Contents

ORIGINAL ARTICLE

PROBLEM – SOLVING ARTICLE

CASE REPORT

ORIGINAL ARTICLE

The Characteristics of Hereditary Colorectal Cancer Syndromes by Population Screening

Andrejs Vanags, Ilze Strumfa, Andris Gardovskis, Inga Melbarde–Gorkusa, Arnis Abolins, Genadijs Trofimovics, Janis Gardovskis
Hereditary Cancer Institute, Riga Stradins University, Riga, Latvia

Summary
Introduction. Colorectal cancer is important medical problem due to frequent occurrence and serious prognosis. Recent advances help to understand the role of heredity of colorectal carcinogenesis with possible implications for prevention.
Aim of the Study. Is to characterise hereditary colorectal cancer by population screening in order to evaluate the needs and possibilities of prevention.
Materials and methods. Population screening was performed in Valka district, evaluating the family cancer history by questionnaire. Hereditary colorectal cancer syndromes were diagnosed by internationally accepted clinical criteria.
Results. The following population frequencies were identified: hereditary non–polyposis colorectal cancer (HNPCC), 0.059% (95% CI = 0.033–0.106%); suspected HNPCC and familial colorectal cancer, 0.107% (95% CI = 0.069–0.166%). The cancer burden among blood relatives of the affected families ranged 15.5–30.1%. The mean age of colorectal cancer diagnostics was 53.7–72.0 years. The probands were mostly oncologically healthy and up to 81.8% – below 50 years of age.
Conclusions. The population frequencies of hereditary colorectal cancer syndromes correspond to significant number of cases. The high cancer burden among blood relatives of the affected families necessitates surveillance, and the age structure and health status of probands is well–suited for this.
Key words: colorectal cancer, hereditary non–polyposis colorectal cancer, population screening.

INTRODUCTION

The high incidence and mortality of colorectal cancer define this malignancy as an important medical problem (3). The role of heredity in the development of colorectal cancer is well–described (5, 6, 9, 10). Hereditary non–polyposis colorectal cancer (HNPCC) is considered the most frequent hereditary cancer syndrome involving the large bowel (4). HNPCC is well–substantiated in the international medical literature devoted to its diagnostic criteria, molecular basis, risk evaluation and possibilities of intervention (4, 8, 10). It has also been studied in Latvian population on hospital patient basis (5).

AIM OF THE STUDY

The aim of the present study is to characterise the hereditary colorectal cancer syndromes in Latvia by population screening approach.

MATERIALS AND METHODS

The population screening for hereditary cancer was performed in the Valka district. In collaboration with 22 family physicians, 18642 family cancer histories were collected from adult inhabitants of Valka district representing 76.6% of the population. No recruitment restrictions were applied for upper age level, gender, ethnicity or health status. Written informed consent was obtained from all patients. All patients filled in the questionnaire reporting the presence and localisation of malignant tumours in blood relatives as well as the age of patient at the time of tumour diagnosis. If the patient has died because of the tumour the death age was ascertained as well. Additional questions were asked about the treatment modalities (e.g. radiation therapy and chemotherapy, extent of operation) of affected persons in order to verify the presence of malignant tumour and to specify its location. The filled forms of family cancer history were analysed in the Hereditary Cancer Institute. HNPCC was diagnosed by Amsterdam Criteria II (4) but suspected, if at least 2 first degree relatives had HNPCC–associated cancer (colorectal, endometrial, small bowel, ureteric, renal pelvis) and at least one cancer was diagnosed before age 50. Familial colorectal cancer, variety 1 (FCC1) was diagnosed if colorectal cancer has been present in at least 2 first degree relatives after the age of 50. Familial colorectal cancer, variety 2 (FCC2) was diagnosed if colorectal cancer has been present in at least 2 second degree relatives at any age. The following approach to analysis was undertaken. The population frequency was calculated as the ratio between the number of diagnosed cases and the studied group. In order to characterise the course of malignant tumour, the data about the age of tumour diagnostics, age of tumour–related death and survival of the affected persons were retrieved from the questionnaires. The cancer burden was calculated as the ratio between affected persons and the whole number of blood relatives in the affected blood line. Descriptive statistical analysis using CIA software (1) was performed involving 95% confidence interval (CI) analysis.

RESULTS

During the population screening, 51 probands were diagnosed with hereditary colorectal cancer syndromes, including 11 cases of HNPCC syndrome (Figure 1), 20 – suspected HNPCC (sHNPCC) syndrome, 15 – FCC1 and 5 – FCC2 syndrome. The corresponding population frequencies were following: HNPCC, 0.059% (95% CI = 0.033–0.106%); sHNPCC and FCC, 0.107% (95% CI = 0.069–0.166%) each. No cases of familial adenomatous polyposis were revealed. The characteristics of the probands are provided in Table 1. The age distribution (Figure 2) of probands suggests elimination of HNPCC probands with advancing age. In contrast, the chance to be diagnosed with FCC increases with age.

In order to evaluate the cancer burden and course, data about presence and location of HNPCC–related tumours were retrieved. There were 23 cases of colorectal cancer and 19 cases of endometrial cancer in HNPCC pedigrees as well as single cases of cancer in the small intestine and renal pelvis, respectively. Endometrial cancer was the dominant manifestation of the hereditary cancer syndrome in some pedigrees (Figure 3). In sHNPCC kindreds, 28 colorectal and 13 endometrial cancers were the only HNPCC–related cancers. In FCC families, 41 cases of colorectal cancer were identified. The burden of index cancers was generally high (Table 2). The mean age of cancer diagnostics and age of cancer related death is shown in the Table 3. Notably, in most groups except endometrial cancer in HNPCC, the mean age exceeds 50 years. In HNPCC, endometrial cancer is diagnosed statistically significantly earlier than colorectal cancer. The higher mean age of colorectal cancer diagnostics in FCC is related to the diagnostic criteria. The course of the malignant tumours within hereditary and familial colorectal cancer syndromes is presented in the Table 4. The following evidence of genetic anticipation was found in HNPCC and sHNPCC kindreds. The mean age of cancer diagnostics in the oldest affected generation was 61.4 years (95% CI for the mean (CIM) = 56.4–66.4 years) but in the next generation – 49.8 years (95% CIM = 44.9–54.7 years).

In HNPCC pedigrees, 3/11 (27.3%; 95% CI = 9.7–56.6%) families reported presence of cancers, not included in the diagnostic criteria (i.e., colorectal, endometrial, small intestinal and renal pelvis cancer). Single cases of brain tumour (0.7%; 95% CI = 0.1–0.3%), breast cancer, lung cancer and head–and–neck cancer were reported. In 1 case, proband reported malignancy located in the abdominal cavity but not further specified. In suspected HNPCC, 22 additional cancers were present in 14/20 (41.2%; 95% CI = 26.3–57.8%) pedigrees. These included 4 cases of breast cancer (3.0% of female blood relatives; 95% CI = 1.2–7.4%), 4 cases of prostate cancer (3.1% of male blood relatives; 95% CI = 1.2–7.6%), 2 cases of lung cancer (0.8%; 95% CI = 0.2–2.7%), 2 cases of pancreatic cancer, 2 cases of brain tumours as well as isolated cases of head–and–neck cancer (0.4%; 95% CI =

0.1–2.1%), urinary bladder cancer, melanoma, Wilms tumour, gastric cancer, renal cancer, cancer of the vulva (0.7% of female blood relatives; 0.1–4.1%) and ovarian cancer. In FCC, 14 additional tumours were present in 10/20 (33.3%; 95% CI = 19.2–51.2%) families. There were 3 cases of sarcoma (1.2%; 95% CI = 0.4–3.6%), 2 cases of gastric cancer (0.8%; 95% CI = 0.2–3.0%), 2 cases of prostate cancer, 2 cases of brain tumours (both in the same kindred), as well as single cases of lung cancer (0.4%; 95% CI = 0.1–2.3%), haematological malignancy, breast cancer. In 2 cases, the location of cancer was unknown to the proband.

DISCUSSION

During the Valka district population screening, both HNPCC families and pedigrees affected by other hereditary colorectal cancer syndromes were identified. The population frequencies of these syndromes were determined. In a hypothetic population of 2 294 590 persons that equals in size the population of Latvia in 2006 (Data bases of the Central Statistics Board, accessed 09.11.2009) but would be identical to Valka population in the age structure, gender and national composition, these frequencies would correspond to 1377 (interval, based on the 95% CI of the relative value, 688–2295) persons diagnosed with HNPCC syndrome and 5048 (interval, based on the 95% CI of the relative value, 3671–6654) persons diagnosed with suspected hereditary colorectal cancer syndromes. The population estimates providing the approximation of probands that might benefit from surveillance have not been described previously.

In order to estimate the magnitude of cancer risk in these pedigrees, the colorectal and endometrial cancer burden among blood relatives in the affected branch was analysed. In all syndromes, colorectal cancer burden exceeds significantly the described cumulative incidence (0–74 years) of colorectal cancer in EU that constitutes 4.53% in males and 2.70% in females (3). Although there is a trend towards higher frequency of colorectal cancer in HNPCC and FCC syndromes in comparison with sHNPCC, the difference is not statistically significant. Two important conclusions can be inferred from these data – the high frequency of colorectal cancer prompts prophylactic follow–up of persons belonging to the affected blood line. The surveillance for colorectal cancer should be equally intense for all the mentioned syndromes as the colorectal cancer frequency shows no statistically significant differences among the syndromes. The colorectal cancer burden in the evaluated families is lower than the described 80% lifetime risk in mutation carriers (8) as we had no possibility to exclude non–carriers by clinical means. However, parameter that can be evaluated on clinical basis is easy and cheap for general medical use, and can give insight in the importance of the problem.

Probands' age structure revealed that significant proportion of probands diagnosed with hereditary cancer syndromes is younger than 50 years of age. In addition, the younger age is more frequent in proband diagnosed with HNPCC and thus subjected to higher cancer risk. Thus, the age structure of probands is well–suited for

timely initiation of surveillance. The age distribution of probands suggests elimination of HNPCC probands with advancing age. In contrast, the chance to be diagnosed with FCC increases with age as the older relatives enter the risk group. The probands mostly were oncologically healthy themselves – a finding that also suggests the possibility to reveal the persons at risk timely.

The mean age of colorectal cancer diagnostics (59.3 (95% CI = 53.8–64.8) years in HNPCC, 55.2 (95% CI = 49.1–61.3) years in sHNPCC) was slightly larger than the published result of 44 years (8). However, relatively young persons at the economically active age are affected. Once the person is affected by hereditary colorectal cancer, the prognosis is serious as reflected by low survival. The death also occurs prematurely: at the mean age of 61.5 (95% CI = 52.9–70.0) years in HNPCC, 56.7 (95% CI = 49.9–63.5) years in suspected HNPCC and 58.7 (95% CI = 53.6–63.8) years in the whole group of definitive and suspected HNPCC. Occasionally, colorectal cancer has caused death of the patients as early as 28 years of age. This early occurrence corresponds to the literature data about HNPCC (7) including even description of colorectal cancer in 19 years old patient. This also emphasizes the need to identify the persons at risk properly and to provide adequate follow–up possibilities. Onset of hereditary colorectal cancer after the age of 50 is also well–known phenomenon that is described even in known mutation carriers (7). Thus, surveillance measures in risk persons should not be cancelled at this age as both the obtained data and literature publications suggest permanent cancer risk.

The age of colorectal cancer diagnostics in FCC families was higher (mean, 72.0 years; 95% CI = 67.3–76.7 years) as predicted by the diagnostic criteria. However, the frequency of colorectal cancer among blood relatives in these pedigrees was not lower.

The frequency of endometrial cancer among females was significant: 22.4% (95% CI = 14.8–32.3%) among female blood relatives in HNPCC families and 9.6% (95% CI = 5.7–15.8%) in sHNPCC families. It exceeds the cumulative incidence (0–74 years) in the EU estimated as 1.5% (3). There is a trend towards lower endometrial cancer risk in sHNPCC families. Although the difference is not statistically significant, further studies in larger group would be necessary to gain more information in larger group.

The endometrial cancer was diagnosed at the mean age 48.4 (95% CI = 43.4–53.4) years in HNPCC families, 50.5 (95% CI = 43.0–58.0) years in the sHNPCC families and 49.4 (95% CI = 45.1–53.7) years in the whole group of definitive and suspected HNPCC. The youngest case was diagnosed with the endometrial cancer at the age of 27 years. Thus, again, females were affected by endometrial cancer at the economically active age. The affected women mostly were alive at the time when population screening was carried out: 17/19 (89.5%; 95% CI = 68.6–97.1%) in HNPCC, 7/13 (53.8%; 95% CI = 29.1–76.8%) in suspected HNPCC and 24/32 (75%; 95% CI = 57.9–86.7%) in the whole group of definitive and suspected HNPCC. The proportion of living persons in the groups of colorectal and endometrial cancer groups was significantly different. Thus, the prognosis is probably better than in case of colorectal cancer; however, the high frequency suggests the need for surveillance. The beneficial prognosis of endometrial cancer in the setting of HNPCC is in agreement with the published data (2,12).

Although cancers in locations other than colorectal, endometrial, small intestinal and renal pelvis were noted, the frequency was low and no dominant location was observed. Among unusual findings, 2 cases of childhood CNS tumours in a single FCC pedigree and several sarcomas in different FCC families were recorded.

We have shown previously (11) that the population screening has shown higher yield of definitive hereditary colorectal cancer syndrome diagnostics than evaluation of hospital patients treated for cancer (the approach further designated in short as hospital screening). The yield of suspected hereditary colorectal cancer syndromes by population screening also has been high in this comparative aspect. The frequency of definitive hereditary colorectal cancer in Latvia by hospital screening data is less than reported from Sweden, Denmark, Finland, Italy, USA and Israel, where the incidence of definitive hereditary colorectal cancer by Amsterdam criteria is 0.5–1.5% of all newly diagnosed colorectal cancer cases, and significantly less than the frequency 3.2% of hereditary colorectal cancers among all colorectal cancers in German population but is close to the frequency of 0.3% in the United Kingdom (5). Thus, hospital screening yields lower number of definitive colorectal cancer than in other Western type societies. Hypothetically, lower frequency of definitive hereditary colorectal cancer in any particular country can be explained by ethnic differences as well as by frequency of factors causing sporadic colorectal cancer. Alternatively, it may be hypothesised that the trend towards higher frequency of hereditary colorectal cancer as revealed by population screening is more in line with other European data and thus can be considered true.

CONCLUSIONS

1. Blood relatives of the HNPCC, sHNPCC and FCC pedigrees are subjected to increased cancer risk that can be approximated by the clinical evaluation of cancer family history at low cost.
2. The course of cancer is unfavourable; considering the two frequent locations, colorectal cancer has worse prognosis than endometrial cancer. In order to prevent cancer development and to prevent the economic loss caused by death or by durable disability of economically active persons, surveillance should be offered in order to start active treatment at precancerous conditions or the cancer at early stage.
3. The age structure and health status of probands is well–suited for surveillance and/or prophylaxis.
4. Population screening discloses more patients at risk

and also brings more information about the real burden of hereditary colorectal cancer in Latvia despite the fact that population screening faces the same problems as the hospital screening in Latvia – incomplete medical information about malignant tumours in previous generations due to several historical reasons.

Conflict of interest: None

REFERENCES

1. Altman D, Machin D, Bryant T, Gardner S. Statistics with confidence: confidence interval and statistical guidelines // 2nd edition, Bristol: BMJ Books, 2000.
2. Boks DE, Trujillo AP, Voogd AC, Morreau H, Kenter GG, Vasen HF. Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer // Int J Cancer, 2002; 102: 198 – 200
3. Boyle P and Ferlay J. Cancer incidence and mortality in Europe, 2004 // Ann Oncol, 2005; 16: 481 – 488
4. Guillem JG, Wood WC, Moley JF, Berchuck A, Karlan BY, Mutch DG, Gagel RF, Weitzel J, Morrow M, Weber BL, Giardiello F, Rodriguez–Bigas MA, Church J, Gruber S, Offit K. ASCO/SSO review of current role of risk–reducing surgery in common hereditary cancer syndromes // Ann Surg Oncol, 2006; 13:1296 – 1321
5. Irmejs A, Borosenko V, Melbarde–Gorkusa I, Gardovskis A, Bitina M, Kurzawski G, Suchy J, Gorski B, Gardovskis J. Nationwide study of clinical and molecular features of hereditary non–polyposis colorectal cancer (HNPCC) in Latvia // Anticancer Res, 2007; 27: 653 – 658
6. Lynch HT, de la Chapelle A. Hereditary colorectal cancer // NEJM, 2003; 348(10):919 – 932
7. Lynch HT, Riley BR, Weissman S, Coronel SM, Kinarsky Y, Lynch JF, Shaw TG, Rubinstein WS. Hereditary nonpolyposis colorectal carcinoma (HNPCC) and HNPCC–like families: problems in diagnosis, surveillance and management // Cancer, 2004; 100(1):53 – 64
8. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in two large midwestern kindreds // Arch Intern Med, 1996; 117:206 – 212
9. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, Cavalieri RJ, Boland CR. Genetics, natural history, tumor spectrum, and pathology of hereditary non–polyposis colorectal cancer: an updated review // Gastroenterology, 1993; 104:1535 – 1549
10. Trimbath JD, Giardiello FM. Review article: genetic testing and counselling for hereditary colorectal cancer // Aliment Pharmacol Ther, 2002; 16: 1843 – 1857
11. Vanags A, Irmejs A, Borosenko V, Gardovskis A, Miklasevics E, Gardovskis J. Comparison of the expedience of population and hospital screening in hereditary cancer detection // Collection of Scientific papers 2008, Riga Stradiņš University, 2009; 31 – 37
12. Vasen HF, Watson P, Mecklin JP, Jass JR, Green JS, Nomizu T, Müller H, Lynch HT. The epidemiology of endometrial cancer in hereditary nonpolyposis colorectal cancer // Anticancer Res, 1994; 14: 1675 – 1678

ACKNOWLEDGEMENTS

The population screening was carried out within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co–financed by European Union Interreg IIIB Neighbourhood program and including participation of the following Valka district family physicians: Maruta Bindre, Lilita Ezerina, Juris Ezerins, Elvira Freiberga, Alla Grinberga, Sanita Jansone, Alda Karklina, Maija Klavina, Ritma Klavina, Marianna Kire, Valdis Kiris, Zane Lukina, Inga Natra, Maris Natra, Liga Putrina, Olga Ribkina, Anna Sakare, Ilona Uzbeka, Inese Verselo, Sniedze Viksna, Maija Zalite, Liga Ziemele. AV is supported by ESF fellowship, project Nr. 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/00

Address:
Andrejs Vanags,
Hereditary Cancer Institute,
Riga Stradins University,
Dzirciema Street 16, LV-1007,
Riga, Latvia,
E-mail: vanags314@inbox.lv

Table 1. Characteristics of the probands diagnosed with hereditary or familial colorectal cancer syndromes

Syndrome	< 50 years: F,% [95% CI]	Females: F,% [95% CI]	Males: F,% [95% CI]	Oncologically healthy: F,% [95% CI]	Cancer location
HNPCC	81.8 [52.3–94.9]	70.0 [39.7–89.2]	30.0 [10.8–60.3]	81.8 [52.3–94.9]	2 CRC
sHNPCC	45.0 [25.8–65.8]	90.0 [69.9–97.2]	10.0 [2.8–30.1]	90.0 [69.9–97.2]	CRC, Br
FCC	27.8 [12.5–50.9]	89.5 [68.6–97.1]	10.5 [2.9–31.4]	95.0 [76.4–99.1]	CRC

Abbreviations in the Table: F, frequency; CI, confidence interval; HNPCC, hereditary non–polyposis colorectal cancer; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC, familial colorectal cancer; CRC, colorectal cancer; Br, breast cancer

Table 2. Comparison of different hereditary and familial colorectal cancer syndromes by frequency of index cancers in blood relatives of the affected pedigrees

Syndrome	Tumour location	Frequency, %	95% CI, %
HNPCC	Index cancers	30.1	23.3 – 38.0
	Colorectal cancer	15.8	10.7 – 22.5
	Endometrial cancer[1]	22.4[1]	14.8 – 32.3[1]
sHNPCC	Index cancers	15.5	11.6 – 20.3
	Colorectal cancer	10.6	7.4 – 14.8
	Endometrial cancer[1]	9.6	5.7 – 15.8[1]
FCC	Colorectal cancer	17.0	12.8 – 22.3

[1] in female

Abbreviations in the Table: CI, confidence interval; HNPCC, hereditary non–polyposis colorectal cancer; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC, familial colorectal cancer

Table 3. Comparison of hereditary and familial colorectal cancer syndromes by age of tumour manifestation

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HNPCC	30 –77	54.2 (50.2 – 58.2)	28 – 89	61.7 (54.2 – 69.2)
CRC	36 – 77	59.3 (53.8 – 64.8)	28 – 89	61.5 (52.9 – 70.0)
Ut	30 – 65	48.4 (43.4 – 53.4)	37 – 72	NA
sHNPCC	27 – 82	53.7 (49.1 – 58.3)	28 – 88	55.5 (49.5 – 61.5)
CRC	28 – 82	55.2 (49.1 – 61.3)	32 – 88	56.7 (49.9 – 63.5)
Ut	27 – 72	50.5 (43.0 – 58.0)	28 – 73	51.2 (33.1 – 69.3)
FCC	41 – 89	72.0 (67.3 – 76.7)	52 – 90	76.3 (73.1 – 79.5)

Abbreviations in the Table: CIM, confidence interval for the mean; HNPCC, hereditary non–polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC, familial colorectal cancer

Table 4. The course of the malignant tumours within hereditary and familial colorectal cancer syndromes

Syndrome	First–year lethality		Survival, years (95% CI)	Alive	
	N	F, % (95% CI)		N	F, % (95% CI)
HNPCC	8/44	18.2 (9.5–32.0)	2.6 (0–5.2)	23/44	52.3 (37.9–66.2)
CRC	6/23	26.1 (12.5–46.5)	1.7 (0.6–2.7)	6/23	26.1 (12.5–46.5)
Ut	1/19	5.3 (0.9–24.6)	8.5	17/19	89.5 (68.6–97.1)
sHNPCC	14/42	25.0 (15.5–37.7)	2.3 (1.1–3.5)	14/42	33.3 (21.0–48.4)
CRC	10/29	34.5 (19.9–52.6)	2.5 (1.2–3.8)	7/29	24.1 (12.2–42.1)
Ut	4/13	30.8 (12.7–57.6)	1.5 (0–3.5)	7/13	53.8 (29.1–76.8)
FCC	10/41	24.4 (13.8–39.3)	2.2 (1.3–3.1)	5/41	12.2 (5.3–25.5)

Abbreviations in the Table: N, absolute number; F, frequency; CI, confidence interval; HNPCC, hereditary non–polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC, familial colorectal cancer

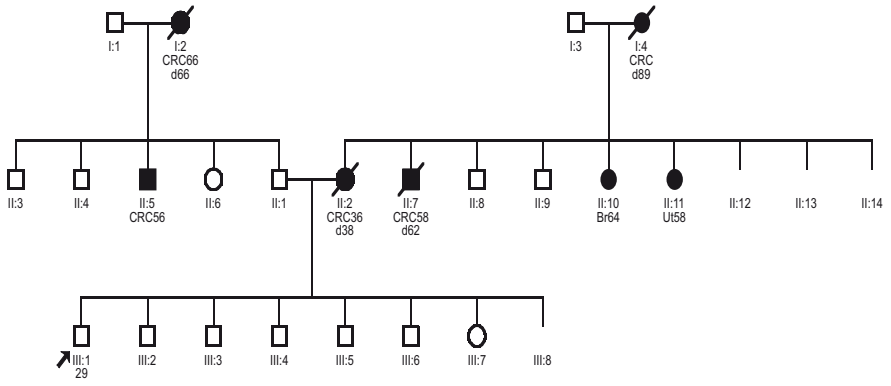


Fig. 1. Pedigree corresponding to the diagnostic criteria of hereditary non–polyposis colorectal cancer syndrome. The pedigree shows also 2 late–onset cases of colorectal cancer in the paternal line that should be considered separately. Abbreviations in the Figure: CRC, colorectal cancer; Br, breast cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow

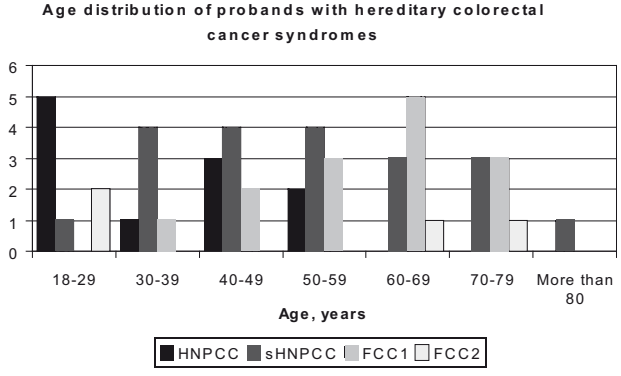


Fig. 2. Age distribution of probands diagnosed with hereditary colorectal cancer syndromes. Abbreviations in the Figure: HNPCC, hereditary non–polyposis colorectal cancer; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC1, familial colorectal cancer, variety 1; FCC2, familial colorectal cancer, variety 2

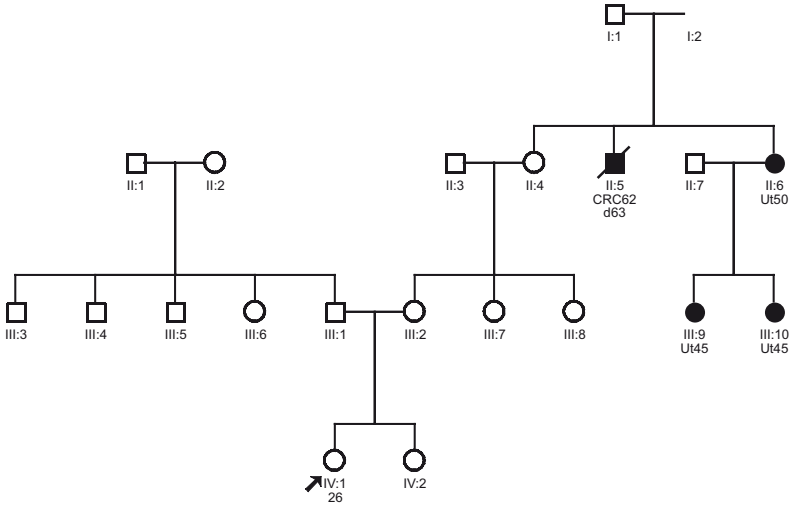


Fig. 3. Hereditary non–polyposis colorectal cancer kindred with predominance of endometrial cancer. Abbreviations in the Figure: CRC, colorectal cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow

ORIGINAL ARTICLE

The Upgrade of Hereditary Cancer Surveillance Schedule by Valka District Population Screening Data

Andrejs Vanags, Ilze Strumfa, Andris Gardovskis, Inga Melbarde–Gorkusa, Arnis Abolins, Genadijs Trofimovics, Janis Gardovskis
Hereditary Cancer Institute, Riga Stradiņš University, Riga, Latvia

Summary
Introduction. The concept of hereditary cancer is one of the most important achievements in modern oncology. It has major scientific implications as well as high practical value in surveillance, prevention and adjustment of treatment for hereditary and familial malignancies. Identification of the persons–at–risk allows recommending a follow–up schedule for timely diagnostics of the corresponding cancers.
Aim of the Study is to evaluate the need for hereditary cancer surveillance program in Latvia and to adjust the surveillance schedule by population screening data.
Materials and methods. The study was performed as population screening in the Valka district, evaluating the family cancer history of 18642 respondents. Hereditary cancers were diagnosed by internationally accepted clinical criteria. Descriptive statistical analysis was carried out by CIA software.
Results. There were 885 persons, fulfilling the clinical diagnostic criteria of hereditary and familial cancer syndromes. The full spectrum of hereditary malignancies was identified thus indirectly characterising the familial background of oncological diseases in the local population. The cancer burden among blood relatives was high for all syndromes, exceeding 8.6%. The mean age of cancer diagnostics was significantly different among the syndromes, ranging 38.0–72.0 years.
Conclusions. The presence of familial background in all most frequent cancer locations and the high cancer burden in the affected kindreds justify the need for familial cancer surveillance. The data about the age of cancer manifestation can be used to adjust the follow–up schedule for most syndromes. Specific recommendations are elaborated and described in the article.
Key words: hereditary cancer, population screening, cancer surveillance.

INTRODUCTION

At present, it is considered that 5–10% of tumours might have hereditary basis – an inherited gene mutation that significantly increase the risk of cancer (12). Hereditary cancers frequently arise early in life (6). In order to prevent hereditary cancer or at least to diagnose it early, follow–up programs could be offered to persons subjected to increased hereditary cancer risk.

AIM OF THE STUDY

To evaluate the need for hereditary cancer surveillance program in Latvia and to adjust the surveillance schedule by population screening data.

MATERIALS AND METHODS

The investigation was designed as population screening for hereditary cancer within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co–financed by European Union Interreg IIIB Neighbourhood programme. The population screening was carried out in the Valka district. There were 18642 respondents in the study (76.6% of the Valka district adult population). Adult persons voluntarily filled out questionnaire concerning family cancer history. No recruitment restrictions were applied for upper age level, gender, ethnicity, presence or absence of cancer, cancer stage and other diagnoses. The participants of the study were asked if his / her relatives (father, mother, grandparents, siblings, children, grandchildren, aunts, uncles and other blood relatives) have had any tumour. If any positive answers were given the participants were asked about the localisation of the tumour. The data about the age of patient at the time of tumour diagnosis were obtained. If the patient has died because of the tumour the death age was ascertained as well. Additional questions were asked about the treatment modalities (e.g. radiation therapy and chemotherapy, extent of operation) of affected persons in order to verify the presence of malignant tumour and to specify its location.
The analysis was performed in the Hereditary Cancer Institute. Cases corresponding to the international diagnostic criteria of any hereditary cancer syndrome (Table 1) were identified and invited for additional medical consultation.

Table 1. The applied diagnostic criteria of hereditary cancer

Hereditary syndrome	Diagnostic criteria
Definitive hereditary non–polyposis colorectal cancer (HNPCC)	Amsterdam II criteria: • At least 3 relatives affected by HNPCC associated cancer (colorectal, endometrial, small bowel, ureteric, renal pelvis); at least one should be first–degree relative of the other two AND • At least two successive generations should be affected AND • At least one cancer should be diagnosed before age 50 AND • Familial adenomatous polyposis (FAP) should be excluded
Suspected HNPCC (sHNPCC)	At least 2 first degree relatives with HNPCC associated cancer (colorectal, endometrial, small bowel, ureteric, renal pelvis) AND at least one cancer is diagnosed before age 50
Familial colorectal cancer, variety 1 (FCC1)	Colorectal cancer in at least 2 first degree relatives after the age of 50. HNPCC and FAP should be excluded
Familial colorectal cancer, variety 2 (FCC2)	Colorectal cancer in at least 2 second degree relatives at any age. HNPCC and FAP should be excluded
Hereditary breast cancer (HBC)	At least 3 breast cancer patients in family at any age AND one of those patients is first degree relative to other two or second degree relative through male
Suspected HBC, variety 1 (sHBC1)	At least one of the following criteria: 1) Breast cancer diagnosed under the age of 40; 2) Medullary or atypical medullary breast cancer; 3) Male breast cancer; 4) Bilateral breast cancer, one of them diagnosed under the age of 50.
Suspected HBC, variety 2 (sHBC2)	Two breast cancers among first degree relatives (or second through male) at any age
Hereditary ovarian cancer (HOC)	At least 3 ovarian cancer cases in family at any age AND one of those patients is first degree relative to other two or second degree relative through male
Suspected HOC (sHOC)	Two ovarian cancer cases among first degree relatives
Hereditary breast/ovarian cancer (HBOC)	At least 3 breast/ovarian cancer patients in family at any age AND one of those patients is first degree relative to other two or second degree relative through male
Suspected HBOC, variety 1 (sHBOC1)	Breast and ovarian cancer in the same individual at any age
Suspected HBOC, variety 2 (sHBOC2)	Two breast or ovarian cancers among first degree relatives (or second through male) at any age
Hereditary endometrial cancer (HEC)	At least 3 first degree relatives with endometrial cancer and at least one of them diagnosed before age of 50
Suspected HEC (sHEC)	Two first degree relatives with endometrial cancer and at least one of them diagnosed before age of 50
Familial endometrial cancer (FEC)	At least 3 first degree relatives with endometrial cancer at any age
Suspected FEC, variety 1 (sFEC1)	At least 2 first degree relatives with endometrial cancer at any age
Suspected FEC, variety 2 (sFEC2)	At least 2 second degree relatives with endometrial cancer at any age
Familial lung cancer (FLC)	At least 3 first degree relatives with lung cancer at any age
Suspected FLC (sFLC)	Two first degree relatives with lung cancer at any age
Hereditary stomach cancer (HSC)	At least 3 first degree relatives with stomach cancer at any age
Suspected HSC (sHSC)	Two first degree relatives with stomach cancer at any age
Hereditary prostate cancer (HPC)	At least 3 blood relatives with prostate cancer at any age OR 2 blood relatives with prostate cancer diagnosed before age of 55 in both of them
Suspected HPC (sHPC)	Two blood relatives with prostate cancer at any age OR Case of prostate cancer diagnosed before age of 55
Familial brain tumour (FBtT)	At least 3 first degree relatives with brain tumour at any age
Suspected FBtT (sFBtT)	Two first degree relatives with brain tumour at any age

Familial haematological tumours (FHemT)	At least 3 first degree relatives with malignant haematological tumour at any age
Suspected FHemT (sFHemT)	Two first degree relatives with malignant haematological tumour at any age
Familial pancreatic tumour (FPan)	At least 2 first–degree relatives with pancreatic tumour or melanoma at any age
Familial cancer of urinary bladder (FBlaC)	At least 3 first degree relatives with urinary bladder cancer at any age
Suspected FBlaC (sFBlaC)	Two first degree relatives with urinary bladder cancer at any age

The diagnosis was updated according to additional data presented by participants. Additional data obtained during consultations were applied in order to identify inter–related families. In this way, the possibility to include any person repeatedly in the analysis due to several kindred relationships was eliminated. Written preventive recommendations were given as well.

The following approach to analysis was undertaken. After the respective cases were diagnosed by clinical hereditary/ familial cancer syndrome, the population frequency was calculated as the ratio between the number of diagnosed cases and the studied group. In order to characterise the course of malignant tumour, the data about the age of tumour diagnostics and age of tumour–related death were retrieved from the questionnaires and subjected to descriptive statistical analysis using CIA software (1). The cancer burden was calculated in a descriptive approach as the ratio between affected persons and the whole number of blood relatives in the affected blood line. The estimates were performed for all hereditary and familial cancer syndromes. In cases when the diagnosis was substantiated on peculiar characteristics of a single case in accordance with the criteria provided in Table 1, the number of relatives was counted in the whole kindred.

The project was accepted by the Central Committee of Medical Ethics. Written informed consent was obtained from all participants.

RESULTS

Analysing 18642 family cancer histories, 885 persons fulfilled the clinical diagnostic criteria of hereditary cancer syndromes. The syndromes were characterised by the population frequency, the index cancer burden in blood relatives, age of tumour diagnostics and age of tumour–related death as shown in Table 2. The population frequency of individual syndromes ranged 0.005 – 0.628%. The most common cancers as breast, lung, colorectal and gastric cancer were characterised also by the highest population frequencies of the respective hereditary cancer syndromes, reaching 1.181% for breast–involving syndromes, 0.569% for familial lung cancer, 0.510% for hereditary and familial gastric cancer and 0.273% for colorectal cancer–involving syndromes. The index cancer burden was generally high invariably exceeding 8.6% (in sHBC1) and reaching high values in common syndromes: 30.1% in HNPCC, 25.5% in familial lung cancer and 25.2% in hereditary stomach cancer. In combination with the mostly close values of the age of cancer diagnostics and age of tumour–related death, the high cancer burden confirmed the significance of the problem. The cancer burden was also evidently greater than the cumulative incidence of the respective tumours in EU population (2). The frequency of non–index cancers in the identified pedigrees also was analysed. In contrast to the index cancer burden, the frequency of breast, ovarian cancer or brain tumours in HNPCC pedigrees did not exceed the cumulative incidence in EU (2). The brain tumour burden was 0.7%; (95% CI = 0.1–0.3%) in HNPCC and 0.8% (95% CI = 0.2–2.7%) in sHNPCC. No ovarian cancer cases were reported in HNPCC, but in sHNPCC the ovarian cancer burden in female blood relatives was 0.7% (0.1–4.1%). The breast cancer burden in females was 1.2% (95% CI = 0.2–6.4%) in HNPCC and 3.0% (95% CI = 1.2–7.4%) in sHNPCC.

Table 2. Characteristics of hereditary and familial cancer syndromes in local population

Syndrome	PF	Cancer burden, %		Age of diagnosis, years		Age of death, years	
		F	95% CI	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HBC	0.011	40.0[1]	19.8–64.3[1]	40–55	47.5 (37.1–57.8)	50–60	54.7 (50.0–59.4)
sHBC1	0.628	8·6	7.2–10.2	20–70	38.0 (36.2–39.7)	26–78	44.7 (41.7–47.7)
sHBC1	0.628	16.3[1]	13.8–19.1[1]	20–70	38.0 (36.2–39.7)	26–78	44.7 (41.7–47.7)
sHBC2	0.343	31.8[1]	27.5–36.4[1]	25–82	51.8 (48.9–54.6)	25–66	60.9 (56.7–65.1)
HBOC	0.011	60.0[1]	31.3–83.2[1]	34–82	61.0 (46.9–75.0)	58–85	71.4 (54.9–87.9)
sHBOC1	0.032	19.3[1]	9.2–36.3[1]	40–60	48.8 (44.2–53.3)	47–69	54.3 (42.3–66.3)
sHBOC2	0.156	30.8[1]	25.0–37.3[1]	18–86	56.6 (51.8–61.4)	23–87	66.1 (61.2–71.0)
HOC	0.005	33.3[1]	12.1–64.6[1]	34–70	49.7 (4.0–95.4)	72	72
sHOC	0.021	36.4[1]	19.7–57.0[1]	45–70	54.2 (46.4–61.9)	47–72	57.2 (50.1–64.3)
HNPCC	0.059	30.1	23.3–38.0	30–77	54.2 (50.2–58.2)	28–89	61.7 (54.2–69.2)
CRC		15.8	10.7–22.5	36–77	59.3 (53.8–64.8)	28–89	61.5 (52.9–70.0)
Ut		22.4[1]	14.8–32.3[1]	30–65	48.4 (43.4–53.4)	37–72	NA
sHNPCC	0.107	15.5	11.6–20.3	27–82	53.7 (49.1–58.3)	28–88	55.5 (49.5–61.5)
CRC		10.6	7.4–14.8	28–82	55.2 (49.1–61.3)	32–88	56.7 (49.9–63.5)
Ut		9.6	5.7–15.8[1]	27–72	50.5 (43.0–58.0)	28–73	51.2 (33.1–69.3)
FCC	0.107	17.0	12.8–22.3	41–89	72.0 (67.3–76.7)	52–90	76.3 (73.1–79.5)
HEC	0.027	41.5[1]	27.8–56.6[1]	40–75	52.1 (47.2–57.0)	44–76	57.7 (49.6–65.8)
sHEC	0.139	32.2[1]	25.7–39.4[1]	30–81	48.5 (44.4–52.6)	35–87	58.7 (53.6–63.8)
FEC/ sFEC1	0.139	30.0[1]	23.8–37.1[1]	52–90	66.2 (63.5–69.9)	54–91	72.4 (69.4–75.4)
sFEC2	0.048	32.4[1]	22.4–44.2[1]	26–82	57.6 (49.9–65.3)	26–83	63.3 (54.7–71.9)
FLC d/s	0.569	18.4	16.4–20.7	18–90	57.9 (55.9–59.9)	13–90	61.2 (58.5–62.1)
FLC	0.070	25.5	19.3–32.8	35–78	56.0 (53.0–59.0)	36–79	57.1 (54.1–60.1)
sFLC	0.499	17.2	15.0–19.7	18–90	58.5 (56.1–60.9)	13–90	61.2 (59.1–63.3)
HSC	0.113	25.2	20.6–30.4	30–83	56.9 (53.4–66.3)	30–90	58.3 (55.3–61.3)
sHSC	0.397	16.0	13.8–18.5	34–95	62.5 (60.1–64.8)	37–96	65.6 (63.4–67.6)
HPC d/s.	0.118	22.2[2]	16.5–29.0[2]	35–75	57.7 (53.3–62.1)	37–80	60.7 (55.0–66.4)
HPC	0.005	21.4[2]	7.6–47.6[2]	70–74	72.0 (67.0–76.9)	76	NA
sHPC	0.113	22.2[2]	16.4–29.4[2]	35–75	56.8 (52.8–60.8)	59.7	54.6–64.8
FBlaC	0.064	22.8	14.9–33.2	60–87	70.7 (66.7–74.7)	65–92	75.7 (71.6–79.8)
FHemT	0.091	16.3	12.1–21.2	3– 88	47.5 (38.9–56.1)	4–86	49.8 (40.5–59.1)
FPan	0.054	14.7	9.1–22.9	51–72	61.6 (57.3–65.9)	51–83	63.4 (58.2–68.6)
FBtT d/s.	0.102	16.5	12.5–21.5	2–77	43.9 (35.0–52.8)	2–77	47.8 (39.7–55.9)
FBtT	0.016	32.3	18.6–49.9	59–60	59.7 (58.2–61.2)	50–65	59.7 (54.3–65.1)
sFBtT	0.086	14.4	10.4–19.5	2–77	41.8 (32.0–51.5)	2–77	45.2 (35.9–54.5)

[1] in female

[2] in male

Abbreviations in the Table: PF, population frequency; F, frequency; CI, confidence interval; CIM, confidence interval for the mean; HBC, hereditary breast cancer; sHBC1, suspected hereditary breast cancer, variety 1; sHBC2, suspected hereditary breast cancer, variety 2; HBOC, hereditary breast ovarian cancer; sHBOC1, suspected hereditary breast ovarian cancer, variety 1; sHBOC2, suspected hereditary breast ovarian cancer, variety 2; HOC, hereditary ovarian cancer; sHOC, suspected hereditary ovarian cancer; HNPCC, hereditary non–polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; NA, not applicable; sHNPCC, suspected hereditary non–polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; sFEC1, suspected familial endometrial cancer, variety 1; sFEC2, suspected familial endometrial cancer, variety 2; FLC, familial lung cancer; d/s, definitive and suspected; sFLC, suspected familial lung cancer; HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer; HPC, hereditary prostate cancer; sHPC, suspected hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; FHemT, familial haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour; sFBtT, suspected familial brain tumour

DISCUSSION

The Valka district population screening has confirmed the presence of hereditary or familial background in all major cancer localisations. The high cancer burden among blood relatives justifies the need for surveillance in the families–at–risk.

Hereditary breast–ovarian cancer is the most common hereditary cancer syndrome in Valka population. In all hereditary breast–ovarian cancer syndromes the index cancer burden among female blood relatives exceeds the respective cumulative frequencies in EU females (2) indicating the need for the surveillance. Although the cancer burden is different in various syndromes, e.g. sHBC1 and sHBC2, it does not characterize the biological properties of cancer, such as growth rate, therefore intensity of follow–up cannot be lowered in syndromes characterised by lower frequency of affected female blood relatives.

According to the literature, annual mammography remains the gold standard of follow–up of female, if her family cancer history corresponds to the criteria of hereditary breast cancer (5). The surveillance is recommended from 25–30 years of age (5, 12) and may include annual breast self–examination (12). Clinical and ultrasound (US) evaluation of breast twice per year also is suggested as well as additional fine needle aspiration or core biopsy if indicated clinically or by US data. In carriers of the *BRCA1/2* mutations, the main genetic background of hereditary breast–ovarian cancer, breast tumours tend to be of high grade and lack calcifications thus decreasing sensitivity of mammography therefore magnetic resonance imaging is considered for screening (6). Surveillance for ovarian cancer includes pelvic US examination and serum testing for tumour markers, e. g. CA125, recommended to start from 25 years of age (5). However, due to lack of recognisable precancerous changes in the ovaries none of methods have been shown to detect ovarian cancer in earlier stage than in symptomatic patients (6).

As revealed by the 95% confidence interval of the mean (CIM) age of tumour diagnostics, clinical tumour manifestation in local hereditary breast–ovarian cancer syndrome patient is expected after 35 years of age. The follow–up aiming at early, preclinical diagnostics must be started earlier. According to literature (5, 6, 12) and results of the present study the following schedule is recommended – annual breast self–examination, clinical and US examination twice per year from 25 years as well as mammography and MRI examination every year from 25 years age, if clinically hereditary breast–ovarian cancer syndrome is established. Transvaginal US examination and serum testing for tumour marker CA125 can be advised from 35 years of age as the lower border of 95% CIM for ovary–involving syndromes is generally higher.

In HNPCC pedigrees, the described life time risk of colorectal cancer in MMR gene mutation carriers reaches 80% (11). HNPCC is characterised by early age at onset of colorectal cancer (10): the mean age of diagnosis is approximately 44 years (11). Due to early cancer development, the surveillance in HNPCC and in suspected HNPCC should include colonoscopy every 1–2 years beginning from 20–25 years and annually after 40 years of age (15).

In Valka HNPCC patients, the mean age of tumour diagnostics is significantly higher. The data of the present study might validate the offered recommendation plan, accounting also for early diagnostics in the few younger cases. Alternatively, the surveillance might be started later. In contrast, FCC probands should consider starting colonoscopy from 35 years of age but in 95% of cases it can be postponed even until 57 years. Thus, the possibility of late–onset familial cancer should be recognised.

According to the literature the risk of extracolonic tumours in HNPCC, e.g. endometrial cancer and ovarian cancer, could be high. The surveillance therefore should include endometrial aspiration or transvaginal ultrasound, and it is recommended for females beginning from 25–35 years of age (7, 15). The endometrial cancer burden among female blood relatives in the presented study is as high as 22.4%, 95% CI=14.8–32.3%. Therefore the proposed surveillance as mentioned above is advised also in the result of the performed research. The highest above mentioned age border would be more appropriate starting point.

In agreement with the published data (17) the results of Valka population screening do not justify surveillance for breast cancer as a part of HNPCC–related person follow–up. The risk of ovarian cancer in HNPCC families is estimated as 6.7–9% by the age of 70 (15, 17). However, the Valka population screening data do not substantiate surveillance for ovarian cancer as the frequency is low and does not exceed the cumulative incidence in EU women (2). Frequency of brain tumours in HNPCC families has been a matter of dispute (17). The Valka population screening data reveal frequency of brain tumours that is very close to the cumulative risk for brain tumour in EU (2). Taking into account this finding and the limited possibilities of early treatment, surveillance for brain tumour cannot be justified.

The cumulative risk of incident endometrial cancer in EU women is estimated as 1.5 (2). The cancer burden was significantly higher in all hereditary endometrial cancer groups, substantiating necessity of surveillance. In the whole hereditary endometrial cancer syndrome groups the lowest observed border of the 95% confidence interval of the mean age was 44.4 years. Starting the surveillance at the age of 35 would be appropriate in at least 95% of affected females. However, the youngest cases were diagnosed at 26 and 30 years of age. Therefore, it would be possible to consider the beginning of surveillance at the age of 25 by endometrial aspiration or transvaginal ultrasound. Prophylactic surgery can be considered in proved mismatch repair gene mutation carriers.

For lung cancer, screening benefit has been reported by some (8) but doubted by other groups (16). The cumulative risk of incident lung cancer in EU is estimated as 6.47 and 1.64 in males and females respectively (2).

The cancer burden was significantly higher both in FLC and sFLC in the Valka population. The mean age of lung cancer diagnostics was: in FLC 56.0 (95% CI=53–59) years, in sFLC 58.5 (95% CI=56.1–60.9) years of age. However, presence of younger lung cancer cases also could be revealed in family cancer history. Thus, the surveillance should be started either at 45 years or 10 years before the younger case of lung cancer in family, whatever comes first, and should consist of lung X–ray twice a year. As synergistic influence of smoking and hereditary factors has been observed (13), cessation of smoking should be strongly recommended for high risk persons.

Both HSC and sHSC in Valka district were characterised by remarkable gastric cancer burden: HSC, 25.2% (95% CI=20.6–30.4%) and sHSC, 16.0% (95% CI=13.8–18.5%) exceeding the cumulative risk of stomach cancer in EU: in females, 0.68 % and in males 1.62% (2). Therefore, surveillance and /or prevention programme is strongly indicated. The mean age of cancer diagnostics was: in HSC 56.9 (95% CI=53.4–66.3) years of age, in sHSC 62.5 (95% CI=60.1–64.8) years of age that represents part of the published interval ranging from 16 to 82 years of age (9). Therefore the surveillance programme should be started either at the age of 45 years or 10 years before the youngest gastric cancer case in family, whatever comes first.

From the surgical point of view, it is important to distinguish between hereditary diffuse stomach cancer (HDSC) and familial intestinal stomach cancer. HDSC is characterised by tendency to submucosal extension, by dismal prognosis as well as by marked difficulties in early endoscopic detection. Hence, prophylactic gastrectomy in proved mutation carriers can be considered as a gold standard, 5 years earlier than the youngest age of gastric tumour diagnosis in the family (4). Therefore *E–cadherin* gene (*CDH1*) evaluation must be offered if the kindred fulfilled the criteria of hereditary diffuse gastric cancer, due to described frequency of *CDH1* gene mutation in HDSC that ranges 30–50% (4). Taking into account the possible high number of HSC cases in Latvia, the prognosis and intervention possibilities as well as psychological and compliance considerations, it would be of utmost importance to set up the *CDH1* gene mutation analysis in combination with subsequent surgical prophylaxis. The minimal recommendations for the present situation or families lacking older medical documentation include clinical evaluation of family history and surveillance by frequent chromoendoscopy combined with biopsy. The endoscopy should be performed biannually (3, 4). At least 15 mucosal biopsies must be provided for histological evaluation (9).

Familial urinary bladder cancer was an example of late–onset familial cancer, characterised by high cancer burden (22.8%) in contrast to incident urinary bladder cancer frequency in EU estimated as 2.82% and 0.52% (2). Thus, surveillance also is recommended by urine cytology, beginning from 50 years of age and continuing annually.

Once familial pancreatic cancer syndrome is established there is a choice to undergo surveillance like endoscopic US, MRI or computed tomography. However, there is no acceptable screening protocol (18). Prophylactic pancreatectomy is not recommended in asymptomatic individuals belonging to familial pancreatic cancer high–risk families (14) due to insufficient data of efficiency as well as severe morbidity of offered procedure.

The frequency of affected persons among blood relatives in the definitive and suspected familial brain tumour and haematological tumour families is high. However, in contrast to the previously discussed types of inherited tumours, no reasonable surveillance program is available.

CONCLUSIONS

1. The presence of familial background in all most frequent cancer locations and the high cancer burden in the affected kindreds justify the need for familial cancer surveillance. The data about the age of cancer manifestation can be used to adjust the follow–up schedule for most syndromes.
2. The follow–up of hereditary breast–ovarian cancer should include breast self–examination, clinical and ultrasound examination from 25 years of age twice per year, mammography and MRI examination annually from 25 years of age, transvaginal examination and serum testing for tumour marker CA125 from 35 years of age.
3. n HNPCC/suspected, HNPCC the follow-up should include colonoscopy every two years from 25 years of age. Annual colonoscopy is indicated after 35 years of age in HNPCC/suspected HNPCC/FCC1/FCC2. For females, transvaginal ultrasound from 25 years of age should be included in cases of HNPCC and in suspected HNPCC. In female matching the criteria of hereditary and familial endometrial cancer syndrome it would be reasonable to start the surveillance programme at the age of 25 by the transvaginal ultrasound annually. Prophylactic hysterectomy is recommended to HEC syndrome patients with proved mismatch repair gene mutation.
4. In familial lung cancer the surveillance should be started at 45 years of age consisting of X–ray twice per year.
5. In hereditary stomach cancer syndrome, biannual chromendoscopy surveillance combined with at least 15 biopsies is indicated from 45 years of age. *E–cadherin* gene (*CDH1*) evaluation should be set up as prophylactic gastrectomy can be recommended to *CDH1* gene mutation carriers.
6. The surveillance for familial urinary bladder cancer include urine cytology annually beginning from 50 years of age.
7. No reasonable surveillance schedule can be recommended for familial pancreatic cancer, familial brain tumour and familial haematological malignancies.

Conflict of interest: None

REFERENCES

1. Altman D, Machin D, Bryant T, Gardner S. Statistics with confidence: confidence interval and statistical guidelines. 2nd edition, Bristol: BMJ Books; 2000.
2. Boyle P and Ferlay J. Cancer incidence and mortality in Europe, 2004 // Ann Oncol, 2005; 16: 481 – 488
3. Caldas C, Carneiro F, Lunch HT, Yokota J, Wiesner GL, Powell SM, Lewis FR, Huntsman DG, Pharoah PDP, Jankowski JA, McLeod P, Vogelsang H, Keller G, Park KGM, Richards FM, Maher ER, Gayther SA, Oliveira C, Grehan N, Wight D, Seruca R, Roviello F, Ponder BAJ, Jackson CE. Familial gastric cancer: Overview and guidelines for management // J Med Genet 1999; 36:873 – 880
4. Cisco RM, Ford JM, Norton JA. Hereditary diffuse gastric cancer: implications of genetic testing for screening and prophylactic surgery // Cancer, 2008; 113(Suppl 7):1850 – 1856
5. Cortesi L, Turchetti D, Marchi I, Fracca A, Canossi B, Rachele B, Silvia R, Rita PA, Pietro T, Massimo F. Breast cancer screening in women at increased risk according to different family histories: an update of the Modena Study Group experience // BMC Cancer, 2006; 6:210 – 218
6. Eccles DM. Hereditary cancer: guidelines in clinical practice. Breast and ovarian cancer genetics // Ann Oncol, 2004; 15 (Supplement 4): iv133 – iv138
7. Guillem JG, Wood WC, Moley JF, Berchuck A, Karlan BY, Mutch DG, Gagel RF, Weitzel J, Morrow M, Weber BL, Giardiello F, Rodriguez–Bigas MA, Church J, Gruber S, Offit K. ASCO/SSO review of current role of risk–reducing surgery in common hereditary cancer syndromes // Ann Surg Oncol, 2006; 13:1296 – 1321
8. International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening // N Engl J Med, 2006; 355(17):1763 – 1771
9. Lynch HT, Kaurah P, Wirtzfeld D, Rubinstein WS, Weissman S, Lynch JF, Grady W, Wiyrick S, Senz J, Huntsman D. Hereditary diffuse gastric cancer: diagnosis, genetic counselling, and prophylactic total gastrectomy // Cancer, 2008; 112(12):2655 – 2663
10. Lynch HT, Riley BR, Weissman S, Coronel SM, Kinarsky Y, Lynch JF, Shaw TG, Rubinstein WS. Hereditary nonpolyposis colorectal carcinoma (HNPCC) and HNPCC–like families: problems in diagnosis, surveillance and management // Cancer, 2004; 100(1):53 – 64
11. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in two large midwestern kindreds // Arch Intern Med, 1996; 117:206 – 212
12. Olopade OI, Pichert G. Cancer genetics in oncology practice // Ann Oncol, 2001; 12:895 – 908
13. Rachtan J, Sokolowski A, Niepsuj S, Zemła B, Zwierko M. Familial lung cancer risk among women in Poland // Lung Cancer, 2009; 65(2):138 – 43
14. Rieder H, Sina–Frey M, Ziegler A, Hahn SA, Przypadlo E, Kress R, Gerdes B, Colombo Benkmann M, Eberl T, Grützmann R, Lörken M, Schmidt J, Bartsch DK. German national case collection of familial pancreatic cancer – clinical–genetic analysis of the first 21 families // Onkologie, 2002; 25: 262 – 266
15. Trimbath JD, Giardiello FM. Review article: genetic testing and counselling for hereditary colorectal cancer // Aliment Pharmacol Ther, 2002; 16: 1843 – 1857
16. US Preventive Services Task Force. Lung cancer screening: recommendation statement // Ann Intern Med 2004; 140(9):738 – 739.
17. Watson P, Vasen HF, Mecklin JP, Bernstein I, Aarnio M, Järvinen HJ, Myrhøj T, Sunde L, Wijnen JT, Lynch HT. The risk of extra–colonic, extra–endometrial cancer in the Lynch syndrome // Int J Cancer, 2008; 123(2):444 – 449
18. Windsor JA. An update on familial pancreatic cancer and the management of asymptomatic relatives // HPB, 2007; 9:4 – 7

ACKNOWLEDGEMENTS

The pilot project of the population screening was carried out within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co–financed by European Union Interreg IIIB Neighbourhood program and including participation of the following Valka district family physicians: Maruta Bindre, Lilita Ezerina, Juris Ezerins, Elvira Freiberga, Alla Grinberga, Sanita Jansone, Alda Karklina, Maija Klavina, Ritma Klavina, Marianna Kire, Valdis Kiris, Zane Lukina, Inga Natra, Maris Natra, Liga Putrina, Olga Ribkina, Anna Sakare, Ilona Uzbeka, Inese Verselo, Sniedze Viksna, Maija Zalite, Liga Ziemele. AV is supported by ESF fellowship, project Nr. 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009.

Address:
Andrejs Vanags
Hereditary cancer institute,
Riga Stradins University,
Dzirciema Street 16, LV-1007, Riga, Latvia,
E-mail: vanags314@inbox.lv

DOI: 10.2478/v10163-011-0003-3

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

ORIGINAL ARTICLE

Apolipoprotein A1 and Transferrin as Biomarkers in Ovarian Cancer Diagnostics

Ronalds Macuks*, Ieva Baidekalna*, Julia Gritcina*, Arina Avdejeva*, Simona Donina, *****
*Riga Stradins University, Riga, Latvia
**Latvian Oncology Center, Riga Eastern Clinical University Hospital, Riga, Latvia
***Riga Stradins University, A.Kirhensteins Institute of Microbiology and Virology, Riga, Latvia

Summary
Introduction. Advanced technologies such as matrix assisted laser desorption/ionization and surface enhanced laser desorption/ionization mass spectrometry has introduced promising insights into ovarian cancer detection. Several highly sensitive and specific protein peaks have been identified that discriminates ovarian cancer patients from patients with benign ovarian tumors and controls.
Aim of the Study. Objective of this study is to evaluate diagnostic accuracy each individual marker and combined serum biomarker assay consisting of apolipoprotein A1, transferrin and Ca125.
Materials and methods. A case–control study consisted of 99 women – 37 patients with ovarian cancer, 31 patients with benign ovarian diseases, and 31 age–matched healthy controls. Apolipoprotein A1 and transferrin was measured in sera using immunological turbidimetric assay. Tumor marker CA125 was analyzed by standard enzyme–labeled chemiluminescent immunometric assay. To compare the difference between variables in the study groups, ANOVA test was performed and for correlation Pearson's correlation analysis applied. Sensitivity and specificity of the diagnostic tests was calculated using statistical program Vassarstat.
Results. Serum apolipoprotein A1 and transferrin were down regulated, controversially to Ca125, which was up regulated among ovarian cancer patients. Negative correlation between transferrin and Ca 125 ($p<0.00$), apolipoprotein A1 and Ca 125 ($p<0.00$) and positive correlation between transferrin and apolipoprotein A1 ($p<0.00$) was observed. For single biomarker test highest diagnostic sensitivity and specificity for Ca125 was observed. Addition of apolipoprotein A1 or transferrin to serum level of Ca125 with the condition, that both have to overlap the threshold (Ca125 > 21U/ml and apolipoprotein A1 ≤139.1 mg/dl or transferrin ≤ 2.3 g/l), yielded test specificity of 96.7%. Addition of apolipoprotein A1 to Ca125 improved test sensitivity up to 94.5% maintaining high sensitivity at the same time 91.1%, respectively, when discriminating controls from ovarian cancer patients. Biomarker test consisting of apolipoprotein A1, transferrin and Ca125 had high specificity at unacceptable sensitivity.
Conclusions. Combined biomarker tests discovered using advanced technologies can aid more accurate ovarian cancer detection. Use of apolipoprotein A1 in combination with Ca125 at distinct thresholds can improve ovarian cancer detection.
Key words: apolipoprotein A1, transferrin, ovarian, cancer; screening.

INTRODUCTION

Ovarian cancer is the 5th leading cause of death between all cancers and most common between gynecological cancers worldwide. In year 2007–2008 mortality rates in Latvia were 194 and 200 cases each year with an incidence of 309 and 280 cases, respectively.

Cancer antigen 125 is the most studied and well characterized serologic tumor marker for advanced epithelial ovarian cancers. However, its use as a population–based screening tool for early detection and diagnosis of ovarian cancer is limited by its low sensitivity and specificity, therefore a variety of biomarkers have been investigated to improve ovarian cancer detection (9,12,21). Promising results have implemented advanced technologies such as matrix assisted laser desorption/ionization and surface enhanced laser desorption/ionization mass spectrometry. Several protein peaks have been identified that discriminates ovarian cancer patients from patients with benign ovarian tumors and controls. Particular technologies already have been used to detect other tumors such as prostate cancer, transitional cell carcinoma of the bladder, and cervical cancer (1,18,24,25).

A comprehensive review of these technologies and clinical applications are described in literature (4, 5 ,8, 13, 17, 26).

Several authors have reported about different expression of transferrin and apolipoprotein A1 in serum among ovarian cancer patients and healthy controls improving sensitivity of ovarian cancer diagnostic tests to 74–98% at specificity of 92–98% (3,16,19,27).

AIM OF THE STUDY

Objective of this study is to evaluate diagnostic accuracy of each individual marker and combined serum biomarker assay consisting of apolipoprotein A1, transferrin and Ca125.

MATERIALS AND METHODS

Ethical approval was taken for this study from the Ethics Committee of Riga Stradins University. A case–control study consisted of 99 women – 37 patients with ovarian cancer in Group A, 31 patients with benign ovarian diseases in Group B, and 31 age–matched healthy controls in Group C. Patients were divided into the 2 study groups after surgery according to final histological

diagnosis. In Group B were patients thought to have had ovarian cancer before the operation. Patients with severe co–morbidities, previous or coexisting other malignancy were not included in the study. In the both study groups tumors arising only from epithelial origin were included (Table 1).

Table 1. Clinical characteristics and age distribution of 99 study samples

Diagnostic group	Age range	Mean age	Pathology		
			Serous	Endo–metroid	Mucinous
Group A	36–87	60.6	35	1	1
Group B	40–79	58.0	19	5	7
Group C	37–81	58.2	–	–	–

Serum samples from patients were collected into two Becton and Dickenson 6ml serum vaccutainers in the early morning of the planned surgery day. Vaccutainers according to protocol were shaked 6–8 times, left for clot formation between 60 and 120 minutes and centrifuged during the interval for 10 minutes at 1300 RPM. After that serum was aliquoted, divided and transferred into nine 0.5ml eppendorfs for storage at – 80 degrees C. For the control group women serum samples were taken after transvaginal ultrasonographic examination and ensuring of having no gynecological pathology.

In the control group were women chosen who attended gynecologist in out patient clinic.

Tumor marker CA125 was detected in patient's serum by standard enzyme–labeled chemiluminescent immu–nometric assay ADVIA Centaur CA125 II™, Multi–Diluent 1, Bayer, using Siemens analyzer Immulite–2000 (1,24).

Apolipoprotein A1 was measured in sera using immunological turbidimetric assay manufactured by Roche Diagnostics (2,16,20,22).

Transferrin was similarly measured in sera using immunological turbidimetric assay manufactured by Roche Diagnostics (7,11,23). Upper limit of 95% confidence interval from control group women was chosen as a cutoff level for apolipoprotein A1 and transferrin serum concentration.

For ovarian cancer patients a total abdominal hysterectomy with bilateral salpingoophorectomy and omentectomy was performed. Some ovarian cancer patients were subjected for pelvic lymphadenectomy as a staging or cytoreductive procedure. For patients with benign gynecological tumors a total abdominal hysterectomy with or without bilateral salpingoophorectomy was performed.

To evaluate mean biomarker concentrations in the groups, descriptive analysis were performed using statistical program SPSS 17.0. To reflect the standard deviations for the calculated values standard error of the mean was used. To compare the difference between variables in the study groups, ANOVA test was performed and for correlation Pearson's correlation analysis applied. Sensitivity and specificity of the diagnostic tests was calculated using statistical program Vassarstat. To display diagnostic performance of each individual and combined biomarker test, receivers operating curve was drawn.

RESULTS

Both patient and control groups were similar according to the mean age (p=0.59). Level of Ca125 was analyzed as it is considered as a standard biomarker for ovarian cancer detection.

Serum apolipoprotein A1 and transferrin were down regulated in Group A, controversially to Ca125, which was up regulated among ovarian cancer patients (Figure 1)

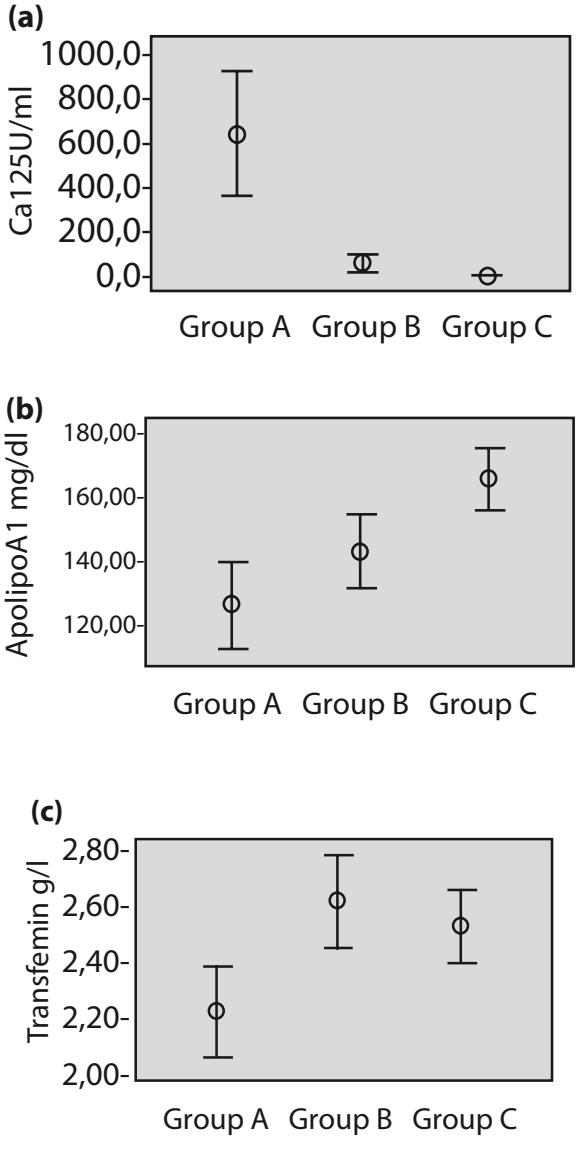


Fig. 1. Distribution of mean serum Ca125 (a), Apolipoprotein A1 (b) and Transferrin (c) concentrations among study and control groups

Difference between mean serum concentrations in the study and control groups were statistically significant, except transferrin concentrations when compared between groups B and C (Tables 2, 3).

Table 2. Mean serum concentrations of serum Transferrin, Apolipoprotein A1 and Ca 125 in study and control groups

Diagnostic group	Transferrin, g/l (95% CI)	Apolipo A1, mg/dl (95% CI)	Ca 125, U/ml (95% CI)
Group A	2.21 ± 0.08 (2.0 – 2.3)	125.42 ± 6.75 (111.7 – 139.1)	627.80 ± 134.52 (353.7 – 901.8)
Group B	2.61 ± 0.08 (2.4 – 2.7)	142.36 ± 30.79 (131 – 153.6)	63.70 ± 17.29 (28.3 – 99.0)
Group C	2.52 ± 0.06 (2.4 – 2.6)	165.35 ± 26.74 (155.5 – 175.1)	7.37 ± 0.63 (6.0 – 8.6)

Table 3. Differences among study and control groups mean Transferrin, Apolipoprotein A1 and Ca 125 serum concentrations (p value)

Diagnostic group	Transferrin	Apolipo A1	Ca 125
Group A vs. B	0.00	0.06	0.00
Group B vs. C	0.41	0.00	0.00
Group C vs. A	0.00	0.00	0.00

Negative correlation between transferrin and Ca 125 ($p<0.00$), apolipoprotein A1 and Ca 125 ($p<0.00$) and positive correlation between transferrin and apolipoprotein A1 ($p<0.00$) was observed.

For single biomarker test highest diagnostic sensitivity and specificity for Ca125 was observed. Addition of apolipoprotein A1 or transferrin to serum level of Ca125 with the condition, that both have to overlap the threshold (Ca125 > 21U/ml and apolipoprotein A1 ≤139.1 mg/dl or transferrin ≤2.3 g/l), improved specificity of the test up to 96.7%. But addition of apolipoprotein A1 or Transferrin to serum level of Ca125 with the condition, that one of them have to overlap the threshold, improved test sensitivity up to 94.5% with decrease in specificity to 59.6% – 62.9%. Further addition of third biomarker yielded prominent specificity with dramatic decrease in sensitivity (Table 4).

Table 4. Accuracy of individual and combined biomarker diagnostic tests evaluated between Groups A vs. B and C

Biomarkers (threshold)	Sensitivity	Specificity
Apolipoprotein A1 (≤139.1 mg/dl)	75.6%	70.9%
Transferrin (≤2.3 g/l)	72.9%	74.1%
Ca 125 (>21 U/ml)	91.9%	80.6%
Apolipoprotein A1 (≤139.1 mg/dl) and Ca 125 (>21 U/ml)	72.9%	88.7%
Apolipoprotein A1 (≤139.1 mg/dl) or Ca 125 (>21 U/ml)	94.5%	62.9%
Apolipoprotein A1 (≤ 139.1 mg/dl) and Transferrin (≤ 2.3 g/l)	64.8%	93.5%
Apolipoprotein A1 (≤ 139.1 mg/dl) or Transferrin (≤ 2.3 g/l)	83.7%	51.6%
Transferrin (≤ 2.3 g/l) and Ca 125 (>21 U/ml)	70.2%	96.7%
Transferrin (≤ 2.3 g/l) or Ca 125 (>21 U/ml)	94.5%	59.6%
Apolipo A1 (≤ 139.1 mg/dl) , Transferrin (≤ 2.3 g/l) and Ca 125 (>21 U/ml)	62.1%	100.0%

Similarly, the highest sensitivity and specificity was observed for Ca125 alone when applied to distinguish cancer patients from healthy controls in groups A and C. Only addition of apolipoprotein A1 improved test sensitivity up to 94.5% maintaining high sensitivity at the same time – 91.1% (Table 5). For all other biomarker combinations sensitivity or specificity was low.

Table 5. Accuracy of individual and combined biomarker diagnostic tests evaluated between Groups A and C

Biomarkers (treshold)	Sensitivity	Specificity
Apolipoprotein A1 (≤139.1 mg/dl)	75.6%	90.3%
Transferrin (≤2.3 g/l)	78.3%	70.9%
Ca 125 (>21 U/ml)	91.9%	100.0%
Apolipoprotein A1 (≤139.1 mg/dl) and Ca 125 (>21 U/ml)	72.9%	100.0%
Apolipoprotein A1 (≤139.1 mg/dl) or Ca 125 (>21 U/ml)	94.5%	91.1%
Apolipoprotein A1 (≤ 139.1 mg/dl) and Transferrin (≤ 2.3 g/l)	67.5%	100.0%
Apolipoprotein A1 (≤ 139.1 mg/dl) or Transferrin (≤ 2.3 g/l)	78.3%	61.2%
Transferrin (≤ 2.3 g/l) and Ca 125 (>21 U/ml)	78.3%	100.0%
Transferrin (≤ 2.3 g/l) or Ca 125 (>21 U/ml)	94.5%	70.9%

Ca125 alone was more accurate predictor of the disease when compared to combinations of Ca125+Apolipoprotein A1 or Ca125+Transferrin (Figure 2).

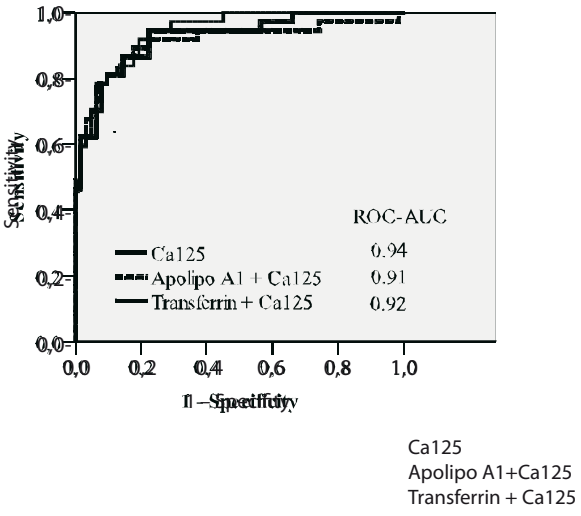


Fig. 2. Ability to separate ovarian cancer patients of single and combined biomarker tests

DISCUSSION

This study reflects facilities of advanced technologies which can separate differently expressed protein levels in ovarian cancer patients and healthy women. Information derived from innovative technologies can aid usage of conventional investigation methods more targeted.

Our sample set contained only 6 patients with early stage ovarian cancers; therefore we were not able to perform comparison of protein expression among early and late stage ovarian cancers.

Despite efforts to find new highly sensitive and specific biomarkers, CA125 still is a most accurate single biomarker for ovarian tumor malignancy prediction. Addition of new biomarkers can only improve diagnostic precision of Ca125.

Numerous studies have noted differently expressed protein peaks of apolipoprotein A1 and transferrin in ovarian cancer and control group patients (3,6,10,14,28). Most of studies had significant improvement in sensitivity and specificity of combined diagnostic tests. In literature there have been published articles about different prediction models, which can discriminate normal serum samples from serum samples derived from patients with low malignancy potential tumors with 91% sensitivity at specificity of 92%, and normal samples from early stage ovarian cancer with a sensitivity of 89% at specificity of 92% (3). Higher diagnostic accuracy of particular study can be explained by having another biomarker transthyretin included in malignancy prediction model. In our study merging of all biomarkers resulted in lower malignancy prediction rates than use of algorithm when apolipoprotein A1 should be down regulated or Ca 125 elevated.

Consolidation of all biomarkers offered high specificity with essential decrease of sensitivity. Other authors have reported about high diagnostic sensitivity and specificity reaching 97% and 99% (AUC 99%), respectively, especially combining more than 2 newly discovered serum proteins with Ca125 (3).

CONCLUSIONS

Combined biomarker tests discovered using advanced technologies can aid more accurate ovarian cancer detection. Use of apolipoprotein A1 in combination with Ca125 at distinct thresholds can improve ovarian cancer detection. Other biomarker incorporation in diagnostic tests should be investigated and further prospective studies with larger sample size are needed to reach clear conclusions.

Conflict of interest: None

REFERENCES

1. Banks RE, Dunn MJ, Forbes MA, Stanley A, Pappin D, Naven T, Gough M, Harnden P, Selby PJ. The potential use of laser capture microdissection to selectively obtain distinct populations of cells for proteomic analysis – preliminary findings // Electrophoresis, 1999; 20:689–700
2. Becker W, Rapp W, Schwick HG, Störiko KZ. Methods for the quantitative determination of plasma proteins by immunoprecipitation // Klin Chem Klin Biochem, 1968; 6:113–22
3. Feng S, Lang J, Kumar A, Carey N, Hsieh B, Suchard MA., Reddy ST, Farias–Eisner R. Validation of Candidate Serum Ovarian Cancer Biomarkers for Early Detection // Biomarker Insights, 2007; 2:369–375
4. Fung ET, Thulasiraman V, Weinberger SR, Dalmasso EA. Protein biochips for differential profiling // (a) Curr Opin Biotechnol, 2001;12:65–69
5. Fung ET, Wright GL Jr, Dalmasso EA. Proteomic strategies for biomarker identification: progress and challenges // (b) Curr Opin Mol Ther, 2000; 2:643–650
6. Goufman EI, Moshkovskii SA, Tikhonova OV, Lokhov PG, Zgoda VG, Serebryakova MV, Toropygin IY, Vlasova MA, Safarova MR, Makarov OV, Archakov AI. Two–dimensional electrophoretic proteome study of serum thermostable fraction from patients with various tumor conditions // Biochemistry (Mosc), 2006; 71(4):354–60
7. Heidelberg M, Kendall FE // J Exp Med, 1935; 62:697
8. Hood BL, Malehorn DE, Conrads TP, Bigbee WL. Serum proteomics using mass spectrometry // Methods Mol Biol, 2009; 520:107–28
9. Jacobs I, Bast RC Jr. The CA 125 tumour–associated antigen: a review of the literature // Hum Reprod, 1989; 4:1–12

10. Kozak KR, Su F, Whitelegge JP, Faull K, Reddy S, Farias–Eisner R. Characterization of serum biomarkers for detection of early stage ovarian cancer // Proteomics, 2005; 5(17):4589–96
11. Lizana J, Hellsing K. Manual immunoephelometric assay of proteins, with use of polymer enhance–ment // Clin Chem, 1974; 20:1181–6
12. MacDonald ND, Jacobs IJ. Is there a place for screening in ovarian cancer // Eur J Obstet Gynecol Reprod Biol, 1999; 82:155–157
13. Merchant M, Weinberger SR. Recent advancements in surface–enhanced laser desorption/ionization time–of–flight mass spectrometry // Electrophoresis, 2000; 21:1164–1177
14. Moore LE, Fung ET, McGuire M, Rabkin CC, Molinaro A, Wang Z, Zhang F, Wang J, Yip C, Meng XY, Pfeiffer RM. Evaluation of apolipoprotein A1 and posttranslationally modified forms of transthyretin as biomarkers for ovarian cancer detection in an independent study population // Cancer Epidemiol Biomarkers Prev, 2006; 15(9):1641–6
15. Naito HK. Reliability of lipid, lipoprotein, and apolipoprotein measurements // Clin Chem, 1988; 34:84–94
16. Nosov V, Su F, Amneus M, Birrer M, Robins T, Kotlerman J, Reddy S, Farias–Eisner R. Validation of serum biomarkers for detection of early–stage ovarian cancer // Am J Obstet Gynecol, 2009; 200:639
17. Palmer–Toy D, Kuzdzal S, Chan, DW. Proteomic approaches to tumor marker discovery // In: Diamandis EP, Fritsche H, Lilja H, Chan DW, Schwartz M, eds. Tumor Markers Physiology, Pathobiology, Technology and Clinical Applications. Philadelphia: AACC Press; 2002; 391–400
18. Paweletz CP, Gillespie JW, Ornstein DK, Simone NL, Brown MR, Cole KA, Wang QH, Huang J, Hu N, Yip TT, Rich WE, Kohn EC, Linehan WM, Weber T, Taylor P, Emmert–Buck MR, Liotta LA, Petricoin EF. Rapid protein display profiling of cancer progression directly from human tissue using a protein bio–chip // Drug Dev Res, 2000; 49:34–42
19. Rai AJ, Zhang Z, Rosenzweig J, Shih I, Pham T, Fung ET, Sokoll LJ, Chan DW. Proteomic Approaches to Tumor Marker Discovery Identification of Biomarkers for Ovarian Cancer // Arch Pathol Lab Med, 2002; 126(12):1518–1526
20. Rifai N, King ME. Immunoturbidimetric assays of apolipoproteins A, AI, AII, and B in serum // Clin Chem, 1986; 32:957–61
21. Shih IM, Sokoll LJ, Chan DW. Tumor markers in ovarian cancer // In: Diamandis EP, Fritsche H, Lilja H, Chan DW, Schwartz M. Tumor Markers Physiology, Pathobiology, Technology and Clinical Applications. Philadelphia: AACC Press; 2002; 239–252Siedel J, Schiefer S, Rosseneu M, Bergeaud R, De Keersgieter W, Pautz B, Vinaimont N, Ziegenhorn J. Immunoturbidimetric method for routine determinations of apolipoproteins A–I, A–II, and B in normo– and hyperlipemic sera compared with immunonephelometry // Clin Chem, 1988; 34:1821–5
22. Tietz NW. Transferrin // In: Tietz NW. Fundamentals of clinical Chemistry. 2nd ed. Philadelphia: WB Saunders; 1976; 278–280
23. Vlahou A, Schellhammer PF, Mendrinos S, Patel K, Kondylis FI, Gong L, Nasim S, Wright Jr. Development of a novel proteomic approach for the detection of transitional cell carcinoma of the bladder in urine // Am J Pathol, 2001; 158:1491–1502
24. Von Eggeling F, Junker K, Fiedler W, Wollscheid V, Dürst M, Claussen U, Ernst G. Mass spectrometry meets chip technology: a new proteomic tool in cancer research // Electrophoresis, 2001; 22: 2898–2902
25. Weinberger SR, Morris TS, Pawlak M. Recent trends in protein biochip technology // Pharmacogenomics, 2000; 1:395–416
26. Zhang Z, Bast RC, Jr, Yu Y, Li J, Sokoll LJ, Rai AJ, Rosenzweig JM, Cameron B, Wang YY, Meng XY, Berchuck A, Van Haaften–Day C, Hacker NF, de Bruijn HWA, Van der Zee AGJ, Jacobs IJ, Fung ET, Chan DW. Three Biomarkers Identified from Serum Proteomic Analysis for the Detection of Early Stage Ovarian Cancer // Cancer Research, 2004; 64:5882–5890
27. Zhao Q, Duan W, Wu YM, Qian XH, Deng XH. Analysis of serum biomarkers of ovarian epithelial cancers based on 2–DE DIGE and MALDI TOF/TOF // Zhonghua Zhong Liu Za Zhi, 2008; 30(10):754–8

Acknowledgement
Study was done within the framework of Latvian University project (number: 2009/0220/1DP/1.1.1.2.0/09/APIA/VIAA/016) and P.Stradins University project (number: 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009)".

Address:
Ronalds Macuks
Mezciema street 23/1–55,
Riga, Latvia, LV-1079
E-mail: r.macuks@gmail.com

ORIGINAL ARTICLE

Surgical Complications in Early Period after Renal Transplantation

Janis Jushinskis, Vadims Suhorukovs, Sergejs Trushkovs, Janis Bicans, Victors Shevelevs, Rafails Rozentals
Riga Stradins University, Transplant Laboratory
Pauls Stradins Clinical University Hospital, Latvian Transplantation Center

Summary.
Introduction. Growing number of elderly transplant recipients and expansion of the criteria for organ donation may increase the risk of post–transplant complications and impact outcomes.
Aim of the Study. The aim of this study was to define the rate of surgical complications needing re–operations and their impact on posttransplant outcomes.
Materials and methods. Study includes 202 consecutive deceased donor renal transplantations performed from 01.01.2004 till 31.12.2006. with further follow–up for 3 years. We analyzed the rate of re–operations, associated donor, recipient and transplantation factors and impact on post–transplant outcomes.
Results. Reasons for re–operations were bleeding and hematoma formation (n=27), urological complications (n=18) and lymphocele (n=26). Hematomas were associated increased donor body mass index (BMI, p=0,067), presence of glomerular sclerosis at zero–time biopsy (p=0,034) and with development of urological complications (p=0,004) and delayed graft function (p=0,012). Urological complications were not associated with donor, recipient and transplant factors. Lymphocele were associated with donor factors (non–traumatic brain death, p=0,034, asystoly and hypotension, p=0,077, BMI, p=0,061, presence of glomerular sclerosis at zero–time biopsy, p=0,030), re–transplantations (p=0,092) and ATG use (p=0,094). Graft loss and patient survival during the follow–up period were not associated with mentioned surgical complications.
Conclusions. Post–transplant surgical complications are associated with donor condition but without impact on three–year graft and patient survival.
Key words: surgical complications, renal transplantation, donor factors, transplantation outcomes.

INTRODUCTION

Surgical complications (SC) after renal transplantation (RT) remain one the main concerns in transplantation (8). By the same time there are two clear tendencies in current transplantation: increasing age and co–morbidity in RT recipients leading to overload in "waiting list" and increasing shortage of donor organs, and expansion of the criteria for deceased donation in order to increase the number of donor organ available for transplantation (2). However, both tendencies may be associated also with increased risk of complications after RT, leading to worse transplantation outcomes, longer hospital stay after transplantation, and, accordingly, higher costs of treatment.

AIM OF THE STUDY

The aim of our study was to evaluate the association of surgical complications needing additional surgical interventions in the early posttransplant period with the condition of deceased donors, graft quality, recipient and transplantation factors, and to determine the impact of surgical complications on later posttransplant outcomes.

MATERIALS AND METHODS

Study included 202 consecutive deceased donor renal transplantations performed in a single center from 01.01.2004 till 31.12.2006. Patients were divided into four groups according to the presence of SC in the early posttransplant period (till the discharge from hospital): group A (n=145) – without complications (control group); group B (n=18) – with urological complications; group C (n=27) – with vascular complications, such as bleeding and/or hematomas; group D (n=26) – with lymphocele formation. In 12 cases there was a combination of two or three mentioned complications, and these patients were included into two or all three "complication" groups according to the complications observed.

We analyzed the rate of SC needing re–operations and surgical interventions in the early posttransplant period in association with donor factors (demographical and clinical factors, laboratory tests, histological findings at donor "zero" biopsy), as also recipient and transplantation factors (recipient age, gender, dialysis modality, cold ischemia time, vascular reconstructions at back–table surgery, etc.). Patients were followed–up for three years in order to evaluate the impact of surgical complications on later posttransplant outcomes. All operations were performed by authors using the same organ explantation and transplantation techniques with retroperitoneal graft positioning in recipient (intraperitoneal approach and graft positioning in 2 cases of third transplantation). Donor kidney "zero" biopsies were performed at donor operations by "True–cut" method. Organ conservation was performed by histidine–tryptophan–ketoglutarate solution (HTK).

Data was collected from transplantation center surgical, transplant coordination and ambulatory follow–up data–bases and records.

Statistical analysis was performed by SPSS 13,0 program (SPSS Inc.). Parametric features are shown as mean ± standard deviation. Groups were compared using χ^2–tests for non–parametric and ANOVA test for parametric variables. Results were considered statistically significant for $p<0,05$.

RESULTS

SC that needed re–operations were observed in 57 patients (28,2%), and in 12 of them (5,9%) there was a combination of two or all three complications. Vascular complications (mainly bleeding and hematoma formation), were observed in 27 cases (13,4%), urological (urine leak and ureteral stenosis) – in18 cases(8,9%), symptomatic lymphocele formation needing repeated punctions and drainage operations – in 26 cases (12,9%). Results of comparison of each "complication" group with the control group are shown in table 1.

Vascular complications showed statistically significant association with the presence of glomerular sclerosis in kidney graft (observed in 18,5% compared with 5,5% in control group, p=0,034), as also tendency to be associated with higher donor BMI (27,0 ± 5,0 vs. 25,4 ± 3,8 in control group, p=0,067). This complication was also more frequently observed in elderly recipients, however, analysis failed to show statistical significance (p=0,090). In postoperative period vascular complications were associated with the development of delayed graft function (29,6% vs. 10,3% in control group, p=0,012), as also with urological complications (combination of those two complications was observed in 7 cases, p=0,004).

Urological complications failed to show statistical association with analyzed factors. The tendency of more frequent development of this complications was observed in transplantations from donors with high BMI (27,1 ± 5,3 vs. 25,4 ± 3,8 in control group, p=0,098). In posttransplant period urological complications were more frequently observed in patients who had delayed graft function (p=0,050).

Lymphocele formations were associated with non–traumatic causes of brain death in donors (p=0,034) and presence of glomerular sclerosis in "zero" biopsies (p=0,030). Lymphocele formations were associated, however, without statistical significance, with higher donor BMI (p=0,061) and hemodynamic disturbances in donors prior or during organ explantation operations (p=0,077), as also with re–transplantations (p=0,092) and with the use of antithymocyte globulin (ATG) for induction immunosuppression (p=0,094). In posttransplant period lymphocele formations were relatively more frequently observed in patients with delayed graft function (p=0,074).

DISCUSSION

Donor organ shortage is one of the main problems in transplantation that leads to more aggressive use of expanded criteria for deceased donation (2). The same situation is observed in Latvia (10), and it became of especial importance during the previous years, when economical crisis resulted in massive emigration of able–bodied population, increase in the number of objections for mostmortem donation associated with public negativism and mistrust, increase in the number of chronically ill persons due to inability to receive valuable medical help in time.

The use of ECD is associated with poorer posttransplant outcomes such as immediate graft function, duration of hospital stay and increased costs of treatment after transplantation (6).

SC in RT are rather frequent (near 30% of all cases) and could be associated with many factors: the use of anti–coagulation therapy in pre– and posttransplant period, immunosuppression and associated problems with increased risk of infections and retarded healing, disturbances caused by uremia and chronic dialysis, etc. (1, 3, 5).

In this study we showed that some donor factors are associated with higher risk of the development of surgical complications. One of the main factors is the presence of glomerular sclerosis in donor kidneys, associated with increased risk of bleeding and development of hematomas and lymphocele in posttransplant period. In our earlier study we have shown that the presence of interstitial and glomerular sclerosis in donor kidneys is associated with worse early posttransplant outcomes (7). Unfortunately, it is still impossible to organize immediate histological analysis in order to get information on the quality of recovered kidneys prior to transplantation, therefore "zero" biopsies have only retrospective value. This one of our main problems, regarding the fact that histological finding are of highest value for appropriate organ allocation (4, 9).

Another factor associated with relatively higher incidence of surgical complications is high donor BMI that could be explained both by difficulties during the organ recovery operation and higher incidence of nephrosclerosis in overweight donors (7).

Relatively higher incidence of vascular complications in elderly recipients is more likely related with initially poorer vascular condition in these recipients (atherosclerosis, arterial stiffening). Higher frequency of lymphocele in transplantations from donors with hemodynamic disturbances may be explained by the necessity to perform rapid organ recovery operation and associated risk of traumatism of lymphatic vessels in grafts. Lymphocele complications after ATG treatment may have several reasons, such as hypocoagulation, retarded healing, etc.

All complications were associated only with the development of delayed graft function and failed to show association with increased risk of graft losses and patient deaths during the next three years after transplantation. Regarding this fact, we can conclude

that transplantation from ECD is a valuable source of donor organs, especially for transplantation in patients with limited life expectancy; however, further follow–up is needed to determine the impact of such complications on later posttransplant period.

Conclusions

SC in early postoperative period are associated with the use of ECD, however, without major impact on first 3 years after transplantation. ECD are a valuable source of donor organs, especially for transplantation in patients with limited life expectancy.

Conflict of interest: None

REFERENCES

1. Akbar SA, Jafri SZH, Amendola MA, Madrazo BL, Salem R, Bis KG. Complications of Renal Transplantation // RadioGraphics, 2005; 25: 1335–1356
2. Delmonico FL, Sheeny E, Marks WH. Organ donation and utilization in the United States, 2004 // Am J Transplant, 2005; 2: 862–873
3. El Atat R, Derouiche A, Guellouz S, Gargah T, Likhoua R, Chebil M. Surgical complications in pediatric and adolescent renal transplantation // Saudi J Kidney Dis Transpl, 2010; 21: 251–257
4. Escofet X, Osman H, Griffiths DF, Woydag S, Adam Jurewicz W. The presence of glomerular sclerosis at time zero has a significant impact on function after cadaveric renal transplantation // Transplantation, 2003; 75: 344–346
5. Hernandes D, Rufino M, Armas S, Gonzales A, Gutierrez P, Barbero P, Vivancos S, Rodriguez C, Rodriguez de Vera J, Torres A. Retrospective analysis of surgical complications following cadaveric kidney transplantation in the modern transplant era // Nephrol Dial Transplant, 2006; 21: 2908–2915
6. Jushinskis J, Trushkov S, Bicans J, Suhorukov V, Shevelev V, Ziedina I, Rozental R. Risk factors for the development of delayed graft function in deceased donor renal transplants // Transplant Proceed, 2009; 41:746–748
7. Jushinskis J, Malcev A. Donor kidney biopsy results as a predictive factor for early graft function // Organs Tissues & Cells, 2009; 12: 55–56
8. Karam G, Maillet F, Braud G, Battisti S, Hétet JF, Glémain P, Le Normand L, Bouchot O, Rigaud J. Surgical complications in kidney transplantation // Annales d'urologie, 2008; 41: 261–275
9. Mazzuccol G, Magnani C, Fortunato M, Todesco A, Monga G. The reliability of pre–transplant donor renal biopsies (PTDB) in predicting the kidney state. A comparative single–centre study on 154 untransplanted kidneys // Nephrol Dial Transplant, 2010; 25: 3401–3408
10. Trushkov S, Jushinskis J, Suhorukovs V. Enhanced criteria donors: Impact of cold ischemia time in "old–to–old" kidney transplantation // Acta Chirurgica Latviensis, 2005; 5: 14–16

Table 1. Comparison of groups
(* – *p* value compared with control group; NC – no complications; UC – urological complications; VC – vascular complications; LC – lymphocele complication; BMI – body mass index; NTD – non–traumatic cause of brain death; ICU – intensive care unit; S–Crea – serum creatinine; S–Urea – serum urea; Hgb – hemoglobin; Hct – hematocrit; Leu – leucocytes; IS – interstitial sclerosis; GS – glomerular sclerosis; PD – peritoneal dialysis; HD – hemodialysis; Re–TX – re–transplantations; CIT – cold ischemia time; ATG – antithymocyte globulin; DGF – delayed graft function; AR – acute rejections)

Factors	**Group A (NC)**	**Group B (UC)**	***p****	**Group C (VC)**	***p****	**Group D (LC)**	***p****
Patients (n)	145	18		27		26	
Donor factors:							
Age (yrs.)	41,8±13,5	43,2±13,7	NS	45,4±12,7	NS	44,3±12,0	NS
BMI (kg/m^2)	25,4±3,8	27,1±5,3	0,098	27,0±5,0	0,067	27,0±4,8	0,061
NTD (%)	44,1%	38,8%	NS	48,1%	NS	65,4%	0,034
Stay in ICU (days)							
Hemodynamic disturbances (%)	3,0±2,3	2,8±2,6	NS	3,0±2,5	NS	3,2±3,0	NS
Laboratory tests:	44,1%	50%	NS	44,4%	NS	61,5%	0,077
S–Crea (mmol/l)							
S–Urea (mmol/l)	0,11±0,04	0,11±0,04	NS	0,11±0,04	NS	0,10±0,04	NS
Hgb (g/dl)	6,7±3,3	7,1±4,2	NS	6,9±3,6	NS	6,2±2,4	NS
Hct (%)	11,6±3,0	11,4±2,0	NS	11,9±2,3	NS	12,2±2,3	NS
Leu (*10^3/ml)	33,7±8,5	33,0±6,1	NS	34,1±6,4	NS	35,9±5,8	NS
Histology:	12,0±5,3	11,4±4,6	NS	12,1±6,1	NS	12,7±4,4	NS
IS (n)							
GS (n)	33 (22,8%)	3 (16,7%)	NS	7 (25,9%)	NS	8 (30,8%)	NS
	8 (5,5%)	2 (11,1%)	NS	5 (18,5%)	0,034	5 (19,2%)	0,030
Recipient factors:							
Age (yrs.)							
Gender (m/f)	44,0±14,5	45,9±17,4	NS	49,2±15,2	0,090	48,0±12,6	NS
Dialysis modality (PD / HD)	75 / 70	10 / 8	NS	13 / 14	NS	15 / 11	NS
Re–TX (n)	26 / 119	2 /16	NS	3 / 24	NS	2/24	NS
	12 (8,3%)	1 (5,5%)	NS	3 (11,1%)	NS	5 (19,2%)	0,092
Transplantation factors:							
CIT (hrs.)	16,6±4,6	16,3±5,3	NS	17,0±4,9	NS	16,1±5,9	NS
Vascular reconstr. (%)	49,7%	50%	NS	48,1%	NS	57,7%	NS
Induction by ATG (%)	17,2%	22%	NS	14,8%	NS	30,1%	0,094
Posttransplant results:							
DGF (%)	10,3%	27,8%	0,050	29,6%	0,012	23,1%	0,074
AR (%)	49,0%	55,5%	NS	37,0%	NS	53,8%	NS
S–Crea (disch., mmol/l)	0,12±0,05	0,13±0,04	NS	0,13±0,04	NS	0,13±0,05	NS
Graft losses (n)	18 (12,4%)	2 (11,1%)	NS	4 (14,8%)	NS	3 (11,5%)	NS
Patient deaths (n)	10 (6,9%)	2 (11,1%)	NS	3 (11,1%)	NS	2 (7,7%)	NS

Address:
Janis Jushinskis
Paul Stradins University Hospital,
Latvian Transplantation Center
Pilsonu str. 13, Riga, LV-1002, Latvia.
e-mail: jushinskis@transplantation.lv

ORIGINAL ARTICLE

Impact of Subclinical Rejection on Kidney Graft Function During the First Year after Transplantation

Vadims Suhorukovs, Janis Jushinskis, Rafail Rozental
Latvian Transplantation Center, Pauls Stradins Clinical University Hospital, Riga, Latvia

Summary
Introduction. There is no unified opinion about the role of subclinical rejection (SR) in further kidney graft function and the necessity of its treatment.
Aim of the Study. The aim of our study is to determine the impact of SR on kidney graft function during the first year after transplantation.
Materials and methods. Totally 144 deceased donor kidney transplantations were performed in a single center between January 1, 2007, and March 16, 2009. The study included patients who developed the primary graft function (n=78). Protocol biopsies were performed in 28 patients. The patients were divided into 4 groups: group A – patients, who had no histological signs of rejection on their protocol biopsy; group B – patients with histological signs of rejection who were treated with steroids; group C – patients with histological signs of rejection and with no treatment; group D – patients who were not biopsied.
All groups were compared for serum creatinine level, glomerular filtration rate (GFR), number of clinical rejection 1, 3, 6, 12 months after the transplantation.
Results. Histological examination revealed that 18 of 28 patients who underwent the protocol biopsy had SR grade from IA to IIA (64.3%). Comparison of the group showed no statistical difference in creatinine level and GFR 12 months after the transplantation ($p > 0,05$ for all groups).
Conclusions. During the first 12 months after transplantation SR does not significantly impact the graft function. However, the graft function was slightly worse in patients with SR and without treatment, and relatively better in patients with SR who were treated by steroids than in patients from others groups. Further follow–up is needed to determine the longer–term results.
Key words: kidney transplantation, subclinical rejection, protocol biopsy.

INTRODUCTION

Recently, there has been a considerable improvement of kidney transplantation results. During the last decade, the number of acute transplant rejection cases and transplant loss within early post transplant period has significantly reduced. But despite the good short–term results the adequate improvement of long–term results has not been achieved and the time limited renal graft function remains the serious problem of current transplantology. Meier–Kriesche et al. reported that relative risk for overall renal transplant loss in 1996 was 1.0, but in 2000 it was 1.14 (2).

The term of subclinical rejection (SR) was introduced during the nineties to denote histological signs of acute rejection in kidney graft with stable function (8). Some studies have established association between SR and chronic allograft nephropathy (CAN) development (4). However, there still exists no unified opinion about the role of subclinical rejection in further kidney graft function (3) and the necessity of its treatment, and protocol biopsy is still not standard of care at many transplant centers (5).

AIM OF THE STUDY

The aim of this study was to determine the impact of SR on kidney graft function during the first year after transplantation and to clarify the effect of its treatment.

MATERIALS AND METHODS

Totally 144 deceased donor kidney transplantations were performed in a single center between January 1, 2007, and March 16, 2009. The study included 78 patients who expressed their informed consent and who developed primary graft function and without any complications during 1 month after transplantation – acute clinical rejection, delayed graft function, severe infection, urinoma, post operation hematoma that needed reoperation etc. Immunosuppression included induction by monoclonal (basilixumab or daclizumab) or polyclonal (ATG) antibodies with a 5–day steroid pulse, and maintenance by per oral steroids, mycophenolate mofetil and Neoral as guided by the blood level – about 150 ng/ml during the first month after transplantation.

Protocol biopsies – the planned biopsy without direct indications – were performed on 28 patients who gave their agreement and who met the following criteria during 10 days before the biopsy: serum creatinine < 0.2 mmol/l, adequate diuresis, normal body temperature and stable renal graft function defined as variability of serum creatinine of less than 20%. Protocol biopsies were performed within the 3rd and 4th weeks after transplantation under ultrasound guidance. Histological changes were diagnosed according to the 1997 Banff criteria[7]. Subclinical rejection was defined as the presence of histological changes grade from IA.

All patients were divided into 4 groups: group A –

patients, who had no histological signs of rejection on their protocol biopsy; group B – patients with histological signs of rejection who were treated by steroid (500 mg i/v for 3 days); group C – patients with histological signs of rejection and with no treatment; group D – patients who underwent no protocol biopsy.

All groups were compared for age and gender of the recipient, age of the donor, cold ischemia time, serum creatinine level and GFR (by Cockcroft–Gault equation) 1, 3, 6 and 12 months after transplantation and number of acute clinical rejection and graft loss during the first year after transplantation.

Descriptive statistics were used to summarize the demographic and clinical features. Results were expressed as mean $\pm$ SD. One–way ANOVA analysis was used to compare groups for parametric variables, and Pearson's Chi–squared test – for non–parametric variables.

Only $p < 0,05$ was considered statistically significant. All statistical analyses were performed using SPSS 13,0 (SPSS Inc.).

RESULTS

Histological examination revealed that 18 of 28 patients who had undergone protocol biopsy had SR grade from IA to IIA (64.3%): grade IA had 13 patients; IB – 4 patients; IIA – 1 patient (Figure 1). Comparison of the groups showed no statistically significant difference ($p>0,05$ between all groups) in age and gender of the recipient, age of the donor, cold ischemia time, acute clinical rejection number and graft loss number during 12 month after transplantation (Table 1). One patient from group B has lost his graft due to non–compliance of immunosuppression therapy.

Comparison of the groups showed statistically significant difference in serum creatinine level at 1 month after transplantation between the group B and group D ($p = 0,043$) and between the group C and group D ($p = 0,027$); but at 3, 6, and 12 months after transplantation this difference became not statistically significant ($p > 0,05$). The differences in serum creatinine level and GFR at 1, 3, 6, 12 months after the transplantation between other groups had no statistical significance ($p > 0,05$). However, group C patients at 12 months had relatively higher mean serum creatinine level and lower GFR compared with other group patients, but group B patients, although statistically insignificant, at 12 months had the mean serum creatinine level slightly lower and GFR slightly higher than in patients from others groups.

DISCUSSION

Most sources currently acknowledge the presence of subclinical rejections. According to the data from various authors, their numbers in early posttransplant period lies between 7 and 46.6% (3,4,9). High SR rate in our study could be explained by a small number of patients who underwent the protocol biopsy and also probably by specificities of immunosuppressive therapy used in our center (rapid decrease of the steroid dose and relatively low doses of Cyclosporine) and high rate of HLA mismatches in our patients.

However, there is no common opinion on the role of SR and on the necessity of its treatment. Some authors note that with time SR could progress into an acute clinical rejection or persist subclinically, facilitating development of chronic transplant nephropathy resulting in graft malfunction (1,4,6). Our study showed that in the first 12 months following the transplantation the number of acute clinical rejections in patients with no signs of SR and those who got steroid treatment because of SR, does not differ from the number of acute clinical rejections in patients with signs of SR who got no treatment. As for the transplant functioning, 12 months after the operation the patients with no treatment revealed deterioration, although statistically insignificant, of the function compared to other groups of patients.

Group D comprised patients who had no protocol biopsies (mostly due to refusals by the patients). However, proceeding from the data we obtained, it could be assumed that this group also includes patients with signs of SR that remained untreated. This confirms the fact that after 12 months the creatinine level in this group is higher, although statistically insignificantly, than in Groups A and B.

At the same time, Group B patients who got steroid treatment, 12 months after reveal, although statistically insignificantly, a lower creatinine level and a higher GFR level compared to other groups.

CONCLUSIONS

Results of our study show that during the first 12 months after transplantation SR does not significantly impact the kidney graft function. However, the graft function was slightly worse in patients with SR and without treatment (group C) and relatively better in patients with SR who were treated by steroids (group B) than in patients from others groups and further follow–up is needed to determine the longer–term results.

Conflict of interest: None

REFERENCES

1. Kumar MSA, Heifets M, Moritz MJ et al. Safety and efficacy of steroid withdrawal two days after kidney transplantation: analysis of results at three years. Transplantation 2006;81:832–839
2. Meier–Kriesche H–U, Schold JD, Srinivas TR et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4:378–383
3. Moreso F., Ibernon M., Goma M. et al. Subclinical rejection associated with chronic allograft nephropathy in protocol biopsies as a risk factor for late graft loss. Am J Transplant 2006; 6:747–752
4. Moriatsu Miyagi, Yukio Ishikawa, Sonoo Mizuiri et al. Significance of subclinical rejection in early renal allograft biopsies for chronic allograft dysfunction. Clin Transplant 2005; 19:456– 465

5. Nankivell BJ, Chapman JR. The significance of subclinical rejection and the value of protocol biopsies. Am J Transplant 2006; 6:2006–2012
6. Nankivell BJ, Borrows RJ, Fungs CLS et al. Natural history, risks factors and impact of subclinical rejection in kidney transplantation. Transplantation 2004; 78:242–249
7. Racusen LC, Solez K, Colvin RB et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999; 55:713–723
8. Rush DN, Jeffery JR, Gough J. Sequential protocol biopsies in renal transplant patients. Transplantation 1995; 59:511–514
9. Terence Y–S Kee, Chapman JR, O'Connell PJ et al. Treatment of subclinical rejection diagnosed by protocol biopsy of kidney transplants. Transplantation 2006; 82:36–42

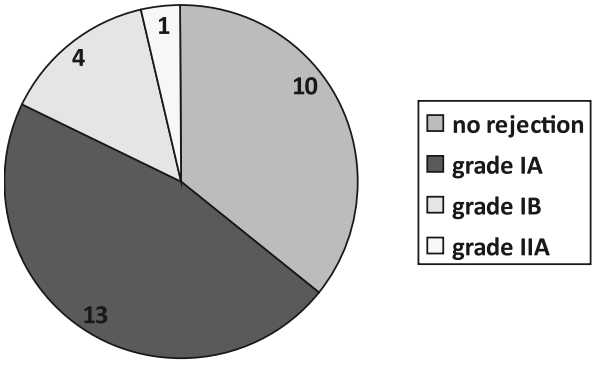


Fig. 1. Number of subclinical rejection cases

Table 1. Demographic and clinical features of the groups

Variables	Group A (n=10)	Group B (n=10)	Group C (n=8)	Group D (n=50)
Donor age (yr) mean±SD	41.4±10.1	52.9±13.4	48.6±8.4	42.4±14.7
Recipient age (yr) mean±SD	50.5±11.4	47.8±15.4	49±7.5	46.4±15.1
Recipient gender (M/F)	5/5	5/5	3/5	18/32
Cold ischemia time (h) mean±SD	16.9±2.9	16.9±1.9	16.3±2.8	15.7±14.7
Clinical acute rejection during 1 year, number of cases	3	2	2	6
Graft loss during 1 year, number of cases	0	1	0	2
Serum creatinine (mmol/l) mean±SD				
1 month	0.112±0.021	0.121±0.027	0.125±0.035	0.106±0.019
3 months	0.116±0.025	0.121±0.027	0.131±0.037	0.113±0.023
6 months	0.122±0.027	0.128±0.023	0.138±0.044	0.122±0.031
12 months	0.131±0.029	0.128±0.023	0.150±0.054	0.135±0.031
GFR (ml/min) mean±SD				
1 month	72.3±15.9	68.4±21.9	59.8±11.6	74.5±16.7
3 months	70.3±16.0	68.4±21.9	57.1±12.3	70.7±17.6
6 months	66.4±13.0	63.2±21.0	55.4±12.8	67.2±18.4
12 months	59.8±15.9	64.0±20.7	52.4±14.5	61.2±17.0

Address:
Vadims Suhorukovs
Pauls Stradins Clinical University Hospital,
13 Pilsonu Street, Riga,
LV-1002, Latvia;
E-mail: vadim.suhorukov@inbox.lv

DOI: 10.2478/v10163-011-0006-0

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

ORIGINAL ARTICLE

Perioperative Predictive Factors Following Splenectomy for Complete Remission of Immune Thrombocytopenic Purpura

Ieva Vidmane–Ozola*/**, Viesturs Boka*/**, Egils Cunskis*, Janis Breikss*, Sandra Lejniece*/***, Uldis Teibe*****
* Riga Eastern Clinical University Hospital, Clinic "Linezers", Latvia
** Riga Stradins University, Department of Surgical Diseases, Latvia
*** Riga Stradins University, Department of Internal Diseases, Latvia
****Riga Stradins University, Department of Continuous Education, Latvia
*****Riga Stradins University, Department of Physics, Latvia

Summary

Introduction. Immune thrombocytopenic purpura (ITP) is one of the most commonly known and widely researched haematological diseases. ITP manifests as decrease in platelet count of various degrees, which can even cause fatal bleeding from 0.4 – 13% annually. Glucocorticoids (GC) and intravenous immunoglobulin (IgG) are used as the first line of treatment, 20–50% of drug therapy is ineffective and splenectomy is "the second stage" of treatment.

Various sources of literature mention the range of ITP remission following splenectomy from 49 – 93%. Current studies are looking for prognostic factors, which would ensure complete ITP remission following splenectomy.

Aim of the Study. To analyse possible perioperative prognostic factors in ITP patients for achieving remission following splenectomy.

Materials and methods. The retrospective study included 13 patients diagnosed with immune thrombocytopenic purpura (ITP), who underwent surgery in the period from 2002 to 2009 at the Riga Eastern Clinical University Hospital "Linezers". From laboratory tests – full blood–count 1 – 2 days before the operation, on the 5th – 7th day following the operation, 1 month after the operation, one year after the operation and during the last follow–up found in the patient's out–patient file. The size of the spleen before the surgery was determined by ultrasonography.

The access to the abdominal cavity and the spleen – conventional or laparoscopic surgery, the duration of the operation, perioperative blood loss, post–operative complications and the patient's day of discharge following the surgery was analysed.

Results. In the period from January 2002 to January 2009 at RECUH clinic "Linezers" 13 ITP patients underwent surgery. As to the gender the average age for both genders was similar (men 39.0 ± 14.1 and women 39.0 ± 16.0). The mean value of the duration of the disease in women (8.0 ± 9.0 months) and men (68.1 ± 58.7 months) has a statistically significant difference, using the independent pair selection t–test (t = 2.38; p = 0.047). In one US case and in one CT case accessory spleens were detected. The pre–operative mean value of PLT count had increased in a statistically significant way in accordance with the independent pair selection t–test (t = 3.087; p = 0.009), and in accordance with Wilcoxon signed–rank test (z = 2,202; p = 0,028) compared to the mean value of PLT count, which was detected during the last follow–up visit on average 35.9 ± 35.9 months after the surgery. Analysis of variance (ANOVA) shows that the average age of cured patients

34.6 ± 9.8 is statistically less significant than for those patients, who continue treatment and whose disease has transformed (F = 7.327; p = 0.011).

Conclusions. The performed research allows concluding that the decisive factors in successful ITP outcome after the operation are the following: 1) in patients, who have undergone the operation in a relatively younger age (34.6 ± 9.8 years) the disease outcome is more successful during the follow – up period – 35.9 ± 35.9 months (F = 7.327; p = 0.011); 2) the visualisation and removal of the accessory spleen decreases the probability of relapse.

Key words: ITP, splenectomy, laparoscopic splenectomy, accessory spleens.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is one of the most commonly known and widely researched haematological diseases. Its incidence is 4.5/100 000 among men and 7.4/100 000 among women (8).

In cases of ITP anti–bodies bind with antigens on platelet surface, causing increased loss of reticuloendothelial system cells in the spleen, to a lesser extent – in the liver and bone marrow. Thus, ITP manifests as decrease in platelet count of various degrees, which can even cause fatal bleeding from 0.4 – 13% annually (17) .

The treatment of ITP is predominantly targeted at restoring the platelet count and decreasing the risk of bleeding. Glucocorticoids (GC) and intravenous immunoglobulin (IgG) are used as the first line of treatment, the second line of treatment is splenectomy. In case of post–splenectomy refractory ITP immunosuppressive therapy (IS) (Cyclosporine, Azatioprin) vinca alkaloids (Vinblastine, Vincristine), Danazol, thrombopoietin analogues (*Eltrombopag*), intravenous anti–D antibody therapy, monoclonal antibodies antiCD20–*Rituximab* are used. Currently

studies on using GC and immunoglobulin in treating ITP have not been randomized (4). Similarly, research on the use of anti–D antibodies and antiCD20 in the treatment of ITP are still ongoing (1, 1).
20–50% of drug therapy is ineffective and splenectomy is "the second stage" of treatment (3, 4, 12, 17, 21). Splenectomy has a dual meaning in the treatment of ITP – elimination of the source producing anti–platelet bodies and elimination of the main site of platelet destruction (1).
For the first time splenectomy in the treatment of ITP was described by Kaznelson in 1916 (3). With the development of modern and minimally invasive surgical technologies, in 1991 Delaitre and Maignien introduced laparoscopic splenectomy (LS) in the treatment of haematological diseases (19). ITP is the most frequent indication for LS because of the unchanged or slightly increased size of the spleen. Several studies have proven that LS is a safe and effective method for treating ITP, due to shorter period of hospitalization, quicker return to active life, smaller post–operative pain and number of complications, and better cosmetic effect compared to conventional splenectomy (CS). The surgical technique has no impact upon ITP outcome following the operation (3, 7, 12, 14, 16). Various sources of literature mention the range of ITP remission following splenectomy from 49 – 93% (3, 9, 14, 22, 23). Current studies are looking for prognostic factors, which would ensure complete ITP remission following splenectomy (2, 3, 8, 9, 13, 17, 20, 23).

AIM OF THE STUDY

To analyse possible perioperative prognostic factors in ITP patients for achieving remission following splenectomy.

MATERIALS AND METHODS

The retrospective study included 13 patients diagnosed with immune thrombocytopenic purpura (ITP), who underwent surgery in the period from 2002 to 2009 at the Riga Eastern Clinical University Hospital "Linezers". Patients' out–patient files and medical records were analysed.
From laboratory tests – full blood–count 1 – 2 days before the operation, on the 5^{th} – 7^{th} day following the operation, 1 month after the operation, one year after the operation and during the last follow–up found in the patient's out–patient file.
To evaluate the coagulogram the activated partial thromboplastine time (APTT), prothrombine index (PI) and the bleeding time according to Duke's method was detected. All patients underwent bone marrow biopsy to exclude primary haematological disease.
The size of the spleen before the surgery was determined by ultrasonography, following the splenectomy the spleen was weighed on scales and its histological examination was performed.
The use of platelet mass (PLTM), erythrocyte mass (EM) and fresh frozen plasma (FFP) during the perioperative period was analysed. The patient's physical condition was assessed in accordance with the generally recognised ASA (*American Society of Anesthesiologists*) classification.
The access to the abdominal cavity and the spleen – conventional or laparoscopic surgery, the duration of the operation, perioperative blood loss, post–operative complications and the patient's day of discharge following the surgery was analysed.
All operations were performed under endothracheal anaesthesia, during the surgery nasogastral tube was inserted, in all patients undergoing CS *Foley* type urinary bladder catheter No.18 was inserted. To ensure perioperative antibacterial prevention measures, all patients during the initial anaesthesia received 2 grams of a third generation cephalosporin antibacterial drug – cefoperazone.
When midline laparatomy is performed, the patient is supine with arched lumbar part, if a n incision under the ribs is performed, then the patient has right lateral position with arched rib arc.
During the laparoscopic operation the patient has a right semi–lateral position in an angle of 45° with arched lumbar part. Initially the abdominal cavity is punctured with *Varesa* needle in the middle of the line connecting the navel with the middle point situated immediately behind the rib arc and filled with CO2 till 12 mmHg (Fig. 1, A). After that a 10 mm optical trocar is placed (30° slanted optics– *Olympus optical, Tokyo, Japan are used*). Following that working trocars are placed. One 10 mm trocar is placed in the epigastrium on the left to the hepatic cord (Fig.1, B), the second 10 mm trocar is placed along *linea axillaris anterior* below the rib arc (Fig. 1, C), a 12 mm trocar is placed along *linea medioclavicularis sinistra* 2–3 cm below the rib arc (Fig. 1, D). All trocar sites can be diverted, depending upon the size of the spleen and its position in the abdominal cavity (Fig.1).

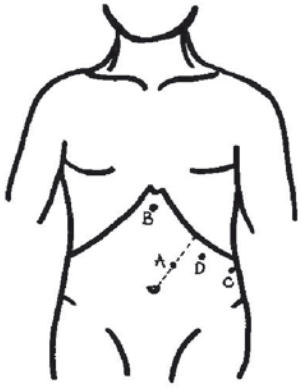


Fig.1 The port sites of patients undergoing laparoscopic splenectomy

During conventional surgery intact spleen is removed from the abdominal cavity. During laparoscopic surgery the spleen is placed in an endoscopic bag (*EndoBag*) and then is removed, by performing a minilparatomy incision ~7 cm long, joining the site of the 10 mm trocar, which is placed on *linea axillaris anterior* below the rib arc

with the trocar placed on *linea medioclavicularis sinistra* 2 – 3 cm below the rib arc. After the surgery the abdominal cavity is closed "layer by layer".A drain is placed in the site of the spleen at the end of both conventional and laparoscopic operation.
Following the surgery all patients are monitored at the intensive care unit (ICU).
All patients who underwent surgery received identical postoperative antibacterial therapy. All patients were vaccinated with *Pneumo – 23*.
This study is a part of Doctoral Thesis and the study application are going to be approved to Ethics commission of the Rīga Stradiņš University.

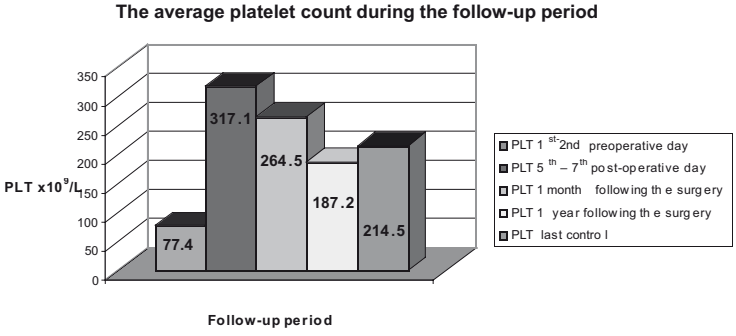
RESULTS

In the period from January 2002 to January 2009 at RECUH clinic "Linezers" 13 ITP patients underwent surgery. See Table 1 for patients' characteristics. The study includes 8 women and 5 men, the average age 39 ± 14.2, the youngest patient was an 18 years old woman, the oldest – a 66 years old man. As to the gender the average age for both genders was similar (men 39.0 ± 14.1 and women 39.0 ± 16.0).
The average duration of the disease prior to the surgery was 45 ± 54.4 months. The shortest period from setting the diagnosis to the surgery was 1 month, the longest – 156 months. The mean value of the duration of the disease in women (8.0 ± 9.0 months) and men (68.1 ± 58.7 months) has a statistically significant difference, using the independent pair selection t–test (t = 2.38; p = 0.047).
Prior to the surgery 2 (15.4 %) patients received only GC therapy, 5 patients (38.5 %) received GC and IS therapy, in 5 cases (38.5 %) GC and IgG was applied. One patient, for whom the duration of the disease prior to the surgery was 7 months, had received both GC and IS, as well as IgG therapy (7.7 %).

Table 1. Patients' characteristics

Total		13 (N)
Gender: female/ male:		8/5
Average age (years ± SD)		39 ± 14.2
Maximum fluctuation of the average age		18 – 66
Duration of the disease prior to the surgery (months ± SD)		45,0 ± 54.4
Maximum fluctuation of the duration of the disease prior to the surgery		1 – 156
Therapy received up to the surgery	GC	2
	GC + IgG	5
	GC + IS	5
	GC + IS + IgG	1
The size of the spleen prior the operation (cm)	Average ± SD	10.7 ± 1.6
	Maximum fluctuation	8.3 – 13
	Auxiliary spleen (cases)	2
ASA I/II/II/IV		1 / 9 / 3 / 0
Day of discharge after the surgery		6.8 ± 2.1
Post–operative follow–up period		35.9 ± 35.9
Disease outcome following the operation	Remission	11
	Continues therapy	1
	Transformation of the disease	1

Fig. 1.



Prior to the operation all patients underwent ultrasonography (US), in 5 cases – computer tomography (CT) examination with i/v infused radiopaque. The average size of the spleen was 10.7 ± 1.6 cm. In one US case and in one CT case accessory spleens were detected, which were removed to prevent failure of ITP treatment following the surgery.
Changes in platelet count (PLT) in the perioperative period are shown in Figure 1. Prior to the operation severe thrombocytopenia (PLT < 50 x 10^9/L) was observed in 6 cases. In these cases the platelet count was adjusted a week before the operation with platelet mass transfusions (6 and 3 units). Thrombocytopenia of medium severity (100 – 50 x 10^9/L) before the operation was detected in 3 cases, mild thrombocytopenia (150 – 100 x 10^9/L) in 4 patients. The average PLT count prior to the surgery was 77.4 ± 52.7 x 10^9/L. On the 5^{th} – 7^{th} day following the surgery the average PLT count was 317.1 ± 119.6 x 10^9/L; one month after the surgery – 264.5 ± 221 x 10^9/L; one year after the surgery – 187.2 ± 148.8 x 10^9/L; the average count during the last follow–up visit on average 35.9 ± 35.9 months after the surgery was 120.2 ± 160.5 x 10^9/L. The pre–operative mean value of PLT count had increased in a statistically significant way in accordance with the independent pair selection t–test (t = 3.087; p = 0.009), and in accordance with Wilcoxon signed–rank test (z = 2,202; p = 0,028) compared to the mean value of PLT count, which was detected during the last follow–up visit on average 35.9 ± 35.9 months after the surgery.The physical condition of all patients prior the surgery was assessed in accordance with ASA classification (See Table 1).

The values of perioperative indicators are included in Table 2

Name	Maximum fluctuations	Average ± SD
APTT (seconds)	23.1 – 37.7	23.9 ± 11.1
PI (%)	76 – 117	82 ± 39.0
Bleeding time (minutes'; seconds")	1'2"– 5'48"	2'32"± 1.7
The size of the spleen before the operation (cm)	8.3 – 14	10.7 ± 1.6
Type of operation LS/CS	11 / 2	
Duration of CS (minutes)	75 – 85	80 ± 7,0
Duration of LS (minutes)	85 – 195	130.6 ± 32.9
Blood loos during LS (millilitres)	100 – 800	372.7 ± 264.9
Blood loss during CS (millilitres)	200 – 400	300 ± 141.4
Weight of the spleen after the operation (g)	64 – 287	161.6 ± 100.6
Number of complications	3	

In 11 cases (84.6 %) laparoscopic splenectomy was performed, in 2 cases (15.4 %) –conventional splenectomy. The duration of LS was 130.5 ± 32.8 minutes, duration of CS – 80 ± 7.1 minutes (See Table 2). Blood loss during LS operation was 372.7 ± 264.9 millilitres (ml) . During CS – average 300 ± 141.4 ml. During the operations 12 units of PLTM, 3 units of EM and 1 unit of FFP were transfused. The transfusion of PLTM during the operation did not differ statistically (applying χ^2 method) depending upon the type of operation (χ^2 = 2.758; df = 3; p = 0.431). In the early post–operative period (ITN) 2 more PLTM units and 3 EM units were transfused.

Following the operation the majority of patients – 9 (81 %) were discharged on the 6^{th} – 8^{th} day.

The average weight of the spleen after the operation – 161.6 ± 100.6 grams. In all cases histological examination revealed changes typical of ITP – the histological pattern of the spleen

blotted, red pulp plethora.

In 3 cases complications developed following the operation. In one case a hematoma of the wound was detected following CS, in two cases – following LC – trocar site hematomas. All wound hematomas gradually disappeared without specific treatment.

The average follow–up period was 35.9 ± 35.9 months (maximum fluctuations from 11 – 135) Analysis of variance (ANOVA) shows that the average age of cured patients

34.6 ± 9.8 is statistically less significant than for those patients, who continue treatment and whose disease has transformed (F = 7.327; p = 0.011).

DISCUSSION

The first splenectomy for treating haematological diseases was performed by Sutherland and Burghad in 1910 to treat hereditary spherocytosis. In 1916 Kaznelson reported on the use of splenectomy in treating ITP. ITP was treated surgically even up to 1958, when Damashek et.al. described the term "hypersplenism" and demonstrated the significance of GC in the treatment of chronic ITP and established it as the first line of treatment (7, 14). The side – effects of GC therapy and the development of minimally invasive surgical techniques facilitated the introduction of laparoscopic splenectomy in the treatment of ITP.

50 – 80 % of the patients are treated with splenectomy, and achieve full remission following the operation in 49 – 93 % of the cases, therefore various perioperative predictive factors are searched that would allow predicting ITP outcome after the operation (3, 9, 14, 22, 23). If 30 days after the operation and longer PLT count is > 150 x 10^9/L (more recent publications > 100 x 10^9/L), without additional therapy, except cases, when GC dose is gradually cancelled after the operation, the remission is considered to be complete. Partial (incomplete) remission – PLT count is 50 x10^9/L (or 30 x 10^9/L in more recent publications) or higher, detected 30 days after splenectomy and longer, with or without additional therapy, except those patients who have complete remission; no response to splenectomy (failure) – PLT count is < 50 x 10^9/L (in more recent publications < 30 x 10^9/L), which has been detected 30 days after splenectomy with or without additional therapy (15).

One of the possible factors causing failure following the operation is the accessory spleen. During post mortems accessory spleen is found in 15 – 20 % of population and their incidence is higher in patients with haematological diseases (14). The accessory spleen can have effect upon ITP treatment outcome following the operation (9, 14, 23). In our study accessory spleen was detected in two cases prior to the operation during US and CT examinations, in both cases they were extirpated. During the operation and upon removal of the spleen from abdominal cavity atraumatic principles are complied with, to avoid injuring the spleen's capsule and prevent the spleen tissue contaminating surrounding tissue, thus avoiding the implantation of spleen tissue in the surrounding tissue. During repeated US and CT examinations after the operation no accessory spleens were detected in those patients with continuing ITP or whose disease had transformed into lymphoproliferative disorder (LPD). More recent research on the possibilities for diagnosing accessory spleen both prior and after the operation the use spiral CT and handheld gamma probe are mentioned (11, 18). It follows from the aforementioned that successful visualisation of accessory spleen tissue before the operation decreases the possibility of relapse after the operation.

The clinical practical guidelines for laparoscopic splenectomy published by European Association of Endoscopic Surgeons in 2008 regard laparoscopic splenectomy as the "golden standard" in the treatment of ITP because of the unmodified or slightly modified size of the spleen (11). In our study the average size of the spleen was 10.7 ± 1.6 cm, i.e., the size of the spleen was unchanged (the normal longitudinal size of the spleen is 10 – 12 cm) and in 9 cases laparoscopic splenectomy was performed. Literature reports that the type of operation does not affect the ITP outcome in a statistically significant way (5,11). One of the most frequently assessed factors, which could influence ITP outcome following an operation is age (3, 7, 8, 14). In our study the mean value of the cured patients' age – 34.6 ± 9.8 years is lower in a statistically significant way compared to those patients, who continue treatment or who have experienced transformation of the disease ($F = 7.327$; $p = 0.011$). Kathkouda et al. mention that the age from 30 to 45 years is an independent predictive factor for successful outcome following the operation (14). Duperier et al. mention that patients, who are below 50 and who have undergone LS, have been successfully cured (7). It can be concluded that a more successful disease outcome following splenectomy can be predicted for younger patients.

Tsereteli et al. write that the duration of the disease prior to the operation is also one of the predictive factors, which should be considered for successful ITP outcome following splenectomy (22). In our study the mean value of the duration of the disease prior the operation (45 ± 54.4 months) did not influence the disease outcome following the operation in a statistically significant way (ANOVA; $F = 0.297$; $p = 0.750$).

Duperier et al. mention that the disease outcome following splenectomy is influenced by PLT count before the operation – it should be > 70 x 10^9/L (7). In our study the mean value of PLT is 77.4 x 10^9/L. The mean value of PLT prior to the operation does not influence ITP outcome after splenectomy in a statistically significant way (ANOVA, $F = 0.429$; $p = 0.663$). PLT is one of the parameters that can be adjusted before the operation. In our clinic the patients are prepared before the operation with PLTM transfusions, taking into consideration the general satus, clinical manifestations and coagulogram. However, currently no specific criteria have been defined for using PLTM while preparing for the operation because of the small number of ITP patients undergoing surgery.

It is mentioned in literature that the increase of PLT in the period from the first to the seventh day after the operation is a good predictive sign with regard to the ITP outcome following splenectomy (2, 5, 14, 15, 17, 23). Katkhouda et al. mention that if PTL count during the first three days following the operation stays within the range of 400 – 600 x 10^9/L, then the number of relapses is smaller (14). In 2004 Balague described that the patients with PTL count of < 100 x 10^9/L compared to patients with PTL count of > 100 x 10^9/L after the operation have a great probability of an unsuccessful disease outcome following splenectomy (2). J.– M. Wu describes two factors for reaching remission – the increase of PTL count immediately after LS ($p = 0.01$) and PTL count ≥ 100 x 10^9/L ($p = 0{,}007$) (23). K.Kojouri et al. in 2004 surveyed the literature available from *Medline* data base covering the period from 1966 to 2004 on the use of splenectomy in ITP treatment. The author concluded that PTL count increased after the operation, but different criteria and post–operative days are used to establish that (15). In our study the mean value of PTL count, which was detected before the operation (77.4 ± 52.7 x 10^9/L), had increased in a statistically significant way both in accordance with independent pair selection t–test ($t = 3.087$; $p = 0.009$), and Wilcoxon signed–rank test ($z = 2.202$; $p = 0.028$) compared with the mean value of PTL detected during the last follow – up visit (120.2 ± 160.5 x 10^9/L). However, PTL count before the operation and PTL count on the 7th day does not influence the disease outcome in a statistically significant way (ANOVA; $F = 0.429$; $p = 0.663$ and $F = 0.950$; $p = 0.41$).

CONCLUSIONS

The performed research allows concluding that the decisive factors in successful ITP outcome after the operation are the following: 1) in patients, who have undergone the operation in a relatively younger age (34.6 ± 9.8 years) the disease outcome is more successful during the follow – up period – 35.9 ± 35.9 months ($F = 7.327$; $p = 0.011$); 2) the visualisation and removal of the accessory spleen decreases the probability of relapse.

Conflict of interest: None

REFERENCES

1. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: Efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura // Ann Intern Med, 2007;146:25 – 33
2. Balague C, Targarona EM, Cerdan G, Novell J, Montero O, Bendahan G, Garcia A, Pey A, Vela S, Diaz M, Trias M. Long–term outcome after laparoscopic splenectomy related to hematologic diagnosis // Surg Endosc, 2004;18(8):1283 – 1287
3. Balague C, Vela S, Targarona EM, Gich IJ, Muniz E, D'Ambra A, Pey A, Monllau V, Ascaso E, Martinez C, Garriga J, Trias M. Predictive factors for successful laparoscopic splenectomy in immune thrombocytopenic purpura: study of clinical and laboratory data // Surg Endosc, 2006 Aug; 20(8):1208 – 1213
4. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy // Br J of Haematol, 2003; 120: 574 – 596

5. Cordera F, Long KH, Nagorney DM, McMurtry EK, Schleck C, Ilstrup D, Donohue JH. Open versus laparoscopic splenectomy for idiopathic thrombocytopenic purpura: clinical and economic analysis // Surgery, 2003; 134(1):45 – 52
6. Cortelazzo S, Finazzi G, Buelli M, et al. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura // Blood, 1991;77:31
7. Duperier T, Brody F, Felsher J, Walsh RM, Rosen M, Ponsky J. Predictive factors for successful laparoscopic splenectomy in patients with immune thrombocytopenic purpura // Arch Surg, 2004; 139(1):61 – 66
8. Fabris F, Tassan T, Ramon R, Carraro G, Randi ML, Luzzatto G, Moschino P, Girolami A. Age as the major predictive factor of long–term response to splenectomy in immune thrombocytopenic purpura // Br J Haematol, 2001; 112: 637 – 640
9. Gadenstätter M, Lamprecht B, Klingler A, Wetscher GJ, Greil R, Schmid T. Splenectomy versus medical treatment for idiopathic thrombocytopenic purpura // Am J Surg, 2002; 184(6):606 – 609
10. George JN, Raskob GE, Vesely SK, et al. Initial management of immune thrombocytopenic purpura in adults: A randomized controlled trial comparing intermittent anti–D with routine care // Am J Hematol, 2003;74:161 – 169
11. Habermalz B, Sauerland S, Decker G, Delaitre B, Gigot JF, Leandros E, Lechner K, Rhodes M, Silecchia G, Szold A, Targarona E, Torelli P, Neugebauer E. Laparoscopic splenectomy: the clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) // Surg Endosc, 2008; 22(4):821 – 848
12. James P. Dolan, Brett C. Sheppard, Thomas G. DeLoughery. Splenectomy for immune thrombocytopenic purpura: Surgery for the 21st century // Am J Hematol, 2008; 83:93 – 96
13. Julia A, Araguas C, Rossello J, Bueno J, Domenech P, Olona M, Guardia R, Petit J, Flores A. Lack of useful clinical predictors of response to splenectomy in patients with chronic idiopathic thrombocytopenic purpura // Br J Haematol, 1990; 76(2):250–255
14. Katkhouda N, Manhas S, Umbach TW, Kaiser AM. Laparoscopic splenectomy // J Laparoendosc Adv Surg Tech A, 2001;11(6):383 – 390
15. K.Kojuri, S.Vasely, D.R. Terrell, J.N.George. Splenectomy for adult patients with idiopathic thrombocytopenic purpura:a systematic review to asses long–term platelet count responses, prediction of response, and surgical complications // Blood, 2004;104(9):2623 – 2634
16. Kumar S., Diehn FE., Gertz MA. Tefferi A. Spleneclomy for immune thrombocytopenic purpura: long–term results and treatment of postsplenectomy relapses // Ann Hematol 2002; 81:312 – 319
17. L. R. Khan, S. J. Nixon. Laparoscopic splenectomy is a better treatment for adult ITP than steroids – it should be used earlier in patient management. Conclusions of a ten–year follow–up study // Surgeon; 2007; 5(1):3 – 8
18. Reyhan Diz–Kucukkaya, MD; Amy Geddis, MD, PhD; Jose A. Lopez, MD. Part XII. Hemostasis & Thrombosis, Chapter 119 Thrombocytopenia // Marshall A. Lichtman, Thomas J. Kipps, Uri Seligsohn, Kenneth Kaushansky, Josef T. Prchal. Williams Hematology, 8e. The McGraw–Hill Companies, Inc.; 2010. 8th DVD format.
19. Park A., Marcaccio M., Sternbach M., Witzke D., Fitzgerald P. Laparascopic vs open splenectomy // Arch Surg, 1999; 134:1263 – 1269
20. Sampath S, Meneghetti AT, MacFarlane JK, Nguyen NH, Benny WB, Panton ON. An 18–year review of open and laparoscopic splenectomy for idiopathic thrombocytopenic purpura // Am J Surg, 2007; 193(5):580 – 583
21. Stanton CJ. Laparoscopic spleneetomy for idiopathic thrombotytopenic purpura (ITP): a five–year experience // Surg Endosc, 1999; 13:1083 – 1086
22. Tsereteli Z, Smith CD, Branum GD, Galloway JR, Amerson RJ, Chakaraborty H, Hunter JG. Are the favorable outcomes of splenectomy predictable inpatients with idiopathic thrombocytopenic purpura (ITP)? // Surg Endosc, 2001; 15(12): 1386 – 1389
23. Wu JM, Lai IR, Yuan RH, Yu SC. Laparoscopic splenectomy for idiopathic thrombocytopenic purpura // Am J Surg, 2004; 187(6):720 – 723

Address:
Ieva Vidmane–Ozola
State Share Company Riga Eastern Clinical University Hospital, Clinic „Linezers"
6, Linezera Street, Riga
Latvia LV-1006
E-mail: ievid@yahoo.com

DOI: 10.2478/v10163-011-0007-z

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

ORIGINAL ARTICLE

The Predictive Value of Thrombelastography and Routine Coagulation Tests for Postoperative Blood Loss in Open Heart Surgery

Agnese Ozolina*, Eva Strike*,, Indulis Vanags****
*Pauls Stradins Clinical University Hospital, Department of Anesthesiology and Cardiothoracic Surgery, Riga, Latvia
**Riga Stradins University, Department of Anaesthesiology and Reanimatology, Riga, Latvia

Summary
Introduction. Hemorrhage after cardiopulmonary bypass remains a clinical problem.
Aim of the Study. Study was performed to compare efficacy of trombelastography (TEG) and routine coagulation tests in relation for postoperative bleeding after cardiac surgery in CPB.
Materials and methods. Forty–seven adult cardiac surgical patients were enrolled in prospective study at Pauls Stradins Clinical University Hospital in 2010. Blood samples for prothrombin time, international normalized ratio, activated partial thromboplastin time (APTT), fibrinogen level, platelet count were collected before surgery, at admission in intensive care unit (ICU) and 6, 12 hours after operation.
Before induction of general anesthesia blood sample was collected to perform kaolin activated TEG (kTEG) and at admission in ICU – kTEG and heparinase– modified kTEG.
Results. Correlation postoperatively was between kTEG reaction time (R) and APTT, as well as heparinase–modified kTEG maximum amplitude (MA) and platelet count. Significant correlation with postoperative bleeding showed heparinase–modified kTEG MA on admission to the ICU.
The highest predictive value preoperatively showed kTEG alpha angle (A), APTT, platelet count and postoperatively kTEG MA, APTT on admission to ICU.
Conclusions. Associated with bleeding are following TEG variables: preoperatively kTEG A, postoperatively kTEG MA and heparinase–modified kTEG MA. APTT and platelet count are also related to postoperative bleeding but to a lesser degree.
Key words: trombelastography, heart surgery, bleeding.

INTRODUCTION

Hemorrhage after cardiopulmonary bypass (CPB) remains a clinical problem. Many risk factors associated with excessive blood loss have been identified (19), but postoperative bleeding remains poorly explained because of the complexity of the hemostatic process and the technical difficulties imposed by operative procedures. It suggests a need for patient testing to determinate hemostatic disorder after CPB and to be able differentiate a surgical cause for abnormal bleeding. Thrombelastography (TEG) has been described as a usefull point–of–care monitor during cardiac surgery (12). It measures in vitro viscoelastic properties of the developing clot in whole blood with specific patterns developing in the presence of clotting factor deficiencies, platelet dysfunction/trombocytopenia, hypofibrinogenemia and fibrinolysis (10). The overall coagulation profile can be qualitatively or quantitatively interpreted in terms of the hypo–, normal, or hypercoagulable state of the sample and the degree of lysis. Initiation of clot formation is defined as the reaction time or r–time (R), kinetics of clot development by angle alpha (A) and strenght of the clot by the maximum amplitude (MA).
Various sample preparations can be used wih the TEG analyzer. Native sample type for global evaluation of coagulation takes aproximately 50 minutes to generate data. Activation (Celite, Tissue factor, Kaolin) of the blood sample is essencial to maintain TEG as a point–of–care test, deriving all of the main parameter in 30 minutes.
Heparinase modified thrombelastography will develope despite anticoagulation with heparin during CPB because heparinase neutralizes the anticoagulation properties of heparin.
Routine coagulation tests as activated parcial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen concentration, platelet count provide no information about the quality of the clot or the dynamics of its formation and they are frequently inadequate for the purpose of monitoring coagulation (10). This was confirmed by several studies. Gravlee and coworkers (7) using 897 cardiac surgical patients concluded that the best multivariate model constructed could explain only 12% of the observed variation in postoperative blood loss. Similar results were obtained by Gelb et al. (6). They showed that PT, APTT, fibrinogen, factors V, VII, VIII and IX and platelet count have no clinical utility as predictors of clinical bleeding. Regarding to TEG Ereth et al. (5) found that blood samples without the use of activator showed that TEG MA parameter has been more predictive after cardiac surgery then isolated tests of platelet function and routine coagulation tests. The

kaolin–activated TEG (kTEG) is associated with early coagulopathic bleeding (18) and kTEG parameters had better correlation with bleeding as routine coagulation tests.

The aspect of hemotranfusion management using TEG shows that celite and tissue factor–activated TEG parameters have been successfully used to guide specifice blood product usage (14). As well as heparinase–modified thrombelastography during CPB has been used to reduced haemostatic factor transfusion (16).

AIM OF THE STUDY

The aim of this study was to compare efficacy of trombelastography and routine coagulation tests in relation for postoperative bleeding after open heart surgery in CPB.

MATERIALS AND METHODS

After obtaining ethics committee approval of the Paul Stradins Clinical University Hospital and written informed patient consent, 47 adult cardiac surgical patients were enrolled in prospective study between 1 December 2009 and 30 March 2010. Inclusion criteria were age 18 to 70 years, coronary artery bypass grafting or/and valve replacement surgery in CPB, baseline coagulation tests in normal values, anticoagulants or antiplatelet agents were discontinued at least 5 days before surgey. The last dose of low–molekular–weight heparin was administered the evening before surgery.

Our exclusion criteria were emergency and redo operations, preoperatively hemostatic disorders or chronic coagulopathy (PT <50%, INR > 2, platelet count < 50 x 10^9/l), renal or/and hepatic failure.

Blood samples testing for PT, INR, APTT, fibrinogen level and platelet count were collected at day before surgery, at admission in intensive care unit (ICU) and 6, 12 hours after operation.

Before induction of general anaesthesia blood sample from radial artery catheter was collected to performe kaolin activated TEG (kTEG) and 1 houre after operation we performed kTEG and heparinase modified kTEG.

The TEG was performed according to the manufacturers instructions using heparinase modified and non heparinase modified samples. Heparinase–containing cups had 2 IU of lypohilized heparinase–1 enzyme from *Flavobacterium heparinum*, which is sufficient to reverse 6 U/ml of heparin in whole blood. Following TEG parameters were recorded: reaction time – R (normal range 4–8 minutes), the alpha angle – A (normal range 47^0–78^0), maximum amplitude – MA (normal range 55–73 mm).

Chest tube drainage (CTD) was recorded at 4 hour and 24 hour postoperatively as milliliters per kilogram. Excessive bleeding was defined as more than 1ml/kg/h in first 4 hours or more than 1000 ml in 24 hours.

Opoid–based anesthesia with fenthanil, midazolam, propafol and cisatracurium was used in all patients. Before the start of CPB heparin was administered in a dose 300 to 400 U/kg initially and 5,000 to 10,000 U as indicated were given to achieve and maintain a target activated coagulation time (ACT) above 480 seconds before and during CPB. After separation from CPB, protamine was administered in a ratio of 1 mg:100 U of heparin, additional protamin was administered until ACT had returned to baseline.

All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS® 16.0). Logistic regression was used to construct the receiver operating characteristic (ROC) curves as there were 8 patients who had a 4–hour CTD more then 1 ml/kg/h. ROC curves for the outcome of excessive bleeding, were plotted for TEG parameters and routine coagulation tests before and after surgery. Secondary outcomes were the correlation (as Pearson's correlation coefficient) of TEG parameters and routine coagulation tests with CTD. As well as the relationship of TEG parameters and routine coagulation tests was analyzed. We evaluated correlation between reaction time – R and APTT, angle alpha – A and fibrinogen and maximum amplitude – MA and platelet count.

Continuous variables were described as mean standart deviation and categorical variables as persentages.

RESULTS

Forty seven adult cardiac surgical patients were examined and 46 completed the study. One patient was excluded after the decision to make off–pump surgery. There were no in–hospital deaths but 3 patients had following postoperative complications: one patient – mediastinitis and two cardiac tamponade two and seven days after operation.

There were 28 males and 18 females from the age of 51 to 80. The mean age of all patients was 67 ± 7.2 years. Coronary artery bypass grafting underwent 16 (34.8%), valve replacement surgery 18 (39.1%) and combined surgery 12 (26%) patients. CPB duration was from 50–252 min., aorta occlusion time 33–164 minutes and reperfusion time 11–82 minutes. Cell saver system was used in 76% cases. Patient demographics are presented in Table 1.

Eight patients (17%) had excessive bleeding and 1 of them had reexploration for major surgical bleeding. Blood loss statistically differed between patients who had excessive bleeding and who did not 4 hour after operation (370 ml vs 155ml) and 24 hour after operation (892ml vs 461 ml).

Preoperatively 44 patients were treated with one or more antiplatelet agents or anticoagulants. Thirty–seven patients received aspirin within 6 ± 4 days before surgery, clopidogrel – 12 patients (8 ± 2 days), low molecular weight heparine – 23 patients, the last injection was given 12 hours before surgery. One patient was treated with warfarin within 5 days before operation. There was no statistically significant difference in blood loss between patients with various antiplatelet agents and anticoagulants.

Preoperatively kTEG parameters were within the normal range excepting R time. Average R time was high 17 ± 13 min. and it statistically differed between patients who

received low molecular weight heparin preoperatively (21 ± 15 vs 12 ± 8, p < 0.003). There were no significant differences in kTEG parameters before and after surgery. Baseline routine coagulation tests were within normal ranges, but postoperatively average platelet count was low 149 ± 48 x 10^9/l and APTT was high 42 ± 7 seconds. We found significant correlation postoperatively between the kTEG R and APTT on arrival to the ICU (r = 0.3, p = 0.03), heparinase–modified kTEG MA and platelet count on arrival to the ICU (r = 0.4, p = 0.003) and platelet count 12 hours postoperatively (r = 0.3, p = 0.02). We did not detect any correlation between any TEG variable and routine coagulation parameter collected before operation.

The strongest correlation with postoperative bleeding showed heparinase–modified kTEG MA on admission to the ICU and bleeding from mediastinal and thoracostomy chest tubes after the first 4 postoperative hours (Fig.1) and after 24 postoperative hours (r = – 0.4, p = 0.04). Additionally heparinase–modified kTEG MA correlated with kTEG A (r = 0.3, p = 0.02) and kTEG MA (r = – 0.3, p = 0.04). Others TEG parameters and routine coagulation tests did not show correlation with blood loss.

To describe predictors for bleeding, ROC curves were done. Preoperatively (Fig.2) the highest predictive value showed kTEG A (c–index 0.58) and APTT (c–index 0.68), platelet count (c–index 0.5) and postoperatively (Fig.3) kTEG MA (c–index 0.64) and APTT on admission to ICU (c–index 0.63).

DISCUSSION

The TEG has developed as a bedside monitor of the coagulation process over the past 25 years. The device was first popularized by Dr Kang and the group in Pittsburg for monitoring during hepatic transplantation (8).

Others have found TEG very useful for the monitoring of the coagulation during cardiac surgery on CPB as its own induces complex disturbances in the coagulation and fibrinolytic systems (4,15). Many studies have tried to find a predictive value of TEG for abnormal bleeding after CPB. Spiess et al. (15) presented the first study concerning TEG and blood loss after CPB. In a group of 38 patients they found that TEG was a significantly better predictor (87% accuracy) of postoperative hemorrhage and need for reoperation than the ACT (30%) or routine coagulation tests (51%). Essell and coworkers (4) found an abnormal TEG representing an increased risk for bleeding. Also Welsby et al (18) found that kaolin–activated TEG is associated with early coagulopathic bleeding in 32 patients. Cammerer et al. (2) compared TEG and platelet function analysis (PFA) for postoperative bleeding including 255 patients. They found that TEG is a better predictor than PFA.

TEG failed to predict blood loss in other studies. Data from the study by Wang et al. (17) of 101 patients indicated no correlation between amount of CTD and TEG variables. Nutall and coworkers (13) found no correlation between TEG done after CPB and 24–hours blood loss after CPB in 82 patients.

Our results indicate that more closely associated with bleeding are following TEG variables: preoperatively kTEG A, postoperatively non–heparinse–modified kTEG MA and heparinase–modified kTEG MA. Regarding to routine coagulation tests APTT and platelet count are also related to postoperative bleeding but to a lesser degree than TEG variables.

Welsby and coworkers (18) found similar results. The strongest correlation with postoperative blood loss showed heparinize–modified and non–heparinse–modified kTEG MA. Weaker correlation with bleeding showed platelet count, fibrinogen level and PT. In contrast to our data they did not find correlation with blood loss and APTT.

The role of fibrinogen in hemostasis after CPB is not well examined. There is overall consensus regarding to the dominant role of platelets in hemostasis after CPB. Welsby et al. (18) identified the value of fibrinogen level in relation to bleeding. In our study it did not show correlation with postoperative blood loss. Fibrinogen did not corellate with TEG parameter angle alpha as well. The explanation could be the fact that most of patients received crioprecipitate transfusions after CPB.

We found angle alpha in TEG samples collected preoperatively as the best predictor of blood loss. Cammerer and coworkers (2) also found angle alpha as the bests predictor for bleeding and in combination with diphosphate–PFA test the predictive value is enhanced. It confirms our finding of predictive role of kTEG angle alpha and platelet count to the bleeding and role of platelets in hemosthasis after CPB.

Narrani K. (12) described that it is not possible to correlate TEG parameters with conventional coagulation profile as both techniques are different. The conventional coagulation tests measures the various components of the haemosthasis in isolation. TEG measures the various components of haemosthasis as they interract with one another in vivo. Althought many authors have tried to correlate TEG variables with routine coagulation tests. Welsby and coworkers (18) found significant correlation for MA with platelet count, fibrinogen level and PT. Regarding to our results there were correlation between kTEG R and APTT preoperatively and heparinase–modified kTEG MA with platelet count after operation.

The present data also challenge current aproaches to interpreting and applying TEG results for hemotransfusion theraphy. R time has previously been used as a guide for factor replacement with fresh frozen plasma (FFP) transfusions, A–angle alpha for crioprecipitate and MA as a guide for platelet transfusions (14,16). R–time was not correlated with bleeding and PT in our study, suggesting that mainly role plays anticoagulation with heparin affecting R–time after operations. Althought marked reductions in plasma levels of coagulation proteins are seen during cardiac surgery (6).

CONCLUSIONS

More accurately TEG variable is MA as it correlated with postoperative bleeding and platelet count suggesting the dominant role of platelets in hemostasis after CPB. It could be used as a guide for platelet transfusions, but it may be desirable to avoid platelet transfusion as a first–line treatment (1). The MA could be used to identify coagylopathic patients who may benefit from therapies such as Desmopresin administration.

Regarding to routine coagulation tests APTT and platelet count are also related to postoperative bleeding but to a lesser degree.

Conflict of interest: None

REFERENCES

1. Blajchman MA, Singal DP. The role of red blood cell antigens, histocompatibility antigens, and blood transfusions on renal allograft survival // Transfus Med Rev, 1989; 3:171–179
2. Cammerer U, Dietrich W, Rampf T, Siegmund LB, Josef AR. The predictive value of modified computerized thrombelastography and platelet function analysis for postoperative blood loss in routine cardiac surgery // Anesth Analg, 2003; 96:51–7
3. Despotis GJ, Levine V, Filos KS. Evaluation of a new point –of–care test that measures PAF–mediated acceleration of coagulation in cardiac surgical patients // Anesthesiology, 1996; 85:1311–23
4. Essell JH, Martin TJ, Salinas J, Thompson JL, Smith VC. Comparision of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass // J Cardiothorac Vasc Anesth, 1993; 7:410–5
5. Ereth MH, Nuttall AG, Klinworth TJ, MacVeigh I, Santrach PJ, Orszulak TA, Harmsen WS, Oliver WC Jr. Does the Platelet–Activated Clotting Test (HemoSTATUS@) Predict Blood loss and Platelet Dysfunction Associated with Cardiopulmonary Bypass // Anesth Analg, 1997; 85:259–64
6. Gelb AB, Roth RI, Levin J, London MJ, Noall RA, Hauck WW, Cloutier M, Verrier E, Mangano DT. Changes in blood coagulation during and following cardiopulmonary bypass:Lack of correlation with clinical bleeding // Am J Clin Pathol, 1996; 106:87–99
7. Gravlee GP, Arora S, Lavender SW, Mills SA, Hudspeth AS, Cordell AR, James RL, Brockschmidt JK, Stuart JJ. Predictive value of blood clotting tests in cardiac surgical patient // Ann Thorac Surg, 1994; 58:216–21Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr, Starzl TE, Winter PM. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation // Anesth Analg, 1985; 64:888–96
8. Kettner SC, Panzer OP, Kozek SA, Seibt FA, Stoiser B, Kofler J, Locker GJ, Zimpfer M. Use of abciximab–modified thrombelastography in patients undergoing cardiac surgery // Anesth Analg, 1999; 89:580–4
9. Mallett SV, Cox DJ. Thromboelastography // Br J Anaesth, 1992; 69:307–313
10. Mittermayr M, Velik–Salchner C, Stalzer B. Detection of proatmine and heparin after termination of cardiopulmonary bypass by thrombelastometry (ROTEM®): results of a pilot study // Anesthesia&Analgesia, 2009; 108(3):743–750
11. Narani K.K. Thrombelastography in the perioperative period // Indian J Anaesth, 2005; 49(2):89–95
12. Nutall GA, Oliver WC, Ereth MH, Santrach PJ. Coagulation tests predict bleeding after cardiopulmonary bypass // J Cardiothorac Vasc Anesth, 1997; 11:815–23
13. Shore–Lesseron L, Manspeizer HE, DePerio M. Thromboelastography–guided transfusion algorithm reduces tranfusions in complex cardiac surgery // 1999; 88:312–319
14. Spiess BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovich AD. Thrombelastography as an indicator of post–cardiopulmonary bypass coagulopathies // J Clin Monit, 1987; 3:25–30
15. Royston D, von Kier S. Reduced haemostatic factor transfusion using heparinase–modified thromboealastography during cardiopulmonary bypass // 2001; 86:575–578
16. Wang JS, Lin CY, Hung WT. Thrombelastogram fails to predict postoperative hemorrhage in cardiac patients // Ann Thorac Surg, 1992; 53:435–9
17. Welsby IJ, Jiao K, Ortel TL, Brudney CS, Roche AM, Bennett–Guerrero E, Gan TJ. The Kaolin–activated thrombelastograph predicts bleeding after cardiac surgery // Journal of cardiothoracic and vascular anesthesia, 2006; 20(4):531–535
19. Wolfe R, Bolsin S, Colson M, Stow P. Monitoring the rate of reexploration for excessive bleeding after cardiac surgery in adults // Quality and Safety in Health Care, 2007; 16:192–196

Address:
Agnese Ozolina
Cardiac Surgery Centre,
Department of Anesthesiology and
Cardiothoracic Surgery
Pauls Stradins Clinical University Hospital
13 Pilsonu street,
Riga, Latvia, LV-1002
E-mail:agnese_krauze@yahoo.com

Table 1. Patients demographics data

Patient data (n = 46)		
Gender	male 28 (60.9%)	female 18 (39.1%)
Age (yr)	67 ± 7.2	
Body mass index (kg/m^2)	29 ± 6.4	
Operation charasteristics		
CABG (%)	16 (34.8%)	
Valve replacement (%)	18 (39.1%)	
Combined surgery (%)	12 (26%)	
CPB duration (min)	106 ± 32	
Aorta occlusion time (min)	69 ± 23	
Reperfusion time (min)	32 ± 12	
Cell saver (%)	35 (76%)	
Blood loss (ml)	> 1ml/kg/h n = 8	< 1 ml/kg/h n = 38
4 h after surgery	370 ± 61*	155 ± 57*
24 h after surgery	892 ± 179*	461 ± 167*

Abbreviations: CABG – coronary artery bypass grafting, CPB – cardiopulmonary bypass

* $p < 0,05$

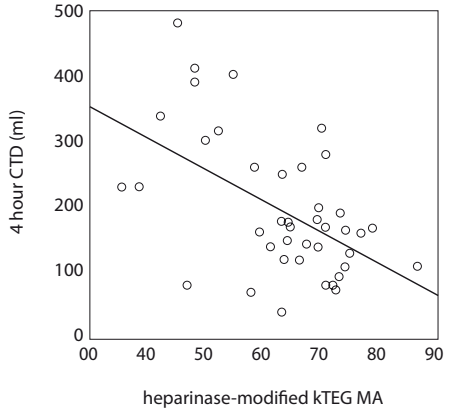


Fig. 1. Negative linear correlation of the heparinase–modified kTEG MA on admission to the ICU with bleeding from the mediastinal and thoracostomy tubes during the first 4 postoperative hours (r = – 0.5, p < 0.001)

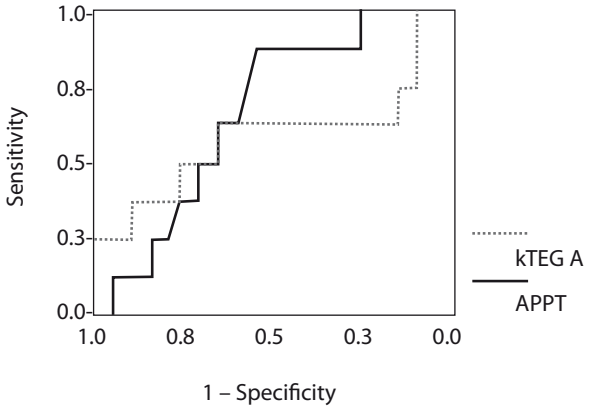


Fig. 2. ROC curves describing the relationship between the kTEG A – angle alpha parameter (c–index, 0.58) and APTT – activated parcial thromboplastin time (c–index, 0.68) before operation and excessive postoperative bleeding

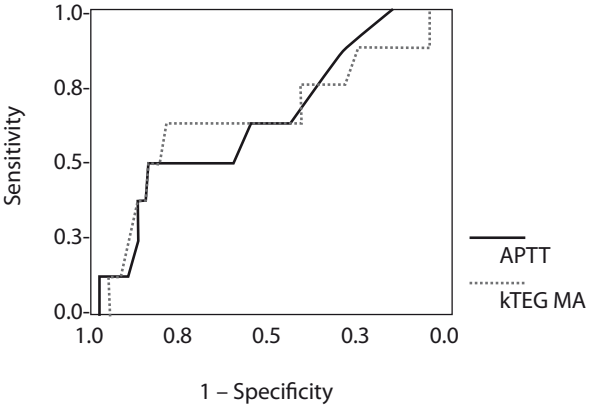


Fig. 3. ROC curves describing the relationship between the kTEG MA – maximum amplitude parameter (c–index, 0.64) and APTT – activated parcial thromboplastin time (c–index, 0.63) on arrival to the ICU and excessive postoperative bleeding

ORIGINAL ARTICLE

Carotid Artery Stenosis Correlation with Hyperhomocysteinemia in Stroke Patient Group: a Prospective Study

Viktorija Kenina*, Zanda Priede*, Pauls Auce, Normunds Suna**, Andrejs Millers***
*Riga Stradins University, Department of Neurology, Riga, Latvia
**Pauls Stardins Clinical University Hospital, Department of Neurology, Riga, Latvia

Summary
Introduction. Stroke is the second most common cause of death worldwide and one of the major causes of long–term disability. Carotid artery stenosis is an independent risk factor for ischemic stroke and related forms of atherosclerotic vascular disease.
Aim of the Study was to examine plasma homocysteine (tHcy) levels in the stroke patient's group with significant carotid artery stenosis, to determine hyperhomocysteinemia correlation with degree of carotid artery stenosis.
Materials and methods. This study was prospective and all patients (n=102) included in the study were hospitalized in Pauls Stradins Clinical University hospital in Clinic of Neurology with diagnosis of acute ischemic stroke. In the group of significant carotidal stenosis we included 48 patients with various degree of stenosis ranging from 50% to total occlusion. Evaluations of stenosis of extracranial carotid arteries were done by duplex ultrasonography method. The blood of these patients was tested for homocysteine level by ELISA (IMMULITE 2000).
Results. Study did not demonstrated statistically significant difference between levels of tHcy in all groups. Mean homocysteine level was not significantly higher in the symptomatic carotid stenosis patient's group. Also there were no significant differences between levels of homocysteine in patient group with different degree of stenosis.
Conclusions. We found no meaningful association between a high tHcy level and extent of carotid stenosis.
Key words: hyperhomocysteinemia, stroke, carotid stenosis.

INTRODUCTION

Stroke is the second most common cause of death worldwide and one of the major causes of long term disability, furthermore mortality from stroke in Latvia compared to neighboring countries is one of the highest in the region(16). One can divide stroke into further subtypes to apply slightly different preventive strategies, for example anticoagulation or surgical carotidal endartectomy. Large artery atherosclerosis is one of the most common causes of stroke and in particular group of younger patient it is also the most frequent one (5). Raised levels of homocystein have been previously described as an independent risk factor of coronary artery disease (3) and stroke (19) and there has been already reported particular association between high homcysteine levels and ischemic stroke due to large artery atherosclerosis (4). Link between hyperhomocysteinemia and external carotid artery has already been previously investigated. Selhub J, et al have demonstrated association between raised level of homocysteine and risk of extracranial carotid artery stenosis in elderly (17), these findings have later been confirmed by several other studies (10), (18)in addition, link to severe stenosis also has been demonstrated (14), but at the same time study from Iran failed to demonstrate this association in their local population (12). Interestingly, several studies have also failed to demonstrate association of early re–stenosis following carotid endartectomy and increased level of homocysteine (2), (7).

AIM OF THE STUDY

The aim of our study was to examine plasma homocysteine (tHcy) levels in the stroke patient's group with significant carotid artery stenosis, to determine hyperhomocysteiemia correlation with degree of carotid artery stenosis.

MATERIALS AND METHODS

This research was conducted as a prospective study, and was approved by the hospital's Ethics Commission. All the research subjects (n=48) were acute ischemic stroke patients admitted to the Pauls Stradins Clinical University Hospital in time period from October, 2008 till May, 2009. Stroke was defined according to WHO definition: as a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin. Inclusion criteria for the study were first – ever stroke or recurring cerebral infarction with carotid artery stenosis of 50% or more; while patients with lacunar strokes, past medical history significant for oncologic or chronic inflammatory diseases, severe impairment of renal function were excluded from the study. Patients in this study were not stratified according to TOAST criteria as a goal for study was to evaluate relationship between degree of stenosis and homocysteine. All patients were separated into two groups according to grade of their stenosis – one group from 50 % to 69 % and those with above 70%. Degree of stenosis was measured

using flow velocity analysis with Philips 33i duplex ultrasound system. For detection of level of tHcy we used IMMULITE 2000 test system, what is chemiluminescent immunoassay highly specific for homocysteine. It is used for quantitative detection of *L – homocysteine*. Testing system consists of two cycles in first release of bound tHcy and its conversion into *S–Adenosyl–L–homocysteine* with following immunoassay using highly specific antibody. In this study we considered result 15 µmol/l as raised level. SPSS for Windows 16.0 was used for data processing and analysis.

RESULTS

Mean level of homocysteine in the patients group (n=48) was 16,73±6,8 mmol/l .

From 48 patients included in study 21 (gender: 14 male, 7 females; mean age: 64,3 ± 11,8 years) had stenosis above 70 % (critical) and 27 (gender: 26 male, 22 females; mean age: 64,3 ± 11,8 years) persons had stenosis between 50 % – 69 % (significant).

Mean level of tHcy in patient group with carotid stenosis above 70 % was 16.26 ±5,4 mmol/l; in the group with stenosis between 50 % – 69 % mean level was 17.14 ±8,06 mmol/l (p=0.18).

Hyperhomocysteinemia was detected in 11 patients out of 21 in group with critical stenosis; as well as in 15 patients out of 27 in other group with significant stenosis from 50 % – 69 %, (p=0.83).

DISCUSSION

In this study we did not demonstrated any statistically significant difference in level of tHcy in blood between stroke patients with critical (above 70%) and significant (50 % – 69 %) carotidal stenosis. Apart from size of this study there is some other weakness of our study – for example we did not recorded nutritional status of included patients (for example vitamin B12 or B6 supplementation) and also we lacked proper control group matched by age and gender without cerebrovascular disease. Lack of statistically significant difference between groups also could be explained with the fact that homocysteine plays a role in atherosclerosis and stroke but not directly in determination of extent of stenosis. Link between raised level of homocysteine and other marker of atherosclerosis and vascular risk factor – Carotidal Intimal Media Tickness (C–IMT) is also controversial still, there are studies that have demonstrated link between raised level of tHcy and C – IMT (11), (8), but interestingly, some studies have demonstrated weaker link with C – IMT (6) or even absence of it(13),(9). Trials of lowering tHcy levels also have failed to show benefit in reduction of vascular events despite lowering homocysteine levels (1), in addition trial that was looking at post stroke patients and effect of lowering homocysteine failed to demonstrate improvement of C – IMT (15). Those controversies might not go against a role of homocysteine in stroke but actually just show that stroke and atherosclerosis is multi factorial illness and later might be a longstanding progradient process with more than one risk and causal factor.

CONCLUSIONS

In our study we did not demonstrate statistically significant difference in levels of blood homocysteine between patient group with critical carotid stenosis (above 70 %) and significant (50 % – 69 %). It demonstrates that there is need for further trials in this field to continue to search for amendable risk factor in development of critical carotidal stenosis.

Conflict of interest: None

Acknowledgment: this work was supported by grant from ESF.

REFERENCES

1. Albert, C.M., et al., Effect of Folic Acid and B Vitamins on Risk of Cardiovascular Events and Total Mortality Among Women at High Risk for Cardiovascular Disease: A Randomized Trial // JAMA, 2008; 299(17): 2027–2036
2. Assadian, A., et al., Homocysteine and early re–stenosis after carotid eversion endarterectomy // Eur J Vasc Endovasc Surg, 2007; 33: p. 144 – 148
3. Christen, W.G., et al., Blood Levels of Homocysteine and Increased Risks of Cardiovascular Disease: Causal or Casual? // Arch Intern Med 2000; 160(4): 422–434
4. Eikelboom, J.W., et al., Association Between High Homocyst(e)ine and Ischemic Stroke due to Large– and Small–Artery Disease but Not Other Etiologic Subtypes of Ischemic Strok // Stroke, 2000; 31(5): 1069–1075
5. Grau, A.J., et al., Risk Factors, Outcome, and Treatment in Subtypes of Ischemic Stroke: The German Stroke Data Bank // Stroke, 2001; 32(11): 2559–2566
6. Held, C., et al., Correlations between plasma homocysteine and folate concentrations and carotid atherosclerosis in high–risk individuals: baseline data from the Homocysteine and Atherosclerosis Reduction Trial (HART) // Vascular Medicine, 2008; 13(4): 245–253
7. Hillenbrand, R., et al., Hyperhomocysteinemia and recurrent carotid stenosis // BMC Cardiovascular Disorders, 2008. 8(1): 1
8. Kazmierski, R., et al., Association of atherosclerotic risk factors with carotid adventitial thickness assessed by ultrasonography // Journal of Clinical Ultrasound, 2009; 37(6): 333–341
9. Linnebank, M., et al., Homocysteine and Carotid Intima–Media Thickness in a German Population: Lack of Clinical Relevance // Stroke, 2006; 37(11): 2840–2842
10. Lupattelli, G., et al., Hyperhomocyst(e)inemia Is Associated with Carotid Atherosclerosis // Angiology, 1999; 50(10): 823–830
11. Malinow, M., et al., Carotid artery intimal–medial wall thickening and plasma homocyst(e)ine in asymptomatic adults. The Atherosclerosis Risk in Communities Study // Circulation, 1993; 87(4): 1107–1113

12. Mousavi, S., M. Ghasemi, and T. Hoseini, Association between plasma homocysteine concentrations and extracranial carotid stenosis // Ann Saudi Med, 2006; 26(2): 120–122
13. Ntaios G, S.C., Hatzitolios A, Ekonomou I, Destanis E, Chryssogonidis I, Chatzinikolaou A, Pidonia I, Karamitsos D., Homocysteine and carotid intima–media thickness in ischemic stroke patients are not correlated // Neuropsychiatr Dis Treat, 2008; 4(2): 477–9
14. Pitoulias GA, T.M., Tsiaousis PZ, Papadimitriou DK., Hyperhomocysteinemia and hypercoagulable state in carotid plaque evolution. Novel risk factors or coincidental risk predictors? // Int Angiol, 2007; 26(3): 270 – 8
15. Potter, K., et al., The effect of long–term homocysteine–lowering on carotid intima–media thickness and flow–mediated vasodilation in stroke patients: a randomized controlled trial and meta–analysis // BMC Cardiovascular Disorders, 2008; 8(1): 24
16. Sarti, C., et al. International Trends in Mortality From Stroke, 1968 to 1994 // Stroke, 2000; 31(7): 1588–1601
17. Selhub, J., et al., Association between Plasma Homocysteine Concentrations and Extracranial Carotid–Artery Stenosis // New England Journal of Medicine, 1995; 332(5): 286–291
18. Wang, H., et al., Serum level of homocysteine is correlated to carotid artery atherosclerosis in Chinese with ischemic stroke // Neurological Research. 28: 25–30
19. Homocysteine Studies Collaboration, Homocysteine and Risk of Ischemic Heart Disease and Stroke: A Meta–analysis // JAMA, 2002; 288(16): 2015–2022

Address:
Viktorija Kenina
Clinic of Neurology
Pauls Stradins University Hospital
Pilsonu iela 13
Riga, LV-1002
Latvia
E-mail: vikakenina@inbox.lv

DOI: 10.2478/v10163-011-0009-x

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

ORIGINAL ARTICLE

Predicting Fetal Prognosis by Assessing Fetal and Maternal Blood Flow Patterns in Pregnancies with Fetal Growth Restriction

Natalija Vedmedovska*, Dace Rezeberga*, Uldis Teibe, Gilbert G.G. Donders*****
* Department of Obstetrics and Gynecology, Riga Stradins University, Riga, Latvia
** Department of Biostatistics, Riga Stradins University, Riga, Latvia
*** Department of Obstetrics and Gynecology of the Regional Hospital Heilig Hart Tienen, University Hospital Gasthuisberg Leuven, University Hospital Citadelle, Liège, Belgium

Summary
Introduction. Fetal growth restriction (FGR) is associated with prematurity and a number of complications, as well as long–term impact on metabolic or cardiac function in adults.
Aim of the Study. To study the prognostic value of staging maternal and fetal Doppler blood flow velocities in women with FGR; and evaluate prenatal characteristics as possible risk factors for severe vascular abnormalities.
Materials and methods. 70 singleton pregnancies complicated by FGR were included in prospective follow–up study. Blood flow velocities in the uterine (UtA), umbilical (AU), middle cerebral (ACM) arteries and ductus venosus (DV) were measured. FGR neonates grouped as follows: I) normal blood velocity waveforms; II) abnormal UtA velocimetry and/or presence of early diastolic "notch"; III) abnormal AU without signs of "brain sparing"; IV) abnormal AU and ACM pulsatility index (PI) and V) AU absent or reversed end diastolic flow and an abnormal DV. Prenatal risk factors and perinatal outcome were assessed in relation to these Doppler blood flow patterns and compared with Fisher exact and Pearson c2 test.
Results. There was a strong correlation between the severity of grouping and birth weight ($p<0.001$), gestational age at delivery ($p<0.001$), low amniotic fluid index ($p<0.001$), low Apgar scores ($p=0.01$) and neonatal transfer rate to NICU or hospital ($p=0.02$). Groups IV and V fetuses had the highest perinatal mortality ($p=0.01$). Women having genital infections (RTI) had significantly worse Doppler flow profile than non–smoking women at term without RTI ($p=0.02$).
Conclusions. Severity of blood flow redistribution correlates with fetal morbidity and mortality. Less severe vascular changes, such as abnormal AU flow without centralization, and even increased uterine artery PI alone are linked to reduced birth weight, higher likelihood of preterm birth and increased risk of morbidity. Genital infections contribute significantly to hemodynamic changes related to the FGR. Screening and preventing of STI as well as optimizing the time of delivery may improve the overall outcome of compromised fetuses.
Key words: intrauterine growth restriction, hemodynamic, outcome, infections.

INTRODUCTION

Fetal growth restriction (FGR) is defined as the inability of a fetus to maintain expected growth, with estimated fetal weight or actual birth weight below the 10th percentile for gestational age (1). Fetal growth restriction is associated with prematurity and a number of complications, such poor neural development and risk of epilepsy in childhood and long–term impact on metabolic or cardiac function in adults (10, 12. 16, 34, 37). The FGR remains the challenge for clinicians, therefore, the different kind of fetal well–being assessment methods incorporated in obstetrics. Doppler ultrasonography has been proposed for identifying pathological growth and predicting fetal compromise (27, 44). The link between abnormal patterns of Doppler velocities of maternal and fetal vessels and fetal outcome was reported in a number of studies (3, 4, 8, 11, 43). Researchers tried hard to understand the etiopathogenesis and the underlying mechanisms of fetal impairment occurring between the diagnosis and the moment of delivery or death (26).

Although in the literature, we could find some scarce data evaluating the effect of smoking on the umbilical blood flow indices (22) or the hemodynamic changes following steroids administration (32, 36), the influence of maternal characteristics, such as genital infections and smoking on blood flow pattern among FGR fetuses were not sufficiently evaluated.

AIM OF THE STUDY

To assess changes in maternal and fetal flow velocity in pregnancies complicated by intrauterine fetal growth restriction, and their correlation with perinatal outcomes on the one hand, and possible interactions of antenatal risk factors on the other.

MATERIALS AND METHODS

We conducted a prospective study from May 2007 to March 2010. Seventy consecutive women with intrauterine growth restriction of singleton fetuses, attending the ultrasound unit at Riga Maternity Hospital in Latvia, were included in the study. Growth restriction

was defined as an estimated weight below the 10th percentile by prenatal ultrasound. Exclusion criteria were rhesus immunization, chromosomal aberrations and morphological malformations. In an estimate to create different levels of prognostic severity, intrauterine growth restricted newborns were divided in 5 groups according to their pattern of flow. Group I consisted of fetuses with normal blood velocity waveforms; Group II of fetuses with an abnormal velocimetry of the *arteria uterine* (UtA) and/or presence of early diastolic "notch"; Group III of fetuses with an abnormal *arteria umbilicalis* (*AU*) pulsatility index (PI); group IV of fetuses with abnormal *AU* and low *arteria cerebri media* (*ACM*) PI and, finally, group V, fetuses with *AU* absent or reversed end diastolic (ARED) flow and/or an abnormal *ductus venosus* (*DV*) flow. Oligohydramnios was considered in presence of amniotic fluid index less than 5 cm (24.

The Ethics Committee of Riga Stradins University approved the study and informed consent was obtained from all patients.

Doppler studies. The patients were examined using a 2–5, 2–7 or 4–8 MHz abdominal transducer (Philips, AU 22, USA) with color Doppler and pulsed Doppler facilities. The high–pass filter was set as low as possible, at 70 Hz. The mechanical and thermal indices were always kept below 1.9 and 1.5.

At each session we measured blood flow velocity in UtA, *AU, MCA and DV*. We applied standardized techniques (14, 19, 25). Briefly, the UtA was identified at the apparent crossing of the uterine and external iliac arteries. Measurements were taken approximately 1 cm distal to the crossover point. Abnormal UtA velocimetry was considered as a mean (left and right) PI value above the 95th percentile for gestational age (GA) based reference ranges (14) and/or presence of early diastolic "notch".

The umbilical artery recordings performed at the free–floating loop of the umbilical cord. Abnormal *AU* velocimetry was defined as PI above the 95th for GA based reference ranges (2).

ACM was assessed in axial section of brain with the sample volume over the proximal section where *ACM* emerges from circle Willis. Abnormal *ACM* velocimetry was defined as PI below the 2.5th for GA based reference ranges (9).

The *ductus venosus* was identified in mid–sagittal transaction as a vessel connecting the umbilical vein with inferior vena cava and exhibiting the typical aliasing of high velocities compared with the umbilical vein. Abnormal *DV* was defined as PI above the 95th for GA based reference ranges and/or ARED (17).

All recordings have been obtained in the absence of fetal breathing and fetal movement. The angle of insonation always was kept lower than 30°. Women were placed in a semi–recumbent position.

When more than one Doppler study was performed in the same fetus, the last Doppler study preceding delivery was used for analysis.

Delivery. The decision on the best mode of delivery was based on the gestation, fetal condition and cervical status as determined by the managing obstetrician. Information regarding birth weight, gestational age at delivery, mode of delivery, and length of hospital stay was obtained from standardized medical records.

Neonates. 5–minute Apgar score below 7, neonatal health, admission to neonatal intensive care unit, transfer to pediatric hospital for further treatment, and neonatal death were assessed.

Statistical analysis. Data were analyzed with SPSS statistical software version 18. Parametric statistics are presented as mean and standard deviation. The differences in the proportion of adverse outcomes in each Doppler groups was compared by the Fisher's exact test, Pearson c^2 test, chi–square for trend or for multiple non–Gaussian samples Krsukal Wallis, p value of <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the study population were described elsewhere (40–41). Doppler waveforms were recorded within seven days of delivery (ranges 2h –7 days). The outcome variables were compared with the results of the Doppler examinations. The mean gestational age at delivery was higher in Group I (38.2± 3.3) compared with other groups (37.2± 4.2; 36.2± 2.6; 36.4± 3.6 and 31.1± 3.1, respectively, c^2 = 60.33; p < 0.001).

The Pearson correlation test showed an overall significant decrease in birth weights among the groups (p< 0.001). The mean birth weight in the first group was 2530± 473 g compared to the 1229 403 g in Group V (*Table N 1*). Placental resistance and low *ACM* PI (Group IV) was associated with reduced birthweight.

Adverse perinatal outcome was lowest when Doppler study profile was normal and highest when Doppler examination on both maternal and fetal side was abnormal (*Table N 1)*. Neonatal morbidity was 67 % for Group III neonates. This was largely attributable to prematurity (nine cases) and RDS (nine cases) see *Table N 1*.

Oligohydramnios was associated with increasing severity of Doppler vascular changes (Normal ®Abnl UtA®Abnl *AU* ® Abnl *AU* and *ACM* ®and *AU* ARED and Abnl *DV*, p<0.001). Unexpectedly, delivery by cesarean section, pre–eclampsia and the incidence of placental abruption were all observed more often in the group with increased umbilical artery PI without "brain–sparing" than in other groups (*e.g.* in Group III) (p=0.007; p=0.25; p=0.62, respectively). In all cases of placental abruption the presence of a "notch" was demonstrated in the UtA Doppler flow patterns.

Absent or reverse diastolic flow of *AU*, abnormal *ACM* and *DV* PI showed a direct correlation with 5–minute Apgar scores below 7, transfer to NICU, transfer to pediatric hospital for further treatment and intranatal mortality (p=0.01; p=0.01; p=0.02; p=0.03, respectively, *Table N 1*).

Perinatal mortality occurred only in Group IV (2/12, 16.7%) and in Group V (2/8, 25%). Three of four deaths occurred during delivery, one due to placental

abruption, and three due to severe pre–eclampsia. Three of eight fetuses of group V were born prematurely, had respiratory distress syndrome and developed severe intraventricular hemorrhage Grade III or IV. The mean length of stay of FGR infants in the NICU was 6 (± 1.6) days, statistically different amongst groups (p=0.016).
Thirteen women from FGR group were smokers and in 10 women reproductive tract infections (*C. trachomatis* n=4; BV n=6) were confirmed during pregnancy. Women with genital infections (p=0.02) had four times more frequent Doppler flow abnormalities compared to women without any other preventable risk factor (genital infections, smoking), p=0.018 (*Table N 1*). Smoking women with FGR have no different Doppler profile compared with normal women (p=0.09).

DISCUSSION

In the human fetuses, placental and fetal compromise are often associated with augmented PI of the umbilical artery (39), and redistribution of the blood flow within the fetal body in order to benefit the cerebral circulation (18, 20, 30). Different staging systems were proposed in order to allow timely delivery of fetuses (13, 28). In the present study, we report on the relation between ultrasonographic and clinical parameters of these high–risk pregnancies. Unlike in the study of Mari *et al*. (27) we also included the maternal uterine artery flow studies in our analysis and found not only that advancing hemodynamic changes are associated with increased perinatal mortality but also that abnormal UtA flow in itself was associated with adverse neonatal outcome in surviving babies (low 5–minute Apgar, increased neonatal morbidity, as evidenced by increased transfer to NICU and pediatric hospitals). Therefore, we support Gosh *et al.*'s (13) suggestion that the uterine artery flow studies should be included in the routine Doppler evaluation of women presenting with impaired fetal growth.
Furthermore, before delivery, the presence of a "notch" was demonstrated in the UtA flow on Doppler examinations in all five cases of placental abruption. As these events all occurred while the patients were hospitalized, four of the five neonates managed to survive.
In this study we hypothesized that fetal prognosis can be assessed by classifying Doppler abnormalities according to the severity in five different groups: from normal flow (Group I), to maternal flow abnormalities only (Group II), fetal uncomplicated flow abnormalities (Group III), abnormalities with brain "sparing effects" (Group IV) and finally to the flow indicating decompensation of the fetal circulation (Group V). We could clearly demonstrate a prognostic link between these groups and both fetal mortality and neonatal morbidity. Furthermore, we demonstrated that the most severe hemodynamic changes (Groups III–V) in FGR fetuses are achieved early in gestation, *i.e*. at the end of second or early in the third trimester. Inevitably, fetuses from Groups III–V were delivered earlier than fetuses of Groups II or I. Other studies have shown that placental compromise is indeed more pronounced if circulatory deprivation occurs before 32 weeks of gestation, and that late–onset cases have minimal placental involvement and more subtle Doppler findings (5, 23).
Unexpectedly, FGR women of III Group (abnormal *AU* without centralization) most often were delivered by cesarean section, which was even a higher rate than the compromised fetuses of Groups IV and V. We presume this might be due to the lack of specific clinical guidelines for the FGR management in Latvia. The prognosis for fetuses in Group III was actually good, with no perinatal deaths in this group. As these babies could have benefitted from delayed delivery as long as the elevated umbilical artery PI is not associated with signs of blood flow redistribution, such as in Groups IV and V, we would recommend conservative management for those fetuses, albeit under close supervision.
In a previous study, our group reported that smoking in association with fetal growth restriction showed more often intervillous hematomas and villous infarction in the placenta (42). In the present study, however, the pattern of Doppler velocities was similar between smoking and non–smoking women with FGR pregnancies. These findings seem to confirm the hypothesis that placental underperfusion in smokers might be periodic rather than continuous (31).
Compared to non–smoking controls delivering at term, we found more genital infections associated with more severe flow abnormalities. Therefore, besides to the known increased risk of preterm birth (15, 29, 33), genital infections like BV are not only linked to the increased likelihood of FGR (41), but also constitute an increased risk for placental abruption as shown by impaired Doppler pattern in the uterine arteries. In former studies we have demonstrated that also aerobic genital infections in the beginning of pregnancy were associated with an increased risk for chorioamnionitis, but also funisitis and fetal infection (35). The pathway of intrauterine ascending infections from abnormal vaginal flora, leading to increased intraamniotic proinflammatory cytokines, periventricular leucomalacia and cerebral palsy, was clearly documented by Yoon and coworkers *(45).* Infants born after the diagnosis of absent or reversed end–diastolic flow in umbilical artery (Group V) are particularly at risk of central nervous system complications and need more frequent parenteral feeding (21). Several abnormal flora types are involved in the causation of such pregnancy complications (7), and therefore, early screening and timely treatment with adequate antibiotics, like clindamycin, might lead to improved pregnancy outcomes (6, 38). However, specific associations between the presence of genital infections and FGR have been documented only sporadically, perhaps because the emphasis of the previous studies was mostly on the prevention of preterm birth and not FGR. We hope our new data inspire researchers to perform more studies on the link between genital infections and FGR, and try to provide evidence that can help to install preventive actions to dampen the severe damage of these small babies by early screening and treatment.

CONCLUSIONS

Severity of blood flow redistribution correlates with fetal morbidity and mortality. Less severe vascular changes, such as abnormal *AU* flow without centralization and even increased uterine artery PI alone are linked with reduced birth weight, higher likelihood of preterm birth and increased risk of morbidity. Genital infections contribute significantly to hemodynamic changes in FGR. Screening and preventing of RTI, as well as optimizing the time of delivery may improve the overall outcome of compromised fetuses.

Conflict of interest: None

REFERENCES

1. ACOG Practice Bulletin. Intrauterine Growth Restriction. No.12 // Int J Gynecol Obstet, 2001; 72:85 – 96
2. Ascharya G, Wilsgaard T, Berntsen, GKR, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy // Am J Obstet Gynecol, 2005; 192:937 – 944
3. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early–onset placental dysfunction // Obstet Gynecol, 2007; 109: 253 – 261
4. Cheema R, Dubiel M, Breborowicz G, Gudmundsson S. Fetal cerebral venous Doppler velocimetry in normal and high–risk pregnancy // Ultrasound Obstet Gynecol, 2004; 24: 147 – 53
5. Crispi F, Domínguez C, Llurba E, Martín–Gallán P, Cabero L, Gratacós E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction // Am J Obstet Gynecol, 2006; 195:201 – 7
6. Donders GG. Treatment of sexually transmitted diseases in pregnant women // Drugs, 2000; 59: 477 – 85
7. Donders GG, Van Calsteren K, Reybrouck R, Van den Bosch T, Riphagen I, Van Lierde S. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy // *BJOG*, 2009; 116:1315 – 24
8. Dubiel M, Breborowicz GH, Gudmundsson S. Evaluation of fetal circulation redistribution in pregnancies with absent or reversed diastolic flow in the umbilical artery // Early Hum Dev, 2003; 71:149 – 56
9. Ebbing C, Rasmussen S, Godfrey KM, Kiserud T. Fetal celiac and splenic artery flow velocities and pulsatility index: longitudinal reference ranges and evidence for vasodilatation at a low ortocaval pressure gradient. *Ultrasound Obstet Gynecol,* 2008; 32: 663 – 72
10. Evensen KA, Steinshamn S, Tjønna AE, Stølen T, Høydal MA, Wisløff U, Brubakk AM, Vik T. Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood // Early Hum Dev, 2009; 85:239 – 45
11. Ferrazzi E, Bozzo M, Rigano S, Belloti M, Morabito S, Pardi G. et al. Temporal sequence of abnormal Doppler changes in the periferal and central circulatory systems of severely growth restricted fetus // Ultrasound Obstet Gynecol, 2002; 19:140 – 6
12. Fortes Filho JB, Valiatti FB, Eckert GU, Costa MC, Silveira RC, Procianoy RS.) Is being small for gestational age a risk factor for retinopathy of prematurity? A study with 345 very low birth weight preterm infants // J Pediatr, 2009; 85:48 – 54
13. Ghosh GS, Gudmundsson S. Uterine and umbilical arteries Doppler are comparable in predicting perinatal outcome of growth–restricted fetuses // BJOG, 2009; 116:424 – 30
14. Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, Puerto B, Gratacos E. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation // Ultrasound Obstet Gynecol, 2008; 32:128 – 132
15. Guaschino S, De Seta F, Piccoli M, Maso G, Alberico S. Aetiology of preterm labour: bacterial vaginosis // BJOG, 2006; 113: Suppl3, 46 – 51
16. Henriksen T. Foetal nutrition, foetal growth restriction and health later in life // Acta Pediatr Suppl, 1999; 88:4 – 8
17. Kessler J, Rasmussen S, Hanson M, Kiserud T. Longitudinal reference ranges for ductus venosus flow velocities and waveform indices // Ultrasound Obstet Gynecol, 2006; 28:890 – 8
18. Kilavuz O, Vetter K. Is the liver of the fetal the 4th preferential organ for arterial blood supply besides brain, heart, and adrenal glands? // J Perinat Med, 1999; 27:103 – 6
19. Kiserud T, Eiknes SH, Blaas HGK, Hellevik LR. Ultrasonographic velocimetryof the fetal ductus venosus // Lancet, 1991; 338:1412 – 1414
20. Kiserud T, Kessler J, Ebbing C, Rasmussen S.). Ductus venosus shunting in growth–restricted fetuses and the effect of umbilical circulatory compromise // Ultrasound Obstet Gynecol, 2006;

28:143 – 149
21. Kornacki J, Kornacka A, Rajewski M, Goździewicz T, Skrzypczak J, Szczapa J. Do abnormal results of Doppler examinations in fetuses with growth restriction increase the frequency of postnatal complications of the central nervous system and gastrointestinal tract? // Ginekol Pol, 2009; 80: 839 – 44
22. Kudielka I, Raimann H, Schurz B, Schatten C, Eppel W, Reinold E Umbilical blood flow indices in smoking women // Z Geburtshilfe Perinatol, 1992; 196:213 – 6
23. Llurba E, Carreras E, Gratacós E, Juan M, Astor J, Vives A, Hermosilla E, Calero I, Millán P, García–Valdecasas B, Cabero L. Maternal history and uterine artery Doppler in the assessment of risk for development of early– and late–onset preeclampsia and intrauterine growth restriction // Obstet Gynecol Int, 2009; 275613
24. Manning FA, Platt LD, Sipos L. Antepartum fetal evaluation: development of a fetal biophysical profile // Am J Obstet Gynecol, 1980; 136:787 – 95
25. Mari G, Abuhamad AZ, Cosmi E, Segata M, Altaye M and Akiyama M. Middle cerebral artery peak systolic velocity–technique and variability // J Ultrasound Med, 2005; 24:425 – 430
26. Mari G, Deter RL, Hanif F, Treadweel M, Kruger M. Sequence of cardiovascular changes occuring in severeIUGR fetuses: Part II // Ultrasound Obstet Gynecol, 2006; 28:390
27. Mari G, Hanif F, Drennan K, Kruger M. Staging of intrauterine growth–restricted fetuses // J Ultrasound Med, 2007; 26:1469–77
28. Mari G, Picconi J. Doppler vascular changes in intrauterine growth restriction // Semin Perinatol, 2008; 32:182 – 189
29. Museva A, Shopova E, Dimitrov A, Nikolov A. Participation of the genital mycoplasmas: Ureoplasma urealyticum and Mycoplasma hominis in the processes of preterm birth // Akush Ginecol (Sofia), 2007; 46 Suppl 4:12 – 5
30. Natanielsz PW, Hanson MA. The fetal dilemma: spare the brain and spoil the liver // J Physiol–London, 2003; 548:33
31. Newnham J, Patterson L, James I, Reid SE. Effect of maternal smoking on ultrasonic measurements of fetal growth and on Doppler flow velocity waveforms // Early Hum Dev, 1990; 24:23 – 26
32. Nozaki AM, Franchisco RPV, Fonseca ESVB, Miyadahira S, Zugaib M. Fetal hemodynamic changes following maternal betamethasone administration in pregnancies with fetal growth restriction and absent end diastolic flow in the umbilical artery // Acta Obstet Gynecol, 2009; 88:350 – 354
33. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth // J Perinat Med, 2007, 35:93 – 9
34. Procianoy RS, Koch MS, Silveira RC. Neurodevelopmental outcome of appropriate and small for gestational age very low birth weight infants // J Child Neurol, 2009; 24: 788 – 94
35. Rezeberga D, Lazdane G, Kroica J, Sokolova L, Donders GGG. Placental histological inflammation and reproductive tract infections in a low risk pregnant population in Latvia // Acta Obstet Gynecol Scand, 2008; 87:360 – 5
36. Simchen MJ, Alkazaleh F, Adamson SL, Windrim R, Telford J, Beyene J. et al. The fetal cardiovascular response to antenatal steroids in severe early–onset intrauterine growth restriction // Am J Obstet Gynecol, 2004; 190:296 – 304
37. Sun Y, Vestergaard M, Pedersen CB, Christensen J, Basso O, Olsen J. Gestational age, birth weight, intrauterine growth, and the risk of epilepsy. Am J Epidemiol, 2008; 167:262 – 70
38. Swadpanich U, Lumbiganon P, Prasertcharoensook W, Laopaiboon M. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery // Cochrane Database Syst Rev, 2008; 16:CD006178
39. Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance–clinical significance // BJOG, 1985; 92:23 – 30
40. Vedmedovska N, Rezeberga D, Teibe U, Donders GGG, Polukarova S. Fetal Growth Restriction in Latvia // *IJOG*, 2010; doi: 10.1016/j.ijgo. nt J Gynaecol Obstet. 2010 Nov; 111(2):185-6.
41. Vedmedovska N, Rezeberga D, Teibe U, Donders GGG. Preventable maternal risk factors and association of genital infection with Fetal Growth Restriction // Gynecol Obstet Invest, 2010; 70: 219–226
42. Vedmedovska N, Melderis I, Rezeberga D, Teibe U, Donders GGG. Placental pathology in foetal growth restriction and smoking // Eur J Obstet Gynecol Reprod Biol. 2010 Dec 21. [Epub ahead of print], in press
43. Verburg BO, Jaddoe VW, Wladimiroff JW, Hofman A, Witteman JC and Steegers E A. Fetal hemodynamic adaptive changes related to intrauterine growth // Circulation, 2008; 117:649 – 659
44. Zelop CM, Richardson, Heffner U. Outcomes of severely abnormal umbilical artery Doppler velocimetry in structurally normal singleton fetuses // Obstet Gynecol, 1996; 87:434 – 438
45. Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC, Chi JG. High expression of tumor necrosis factor–alpha and interleukin–6 in periventricular leucomalacia // Am J Obstet Gynecol, 1997; 177:406 – 11

Table 1. Characteristics of FGR groups according to Doppler profile, data are given as numbers and SD, percentage in parenthesis

	Group I (n=18)	Group II (n=14)	GroupIII (n=18)	GroupIV (n=12)	GroupV (n=8)	P value
▪ Preventable risk factors						
Nl* (n)	12	3	7	4	0	Ref
Smoking (n)	3	1	2	2	3	0.09
STI (n)	1	4	1	2	2	0.018
▪ Acute pregnancy complications						
Preeclampsia	1 (6)	1 (7)	4 (22)	0	1 (13)	0.25
Placenta abruption	0 (0)	1(7)	3(16.6)	1 (8)	0	0.62
C–section	6 (33)	9 (64)	17(94)	7(58)	6 (75)	0.007
▪ Perinatal outcome						
Birth weight	2530±473	2270±364	1945±111	1746±516	1229±403	0.001
Gestational weeks	38.2±3.3	37.2±4.2	36.2±2.6	36.4±3.6	31.1±3.1	0.001
Amniotic fluid index <5	2(6)	2(14)	4(22)	3(25)	3(38%)	0.001
Perinatal mortality	0 (0)	0 (0)	0 (0)	2 (16)	2 (25)	0.01
5–min Apgar score<7	0 (0)	1 (7)	1 (6)	2 (17)	5 (63)	0.01
Neonatal morbidity	1 (6)	4 (29)	12 (67)	3 (10)	6 (100)	0.0004
Transfer to NICU	0 (0)	1 (7)	5 (28)	1 (10)	5 (83)	0.01
Transfer to pediatric hospital	1(6)	4 (29)	8 (44)	4 (40)	6 (100)	0.02

**non smoking, no genital infection*
μ: P value versus reference group of women without preventable risk factors only (non smoking, no STI)

Address:
Natalija Vedmedovska
Department of Obstetrics and Gynecology,
Riga Stradins University,
Dzirciema street 16, Riga LV-1013, Latvia
E-mail address: natalyved@apollo.lv

DOI: 10.2478/v10163-011-0010-4

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

ORIGINAL ARTICLE

Internal Fracture Fixation using the Anterior Retroperitoneal Lower Laparotomy Approach in Pelvic Ring and Acetabular Fractures: the First Experience and Outcomes

Andris Vikmanis, Andris Jumtins***
*Riga Stradins University
**Riga Eastern Clinical University Hospital, Clinics"Gailezers"

Summary
Introduction. The ilioinguinal approach is well established for the treatment of pelvic fractures. As an alternative, the anterior retroperitoneal lower laparatomy (modified Stoppa) approach can be used to expose pelvic and acetabular fractures. We describe our experience with this approach in polytrauma patients with pelvic ring and acetabular fractures .
Aim of the Study. The aim of study was to evaluate possibilities and impossibilities of internal fixation of pelvic ring and acetabular fractures using the anterior retroperitoneal lower laparatomy approach.
Materials and methods. This retrospective study describes a series of 20 consecutive patients where a modified Stoppa approach was used for pelvic or acetabular fracture fixation.
Results. 10 patients with acetabular fractures, six patients with a pelvic ring injury not involving the acetabular joint and 4 patients with a combined fracture were operated through a modified Stoppa approach. Anatomic or satisfactory reduction was achieved in 92% of the acetabular fractures. Pelvic ring fractures had an anatomic (displacement <1 cm) postoperative result in 100% .
Conclusions. using this approach may have good the postoperative radiological un surgical results. This is a method of choice for patients with combined trauma with internal organ damage and patients with both side pelvic bone fracture.
Key words: internal fixation, pelvic and acetabular fractures, lower retroperitoneal laparotomy approach.

INTRODUCTION

The ilioinguinal approach is widely used for internal fracture fixation of pelvic ring and acetabular fractures. Although its value has been established in numerous reports, because of the combination of various windows, the ilioinguinal approach is a laborious exposure. In 1993, Hirvensalo(2) and later Cole(3) described an extraperitoneal ("Stoppa") approach through the rectus abdominus muscle as an alternative approach for internal fixation of fractures of the pelvic ring or acetabulum(4.5). In 2008, we started use the modified Stoppa approach through the linea alba in Latvia. The technique uses a single window for obtaining an intrapelvic overview of the operative field by manipulating the entire peritoneal sac and pelvic organs away from the fracture. We report our first experiences and outcomes with this approach in 20 patients with pelvic ring and acetabular fractures that were eligible for anterior approach.

AIM OF THE STUDY

The aim of the study was to evaluate the technical aspects of the procedure with its intraoperative possibilities and impossibilities, the operative results obtained, and the rate and type of complications associated with the anterior retroperitoneal lower laparotomy approach.

MATERIALS AND METHODS

Between October 2008 and April 2010, the Stoppa approach was used in 20 consecutive patients with pelvic, acetabular or combined fractures in which previously we would have used an ilioinguinal approach. Our patient group consisted of primary(14) and secondary(6) referred patients .
Preoperatively, from radiological examinations were performed RTG – AP,LL,inlet,uotlet and always CT of pelvis with 3D reconstructin since most of those patients were with politrauma and as politrauma protocol CT is a must. A neurologist routinely evaluated all patients as well. Postoperatively, in all patients standard physical examination was performed by the attending trauma surgeon.
The operative procedures were performed by head of trauma and orthopedic department and two assistants. The postoperative radiographic results for all fractures were classified . In the acetabular fractures, displacement of 1 mm or less was considered an anatomic reduction, 2 to 3 mm was satisfactory and more than 3 mm was unsatisfactory(1.6) .
Postoperative fracture reduction of pelvic fractures was classified according to Pohlemann(7), considering a reduction within 1 cm as satisfactory.

Operative Technique
All patients were operated under general anesthesia on a radiolucent table in a supine position. The leg on the injured side was draped freely and both hips and knees were slightly flexed to relax the iliopsoas muscle. Prophylactic antibiotics (cefalosporin; 24 hours) and thrombosis prophylaxis (low molecular weight heparin; administered from admission until discharge) were routinely given. Through a midline incision from umbilicus to symphysis the anterior rectus sheath was opened vertically in the midline (Fig. 1).

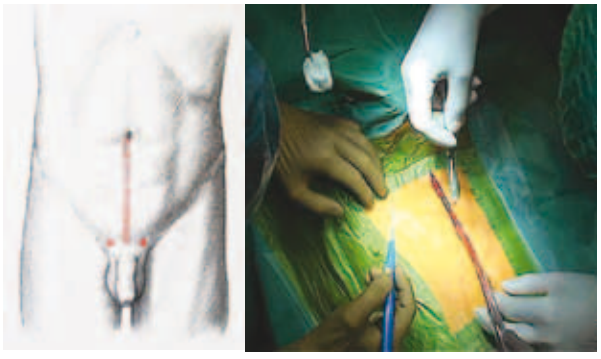


Fig. 1. Lower abdominal midline incision

The preperitoneal space was opened and bluntly dissected to the symphysis pubis. Generally the dissection is facilitated by the fracture hematoma following an anatomic dissection plane.
The fibers of the transverse abdominal muscle were dissected from the peritoneal sac and subsequently the peritoneal sac was freed from its surroundings so that it could be manipulated upwards and away from the fracture side. In all cases, the common femoral artery and vein were identified, mobilized and encircled with a silastic band to facilitate manipulation if necessary; in male patients the spermatic cord was identified and retracted with a silastic band as well . Starting from the superior ramus near the symphysis, the pelvic ring was identified and exposed subperiosteally.

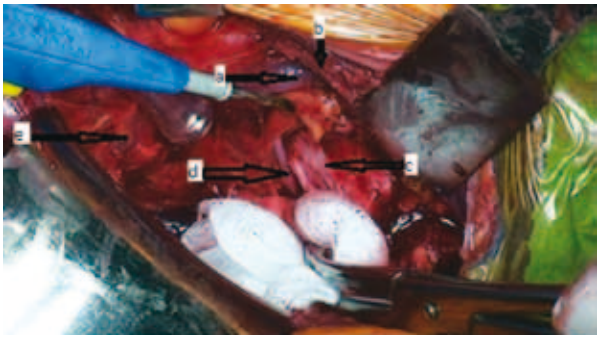


Fig. 2. Wiev of intra–operative situation .a–v.iliaca externa, b–m.rectus abdominis, c–ramus superior os pubis sin., d–corona mortis, e–peritoneum

Connecting vessels between the obturator and femoral vascular system, the corona mortis, were meticulously looked for and, if detected, cut after ligation.

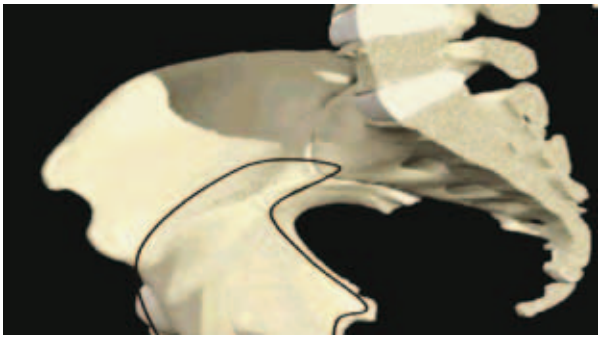


Fig. 3. Exposure of the modified Stoppa approach
Depending on the fracture type and exposure needed, after identifying the femoral nerve, the fascia of the psoas muscle was incised and the psoas muscle mobilized circumferentially if necessary (In this way, full exposure and access of the pelvic iliopectineal line and the quadrilateral plane up to the cranial and medial border of the SI joint is possible (Fig. 3).
If needed, this exposure can be extended to the opposite side of the pelvic ring through the same skin incision. If any peritoneal perforation was encountered during the exposure, it was preferably closed at the time of detection with a running suture. After completion of the exposure the operative field was kept into view with blunt retractors. After the osteosynthesis was completed, a final check on hemostasis and peritoneal sac perforations was performed. A suction drain was left in the preperitoneal cavity. The rectus sheath was closed in a running fashion with a monofilament resorbable suture. The skin was closed according to the preference of the surgeon, usually with interrupted monofilament sutures. The suction drain was removed 24 to 48 hours post–operatively.

RESULTS

Table 1 shows the demographic characteristics of the patients. There were 14 male and 6 female patients with an average age of 40 years (range 18 to 80 years). Of these, 13 were primarily admitted to our hospital , six were referred from surrounding hospitals, and one were transferred from abroad.
Ten patients had isolated acetabular fractures, six patients had pelvic ring fractures, and four patients had a combined pelvic ring and acetabular injury. According to the AO classification there were eight B type and two C type pelvic ring fractures, and according to the Letournel classification 8 both column, 4 T–shape, 1 anterior column, and 1 transverse type fractures of acetabulum.

Table 1. Demographics

Characteristic data		Number
Number of patients		20
Mean age (years)		40
Male:female ratio		14:6
Type of fracture	Acetabulum	10 (60%)
	Pelvic ring	6 (24%)
	Combined	4 (16%)
Laparotomy were performed in acute stage cases		5
Median interval accident to surgery (days)		15,5
Initial treatment with external fixator (cases)		8

In the majority of patients the mechanism of injury was a road accidents (50%) and fall from a height(40%).
The median time from injury to surgery was 6 days (range 0 to 57 days). This interval was mainly determined by the patients' general condition. In eight cases, temporary treatment was preceded by external fixation placement.
Preoperatively in four patients, neurologic abnormalities were found: two patients had sacral plexus injuries, of which two patients had a contusion of plexus lumbaris with a paresthesia. Another two patients with traumatic brain injury.
Surgical data are given in Table 2 and Table 3. The median operative time of the Stoppa–approach, defined as skin incision to skin closure, was 130 minutes (range 65 to 180 minutes). Median blood loss was 1020 ml (range 200 to 3000 ml) for all patients. All patients received packed red blood cells (PRBC) during or after the operation with a median amount of 2 units (range 1 to 6 units). For the 10 patients in whom a cell saver device was used, a median amount of 750 ml was reinfused. Iatrogenic perforation of the peritoneum was detected in two patients and after immediately closing all healed uneventfully.
An anatomic result was achieved in 10 patients (71%), a satisfactory result in three patients (21%) and unsatisfactory results in one patient (8%) – (n_14). For pelvic ring fractures, a displacement of _1 cm on postoperative radiography was considered satisfactory. All pelvic ring fractures were anatomically reduced (n _ 10).

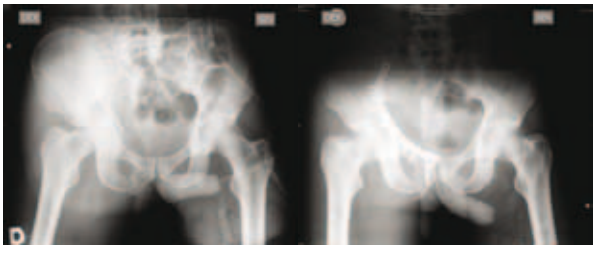


Fig. 4. Example of a patient with both column fractures treated by single modified Stoppa approach

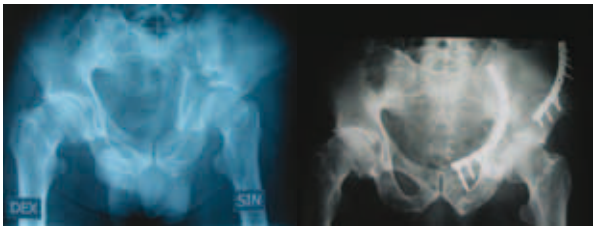


Fig. 5. Example of a patient with both column acetabular fractures treated by the modified Stoppa approach combined with lateral approach

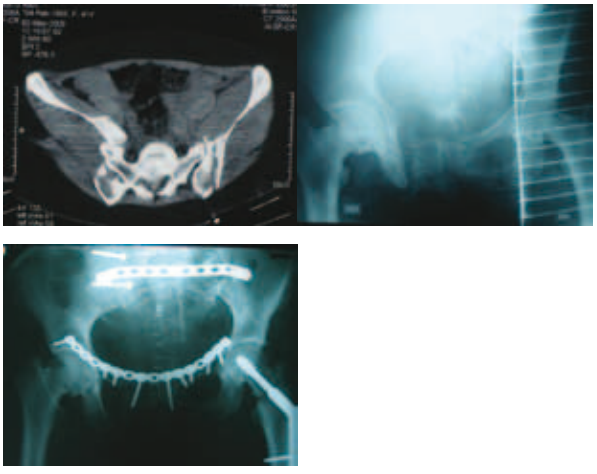


Fig. 6. Example of patient with C type pelvic ring fracture treated by modified Stoppa approach combined with posterior approach

Table 2. Surgical Data

Characteristic data	median	Range
Operation time, minutes	130	65–180
Blood loss, ml	1020	200–3200
Blood transfusions	2	1–6
Iatrogenic pelvic sack lesion	2	

For politrauma patients (ISS greater than or equal to 16) the mean hospital stay was 34 days compared with 21 days for patients with isolated pelvic and/or acetabular injuries . Patients that were operated within 5 days after the injury had an average blood loss of 1000 ml compared with patients that were operated after 5 days who had an average blood loss of 2500 ml.

Table 3. Postoperative reduction

Type of fracture	Number	Displa–cement	Result	%
Acetabulum	14	< 1 mm	10	71
		1–3 mm	3	21
		>3 mm	1	8
Pelvic ring	10	>10 mm	0	0
		<10 mm	10	100

Complications

During the retroperitoneal dissection, sever fibrosis was encountered and an injury of the peritoneal sack occurred, which was treated successfully with the stitches.

There were no iatrogenic lesions of the obturator vessels, nor of the spermatic cord. Three patients had thromboembolic complications: all of these had deep venous thrombosis (DVT) at the injured side (diagnosed by duplex scanning) and one of these developed pulmonary embolism (diagnosed CT). These thromboembolic complications were detected between the 2nd and 10th week postoperatively. All were initially treated by intravenous heparinization followed by oral anticoagulation with uneventful recovery.

Two patients had newly diagnosed neurologic symptoms after surgery – a neuropraxia of the femoral nerve which resolved spontaneously.

At one year follow–up the symptoms had completely resolved. The infectious complications comprised of one urinary tract infections, one pulmonary infection and one superficial wound infection, and all resolved after antibiotic treatment. There were no deep infectious complications encountered.

Table 4. Complications

Complication	number
Infection	3
Injury of peritoneal sack	2
Deep venozus thrombosis	3
Neuropraxia of the femoral nerve	2

DISCUSSION

The treatment of both the pelvic and acetabular fractures is demanding. The operative techniques developed during the last 40 years, have been mainly for the acetabular surgery. However, development is still continuing and optimal treatment protocols are still under scientific evaluation and critical discussion, especially in the treatment of pelvic fractures. Fixation of the anterior part of the ring is still considered unnecessary in many centres although all biomechanical tests show inferior stability of a partially stabilised ring compared to a more extensive fixation of the whole ring. External fixation devices cannot restore enough stability in the unstable type C injuries to allow mobilization of the patient without risk of redisplacement of the injury sites leading to suboptimal functional results. Neither have minimal invasive, percutaneous techniques been able to guarantee good reduction or stability of the entire ring.

The widely used ilioinguinal approach and especially the extended iliofemoral, transtrochanteric and triradiate exposures can be considered extensive and traumatic. The preparation of the neurovascular bundle with lymphatic vessels and funicular structures contains risks, needs extra time for meticulous preparation and always causes scar tissue formation around these important areas when using the ilioinguinal technique. All techniques directed to the joint through lateral or posterior approaches create scar formation, contain a risk of heterotopic ossification and have to be noted as a potential risk for any possible endoprosthetic solution later on.

At the Department of Orthopaedics and Traumatology in Riga Eastern Clinical University Hospital the policy of internal fixation of both the acetabular and pelvic fractures was adopted simultaneously in 2008.

The first operation was performed in 28.10.2008.

The anterior approach was further developed as a route to achieve access to both on the entire pelvic brim and in the acetabular quadrilateral area. The external fixation frames have been used solely as temporary fixation devices to reduce the pelvic volume in open fractures and in severe bleeding when preparing the patient to angiography or internal fixation procedures.

The anterior extraperitoneal approach used in the present study gives a wide view on the true pelvis and can be used in both the pelvic and acetabular fracture treatment. As an anatomical, quite short midline incision between the rectus muscles, it can be considered less invasive when compared to many other approaches on the pelvic area. The approach was combined with lateral, posterior or Kocher—Langenbec approaches depending of the fracture type in each patient.

In acetabular fractures the anterior technique gives access and a direct view on the quadrilateral area, anterior wall area and even more, on the important supratectal area. Especially in those cases where the acetabular roof hides an articular fragment impacted to the weight bearing dome area, this medial window can allow the reduction
of the fragments, transportation of cancellous bone and bone substitution materials and fixation of the fractures without lateral extrapelvic exposures and dislocating the joint. The anterior approach leaves the extrapelvic juxtaacetabular tissues intact which is important in possible secondary osteoarthritis and eventual joint replacement surgery.

As seen in the limited number of complications this approach can be considered relatively safe, although the operation is demanding and needs good surgical skills and good knowledge of intrapelvic anatomy. The low incidence of major surgical complications, as well as deep venous thrombosis and heterotopic ossification(12) was an important finding . Although the risk of major vascular injuries is always present. Although all the patients received antithrombotic prophylaxis during the hospital stay this was an important finding, because the intrapelvic technique always includes some manipulation of the iliac vessels together with other anterior vascular structures. There were the low incidence of femoral nerve injuries which resolved spontaneusly. And there were not any lesions of the obturator nerve, although the nerve always has to be pushed down with a blunt retractor, when
the lateral bony structures have to be revealed.

The neurological recovery in the pelvic group with plexus injuries needs to be noted. Good recovery in

both muscular and sensory deficiencies was observed especially in those patients where the reduction and fixation were successful and were in accordance with earlier studies. Moreover, by anatomical reduction the leg discrepancy could be prevented in most cases leading to normal gait.

The good reduction together with proper stabilization allow early mobilization, prevent complications and thereby lead to a short hospital stay and to an early start of rehabilitation.

The encouraging results with good functional recovery, the possibility of anatomical reduction with the less invasive techniques described above and the relatively low complication rate give a strong indication to continue the policy and efforts to reduce and fix both the pelvic ring and acetabular fractures in an anatomical position, whenever the general condition of the patient allows major reconstructive procedures.

CONCLUSIONS

Our experience with the Stoppa approach in 20 consecutive

patients shows that good operative results can be obtained with this exposure. The rate of complications in this small series of seriously injured patients was considerable but the majority of these resolved with conservative treatment. We consider the Stoppa approach as a useful alternative for the ilioinguinal approach in patients with fractures in the pelvic ring or the acetabulum where open reduction and internal fixation is indicated. Furthermore, this straightforward anatomic approach offers additional advantages in bilateral fractures and combined trauma with internal organ damage. To determine its comparativeness to standard approaches with respect to functional outcome, more studies are warranted.

Conflict of interest: None

REFERENCES

1. Matta JM. Indications for anterior fixation of pelvic fractures // Clin Orthop. 1996; 88 –96
2. Hirvensalo E, Lindahl J, Bostman O. A new approach to the internal fixation of unstable pelvic fractures // Clin Orthop Rel Res. 1993; 28–32
3. Cole JD, Bolhofner BR. Acetabular fracture fixation via a modified Stoppa limited intrapelvic approach. Description of operative technique and preliminary treatment results // Clin Orthop. 1994; 112–123
4. Stoppa RE. The treatment of complicated groin and incisional hernias // World J Surg. 1989; 13: 545–554
5. Stoppa RE, Rives JL, Warlaumont CR, Palot JP, Verhaeghe PJ, Delattre JF. The use of Dacron in the repair of hernias of the groin // Surg Clin North Am. 1984; 64:269 –285
6. Matta JM. Operative treatment of acetabular fractures through the ilioinguinal approach. A 10–year perspective // Clin Orthop. 1994; 10–19
7. Pohlemann T, Gansslen A, Schellwald O, Culemann U, Tscherne H. Outcome after pelvic ring injuries // Injury. 1996; 27 Suppl 2: B31–B38
8. Tornetta P3, Hochwald N, Levine R. Corona mortis. Incidence and location // Clin Orthop. 1996; 97–101
9. Muller M. The comprehensive classification of fractures, Part 2: Pelvis and acetabulum // Berlin: Springer, 2004
10. Letournel E. Acetabulum fractures: classification and management // Clin Orthop. 1980; 81–106
11. Letournel E. The treatment of acetabular fractures through the ilioinguinal approach // Clin Orthop. 1993; 62–76
12. Ghalambor N, Matta JM, Bernstein L. Heterotopic ossification following operative treatment of acetabular fracture. An analysis of risk factors // Clin Orthop. 1994; 96 –105

Address:
Andris Vikmanis
Department of Orthopaedics and Traumatology
Riga Eastern Clinical University Hospital
Clinics"Gailezers"
Hipokrata Street 2, Riga, Latvia, LV-1038
E-mail: vikmanis2@inbox.lv

ORIGINAL ARTICLE

The Evaluation of Early Results after Total Hip Replacement in Dysplastic Hip Patients

Silvestris Zebolds*, Andris Jumtins**
* State Hospital of Traumatology and Orthopaedics, Riga, Latvia
**Riga Stradins University, Riga, Latvia

Summary
Introduction. Dysplasia of hip joint leads to osteoarthritis. Suffer relatively young population in ages between 20 and 40. Due to severe changes of anatomy total hip replacement (THR) in dysplastic hip patients is a challenge for orthopaedic surgeons. Radical anatomical and biomechanical reconstruction may lead to high complication rate. The planning of the rotation center of hip joint is a key of success in the treatment of dysplastic osteoarthritis patients.
Aim of the Study. The aim of the study was to evaluate the early results for dysplastic osteoarthritis patients (DOA), who underwent THR in Riga State Hospital of Traumatology and Orthopaedics in 2008–2009.
Materials and methods. 63 THR were performed in 59 patients (50 women, 9 men). In all cases cementless acetabular components of endoprosthesis were used. Functional evaluation was made due to method of grading functional value of hip – Merle d'Aubigne and Postel. Hip dysplasia was divided in 4 groups due to classification after Crowe. Special digital orthopaedic programmes (AGFA, IMPAX) were used for preoperative planning and radiographic postoperative analysis.
Results. Regarding to method of grading functional value of hip – Merle d'Aubigne and Postel we found out a significant improvement in range of movements, mobility and pain relief. Due to Crowe classification there were 19 patients with Crowe type I dysplasia, 29 with Crowe type II and 15 with Crowe type III. 43 acetabular cups were placed in the primary socket and 20 in the secondary socket. Radiographic analysis showed significant changes in location of rotation center of hip and offset after THR in dysplastic hip patients.
Conclusions. Significant functional improvement was achieved after THR in DOA patients and the radiographic analysis showed significant decrease of horizontal location of RC and increase of offset after THR in DOA patients.
Key words: dysplastic osteoarthritis, rotation center of hip joint, digital planning.

INTRODUCTION

The abnormal loading of joint cartilage leads to developing of osteoarthritis in patients with hip dysplasia. Patients are relatively young and mostly women between the ages of 20 and 40. The signs of osteoarthritis are strongly associated with increasing age and the severity of dysplasia (4). In our study we used classification after Crowe (1). Total hip replacement (THR) in dysplastic hip patients is a challenging procedure. Anatomy of the joint is extremely changed in comparison with normal or primary osteoarthritic hip. Biomechanics of the hip joint, pelvis , lumbar spine and lower extremeties are often severly changed during the life time. Complication rate after THR in dysplastic hip patients is much more higher (3). Anatomical socket placement can result in a hip that is difficult to reduce, and reduction can be associated with considerable limb lengthening and an increased risk of neurological traction injury (6). Radical anatomical and biomechanical reconstruction of hip joint during operation may lead not only to local complications as overstretching of *N.ischiadicus*, contracture of hip joint, early loosening and wear of acetabular component of endoprosthesis, but even to the distress of the whole musculo–skeletal apparatus. For that reason it is very important to plan the best location of the acetabular cup, which depends on the chosen level of the rotation center of the hip joint. Since 2008 in the Riga State Hospital of Traumatology and Orthopaedics (SHTO) we have a possibility to use special digital orthopaedic programms (AGFA, IMPAX) for radiographic preoperative planning and for analysing of postoperative results. 63 THR were performed in 59 dysplastic osteoarthritis patients during 2–years period (2008 and 2009) in Riga SHTO. All patients were clinically and radiographically examined before and after (follow up 3 to 27 months) operation. In addition questionnaires based on the modified method of grading functional value of hip after Merle d' Aubigne and Postel (8) were sent to all patients.

AIM OF THE STUDY

The aim of our study was to evaluate functional and radiographic outcomes after THR in dysplastic hip patients.

MATERIALS AND METHODS

All dysplastic osteoarthritis (DOA) patients who underwent THR in 2008 and 2009 in Riga SHTO were included in our study. In all 63 THR cases uncemented acetabular components of endoprosthesis were used. The distribution of acetabular components (cups): Duraloc – used in 41 cases, W.Link T.O.P. – in 11 cases; Bicon Pluss – in 10 cases, BHR – in 1 case. 55 uncemented femoral components (stems) were used: SLPluss in 54

and Nanos(short stem) in 1 case. Also 8 cemented stems were used: CSPluss – in 6 cases, W.Link LCP – in 2 cases. We applied Crowe classification to divide dysplasia in 4 types due to subluxation of the femoral head:

- Crowe – type I – subluxation less than 50% (see figure 1);
- Crowe – type II – subluxation 50% –75% ;
- Crowe – type III – subluxation 75%–100% (see figure 5);
- Crowe–type IV – subluxation more than 100%.

For evaluation of functional outcome we applied method of grading functional value of hip after Merle d'Aubigne and Postel (8). This method includes evaluation of patients due to 3 criteria: pain, function and mobility (Table 1).

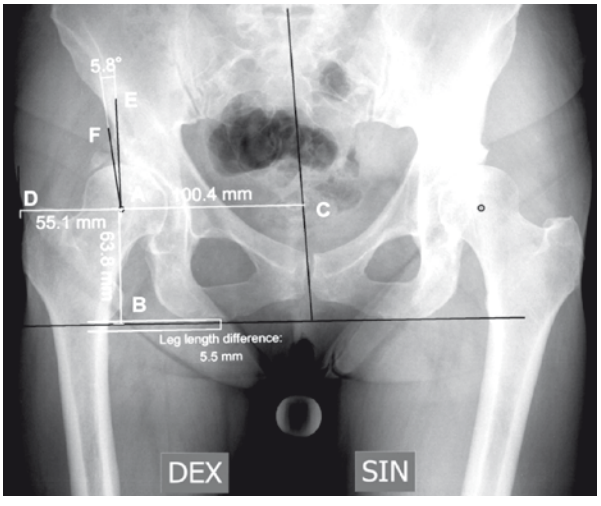
Table 1. Method of grading functional value of hip – Merle d'Aubigne and Postel

Gra–de	Pain	Function	Mobility
0	Pain is intense and permanent	Ankylosis with bad position of hip	None
1	Pain is severe even at night	No movenent;pain or slight deformity	Only with crutches
2	Pain is severe when walking; prevents any activity	Flexion under 40 degrees	Only with canes
3	Pain is tolerable with limited activity	Flexion between 40 and 60 degrees	With one cane, less than 1 hour; very difficult without cane
4	Pain is mild when walking; disappears with rest	Flexion between 60 and 80 degrees; patient can reach his foot	A long time with a cane; short time without cane and with limp
5	Pain is mild and inconstant; normal activity	Flexion between 80 and 90 degrees; abduction of at least 15 degrees	Without cane but with slight limp
6	No pain	Flexion of more than 90 degrees; abduction to 30 degrees	Normal

The worst score is 0 points – for a patient with permanent pain, no movement and bad position of the hip, walking is not possible. The best score is 6 points in each group, it means it is possible to achieve result of maximum 18 points–for a patient with no pain (6 points in pain score), flexion in hip joint more than 90 degrees (6 points in function score), normal walking (6 points in mobility score).

Special orthopaedic programmes (AGFA,IMPAX) were used for preoperative planning and postoperative evaluation of radiographs. Metallic ball marker of known diameter(25 mm) was used for calibration of the radiograph in A–P projection. The rotation center of the hip joint is similar with the center of the head of the femur (point A in figure 1) or center of the head of endoprosthesis after THR (point A in figure 2).

Fig. 1. Preoperative measurements in A–P radiograph – Crowe–type I dysplastic OA of the right hip joint (AB–the vertical location of the rotation center;AC–the horizontal location of the rotation center; AD– the offset; angle FAE– Wiberg lateral center edge angle)



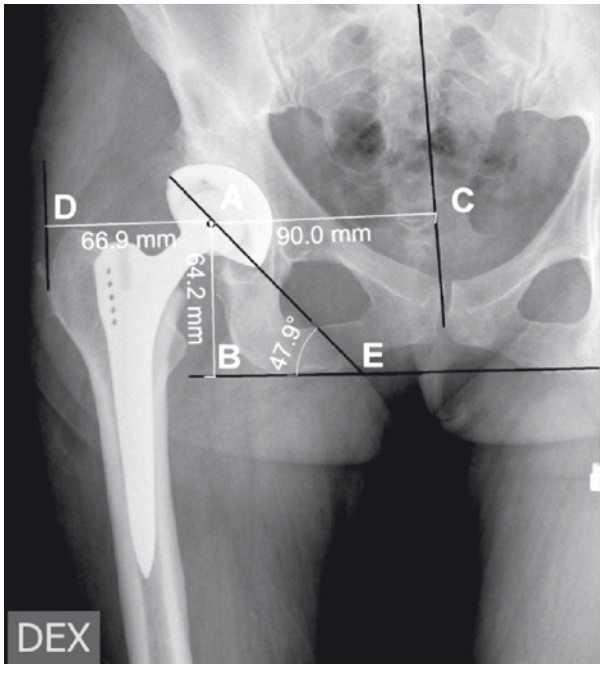


Fig. 2. Postoperative measurements in A–P radiograph– THR of the right hip joint with uncemented EP(W.Link T.O.P. acetabular component of endoprosthesis located into the primary socket,SLPluss stem and ceramic ball head used; AB–the vertical location of the rotation center of the hip joint, AC– the horizontal location of the rotation center of the hip joint; AD– the offset; angle AEB– the inclination angle of the acetabular component of endoprosthesis into the pelvis)

Postoperatively we analysed the placement of acetabular component. If the rotation center of the endoprosthesis was similar with the anatomic hip center, we considered that acetabular cup is placed in the primary socket (figure 2). If the rotation center of endoprosthesis was placed more than 1 cm cranially, then we considered that the cup is placed in the secondary socket (figure 6). We used 3 main measurements for evaluation of the location of the rotation center of hip joint: vertical location – the distance from the ischial tuberosity to the center of the femoral head (distance AB, see figure 1); horizontal location – the distance from the line, which connects processus spinosus of lumbar spine with the center of symphysis to the center of the femoral head (distance AC, see figure 1).The third measurement is Wiberg lateral center edge angle (CEA) which is the angle between vertical line from the center of the femoral head and line which connects the center of the femoral head and lateral edge of the acetabulum (angle FAE in figure 1). Usually Wiberg lateral edge angle in dysplastic hip patients is less than 25 degrees and depends on the severity of dysplasia (7,9). For abductor muscle tension the offset is important. It is the distance from the center of the femoral head to the lateral edge of greater trochanter (distance AD in figure 1). To evaluate postoperative radiographic changes in the location of rotation center of hip joint we measured vertical and horizontal location of the center of the head of endoprosthesis. We compared the planned location of rotation center of the hip joint, inclination angle and size of the acetabular component with postoperative outcome (figure 2,5,6). For evaluation of leg length descrepancy we measured and compared distances from lesser trochanters to the line that connects both ischial tuberosities.

RESULTS

63 THR were performed in 2 years period in 59 patients. 50 patients were women and 9 – men. Mean age was 45,30 (from 20 to74) years. From 59 sent questionnaires we received 40 responses (68%). The follow–up was 3 to 27 month after THR. According to method of grading functional value of hip – after *Merle d Aubigne and Postel* the pain score (in average) increased from 1,30 preoperatively to 5,70 postoperatively (nearly all patient were free of pain after THR). The function score changed from 3,30 to 5,60 and the mobility score also increased from 3,30 to 5,30 points (figure 3).

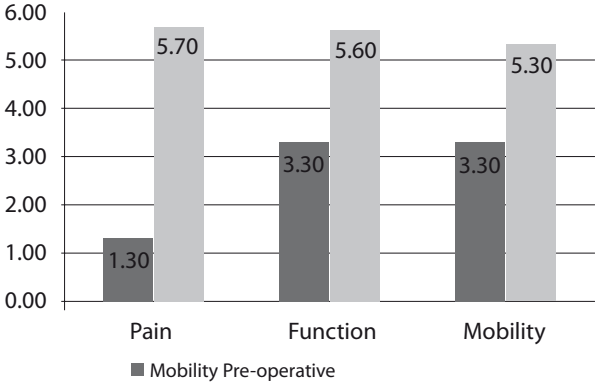


Fig. 3. The evaluation of funcional result pre– and postoperatively according to *Merle d' Aubigne and Postel* grading system

Distribution of patients due to severity of dysplasia (n = 63 THR): Crowe – type I – 19, Crowe – type II – 29, Crowe – type III – 15. We did not have Crowe– type IV patients in 2008 and 2009. Postoperative analysis showed us that in 43 cases the acetabular cup was placed at the anatomical site (in the primary socket), but in 20 cases – in the secondary socket. In all Crowe – type I dysplasia cases (19) the cups were operated in the primary socket, from 29 Crowe – type II dysplasia cases 22 were placed in primary, but 7 in secondary socket. From 15 Crowe – type III dysplasia cases 2 cups were placed in primary, 13 in secondary socket (Figure 4).

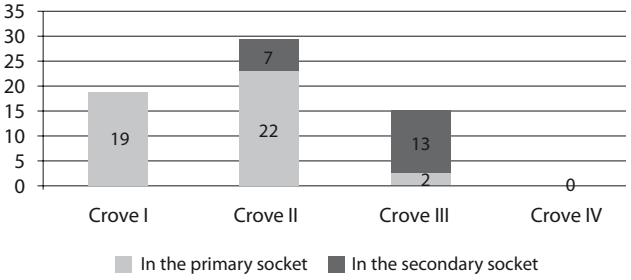


Fig. 4. Distribution of dysplasia due to Crowe classification, placement of acetabular compo–nents in the primary or secondary sockets

Digital radiographic measurements were made for group of 23 patients. The analysis showed the following results after THR: average increase of the vertical location of the rotation center (RC) was 2,5 mm (p=0.03), average decrease of the horizontal location of the rotation center was 7,5 mm (p<0.001), average increase of the offset was 13,5 mm (p<0.001), see table 2. The decrease of horizontal RC can be explained by medialization of acetabular component therefore satisfactory bone coverage of cup was obtained during THR. The offset increase is very important for abductor muscle function as well as the adequate tension of abductors ensures the stability of the hip joint. The increase of the offset depends on the length of the modular necks of the femoral component of endoprosthesis.

Table 2. Change of the rotation center of the hip joint and offset after total hip replacement (THR)

	Before THR	After THR
The vertical location of the rotation center(average)	61,9 (min 30,4 mm; max 77,5 mm)	64,4 mm (min 41,5 mm; max 75,8 mm)
The horizontal location of the rotation center (average)	99,6 mm (min 72,3 mm; max 118,9 mm)	92,1 mm (min 76,4 mm; max 97,8 mm)
Offset (average)	49,7 mm (min 30,0 mm; max 69,2 mm)	63,3 mm (min 49,6 mm; max 80,7 mm)

We compared also the the planned vertical location of RC of hip joint with postoperative result. The mean difference was 0,8 mm (not significant). The planned inclination angle of the acetabular cup was about 44 degrees, but postoperative angle of inclination was 38,5 degrees (Table 3). So significant difference could be explained by try of surgeons to locate the acetabular cups more horizontally for reducing the risks of luxation.

Table 3. The comparison of the planned position of the rotation center of endoprosthesis and inclination angle of acetabular component with the postoperative result

	Preoperative planning	Postoperative result
The vertical location of the rotation center(average)	65,2 mm (min 52,0 mm; max 75,6 mm)	64,4 mm (min 41,5 mm; max 75,8 mm)
The inclination angle (average)	44,4° (min 31,2°; max 49,9°)	38,5° (min 24,7°; max 52,6°)

The average Wiberg lateral CEA was 17.9° (min 0 degrees, max 42.9 degrees).In cases with CEA bigger than 25 degrees, DOA patients usually had collapsed femoral heads due to aseptic necrosis.The sizes of implants were planned precisely.The mean difference was only 0,2 mm (not significant). In our study we did not see any major complications as dislocations, infections, early loosening of components of endoprosthesis etc.

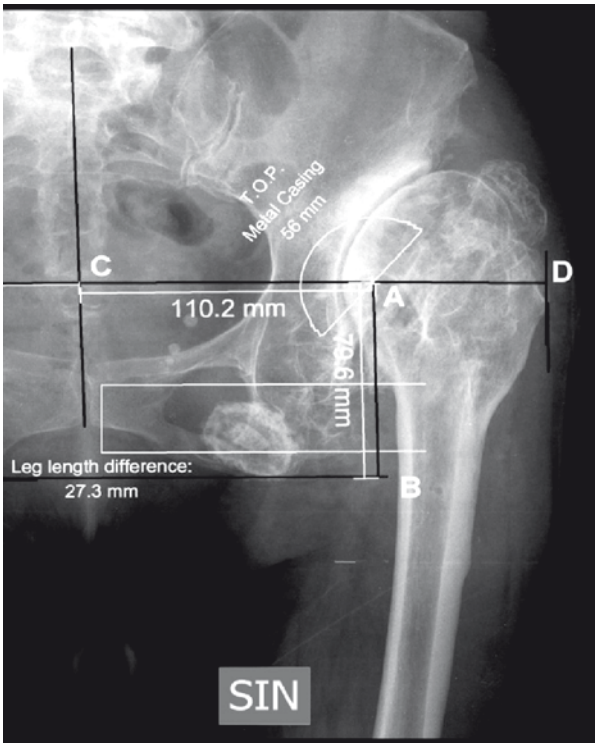


Fig. 5. A–P radiograph of the pelvis– Crowe –type III dysplastic OA of the left hip joint(point A– the planned rotation center of the hip joint after THR;AB– the planned location of the vertical RC; AC–the planned location of the horizontal RC)

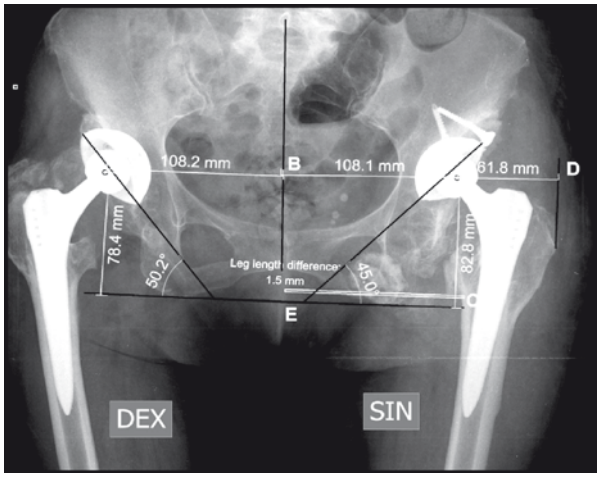


Fig. 6. A–P radiograph of the pelvis– THR of both hip joints with uncemented EP(W.Link uncemented T.O.P. acetabular components located into the secondary sockets, bone grafting of the roof of the left acetabulum is made for better coverage of the cup ,uncemented SLPluss stems and metal ball heads used;point A–the rotation center of the left hip joint;AB–the horizontal location of RC;AC–the vertical location of RC;AD–the offset;angle AEC–the inclination angle of acetabular component into the pelvis)

DISCUSSION

Due to changed anatomy the complication rate in DOA patients (Crowe – typeII, III, IV) is much more higher than in degenerative OA patients.For patients with dysplasia Crowe – typeIV major complication rate can reach even 43 % (Krych,2009).The most common cause (about 33%) for acetabular revision is instability or dislocation (Bozic,2009).The radical anatomical and biomechanical reconstruction of the hip joint during THR and trying always to place the acetabular component at the level of anatomic hip center may lead to limb lengthening, neurological injury and early cup loosening.In our study 20 cups (32%) were placed in secondary socket and we did not see any major complications .We consider that preoperative planning of the location of the RC of hip joint due to grade of dysplasia is a key of success for treatment of DOA patients.

CONCLUSIONS

1. Significant functional improvement and pain relief were achieved after THR in DOA patients in short–term follow–up.
2. The radiographic analysis showed decrease of the horizontal location of the center of rotation of the hip joint and increase of the offset after THR in DOA patients, but there were no significant changes in the vertical location of the rotation center.

Conflict of interest: None

REFERENCES

1. Crowe J.F., Many V.J., Ranawat C.S. Total hip replacemet in congenital dislocation of the hip // JBJS, 1979; 61A: 15 – 23.
2. Bozic K.I., Kurtz S.M., Lau E. Et al., Theepidemiology of revisiontotal hip aarthroplastyin the United States //JBJS Am. 2009;91:128–33.
3. Hendrich C., Engelmaier F., Mehling I., et al. Cementless acetabular reconstruction and structural bone–grafting in dysplastic hips. Surgical tecnique // JBJS, 2007; 89: 54 – 67.
4. Jessel R.H., Zurakowski D., Zilkens C. et. al. Radiographic and patient factors associated with pre–radiographic osteoarthritis in hip dysplasia // JBJS Am., 2009; 91:1120 – 1129.
5. Klapach A.S., Callaghan J.J., Miller K.A., et.al. Total hip arthroplasty with cement and without acetabular bone graft for severe hip dysplasia// JBJS Am., 2005;87:280 –285.
6. Krych A.J., Howard J.L., Trousdale R.T., et.al. Total hip arthroplasty with shortening subtrochanteric osteotomy in Crowe Type–IV developmental dysplasia // JBJS Am., 2009; 91: 2213 – 2221.
7. Maeyama A., Naito M., , Moriyama S., Yoshimura I. Evaluation of dynamic instability of the dysplastic hip with use of triaxial accelerometry // JBJS Am., 2008;90:85–9/
8. Merle d' Aubigne R., Postel M., Functional results of hip arthroplasty with acrylic prosthesis // JBJS, 1954; 36: 45.
9. Wiberg G. Studies of dysplastic acetabula and congenital subluxation of the hip joint.With special reference to complication of osteoarthritis // Acta Chir.Scand., 1939; 58(Suppl):5–135.

Address:
Silvestris Zebolds
State Hospital of Traumatology and Orthopaedics,
Riga, Latvia
Duntes street 22 Riga, Latvia LV-1005
E-mail: szebolds@apollo.lv

DOI: 10.2478/v10163-010-0012-7

ACTA CHIRURGICA LATVIENSIS • 2009 (9)

ORIGINAL ARTICLE

Clinical, Radiographic and Pathohistological Outcomes of Hydroxyapatite (HAp) Ceramics and Dental Implants in Atrophic Posterior Maxilla

Girts Salms*, Andrejs Skagers*, Guntis ZigursJanis Locs***, Liga Berzina-Cimdina***, Laila Feldmane******
*Department of Oral and Maxillofacial Surgery, Institute of Stomatology, Riga Stradins University, Latvia
**Department of Prosthodontics, Institute of Stomatology, Riga Stradins University, Latvia
***Riga Biomaterials Innovations and Development Centre, Riga Technical University, Latvia
****Department of Pathology, Riga Stradins University, Latvia

Summary
Introduction. Implant based prosthodontic rehabilitation of patients with atrophic edentulous posterior maxilla has necessity in reinforcement of alveolar bone using different bone substitutes. It is important to evaluate late outcomes in integration of synthetic HAp as biomaterial in chemical composition close to main natural bone mineral component in elevated maxillary sinus floor and osseointegration of dental implants.
Aim of the study. To evaluate clinical and radiological outcomes of one stage maxillary sinus floor augmentation with synthetic HAp granules and dental implant insertion, mineralization degree of residual bone and augmented sinus part, morphological analysis of biopsies from HAp/ host tissue hybrid and residual alveolar bone was performed.
Materials and methods. One stage maxillary sinus floor elevation with synthetic HAp granules and 147 SEMADOS (BEGO) dental implant insertions in 70 patients were included in this study. Clinical and radiograph analyzes by dental X-rays, digital orthopantomogramms, quantitative radiodensitometry after 3 and 5 years was done. Trephine biopsies of residual alveolar bone and elevated part of maxillary sinus 6 months after implantation was done in 30 cases.
Results. During this period 6 implants (4.2%) were lost. We found the decrease of radiodensity in HAp augmentated maxillary sinus area and increase of radiodensity in the area of residual alveolar bone. In biopsies after 6 months biomaterial/host tissue hybrid consisted of small bone trabecules, fibrous tissue and granules of irregular shape without inflammatory cells. Slow degradation of HAp granules by activity of osteoclast like macrophages was observed.
Conclusions. Osseointegration was lost in 4.2% of inserted in augmented maxillary sinus implants. Radiodensitometry showed decrease of optical density in augmented sinus part and increase in residual alveolar bone. In biopsies of host tissue/biomaterial hybrid was bone newformation, connective tissue and biodegradation of HAp granules by osteoclast like cells.
Key words: atrophic posterior maxilla, synthetic hydroxyapatite, radiodensitometry, biopsy.

INTRODUCTION

Alveolar bone of the jaws is the primary support structure for teeth and after their lost for dental implants with unique continual and rapid remodelling subsequently the functional demands and loading in mastication. It is well recognized that tensional forces stimulate osteogenesis while compressive forces promote osteoclastic activity (16). Maxillary posterior edentulous region from expansion of the sinus after teeth loss and decrease of bone density presents unique challenging conditions in implant dentistry (9). Sinus floor elevation with bone or artificial materials increases availability of bone height, and jaw bone loading during prosthodontic phase of the reconstruction (2). Autogenous bone grafting recognized as gold standard among advantages has also disadvantages as extra surgery with possible morbidity of donor site, limited available volume, difficulties to foresee resorbtion and final outcome of bone grafting, especially in recipient site where active resorbtion of previous host bone occurred (15). Implant loss after one stage sinus auto bone grafting is near 20% (8). Calcium phosphate ceramics have proven to be one of the more successful high technology-based biomaterials that have developed within the past decades (6). HAp is the main natural inorganic compound of bone and essentially has affinity and biocompatibility to the bone tissue. It has superior properties for the stimulation of osteogenesis and bone bonding, both related to the specific interactions of surface with the extracellular fluids and cells, ionic exchanges, superficial molecular rearrangement and cellular activity (1). There are clinical, radiological and morphological methods for the assessment of grafting materials used as bone substitutes for maxillary sinus floor elevation. From the clinical point of view and also for the general assessment not just grafting material but a lot of local and general factors influence the survival of dental implants in host bone/ biomaterial hybrid and stability of implant-supported artificial teeth. Quantitative radiodensitometry was used for the evaluation of tissue density in healing mandibular fractures (17).

MATERIALS AND METHODS

The properties of synthesized powder and sintered ceramics were investigated by chemical compositions of high purity, X-ray diffraction, SEM, FT-IR methods. HAp powder was calcined at 800°C for 1 h, pressed in blocks and sintered for 1 h at 1150 - 1200°C. Granules were prepared by grinding the ceramic blocks. To evaluate up to 5 years late outcomes of one stage sinus floor elevation with synthetic HAp and 142 SEMADOS (BEGO) dental implant insertion in this study were included 68 patients with alveolar bone in posterior maxilla not less than 5 mm in height and more than 4 mm in width - Misch class SA2 – SA3. Clinical and radiographs analyzes by method of quantitative radiodensitometry (CADIA), in cases of 5 lost implants scanning electron microscopy (SEM), electron diffraction X-ray (EDX) chemical microanalysis methods were used. The subject evaluated by quantitative radiodensitometry was the optical density, which is opposite to the traditional interpretation of X-rays where more dark till black corresponds to less dense tissue and white corresponds to density of implants or abnormal high mineralization of bone. As a more logical decision for clinical framework, we chose the conversion of units of absolute optical density to percentage rate assuming the density of titanium implants 100% and the density of oral cavity as 0%; there were the radiodensity of alveolar bone and augmented sinus floor between these marginal values. We have used dental periapical X-rays, panorex and paraxial computer tomography scans to analyze optical density in the residual alveolar bone and elevated maxillary sinus part. The digital image was processed by Leica Quantimet (Leica Corporation, Cambridge, UK) image-processing system using a computer equipped with Image-Pro Plus system software for image analysis. SPSS 7.5 program statistical analysis was used. On 24 patients after one stage sinus floor elevation with synthetic HAp granules and SEMADOS dental implant insertion at second stage surgery average after 6 months 2 mm diameter trepan biopsy of biomaterial/host tissue hybrid and alveolar bone was done. Samples were fixed in 10% neutral formalin and decalcinated. Slices were stained with hematoxyline/eozine and according Masson trichrom, evaluated in light microscope.

RESULTS

There were no acute suppurative inflammations from oral and also nasal-maxillary sides. One implant was lost on the second stage surgery caused by soft alveolar bone and dubious primary stability. Another 5 implants were lost after 2 – 4 years after loading may be from overloading; poor oral hygiene resulted in periimplantitis. Another 136 implants showed no complaints from patient side, clinical stability. On control X-rays was evident osseointegration, increase of residual alveolar bone density, decrease of density in elevated part of maxillary sinus floor.

Figure1a,1b

Radiodensitometry of the elevated sinus floor area and residual alveolar ridge shows 98 % of optical density in the sinus lifts area after implant placement. 82% of sinus lift bone hybrid after uncovering on average 6 months of the dental implants, 76 % after 3 years of initial loading of the dental implants and 65 % after 5 years of the implant loading. However, residual alveolar crest area exhibits 55 % of optical density after the implant and sinus floor elevation with HAp granules, 64 % of sinus host tissue/HAp hybrid after uncovering of the dental implants, 78% after 3 years and 70 % after 5 years of the implant loading.

Figure 2

Our histological study showed decrease of number and activity of osteocytes in atrophic alveolar residual bone, osteoporosis. 6 months after sinus floor elevation with synthetic HAp granules there was no active inflammation, HAp/tissue hybrid consisted of bone trabecules, partially mineralized bone, fibrous and loose connective tissue. Biodegradation of HAp granules by active osteoclast like macrophages was evident.

Figure 3a, 3b

We observed more pronounced inflammation reaction with the xenomaterial bovine Tutodent (Tutodent Gmbh) implantation in the maxillary sinus after 6 months.

Various chemical composition biomaterials after implantation in the maxillary sinus shows different biodegradation mechanisms Ca2CO3 (Algipore, Friadent) – chemical/ dissolution.

Figure 4, 5

There are only some publications on human histological cases on retrieved dental implants from augmented maxillary sinus floor. 2,5 years after sinus floor elevation with combination of 25% freeze dried demineralised bone and 75% OsteoGraft/N700 (CeraMed Dental, Lakewood) and two implant insertion dense lamellar bone was present in direct contact with the threaded HAp coated part of retrieved implant. The particles of inorganic bovine bone (OsteoGraft/N 700) were not completely resorbed; no osteoclasts were present and the graft particles did not seem to be undergoing any type of resorbtion or remodelling (14).

Our clinical case, when we explanted Semados (Bego) implant at the removal caused by periimplantitis in the residual alveolar bone but with stable integration in HAp grafted sinus floor area, in three years demonstrated direct mechanical integration of HAp/tissue hybrid to the titanium implant without any intermediary tissue and sharp border between these different chemical compositions with no chemical interference.

Figure 5a, 5b

DISCUSSION

There are reports on lost 2.5 – 18 % of dental implants inserted in augmented maxillary sinus with different auto and allomaterials (11, 13). Failures in osseointegration of dental implants depends from kind of used bone substitutes. In database including 6 913 implants placed in 2 046 patients in follow-up time ranging from 12 to 75 months implant survival was 87.7% with grafts of 100% autogenous bone, 94.88% in combination of autobone with different bone substitutes and 95.98%

when bone substitutes were used alone (4).
Radiographs are more commonly used methods for the evaluation on alveolar bone/dental implant relations as well in grafted maxillary sinus part. Unfortunately, almost all grafting materials have a tendency to decrease their initial size over the time. Long term average height as estimated at Sinus Grafting Consensus Conference (1996) was 2.1±0.3 mm when freeze-dried bone allograft was used and respectively 1.8±0.4 mm in cases of iliac crest bone and 0.9±0.3 mm when using alloplasts. Our data on sinus floor elevation with pure synthetic HAp confirmed high stability of bioceramic/host tissue hybrid with no lost of height of elevated sinus portion and average loss of 0.7±0.3 mm of crestal bone portion during long period of observation.
The main interest is the morphology of host tissue/ biomaterial hybrid in sinus floor augmented with HAp or another inorganic bone substitutes that are mostly investigated in experiment. The histological and histometrical evaluation of porous Hap as a grafting material for sinus lift done on monkeys gave a solid confirmation of good Hap biocompatibility, its biodegradation and replacement by mineralized bone with high values of direct bone-to-bioceramic contact. Significant difference was obtained in bone-to-implant contact between residual bone and augmented area, but also at 45.8% to 68.7% of dental implant surface had direct contact to mineralized bone; respectively this contact in residual bone area was 60.9% to 92.3% (4). Histological evaluation of 3 different grafting materials for sinus lifting procedure bases on 8 cases after 6 months indicated that demineralised freeze-dried bone powder resorbs earlier than deproteinized bovine bone granules and porous HAp [12]. Histological evaluation of 3 different grafting materials for sinus lifting procedure bases on 8 cases after 6 months indicated that demineralised freeze-dried bone powder resorbs earlier than deproteinized bovine bone granules and porous HAp (12). Histomorphometric study after one year grafting of sinus floor in 21 patients using autogenous particulated bone from the mandibular ramus, bovine HAp and mixture of both showed no differences between the 3 groups, indicating that autogenous bone graft can be substituted with bovine HAp to 80% or 100% (5).
An essential property of bone substitutes is their possibility to be integrated into the natural bone remodelling, which starts with osteoclastic activity followed by osteogenous cell activity. Osteoclastic cells of different origin cultured on calcium phosphate biomaterials produced clear difference in the shape and the depth of resorbtion lacunae. Degradation measurements revealed a significant increase of P and Ca release in the presence of osteoclasts (10). Formation of osteoclast-like cells was more pronounced on HAp surface as on tricalcium phosphate (TCP) and was explained with high dissolution rate of TCP and high Ca concentration in the osteoclast interface and environment (3).

CONCLUSIONS

1) Radiodensitometry in long term evaluation shows increase of optical density in residual alveolar bone and decrease of optical density in augmented with synthetic HAp granules maxillary sinus floor.
2) Biopsies from residual alveolar bone and augmented maxillary sinus floor demonstrate HAp/host tissue hybrid remodelling by activity of osteoclast like cells and bone newformation, slow biodegradation of Hap granules.
3) Our experience as well as previous publications confirms that synthetic porous HAp granules used as artificial material for maxillary sinus floor elevation in one stage with insertion of titanium non –coated dental implants in cases of residual alveolar bone height not less than 5 mm may be the method of choice for implant based prosthetic reconstruction of the atrophic posterior maxilla.

ACKNOWLEDGEMENT

This work was supported by Sate research programme's project "Perspective biomaterials and medical technologies" and grant 041224 from Latvia Council of Science.

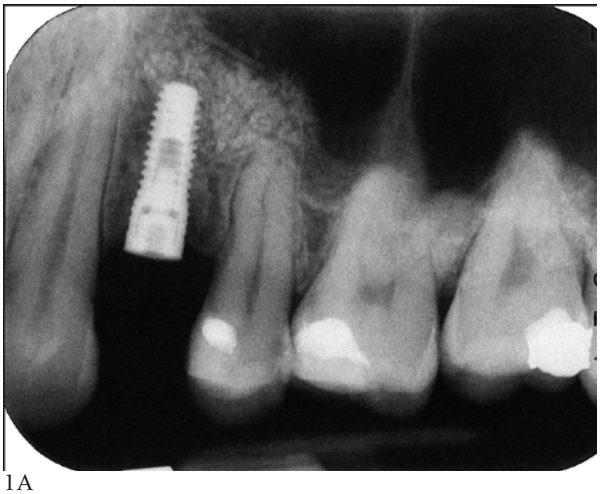
Conflict of interest: None

REFERENCES

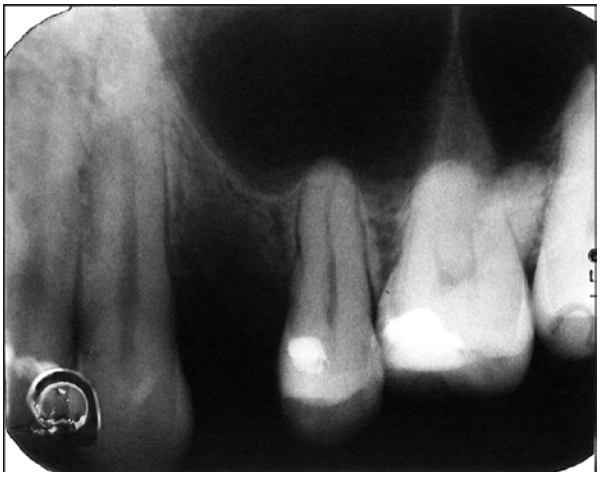
1. Barrere F, Blitterswijk C A, de Groot K. Bone regeneration: molecular and cellular interactions with calcium phosphate ceramics // Int J Nanomedicine, 2006; 3: 317 – 332
2. Boyne P J, James R L. Grafting of the maxillary sinus with autogenous marrow and bone// J Oral Surg, 1980; 38:613 – 616
3. Detsch R, Mayr H, Ziegler G. Formation of osteoclast-like cells on HA and TCP ceramics // Acta Biomater, 2008; 4:139 – 148
4. Del Fabbro M, Testori T, Francetti L, Weinstein R. Systematic review of survival rates for implants placed in the grafted maxillary sinus // J Prothet Dentistry, 2005; 94:266 – 271
5. Hallman M, Sennerby L, Lundgren. SA clinical and histologic evaluation of implant integration in the posterior maxilla after sinus floor augmentation with autogenous bone, bovine hydroxyapatite or a 20:80 mixture // Int J Oral Maxillofac Implants, 2002; 5:635 – 643
6. Lemons J E, Misch C E // Contemporary implant dentistry 2nd ed. 1999; Mosby 189–195
7. Karabuda C, Ozdemir O, Tosun T, Anil A, Olgac V J. Histological and clinical evaluation of 3 different grafting materials for sinus lifting procedure based on 8 cases // Periodontology 2001; 10:1436 – 144
8. McCarthy C, Patel R R, Wragg P F, Brook I M. Sinus augmentation bone grafts for the provision of dental implants // Int J Oral Maxillofac Implants, 2004; 18:377 – 382

9. Misch C E Maxillary sinus augmentation for endosteal implants// Int J Oral Implants, 1987; 4: 49 – 58
10. Monchau F, Lefevre A, Descamps M, Belquin-myrdycz A, Laffargue P, Hildebrand HF. In vitro studies of human and rat osteoclast activity on hydroxyapatite, β-tricalcium phosphate, calcium carbonate // Biomolecul Engin, 2002; 19:143 – 152
11. Olson J W, Dent C D, Morris H F, Ochi S. Long-Term Assessment (5 to 71 Months) of Endosseous Dental Implants Placed in the Augmented Maxillary Sinus // Ann Periodontol, 2000; 5:152 – 156
12. Quinones C, Hülzerer M B, Schüpbach P, Kirsch A et al. Maxillary sinus augmentation using different grafting materials and osseointegrated dental implants in monkeys // Clin Oral Impl Res, 1997; 8:487– 496
13. Raghoebar G M, Timmenga N M, Reinsema H, Stegenga B, Vissink A. Morbidity and complications of bone grafting of the floor of the maxillary sinus for the placement of endosseous implants // Clin Oral Implants Res, 2001; 3:279 – 286
14. Rosenlicht J L, Tarnow D P. Human histological evidence of integration of functionally loaded hydroxyapatite coated implants placed simultaneously with sinus augmentation: a case report 2.5 years post placement // J Oral Implantol, 1999; 25:7 – 10
15. Small S A, Zinner I D, Panno F V, I.I.J. Shapiro, J.L. Stein. Augmenting the maxillary sinus for implants: report of 27 cases // Int J Oral Maxillofac Implants 1993; 8:523 – 527
16. Sodek S, McKee M D. Molecular and cellular biology of alveolar bone // Periodontology, 2000; 24:99 – 126
17. Villarreal P M, Junquera L M, Martinez A. Study of mandibular fracture repair using quantitative radiodensitometry // J Oral Maxillofac Surg, 2000; 58:776 – 781

Address:
Girts Salms
Department of Oral and Maxillofacial Surgery
Riga Stradins University, Institute of Stomatology
20 Dzirciema street,
Riga, Latvia, LV 1007
E-mail – gsalms@latnet.lv



1A



1B

Fig. 1a, 1b. Dental X-rays of patient A.J. with loss of upper premolar with soft, radiolucent alveolar bone before and 2 years after sinus floor elevation with HAp granules 0.2 – 0.4 mm, porosity 40%

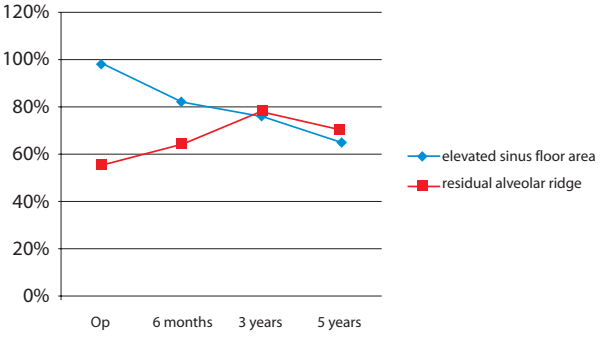
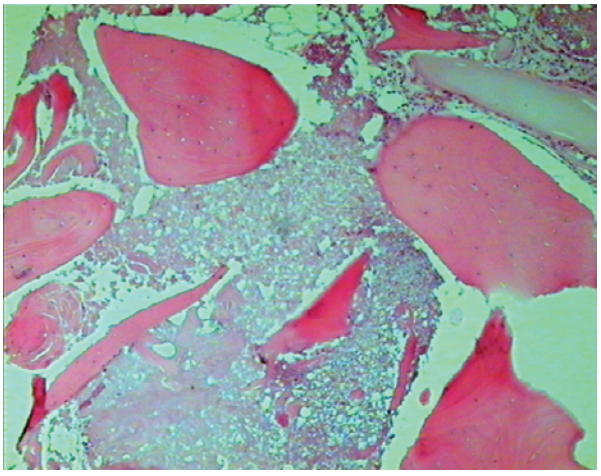


Fig. 2. Results of radiodensitometry of residual alveolar bone and augmented with HAp granules maxillary sinus part immediately after implantation, 6 months, 3 and 5 years after



A x 60

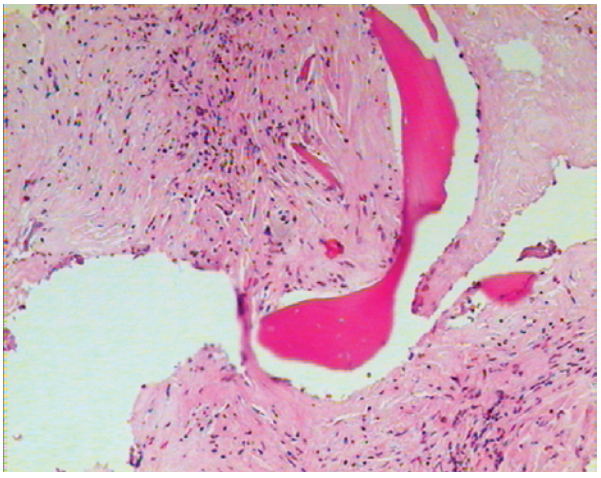
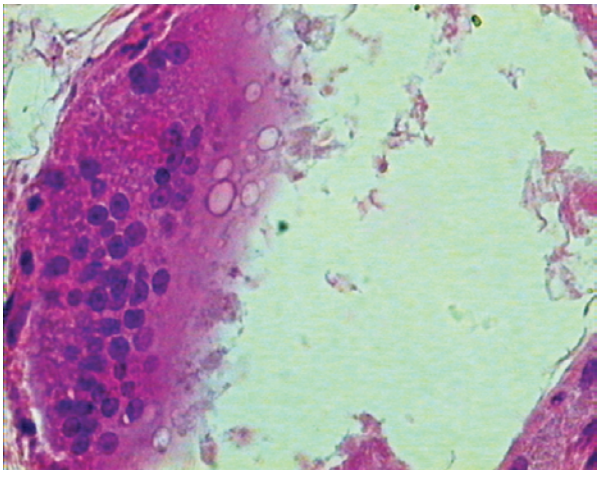


Fig. 4. Maxillary sinus augmented part with Tutodent after 6 months osteogenesis, osteomielofibrosis, no inflammation Hem-eoz x 60B



B x 200

Fig. 3. Microphotogramms of biopsies from residual alveolar bone and augmented with HAp granules sinus after 6 months

A) Biomaterial/host tissue hybrid consisted of small bone trabecules, osteoid, fibrous tissue and granules of irregular shape without inflammatory cells;

B) Degradation of Hap granule by activity of osteoclast like macrophage

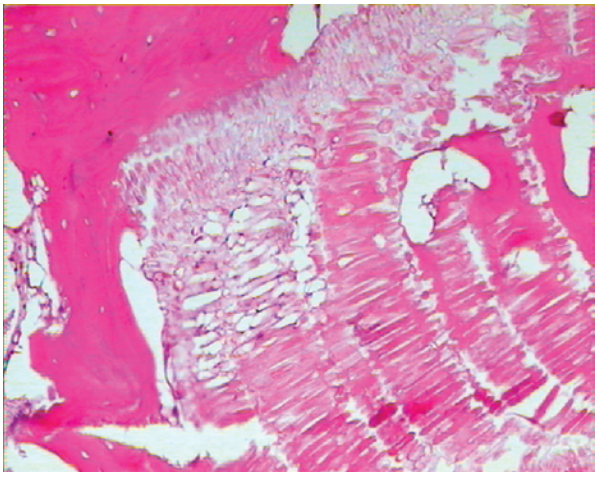


Fig. 5 Algipore, material dissolution without cell activity/Hem-eoz x 60

Fig. 4. Retrieved partially osseointegrated Semados (Bego) titanium dental implant:

A) crossed section of the implant shows bone/HAp hybrid in the threads of implant part from augmented sinus and no osseointegration in crestal part involved in periimplantitis;

B) SEM micrography of titanium dental implant integrated after maxillary sinus floor elevation by synthetic HAp granules (porosity 35 – 40%) 3 years ago

DOI: 10.2478/v10163-010-0013-6

ORIGINAL ARTICLE

Evaluation of Oral Health Status and the Need of Surgical and Therapeutical Preprosthodontic measures in the Elderly Living in Old People`s Homes in Latvia

Aldis Vidzis*, Ingrida Krasta, Anda Brinkmane**, Ingrida Cema*****
* Riga Stradins University, Department of Prosthodontics, Latvia
** Riga Stradins University, Department of Therapeutical Dentistry, Latvia
*** Riga Stradins University, Department of Oral Pathology, Latvia

Summary
Introduction. Demographic evolution indicates enlargement of the older people proportion and increased life expectancy. The oral health is strongly associated with quality of life. In 1992 the main part of Latvian dental care was excluded from the list of the government paid health service. The rules N. 254 (2006) of the Cabinet of Ministers of the Republic of Latvia establish that customers from social old people's homes have to pay for dental care by themselves and the government will prepay only teeth extractions in cases of acute pain. Thereby, there appeared necessity to conduct comparative evaluation of clinical situation among populations of Latvia and other countries.
Aim of the study. The aim of the study was to establish necessary types and ranges of surgical and therapeutical measures before prosthodontical teeth replacement among people who live in old people's homes; to conduct comparative analysis of clinical situation with corresponding groups of age in Latvian population.
Materials and methods. There were examined 212 elderly people living in old people`s homes of Kurzeme region of Latvia (randomly chosen). The indices of bad odour were established by HALIMETER. Caries incidence was assessed with DMFT index (D-decayed, M-missing, F-filling). This study was done in period from November of 2007 to February of 2009.
Results. Out of all examined elderly people living in old people`s homes 32.3% of men and 57.3% of women had complete teeth loss. Caries incidence ratio was 28.7 and 28.8, respectively. Untreated dental caries and filling rate were low (4.5; 2.6 and 0.6; 0.7) while the number of lost teeth was high (23.1 and 25.8). Out of the examined elderly 85.7% of men and 76.5% of women needed emergency surgical treatment (extraction of destroyed teeth). In 45.2% and 57.8% of cases were observed oral mucosal lesions, in 2.4% and 1.6% of cases were found oral precancerous conditions. In 14.3% and 18.8% of cases was noted pain in temporomandibular joints. 97.6% and 87.5% of old people`s homes inhabitants needed prosthodontical teeth replacement.
Conclusions. Oral health care measures for the elderly in old people`s homes is insufficient, the ratio of decayed and missing teeth is high, oral hygiene mostly is unsatisfactory and many of them have halitosis. The elderly from old people`s homes need vast surgical and therapeutical treatment prior to prosthetics and teeth replacement. The prevalent type of prosthodontics is complete removable dentures. There is need to develop the oral health care conception for the elderly living in old people`s homes in Latvia.
Key words: dental care in old people`s homes, oral surgery, dentistry, prosthodontics.

INTRODUCTION

Demographic evolution indicates enlargement of the older people proportion and increased life expectancy. Different oral health conditions such as carious teeth and their complications, untreated roots in the oral cavity, oral mucosal lesions, precancerous conditions, cancers, pain in the temporomandibular joints, xerostomia, unrestored complete or partial teeth loss affect the quality of life. Physiological and social aspects are very important in the given situation. The typical feature of the elderly is contradiction between the subjective treatment requirements and the objective treatment needs. The social aspects are in base of the social support pattern, those are associated with oral health and well-being, as well as, social support and satisfaction of population.

In the 1992 the main part of dental care in Latvia was excluded from the list of the government paid health service. The rules N. 254 (2006) of the Cabinet of Ministers of the Republic of Latvia establish that customers from social old people's homes have to pay for dental care by themselves and the government will prepay only teeth extractions in cases of acute pain. Epidemiologic investigations in numerous countries in the world demonstrate that oral health and dental care of older people are unsatisfactory. WHO researches revealed characterizing parameters of oral health (DMFT index) range from 22 to 32 in developed countries (10). DMFT indices are: in USA – 21.9 (23), in Australia – 24.7 (19), in Turkey – 29.3 (21), in Brazil – 30.17 (13), in Fiji – 23 (4). In Latvia oral health of the elderly has been evaluated in 1993 in the project of ICS-2 (2, 22). In the 1996 the mean DMFT index in the group of 65 – 74 years of age in Latvian population was 24.9 (3). In the research in 2005 (3) this index was 24.84.

In the ICS-2 report (1996) was observed that in Latvia in age group of 65 – 74 95.33% of people have dentures (22). In Latvian population the necessity

of new dentures is 60.4% (15, 14). Each country has own experience how to attract investments for health care and to maintain and to effectively promote the state of health of population. The pattern of health care in every country depends on traditions, historical evolution of state and the role of the government in the adjustment in social care (10, 11). An evaluation of oral health status in Latvian inhabitants (population of 60- 70 age groups) didn't reveal any information about surgical and therapeutical pretreatment measures before prosthodontic dental care in people who live in social old people's homes.

AIM OF THE STUDY

The aim of the study was to establish necessary types and ranges of surgical and therapeutical measures before prosthodontical teeth replacement among people who live in old people's homes; to conduct comparative analysis of clinical situation with corresponding groups of age in Latvian population.

MATERIALS AND METHODS

There were examined 212 randomly chosen elderly people living in old people`s homes of Kurzeme region of Latvia. The examinations were done by dentists worked following unified requirements using dental equipment. The indices of bad odour were established by HALIMETER (Interscan Corporation, Chastworth, California, USA). Caries incidence was assessed with DMFT index (D-decayed, M-missing, F-filling). Oral hygiene was evaluated by Silness & Loe (1964) plaque index. In the study were examinated and evaluated the dental status, the need of replacement of missing teeth by dentures and indicators of the quality of existing dentures; incidence of pain in head and face region, precancerous conditions and oral mucosal lesions. For this purpose was used standard inquiry form. This study was done in the period from November 2007 to February 2009. For assessment of study results was used descriptive statistics. The acquired data was processed by Microsoft Excel.

RESULTS

Out of all the examined elderly people living in old people`s homes 32.3% of men and 57.3% of women had complete teeth loss. 67.7% and 42.7% of them respectively had partial teeth loss and the dental status was assessed as marginal. The caries incidence characterized rate (DMFT index) in people living in old people`s homes was 28.7 and 28.8, respectively. Untreated dental caries and filling rate were low (4.5; 2.6 and 0.6; 0.7) while the number of lost teeth was high (23.1 and 25.8). The lost teeth ratio indicated the multitude loss of teeth (in the average this population have only 2 to 5 residual teeth). The examination revealed that in the average of 58.0% of cases these teeth should be extracted due to medical indications. From all the examined elderly 85.7% of men and 76.5% of women needed emergency surgical treatment (extraction of destroyed teeth). Old people from old people`s homes receive dental care in dental clinics only in acute emergency situations because in Latvia local dental care does not exist for this group of population.

From the elderly with partial teeth loss 45.2% of men and 57.8% of women were observed oral mucosal lesions (Fig. 1.), while from old people with complete teeth loss oral mucosal lesions were found in 35.0% and 45.3% cases respectively (Fig. 2.). The most common oral mucosal conditions were coated tongue (26.0%), erythematous oral mucosa (24.0%), atrophic oral and lips mucosa (14.0%), denture stomatitis (12.0%), varices (12.0%), local hyperplasia (10.0%), hemangiomas (12.0%), angular cheilitis (8.0%), actinic cheilitis (4.0%), lichen planus (2.0%). Several oral mucosal lesions were found in 32.0%. Angular cheilitis, hyperkeratosis at the commissures, white coating on the mucosa and papillary hyperplasia on the palate, erythematous oral mucosa and complaints about dry mouth indicate potential candidiasis in oral cavity.

From all the examined old people with partial teeth loss 26.2% and 50.0% of them (men/women) had complaints about dry mouth (Fig. 1.) (suspicion of xerostomia). For the elderly with total teeth loss (Fig.2.) this ratio was 30.0% and 46.5%, respectively. In 2.4% and 1.6% of all older people with retained teeth were found out precancerous conditions such as lichen planus and leukoplakia. In the group of totally edentulous old people precancerous lesions were not found (Fig.1. and Fig 2.). This difference is associated with chronical traumatization of oral mucosa by sharp edges of decayed teeth and roots. The pain in temporomandibular joints (TMJ) was detected in 14.3% and 18.8% of those with partial teeth loss, in patient group with total teeth loss only 11.6% of women had complaints of obnoxious, easily provocable pain in region of TMJ. Data of our research show that the incidence of good oral hygiene practice was 46.1%. However, 28.9% of respondents have never practiced oral hygiene. Among old people`s homes patients with retained teeth satisfactory hygiene was found in 7.1% and 7.8% of cases (Fig.1.). In group of old people with total teeth loss satisfactory oral hygiene was observed in 25.0% and 16.3% of cases, unsatisfactory in 30.0% and 14.0% of cases and medium oral hygiene was found in 45.0% and 69.8% of cases, respectively (Fig.2.). The results of our study indicate that the elderly living in old people`s homes with partial teeth loss need prosthodontical teeth replacement with removable partial dentures (RPD) in 97.6% of men and 87.5% of women. 7.1% of men and 30.0% of women had dentures but the quality of those is acceptable only in 2.4% and 9.4%, respectively. 85.0% and 84.9% of all respondents with total teeth loss need prosthodontical teeth replacement. 30.0% and 19.8% of old people`s homes inhabitants had total dentures but their quality was satisfactory only in 15.0% and 9.3% of cases. Our study revealed that old people becoming older lose wish to take care of their oral health and receive the dental care and lost teeth replacement (Fig.3.). It is motivated by financial pressure and overall depression.

DISCUSSION

Oral health of the examined old people living in old people`s homes differs from the same age group old people`s oral health status in general population in Latvia. Such parameters as DMFT (number of decayed, missed

and filled teeth) among old people in Latvia are higher (worse) than the same parameters in others European countries: in Germany – 22.0 (16), in Denmark – 16.7 (11), in Croatia – 27.0 (17).

In Latvia the oral health status of the elderly was studied in 1993 in the Project of ICS-2 (2, 22). In this research were included inhabitants of 65-74 age group. DMFT index was 24.9 (the mean number of decayed – 1.69, filled – 3.23, and missed – 20.0). In the study in 2005 (3) DMFT index was 24.84 (the mean number of decayed – 2.46, filled – 2.53, and missed – 19.85). In our research DMFT index in inhabitants of old people`s homes was considerably higher At present, old people from old people`s homes visit the dentist only for emergency extractions of teeth in cases of acute pain. No one from the examined 212 old people had intact set of teeth. The oral mucosal changes and lesions were detected in 41.9% and 50.7%, respectively. The results of oral mucosal lesions studies in Latvia for the corresponding age group were not found. Results of oral mucosal researches in the world are quite different: in Germany – 19.55% (18), in Hungary – 10.14% (7), in China – 12-26% (8), in Greece – 47.0% (20), in Turkey – 40.7% (5) and in Chile – 53.0% (6). In these studies dominate angular cheilitis, hyperplasias, varices and denture stomatitis. In 57.0% of all the elderly in old people`s homes had several oral mucosal lesions. Xerostomia was found in 27.4% and 48.0% of these old people group. This quantity is close to average similar rate in corresponding age of group in Europa (52.0%) (9, 12). The high ratio of hyposalivation and xerostomia is associated with excessive use of medication. In 1.6% of men and in 0.7% of women were found precancerous conditions (lichen planus, leukoplakia). The results of our research indicate that old people with partial teeth loss need teeth replacement in 97.6% and 87.5% of cases while the replacement of complete teeth loss is necessary in 85.0% and 84.9% of cases. The need of prosthodontic teeth replacement in Latvian population is 60.4% (14, 15). Halitosis was observed in 42.9% and 39.1% of respondents with partial teeth loss and in 40.0% and 14.0% of the elderly with complete teeth loss. The mean ratio of halitosis in corresponding age group in Latvia is 33.1% (1). Evaluation of dental status of residents of old people`s homes, development and distribution of curative and preventive measures considerably will improve the quality of life in this group of residents in Latvia.

CONCLUSIONS

1. Oral health care measures for the elderly in old people`s homes is insufficient, the ratio of decayed and missing teeth is high, oral hygiene mostly is unsatisfactory and many of them have halitosis.
2. The elderly from old people`s homes need vast surgical and therapeutical treatment prior to prosthetics and teeth replacement. The prevalent type of prosthodontics is complete removable dentures.
3. There is need to develop the oral health care conception for the elderly living in old people`s homes in Latvia.

Conflict of interest: None

REFERENCES

1. Brinkmane A., Senakola E., Selga G. et al. Mutes veselibas stavokla novertejums Latvijas iedzivotajiem, izmantojot parvietojamo zobarstniecibas iekartu // RSU Zinatniskie raksti, 2004; 332 – 336
2. Care R, Urtāne I. Kariesa epidemioloģija Latvijā no 1990. līdz 1998. gadam // AML/RSU Zinātniskie raksti, 1999; 197 – 201
3. Care R, Ārne G. Kariesa intensitāte Latvijā 2005. gadā pieaugušajiem iedzīvotājiem 35-44 un 65-74 gadu vecuma grupās // RSU Zinātniskie raksti, 2007; 340 – 344
4. Comfort AO, King T, Moveni M, Tuisuva J. Dental health of Fiji institutionalized elderly // Pac Health Dialog, 2004; 11(1):38 – 43
5. Dundar N, Kal I. Oral mucosal conditions and risk factors among elderly in a Turkish school of dentistry // J Gerontology, 2007; 53:165 – 172
6. Espinosa I, Rojas R, Aranda W, Gamonal J. Prevalence of oral mucosal lesions in elderly people in Santiago, Chile // Oral Pathol Med J, 2003; 32(10):571– 575
7. Jahn M, Schmidt J, Fejerdy L, Tollas OL, Fejerdy P, Madlena M. The prevalence of oral mucosal lesions in Hungary // J Fogorvosi szemle, 2007; 100: 59 – 63
8. Lin HC, Cobert EF, Lo ECM. Oral mucosal lesions in adult Chinese // J of Dental Research, 2001; 80: 1486 – 1490
9. Petersen PE, Yamamoto T. Improving the oral health of older people: the approach of the WHO Global Oral Health Programme // Community Dent Oral Epidemiol, 2005; 33:81 – 92
10. Petersen PE, Krustrup U. Dental caries prevalence among adults in Denmark – the impact of socio-demographic factors and use of oral health services // Community Dental Health, 2007; 24:225 – 232
11. Putten GJ, Brand HS, Bots CP, van Nieuw Amerongen A. Prevalence of xerostomia and hyposalivation in the nursing home and the relation with member of prescribed medication // J Gerontology Geriatrics, 2003; 34:30 – 36
12. Reis SCGB, Higino MASP, Melo HMD, Freire MCM. Oral health status of institutionalized elderly in Goiânia-GO, Brazil 2003 // J Brazil epidemiology, 2005; 8: 67 – 73
13. Soboleva U, Ragovska I, Pugacha I. Assessameru of the received prasthetic treatment in the Latvian population // Stomatologija, 2006; 3:36
14. Soboļeva U, Urtāne I. Protezēšanas nepieciešamības izvērtējums Latvijas populācijā // RSU Zinātniskie raksti, 2003; 357 – 362
15. Schiffner U, Hoffmann T, Kerschbaum T, Micheelis W. Oral health in German children, adolescents, adults and senior citizens in 2005 // Community Dental Health, 2009; 26: 18 – 22
16. Simunković SK, Boras VV, Pandurić J, Zilić IA. Oral health among institutionalised elderly in Zagreb, Croatia // Gerontology, 2005; 22:238 – 241
17. Splieth CH, Sumnig W, Bessel F, John U, Kocher T. Prevalence of oral mucosal lesions in a representative population // J Quintessence Int, 2007; 38:23–29

18. Stubbs C, Riordan PJ. Dental screening of older adults living in residential aged care facilities in Perth // Aust Dent J, 2002; 47:321 – 326
19. Triantos D. Intra-oral findings and general health conditions among institutionalized and non-institutionalized elderly in Greece // J Oral Pathol Med, 2005; 34:577 – 582
20. Unlüer S, Gökalp S, Doğan BG. Oral health status of the elderly in a residential home in Turkey // Gerodontology, 2007; 24:22 – 29
21. Urtāne I, Care R, Petersen PE. Pasaules Veselības Organizācijas starptautiskās sadarbības pētījums Latvijā 1993.g. ICS-II ziņojums. Rīga: 1996; 2 – 175
22. Vargas CM, Yellowitz JA, Hayes KL. Oral health status of older rural adults in the United States // J Am Dent Assoc, 2003; 134:479 – 486

Adress:
Aldis Vidzis
Riga Stradins University
Department of Prosthodontics
20 Dzirciema Street,
Riga, Latvia, LV-1007
E-mail: Aldis.Vidzis@rsu.lv

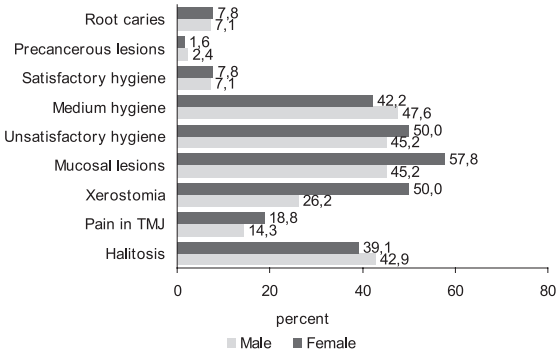


Fig. 1. The rate of clinical manifestations in respondents with partial teeth loss

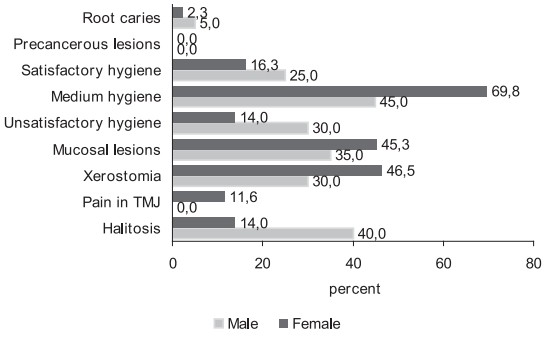


Fig. 2. The rate of clinical manifestations in respondents with complete teeth loss

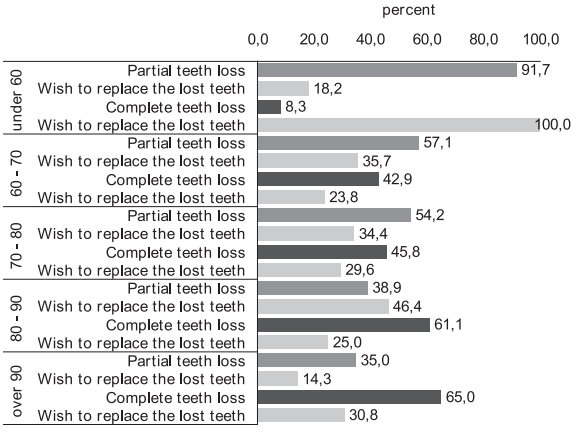


Fig. 3. Wishes of respondents to replace the lost teeth

ORIGINAL ARTICLE

Role of Human Skin Antimicrobial Peptides in Psoriasis

Elga Mozeika*, Mara Pilmane, Janis Kisis***
*Department of Infectology and Dermatology, Riga Stradins University, Riga, Latvia
**Institute of Anatomy and Anthropology, Riga Stradins University, Riga, Latvia

Summary
Introduction. Psoriasis is a chronic inflammatory skin disease with various biochemical, immunologic and vascular changes, and a vague relationship to nervous system function. Skin defends the body by rapidly setting an innate immune response and providing a swift first–line defense against infection or injury. Hundreds of naturally occurring antimicrobial peptides have been discovered and it has been shown that psoriatic epidermis expresses high levels of host defense proteins.
Aim of the Study. To evaluate human antimicrobial peptides in correlation with inflammation level in skin biopsy material of psoriatic lesions.
Materials and methods. We evaluated 9 psoriasis patients and 1 healthy volunteer. Skin biopsies were obtained from using the routine punch biopsy method. All tissue specimens were stained with hematoxylin and eosin and by immunochemistry for human β defensin 2, PGP 9.5, MMP2. The intensity of immunostaining was graded semiquantitatively. For apoptosis evaluation, we used TUNEL method.
Results. We found a distinct inflammatory cell infiltration with diffusive character in subepithelial layer, epithelium and hair follicle outer epithelial sheath. Defensin–containing cell number, PGP 9.5–containing nerve fibers and number of MMP2 positive macrophages, fibroblasts and epitheliocytes varied from few to abundant in the visual field. Apoptosis affected epithelial cells, connective tissue cells and inflammatory cells focally.
Conclusions. Histological findings vary from marked inflammatory cell infiltration to granulation tissue. Psoriatic lesions of patients with no previous active psoriasis treatment feature marked activation of defensin, matrix metalloproteinase, apoptosis and neuropeptides–containing innervation. In skin of psoriasis patients with long–term ineffective treatment psoriatic lesions show abundance of positive structures of defensin, matrix metalloproteinase and neuropeptides–containing innervation. Close correlation between expression of defensin–containing cells, apoptotic cells, and inflammation in the skin was found suggesting about possible stimulation of AMPs and apoptosis by specific inflammation.
Key words: antimicrobial peptides, human keratinocytes, immunity, psoriasis.
Abbreviations: AMPs – Antimicrobial peptides; HBD–2 – Human beta defensin 2; HNP – Human neuthrophil peptides; IMH – Immunohistochemical method; MMP2 – Matrix metalloproteinase 2; PGP 9.5 – Protein gene product 9.5; PKC – Protein kinase C.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease, with a strong genetic basis, characterized by complex alterations in epidermal growth and differentiation and multiple biochemical, immunologic and vascular abnormalities, and a poorly understood relationship to nervous system function (10).

The skin is situated at the interface between an organism's internal milieu and an external environment characterized by constant attack with potential microbial pathogens. Now it is evident that a major role of the skin is to defend the body by rapidly setting an innate immune response and providing a swift first–line defense against infection or injury. Both resident and infiltrating cells in the skin synthesize and secrete small peptides that demonstrate broad–spectrum antimicrobial activity against bacteria, fungi, and viruses. Antimicrobial peptides (AMPs) also act as multifunctional immune effectors by stimulating cytokine and chemokine production, angiogenesis, wound healing, cell proliferation, chemotaxis, immune induction, and protease–antiprotease balance (3, 5).

Hundreds of naturally occurring antimicrobial peptides have been discovered based on their potency to inhibit the growth of microbial pathogens. There are two major families of AMPs – defensins and cathelicidins. Current evidence shows that both above mentioned families of AMPs act as natural antibiotics and as well as signaling molecules that activate host cell processes involved in immune defense and tissue repair. Modifications in the expression pattern of AMPs have been associated with a variety of pathological processes (2).

Antimicrobial peptides are predominantly small cationic polypeptides that are classified together due to their capacity to inhibit microbes. Defensins and cathelicidins comprise the major families of antimicrobial peptides in the skin, although other cutaneous peptides, such as proteinase inhibitors, chemokines, and neuropeptides, also demonstrate antimicrobial activity. Together, these multifunctional antimicrobial peptides play an important role in skin immune defense and pathogenesis of disease (4).

Antimicrobial peptides are produced by leukocytes and epithelial cells not only in skin, but also in the gastrointestinal and genitourinary tracts, tracheobronchial tree. They include defensins, cathelicidin, histatins, cathepsin G, azurocidin, chymase, eosinophil derived neurotoxin, high mobility group 1 nuclear proteins, lactoferrin (17).

The defensins can be classified into two subfamilies (α– and β–defensins) based on their tertiary structure. The alfa defensins also are known as the human neuthrophil peptides (HNP 1–3) and are largely stored in the granules of neuthrophils and macrophages. There are also many β defensins (HBD). HBD1 is expressed constitutively by keratinocytes, HBD2–4 on the other hand is inducible and produced by keratinocytes and epithelial cells in response to proinflammatory stimuli. Evaluation of the human genome suggests that there may be an additional 25 β defensins that have not yet been identified (17).

Several studies compare psoriasis and atopic dermatitis as the two most common chronic skin diseases. Patients with atopic dermatitis, but not psoriasis, suffer from frequent skin infections. The expression of innate immune response genes and antimicrobial peptides has been found to be decreased in atopic dermatitis, as compared with psoriasis, despite that both skin diseases are characterized by defective skin barriers. Psoriatic epidermis expresses high levels of host defense proteins compared with atopic dermatitis epidermis (13, 14, 16). Psoriatic–scale extracts have been identified as a unique source of human–inducible antibiotic peptides and proteins, among them psoriasin, HBD–2, and RNase 7, as by far, the quantitatively dominating antimicrobial peptides. These peptides and proteins can also be found at much lower levels in healthy skin, where they are expressed focally (11).

Other researches consider protein kinase C (PKC) inhibitor AEB071 and type I interferon as potential therapeutic options or targets for psoriasis (20, 22).

Great involvement in the pathogenesis of psoriasis have demonstrated neuropeptides – increased findings of antibodies to vasoactive intestinal polypeptide, substance P, calcitonin gene–related peptide, neuropeptide Y, and the general neuronal marker protein gene product 9.5 have been found. These substances can not only be released by nerve endings, but may also be synthesized directly in the skin and released from various dermal cells (1, 18).

Despite to all above mentioned data, still there is a lack of knowledge about distribution and relative appearance in antimicrobial peptides in the skin of patients with psoriasis, especially in different stages of disease. Thus, the aim of this study was to research of appearance in skin antimicrobial peptides in correlation with inflammation level in ontogenetic aspects of patients with psoriasis.

AIM OF THE STUDY

The aim of the study was to evaluate human antimicrobial peptides in correlation with inflammation level in skin biopsy material of psoriatic lesions.

MATERIALS AND METHODS

Patients. All psoriasis patients were diagnosed by a dermatologist. Skin biopsies were obtained from the skin lesions of nine different psoriasis patients using the routine punch biopsy method and one healthy volunteer using excision. All patients were off topical and systemic medication for more than 4 weeks before their skin biopsy was taken.

Patient selection criteria were created to achieve as much as possible accurate results with less affecting side factors.

Inclusion criteria were developed in accordance to previously realized researches, as well as to knowledge of immunological changes in skin due to exposure to sun and treatment with topical vitamin D analogue calcipotriol (13, 16, 24): patient 18 and older; patient has psoriasis symptoms for at least 6 weeks, preferable diagnosed for the first time; visible characteristic psoriatic eruptions in typical localization sites; patient hasn't received any previous treatment for at least a month; skin is not fiercely tanned; patient hasn't received any antibiotic treatment during last month.

Exclusion criteria were following: patient has received psoriasis or antibiotic treatment during last month; other confirmed skin diseases – such as various origin urticaria, eczema, atopic dermatitis, folliculitis; much tanned skin; other systemic diseases – such as inflammatory bowel diseases, acute liver diseases, diabetes mellitus, plodding cardiovascular diseases, autoimmune diseases, and oncology.

As a result we selected nine psoriasis patients – seven male and two female in age group from 25 to 68, average age 44,7; volunteer – 33 years old female.

The study was approved by the Ethical Committee at Riga Stradins University, permit issued on September 10, 2009.

Methods

1) Skin biopsies were fixed in Stefanini's solution, dehydrated and embedded in paraffin. Four micrometer thick sections were prepared from each tissue specimen and stained routinely with hematoxylin and eosin (Lillie, 1969).

2) Immunohistochemical method (IMH). Human beta defensin 2 (cat No AF 2758, LOT VJU015051, obtained from goat, 1:100 dilution, R&D Systems, Germany), PGP 9.5 (code Z5116, obtained from rabbit, 1:600 dilution, DakoCytomation, Denmark) and MMP2 (cat No AF902, LOT DUB034081, obtained from goat, 1:100 dilution, R&D Systems, Germany) were used by biotin – streptavidin IMH (Hsu et al., 1981).

3) For TUNEL method we used In situ Cell Death Detection, POD cat No 1684817 (Roche Diagnostics, Negoescu et al., 1998).

4) For visual illustration of our findings we used Leica DC 300F digital camera and image processing and analysis software Image Pro Plus.

The intensity of immunostaining was graded semiquantitatively and few positive structures in the visual field were labelled with +, moderate number of positive structures in the visual field was labeled

with ++, numerous positive structures in the visual field were labeled with +++, and abundance of positive structures in the visual field was marked with ++++.
Results of TUNEL method were obtained by counting apoptosis positive cells in three unintentionally chosen fields of vision. The mean ± SD was calculated for each specimen.

RESULTS

Intraepithelial lymphocytes, a distinct inflammatory cell infiltration in subepithelial layer as well as the presence of epithelioid cells and macrophages were detected in all patients (Fig. 1 – 2). Similar inflammatory cell infiltration was detected also in hair follicle outer epithelial sheath and in epithelium. Arteriole sclerosis and sweat gland cell vacuolization were established (Fig. 3). Inflammatory infiltration showed diffusive character. Patient with long–drawn psoriasis demonstrated granulations in the tissue. Also vacuolization in epithelial layer and Munro's microabscess were observed focally.
Defensin–containing cell number varied from few to abundant (Fig. 4 – 6). Pronounced correlation was observed between defensin–containing cells and apoptosis findings. Explicit increase of defensin–containing cells and apoptosis was noticed in sites of active inflammation; meanwhile in areas of granulation both findings were negative.
PGP 9.5–containing nerve fibers were found in all specimens and their number varied from few to abundant (Fig. 7). Fine PGP 9.5 positive nerves occupied subepithelial area and reached the epithelium.
Number of MMP2 positive macrophages, fibroblasts and epitheliocytes varied from few to abundant mainly in the subepithelium (Fig. 8). The results are summarized in Table 1.
Marked apoptosis affected epithelial cells, connective tissue cells and inflammatory cells focally (Fig. 9 – 10). However, there was also an interesting observation found in patient with very long psoriasis anamnesis and previous unsuccessful treatment, when in the region of granulation tissue number of apoptotic cells notably decreased (Table 2).

DISCUSSION

Antimicrobial peptides represent efficient innate defense mechanism which protects interfaces from infection with pathogenic microorganisms. In human skin AMPs mainly are produced by keratinocytes, neutrophils, and sweat glands and are either expressed constantly or after an inflammatory trigger. In several human diseases there is an inverse correlation between severity of the disease and the level of AMPs production. Decreased levels of AMPs are associated with burns and chronic wounds. In contrast, overexpression of AMPs can lead to increased protection against skin infections as seen in patients with psoriasis and *rosacea*, inflammatory skin–diseases which rarely result in superinfection. Increased levels of AMPs are often found in inflamed or infected skin areas in patients with *acne vulgaris* indicating a role of these peptides in the protection of infection. These data indicate that AMPs have a therapeutical potential as topical agents in several skin diseases (6, 19).
Antimicrobial peptides have maintained broad–spectrum antimicrobial activity and resisted most microbial strategies, which suggests that antimicrobial peptides may be strong alternatives to current antibiotic regimens in select disease situations (15).
The number of human beta defensin 2 positive structures in our study varied very broadly. Abundance of positive structures was found in specimens of two patients, both with a very long anamnesis of the disease (15 and 44 years) and previous unsatisfactory outcome of the treatment. Meanwhile, the number of positive structures found in specimen of volunteer and other patients was moderate to numerous. Increased number of HBD–2 in psoriatic lesions as well as increased serum level compared to healthy controls earlier has been shown and is tightly related also with the macroscopical clinical activity (12).
In the present study, the number of PGP 9.5 positive nerve fibers was found at an average amount of numerous positive structures in the visual field. Likewise abundance of positive structures was found in specimen of the patient with 44 years of anamnesis of psoriasis and no treatment for past six months. On the contrary, in patient with 15 years of psoriasis diagnosis finding of PGP 9.5 was from few positive structures to moderate number. Various earlier studies have investigated the role of stress and changes in expression of neuropeptides in psoriasis. Recent study by El–Nour et al. (8) suggests a down–regulation of innervation during psoriasis exacerbation. An unexpected reduction in the number of nerve fibers labeled for PGP 9.5 was found in skin biopsies from involved skin from psoriasis patients who believed that their psoriasis was influenced by stress. No association with additional stress was observed in our study, thought acquired data propose more profound investigation in circumstances of the disease in patient with noticeably higher results of PGP 9.5.
Appearance of MMP2 positive cells in current study varied from few positive structures to abundance of positive structures in visual field in previously mentioned patient with long–drawn progress of the disease. In earlier studies higher levels of MMP2 in psoriatic lesions as compared to healthy individuals has been found in both involved, and uninvolved skin (9).
Apoptosis was detected by TUNEL method and acquired data diversified in very extensive limits. No positive staining was detected in two of our cases, material of control patient showed few positive structures in the visual field, meanwhile also maximal intensity of staining could be found in specimens from patients with recent onset of psoriasis. Apoptosis has been evaluated in accordance with topical vitamin D analogue calcipotriol therapy after which number of apoptotic cells is significantly higher than in non–treated psoriatic lesions (7, 21). Biopsies from all patients enrolled in our study were taken from places with reduced exposure to sun and no previous treatment for at least four weeks to exclude such outreach. For all that our broad data

suggests that apoptosis expression may also be regulated by other factors.

We discovered pronounced correlation between defensin–containing cells and apoptosis findings. Considerable increase of defensin–containing cells and apoptosis was noticed in sites of active inflammation; meanwhile in areas of granulation defensin–containing cells and apoptosis findings were negative. Our discovery shows firm correlation between expression of defensin–containing cells, apoptotic cells, and inflammatory infiltration in skin of psoriatic lesions. To our knowledge, there is no previous data of such revelation. While as a control we have examined one healthy skin sample which might not be sufficient for strong statistics, our material is unique, based on a generally accepted norm and gives the first insight in a tendency. Acquired data show the complicated nature of skin innate immune system.

As AMPs are of peptide nature, they could present such problems as high manufacturing costs, short half life, lost of activity in physiological conditions, application problems, unwanted systemic reactions, and interference with normal flora bacteria when trying to use as antimicrobial agents. And also there remain unresolved issues to consider: standardized techniques to assess the activity, molecular regulation mechanisms, the ability to target the site of disease, tolerance and toxicity issues, understanding of the role and expression of AMPs in health and disease remains a challenging area of research (23).

CONCLUSIONS

Histological findings vary from marked inflammatory cell infiltration to granulation tissue and are much inwrought with anamnesis of psoriasis: psoriatic lesions of patients with no previous active psoriasis treatment feature marked activation of defensin, matrix metalloproteinase, apoptosis and neuropeptides–containing innervation. In skin of psoriasis patients with long–term ineffective treatment psoriatic lesion showed abundance of positive structures of defensin, matrix metalloproteinase and neuropeptides–containing innervation. Exception from this should be validated as individual variations due to the other unknown systemic / local factors affecting tissue changes. Close correlation between expression of defensin–containing cells, apoptotic cells, and inflammation in the skin was found suggesting about possible stimulation of AMPs and apoptosis by specific inflammation.

Conflict of interest: None

REFERENCES

1. Al'Abadie M. S., Senior H. J., Bleehen S. S., Gawkrodger D. J. Neuropeptides and general neuronal marker in psoriasis – an immunohistochemical study // Clin Exp Dermatol, 1995 Sept; 20(5):384 – 389
2. Bardan A., Nizet. V., Gallo R.L. Antimicrobial peptides and the skin // Expert Opin Biol Ther, 2004 Apr; 4(4):543 – 549
3. Beisswenger C., Bals R. Functions of antimicrobial peptides in host defense and immunity // Curr Protein Pept Sci, 2005 Jun; 6(3):255 – 264
4. Braff M. H., Bardan A., Nizet V., Gallo R. L. Cutaneous Defense Mechanisms by Antimicrobial Peptides // J Invest Dermatol, 2005; 125:9 – 13
5. Braff M. H., Gallo R. L. Antimicrobial peptides: an essential component of the skin defensive barrier // Curr Top Microbiol Immunol, 2006; 306:91 – 110
6. Braff M. H., Zaiou M., Fierer J., Nizet V., Gallo R. L. Keratinocyte Production of Cathelicidin Provides Direct Activity against Bacterial Skin Pathogens // Infect Immun, 2005 Oct; 73(10):6771 – 6781
7. El–Domyati M., Barakat M., Abdel–Razek R., El–Din Anbar T. Apoptosis, P53 and Bcl–2 expression in response to topical calcipotriol therapy for psoriasis // Int J Dermatol, 2007 May; 46(5):468 – 474
8. El–Nour H., Santos A., Nordin M., Jonsson P., Svensson M., Nordlind K., Berg M. Neuronal changes in psoriasis exacerbation // J Eur Acad Dermatol Venereol, 2009 Nov; 23(11):1240–1245
9. Fleischmajer R., Kuroda K., Hazan R., Gordon R. E., Lebwohl M. G., Sapadin A. N., Unda F., Iehara N., Yamada Y. Basement Membrane Alterations in Psoriasis are Accompanied by Epidermal Overexpression of MMP–2 and its Inhibitor TIMP–2 // J Invest Dermatol, 2000 Nov; 115(5):771 – 777
10. Gudjonsson J. E., Elder J. T. Psoriasis // In: Wolff K., Goldsmith L. A., Katz S. I., Gilchrest B. A., Paller A. S., Leffell D. J. Fitzpatrick's Dermatology in General Medicine. 7th ed. McGraw–Hill Companies; 2008; 169 – 193
11. Harder J., Schröder J. M. Psoriatic Scales: a Promising Source for the Isolation of Human Skin–derived Antimicrobial Proteins // J Leukoc Biol, 2005; 77:476 – 486
12. Jansen P. A. M., Rodijk–Olthuis D., Hollox E. J., Kamsteeg M., Tjabringa G. S., et al. β–Defensin–2 Protein Is a Serum Biomarker for Disease Activity in Psoriasis and Reaches Biologically Relevant Concentrations in Lesional Skin // PLoS ONE, 2009; 4(3):e4725
13. Jongh G. J., Zeeuwen P. L. J. M., Kucharekova M., Pfundt R., van der Valk P. G., Blokx W., Dogan A., Hiemstra P. S., van de Kerkhof P. C., Schalkwijk J. High Expression Levels of Keratinocyte Antimicrobial Proteins in Psoriasis Compared with Atopic Dermatitis // J Invest Dermatol, 2005; 125:1163 – 1173
14. Kim J. E., Kim B. J., Jeong M. S., Seo S. J., Kim M. N., Hong C. K., Ro B. I. Expression and Modulation of LL–37 in Normal Human Keratinocytes, HaCaT cells, and Inflammatory Skin Diseases // J Korean Med Sci, 2005; 20:649 – 654
15. Lee P. H. A., Ohtake T., Zaiou M., Murakami M., Rudisill J. A., Lin K. H., Gallo R. L. Expression of an additional cathelicidin antimicrobial peptide protects against bacterial skin infection // Proc Natl Acad Sci U S A, 2005 Mar 8; 102(10):3750 – 3755

16. Nomura I., Goleva E., Howell M. D., Hamid Q. A., Ong P. Y., Hall C. F., Darst M. A., Gao B., Boguniewicz M., Travers J. B., Leung D. Y. M. Cytokine Milieu of Atopic Dermatitis, as Compared to Psoriasis, Skin Prevents Induction of Innate Immune Response Genes // J Immunol, 2003 Sep 15; 171(6):3262 – 3269
17. Oppenheim J. J., Biragyn A., Kwak L. W., Yang D. Roles of Antimicrobial Peptides Such as Defensins in Innate and Adaptive Immunity // Ann Rheum Dis, 2003; 62:17 – 21
18. Reich A., Szepietowski J. C. Vasoactive peptides in the pathogenesis of psoriasis // G Ital Dermatol Venereol, 2008 Oct; 143(5):289 – 298
19. Schittek B., Paulmann M., Senyürek I., Steffen H. The role of antimicrobial peptides in human skin and in skin infectious diseases // Infect Disord Drug Targets, 2008 Sep; 8(3):135 – 143
20. Skvara H., Dawid M., Kleyn E., Wolff B., Meingassner J. G., Knight H., Dumortier T., Kopp T., Fallahi N., Stary G., Burkhart C., Grenet O., Wagner J., Hijazi Y., Morris R. E., McGeown C., Rordorf C., Griffiths C. E. M., Stingl G., Jung T. The PKC Inhibitor AEB071 May Be a Therapeutic Option for Psoriasis // J Clin Invest, 2008 Sept 2; 118(9):3151 – 3159
21. Tiberio R., Bozzo C., Pertusi G., Graziola F., Gattoni M., Griffanti P., Boggio P., Colombo E., Leigheb G. Calcipotriol induces apoptosis in psoriatic keratinocytes // Clin Exp Dermatol, 2009 Sep 15
22. Yao Y., Richman L., Morehouse C., de los Reyes M., Higgs B. W., Boutrin A., White B., Coyle A., Krueger J., Kiener P. A., Jallal B. Type I Interferon: Potential Therapeutic Target for Psoriasis? // PLoS ONE, 2008 Jul 16; 3(7):e2737
23. Zaiou M. Multifunctional antimicrobial peptides: therapeutic targets in several human diseases // J Mol Med, 2007; 85:317 – 329
24. Zasloff M. Sunlight, Vitamin D, and the Innate Immune Defenses of the Human Skin // J Invest Dermatol, 2005 Nov; 125(5):1072 – 1074

Address:
Elga Mozeika
Ozolu str. 11, Adazi
LV-2164, Latvia
E-mail: elga.mozeika@yahoo.com

Table 1. Relative appearance of defensin, neuropeptides–containing innervation and MMP2 positive structures in patients with psoriasis

Patient	Human Beta Defensin 2	PGP 9.5	MMP2
Nr. 1	++/+++	++	+
Nr. 2	++	+/++	++
Nr. 3 first biopsy	+++	+++	+++
Nr. 3 recurrent biopsy	+++	+++	+++
Nr. 4	++++	+/++	++
Nr. 5	+++	+++	++
Nr. 6	+	+++	+
Nr. 7	++	++	++
Nr. 8	+++/++++	+++/++++	+++/++++
Nr. 9	+++	+/++	+++
Volunteer	++	++	++

+ few positive structures in the visual field,
++ moderate number of positive structures in the visual field,
+++ numerous positive structures in the visual field,
++++ abundance of positive structures in the visual field.

Table 2. Apoptosis detected with TUNEL method in patients with psoriasis

Patient	1	2	3,1	3,2	4	5	6	7	8	9	Volunteer
1.	39.29	46	23.1	52.05	75.32	62.5	0	0	13.46	25.93	20.6
2.	50.8	45.65	13.84	45.71	87.5	65.57	0	0	23.08	24.24	12
3.	41.66	52.5	27.14	56.81	27.27	60.15	0	0	26.54	24.58	15
Mean ± SD	43.92 ± 6.08	48.05 ± 3.86	21.36 ± 6.82	51.52 ± 5.57	63.36 ± 31.85	62.74 ± 2.72	0.00	0.00	21.03 ± 6.78	24.92 ± 0.89	15.87 ± 4.37

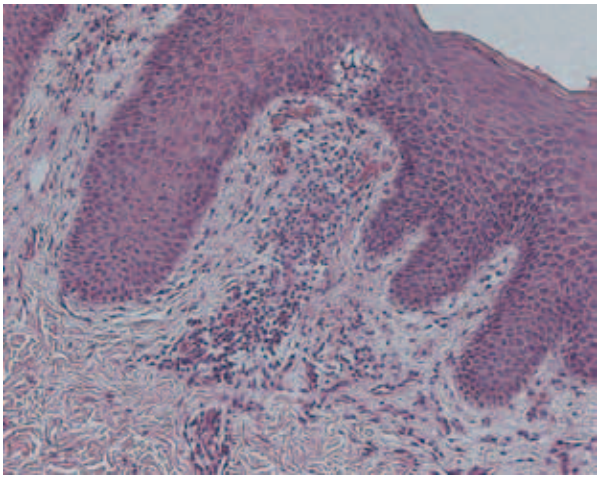


Fig. 1. Marked inflammatory cell infiltration in subepithelial layer. Hematoxylin and eosin, X 200

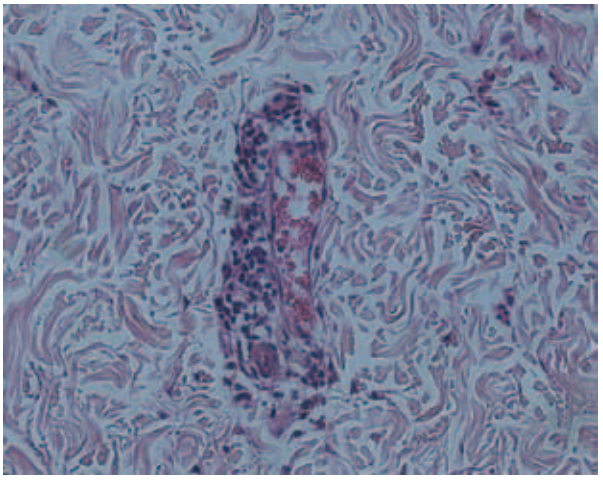


Fig. 2. Diapedesis in blood vessel due to pronounced inflammation. Hematoxylin and eosin, X 400

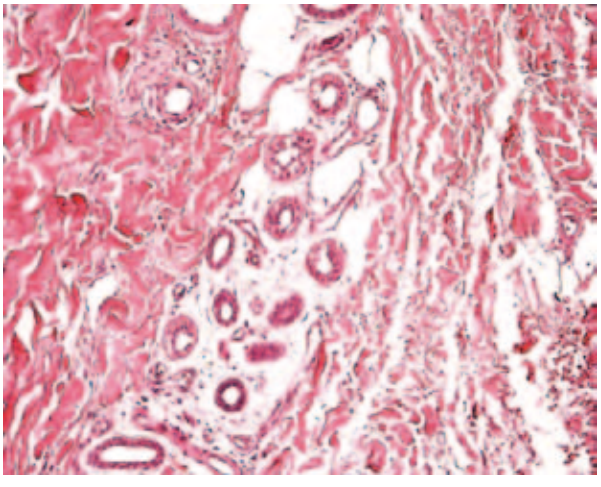


Fig. 3. Sweat gland cell vacuolizati on. Hematoxylin and eosin, X 250

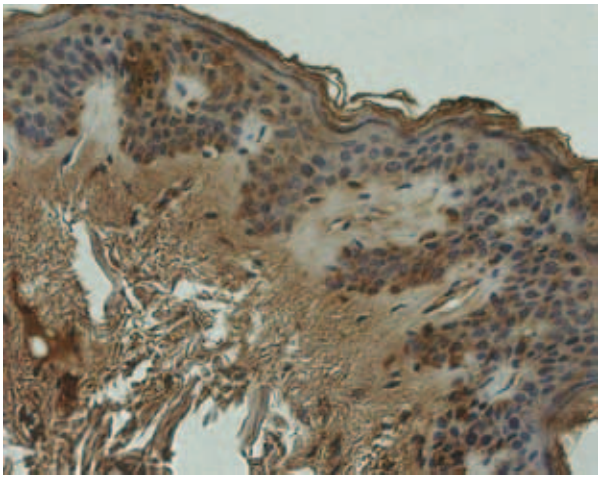


Fig. 4. Moderate number of defensin–containing cells in volunteer patient's biopsy material. Human beta defensin 2 IMH, X 400

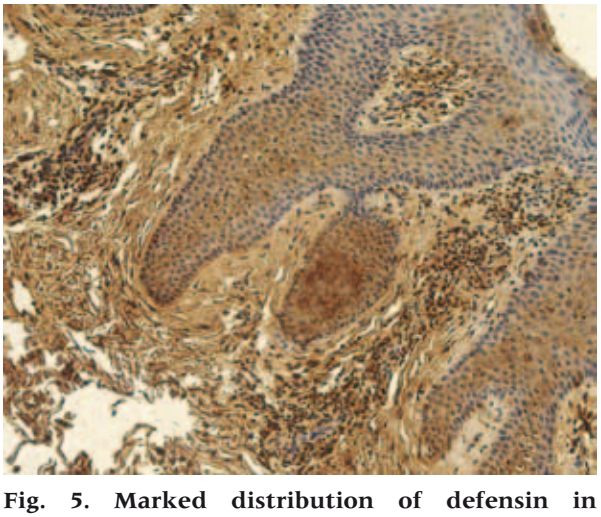


Fig. 5. Marked distribution of defensin in subepithelial tissue in psoriatic skin lesion. Human beta defensin 2 IMH, X 200

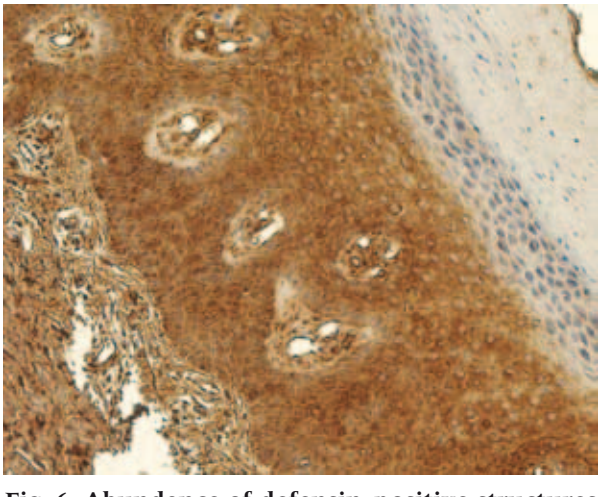


Fig. 6. Abundance of defensin–positive structures in the visual field, both epithelial and subepithelial tissue in psoriatic skin lesion. Human beta defensin 2 IMH, X 200

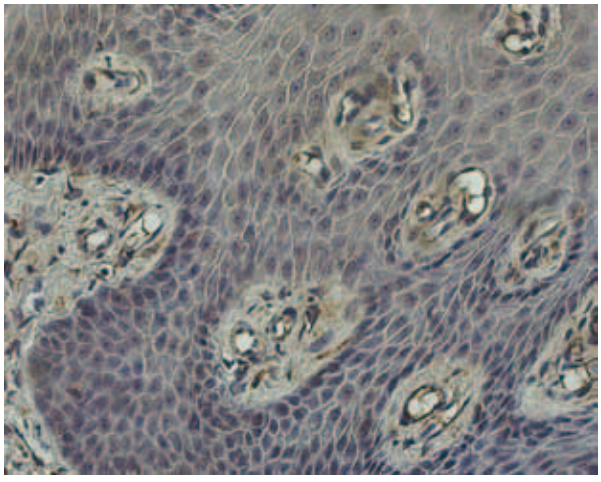


Fig. 7. Fine PGP 9.5–containing nerve fibres in subepithelium of patient's skin. PGP 9.5 IMH, X 400

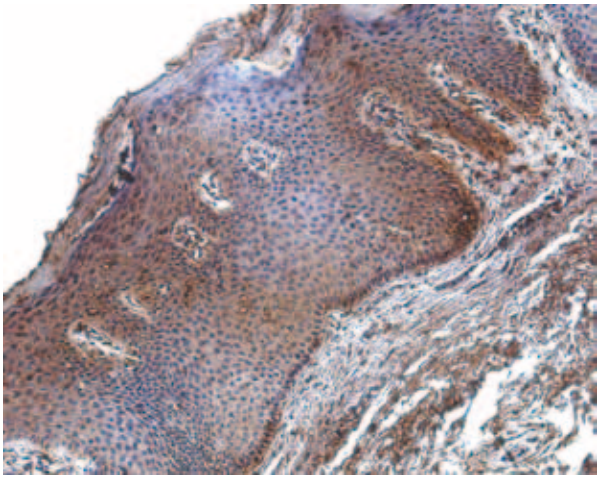


Fig. 8. Focal expression of matrix metalloproteinase 2 positive structures in epithelium and subepithelium of patient. MMP 2 IMH, X 200

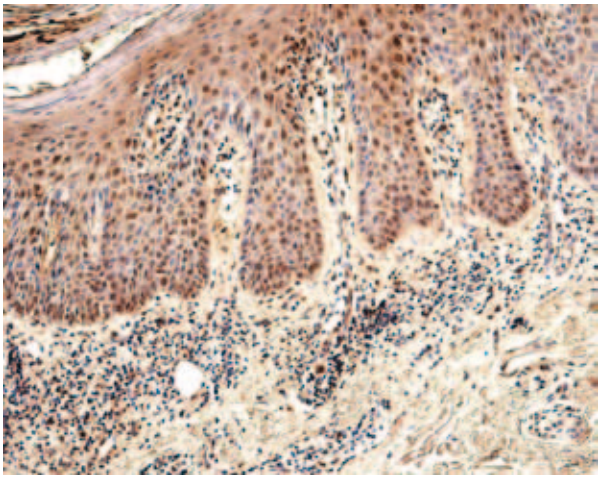


Fig. 9. Marked apoptosis of epitheliocytes and inflammatory cells in patient. TUNEL, X 200

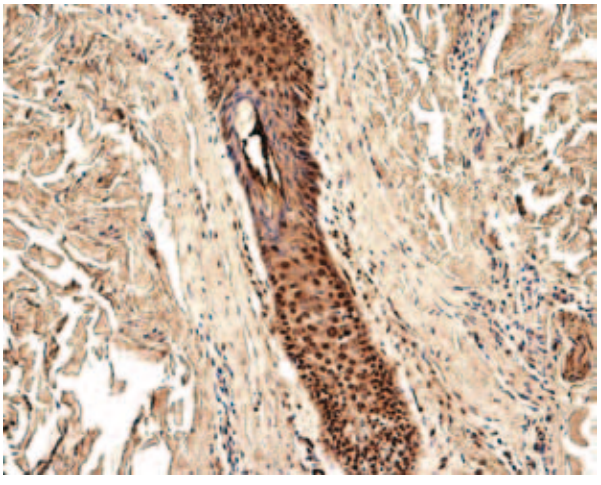


Fig. 10. Marked apoptosis in hair follicle cells of patient. TUNEL, X 250

DOI: 10.2478/v10163-010-0015-4

ORIGINAL ARTICLE

Assessment of Postoperative Pain in Nursing

Iveta Strode*, Inara Logina**
*Pauls Stradins Health and Social Care College, Riga, Latvia
**Riga Stradins University, Department of Neurology, Latvia

Summary
Introduction. Postoperative pain is a typical form of acute pain and is connected with extensive traumatization of tissue and operation wound traumatic edema, which in its turn, becomes a source of permanent nociceptive impulses. Insufficiently controlled postoperative pain is a factor of risk for the development of various pathologies, postoperative complications, as well as chronic pain.
Aim of the study. To study the usage of postoperative period pain intensity and quality assessment scales in the clinical practice of nursing, as well as availability of methods.
Materials and methods. Inquiry utilized quantitative research method - questionnaire. The questionnaire embraced 263 patients and 309 nurses, working in surgical profile. Survey was carried out in surgical profile wards in Riga and regional clinics of Latvia.
Results. Prevalent method, in our investigation of pain intensity evaluation, is patient's oral subjective and objective assessment of condition. Such method is mentioned by 87% (269/309) of respondents. A conventional and acknowledged method of pain objectivization – verbal descriptor pain intensity scale is applied by 22% (69/309) respondents, but visual analogue scale is utilized only by 5% (15/309) respondents. Assessment of postoperative pains as systematic and planed operation was marked by 41% (126/309) of surgical nurses.
Conclusions. Prevailing method in the clinical practice of pain assessment is patient's subjective and objective evaluation of condition. However, this method is insufficiently recorded and objectivizated. Therefore, it is an actual problem in surgical patient care and shows necessity for standards and improvement of postoperative pain management.
Key words: acute pain, assessment of pain, assessment of psychological factors, nursing, pain management, postoperative pain in adults, postoperative patient care.

INTRODUCTION

International Association for the Study of Pain defines pain as an unpleasant sensations and emotions related to real or potentially possible damage of tissue or is described as such damage (1). Despite its various mechanisms of origin and causes, pain always is a subjective feeling with multidimensional nature, formed by physical, emotional and cognitive components.

Postoperative pain is a typical form of acute pain and is connected with extensive traumatization of tissue and operation wound traumatic edema, which in its turn, becomes a source of permanent nociceptive impulses. Insufficiently controlled postoperative pain is a factor of risk for the development of various pathologies, postoperative complications, as well as chronic pain. Pain causes response from the cardiovascular system. It results in disturbances of the heart rhythm, tachycardia, hypertension, disturbance of microcirculation, venous obstruction. Pain gives unfavorable effect on other body systems and can trigger different complications. Therefore, care should ensure the complete control over rational influence and maximal decreasing of pain.

The aim of the patients with acute pain is maximal reduction of pain, lesser effective dose of medication, maximal level of activity, improvement of psychological effects, utilizing continuity principle in objective assessment of pain.

Scales and questionnaires, based on critical self-analyses and self-assessment of pain from an individual's subjective feelings, are used in the clinical practice in order to assess intensity and quality of pain. Simple one-dimensional pain assessment scales are a visual analogue scale, a numerical analogue scale and a verbal pain intensity scale (4). Utilization of the pain assessment scales in patient care process is a prerequisite for a purposeful care.

Professional competence of a nurse is characterized by her ability to solve the health care problems of a patient, analyzing her own experience and taking advantage of theoretical knowledge. Two sisters – scientists Patricia Benner and Judith Vrubel in professional competence theory describe skills and levels of nurse knowledge. They update the levels of competence – from trainee to expert. This competence is complicated and bases on scientific studies and theoretical acknowledgement. Benner defines competence as "comprehension of definite area, performance of skills in this area as well as identification of this area, understanding and utilization of aims and idea" (8).

In pain care nurse is an integral and essential member of team, working together with an anesthetist, surgeon and other nursing personnel.

AIM OF THE STUDY

To study the usage of postoperative period pain intensity and quality assessment scales in the clinical practice of nursing, as well as availability of methods.

MATERIALS AND METHODS

Survey utilized quantitative research method. As an investigation tool was chosen questionnaire. Inquiry forms for surgical profile patients and nursing staff were created during the study. Survey was carried out in surgical profile wards in Riga and regional clinics of Latvia. Questionnaire embraced 263 patients and 309 nurses, working in surgical profile.

Questions of the questionnaire for surgical profile nursing staff were subdivided in the following groups:

- general part (age, gender, professional education, professional work experience);
- questions on utilization of postoperative pain assessment methods and its efficiency in the daily nursing process;
- questions characterizing model of postoperative pain assessment organization and the factors influencing usability of postoperative pain assessment methods.

Questions of the questionnaire for surgical profile patients were subdivided in the following groups:

- general part (age, gender, education, occupation);
- questions on the utilization of pain assessment methods in postoperative period;
- questions characterizing subjective feelings and factors in postoperative period, influencing patient's perception of pain.

RESULTS

Demographic analysis of 309 nurses – respondents: 18% of them are 21–30 years old, 28% – 31-40 years old, 33% – 41-50 years old, 13% – 51-60 years old, 8% is older than 60 years. More than 50% of respondents have length of service in profession 20-25 years, 66% have work experience in surgical profile patient nursing more than six years. 53% of respondents have secondary vocational education, 18% – the first level higher vocational education and 29% have higher education. 98% of respondents were women, 2% – men.

Demographic analysis of 263 patients- respondents: 156 women and 107 men. 62% (163/263) of them have secondary or secondary vocational education, 29% (76/263) – higher education and only 9% (24/263) – primary school education. Most of them – 36% (95/263) undergo treatment in abdominal surgery, 11% (29/263) in blood vessel surgery, others in neurosurgery, cardiosurgery, traumatology and other wards 69% (181/263) patients had planned operations.

Characterization of Pain Assessment Methods

In clinical wards, included in our study, dominant pain assessment method is patient's subjective and objective oral evaluation of situation (Fig.1).

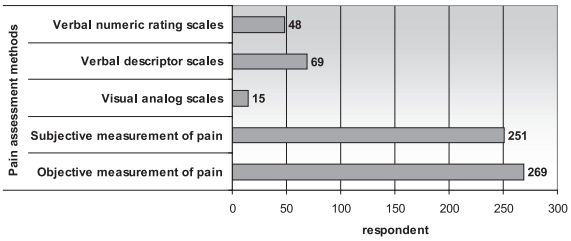


Fig. 1. Application of postoperative pain assessment methods according to the results of nurse questionnaire

Analyzing frequency of pain assessment application, the visual analogue scale in everyday postoperative patient care use only 3% (9/309) respondents, the verbal descriptor scale – 8% (24/309) and the verbal numeric rating scale – 6% (18/309).

Point of view of nurses- respondents is that assessment of pain is area of responsibility of nurse and one of components of nursing, whereas from the point of view of patients only 236 respondents is of same opinion.

Performing statistical credibility evaluation on frequency of usability of assessment of the subjective condition method between the nurses with secondary vocational and higher education (t- 4.386, degree of freedom 238, $p < 0.00$), conclusion is that the nurses with higher education use this method more often. Similar coherence is seen between the nurses with the first level higher education and higher education (t -4.093, degree of freedom 142, $p < 0.00$), indicating that nurses with the first level higher education use this method more often then the nurses with higher education.

Evaluating usability of the visual analogue scale between the nurses with secondary vocational education and the nurses with the first level vocational higher education (t – 3.79, degree of freedom 204, $p < 0.00$), one can observe that this method is more frequently used by the nurses with the first level vocational higher education.

Usage of the verbal descriptor scale shows that the nurses with the first level vocational higher education prefer this method more often than the nurses with secondary vocational education (t –2.87, degree of freedom 204, $p < 0.00$) and similar coherence is seen between the nurses with secondary vocational education and the nurses with higher education (t -2.431, degree of freedom 238, $p < 0.01$). The nurses with higher education prefer this method more often than nurses with secondary vocational education.

Frequency of the verbal numeric rating scale usability among the nurses with secondary vocational education and the nurses with the first level vocational higher education (t –3.79, degree of freedom 204, $p < 0.00$) shows that the nurses with the first level vocational higher education use this method more often than the nurses with secondary vocational education. Resembling connectedness is recognized among the nurses with secondary vocational education and the nurses with higher education (t -3.399, degree of freedom138, p <

0.00), where the nurses with higher education employ this method more often than the nurses with secondary vocational education.

Medical Therapy in Postoperative Period

237 (n=263) respondents answer that in postoperative period they regularly receive painkillers, whereas 55 (n=263) respondents mention additional medical therapy for reduction of pain.

In the first day after operation 32% (84/263) of respondents feel moderate pain (4-6 points), 38% (101/263) - severe aches (7 and more points) and 30% (78/263) of respondents have only mild pain (Fig.2.).

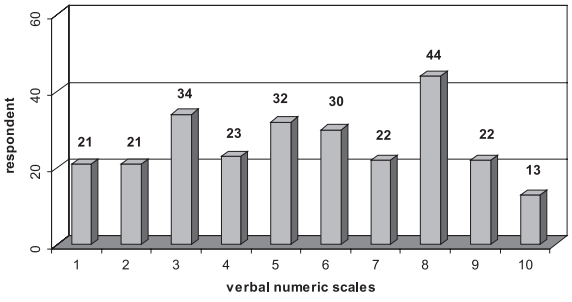


Fig. 2. Postoperarative pain assessment is based upon verbal numeric scales of the first day after surgery

Assessment of postoperative pain as methodical and systematic activity was mentioned by 126 nurses working in surgical profile and 47 respondents consider it as documenting action. Others emphasize that assessment is chaotic, unscheduled and unrecorded action. It is necessary to ensure regular pain assessment organization taking into account also side effects in order to successfully determine appropriate pain management.

DISCUSSION

Several independent surveys on pain management in postoperative period are carried in different countries. They analyze efficiency of both, medical measures and measures without medication in the reduction of pain syndrome. In spite of the development of pain management in postoperative period, frequency of postoperative pain increases. Inquiry shows that 75% of patients in postoperative period complain on moderate postoperative pain. Therefore, in clinical nursing the problem of pain is urgent. For example, in the study of postoperative pain in out-department patients, 40% of the respondents feel moderate pain and 25% consult medical professionals on the methods of pain reduction (3). In survey on postoperative pain monitoring in early postoperative period, conducted in Germany (110 respondents), were noticed that in the first day after operation intensity of pain is not adequately observed – pain is not assessed accordingly or the moderate pain is overestimated. There are many independent studies on postoperative pain in the research of nursing (2).

Nurse - professor J.Travelby (USA) accents that nursing is an interpersonal process in which nurse helps individual, family or society to delay or overcome experience related to illness or suffering (5).

Nursing is a systematic method for determination and problem solving with the planned actions in order to ensure for patient individual care in different health conditions. However, in this inquiry assessment of pain as a regular action mention only 126 respondents (nurses).

One of the tasks in perioperative period is to give a patient information how to assess postoperative pain and possibilities of pain reduction therapies. Management model of anaesthetics is closely connected with the action plan of a particular clinic (6). Efficiency of analgezia, quality of seizure prevention and potency length of medicine should be evaluated. It is important to clarify the time, when analgetic was last time injected and the length of time till pain recrudesce in order to evaluate the signs of tolerance. The first sign of tolerance is decrease of anaesthetic potency length. It is important that assessment of pain should be considered as the fifth vital indicator in nursing. Study of Danish nurses on pain monitoring, conducted in five clinics, conclude that 83,6% nurses postoperative pain assessment consider as a routine. Whereas 78,1% of nurses assessment of pain put forward as a vital sign in postoperative period. This inquiry stresses that documentary assessment of pain plays a great role in postoperative pain management (7).

One of essential tasks in postoperative period is to release a patient from distress caused by pain in order to provide comfort for a patient. This is a motivation for humane and ethical nurse practice ensuring to relieve pain for postoperative patient. Still in Latvia there are a few studies on acute pain influence on recovery, progress of disease and outcome as well as assessment of pain intensity and quality.

CONCLUSIONS

Prevailing method in the clinical practice of pain assessment is patient's subjective and objective evaluation of condition. However, this method is insufficiently recorded and objectivizated. Therefore, it is an actual problem in the surgical patient care and shows necessity for standards and improvement of postoperative pain management.

ACKNOWLEDGEMENT

Article was created with support of European Social Fund.

Conflict of interest: None

REFERENCES

1. Classification of chronic pain. 2nd edition // IASP Press, 1994
2. Gross T., Pretto M., Aeschbach A. Pain management in surgical wards. Quality and solutions for

improvement in the early postoperative period // Chirurg, 2002; 73:818 – 826
3. Karanikolas M., Swarm R.A. Perioperative medicine: current trends in perioperative pain management // Anesthesiology Clinics of North America, 2000; 18:579 – 599
4. Le Bel A.A. Assessment of pain // In: Ballantyne J.C. The Massachusetts general hospital handbook of pain management. Third Edition. Philadelphia: Lippincott Williams & Wilkins; 2006; 58 – 75
5. Meleis A.I. Theoretical nursing: Development& Progress. Philadelphia: J.B. Lippincott Company; 1985; 254 – 263
6. Odom J. Postoperative patient care and pain management // In: Rothrock J.C. Care of the Patient in Surgery. Printed in the United States of America: Mosby; 2003; 253 – 280
7. Rond M., Wit R., Dam F. The implementation of a pain monitoring programme for nurses in daily clinical practice: results of a follow-up study in five hospitals // Journal of Advanced Nursing, 2001; 35:590 _ 598
8. Šiliņa M., Dupure I. Pacientu izglītošana – māsas kompetence. Rīga: Nacionālais apgāds; 2004; 104

Address:
Iveta Strode
Pauls Stradins Health and Social Care College
Vidus prospects 36/38,
Jurmala, Latvia, LV-2010
E-mail: ivetastrode@inbox.lv

DOI: 10.2478/v10163-010-0016-3

ORIGINAL ARTICLE

Primary Cardiac Tumours in Infancy and Youth in the Small Population: a Seven Year Review

Teivane Elina, Zidere Vita, Lacis Aris
University Clinical Children's Hospital, Riga, Latvia
Department for Pediatric Cardiology and Cardiac Surgery

Summary

Introduction. Primary tumours of the heart are rare in fetuses, neonates and children; the incidence varies from 0.003% - 0.08% (4, 6, 9, 10) up to 0.2% in children referred for cardiac examination (3, 15). Rhabdomyoma is the most common cardiac tumour during fetal life (60-75%). Teratoma is less common (14 to 19%) with fibroma, myxoma, hemangioma also being described (3, 4, 6, 10, 16, and 18). Multiple rhabdomyomas are associated with tuberous sclerosis in up to 90-95% of cases (3, 4, 5, 6, 10, 12, and 16). No previous study was done on this topic in Latvia so our aim was to determine the incidence, the course and the outcome of primary cardiac tumours in children in our small population.

Aim of the study. The aim of our study was to determine the incidence of primary cardiac tumours in our paediatric population, to investigate the nature of the pathology, the course and the outcome of the disease in childhood in Latvia and to compare our results with data from the international literature.

Materials and methods. We reviewed retrospectively the clinical, echocardiographic, operative, histological and follow-up data on 17 cases of a primary heart tumours detected within the period of January 1, 2000 till December 31, 2006 in the Clinic for Pediatric Cardiology and Cardiac Surgery of the University Children's Hospital in Riga, Latvia.

Results. the incidence of primary heart tumours in the paediatric population in Latvia is 2.4+/-1.4 cases per year. 94% (16) of the primary cardiac tumours in children were benign and 6 %(1) malignant. Radical excision performed in all 7 cases of surgical treatment. Rhabdomyomas comprise 47% (n=8) of all the benign tumours with tuberous sclerosis present in 88% of the cases.

Conclusions. Most primary cardiac fetal tumours tend to appear in the third trimester of pregnancy, a normal early fetal scan might not rule out cardiac tumours. Relatively often (29% of the cases) the cardiac tumours were an incidental finding. The localization, number and visual appearance of the tumours in echocardiography was indicative of the type of tumour. 41% of the patients with primary cardiac tumours were in need of urgent surgical treatment. Almost all benign primary cardiac tumours were not the cause of death and with the exception of tuberous sclerosis there is good overall prognosis, in the case of malignant primary cardiac tumour the prognosis is poor.

Key words: primary cardiac tumour, echocardiography, congenital heart disease.

INTRODUCTION

Primary tumours of the heart are rare in fetuses, neonates and children. They are found in 1/10,000(0.01%) of routine autopsies of patients of all ages (10) and in 0.0017% of autopsies in the paediatric age group (6, 18). According to the literature, the incidence of primary heart tumours in infancy and childhood varies from 0.003% to 0.08% (4,6,9,10) with a reported incidence of up to 0.2% in children referred for examination for cardiac disease (4,15). The incidence of primary heart tumours in fetal echocardiography is 0.14% (9, 18)-0, 2 %(10). Most of the evidence in this article is based on case reports rather than large cohort studies. The frequency and type of cardiac tumours in children differ from those in adults. The majority of primary cardiac tumours in children are benign. Rhabdomyoma is the most common cardiac tumour during fetal life and childhood and accounts for 60-75%. Teratoma is less common (from 14 to 19%) with fibroma, myxoma, hemangioma also being described (3, 6, 10, 15, 16, and 18). Multiple rhabdomyomas are associated with tuberous sclerosis in up to 90-95% of cases but these tumours tend to regress with time (3, 5, 6, 10, 15, 16, and 18) although some authors (12) suggested rhabdomyomas could develop during childhood in tuberous sclerosis. Malignant primary cardiac tumours are extremely rare and are observed in 4-9% of cases with rhabdomyosarcoma as the leading malignancy.

During the past decade the number of cardiac masses detected in paediatric population has increased significantly because of the widespread use of non-invasive imaging techniques.

AIM OF THE STUDY

The aim of our study was to determine the incidence of primary cardiac tumours in our paediatric population, to investigate the nature of the pathology, the course and the outcome of the disease in childhood in Latvia and to compare our results with data from the international literature. There are no previous studies on this subject available in Latvia and we suspected a primary heart tumour is a relatively frequent pathology in our small population. The number of primary heart tumours cases in our study demonstrated unusual appearance in infancy which were unexpected to us, and which we felt were worthy of description.

MATERIALS AND METHODS

There were 2,294, 000 inhabitants in the year 2006 in Latvia, 18.9 % (433,566) of them children (17). The life births rated from 19 664 in year 2001 to 22 264 in year 2006 (17) and there are approximately 250 newly diagnosed congenital heart diseases in the paediatric population in Latvia annually. All children with a suspected heart anomaly and those with known cardiac pathology are treated and followed-up in our centre, the only paediatric cardiology clinic in our country.

It was a retrospective descriptive study; all the patients with primary heart tumours diagnosed within the time between January 1, 2000 until December 31, 2006 from the local database of the Clinics for Pediatric Cardiology and Cardiac Surgery of University Children's Hospital, Riga, Latvia were included in the study. Retrospective review of our database detected 18 cases, including four diagnosed prenatally, with a diagnosis of a primary heart tumour seen between January 1, 2000 until December 31, 2006 in our centre. In one prenatally diagnosed case (rhabdomyosarcoma) the pregnancy resulted in a stillbirth and this patient was excluded from further study.

The confidentiality of the patients included in the study was fully preserved and the design of the study in based under the existing legislation of our country.

The patients were analysed according to the localization of the tumour and its morphology on echocardiography and/or the histology of the tumour, the surgical therapy and the follow up. The demographic, clinical and diagnostic data were collected and analyzed. The data were obtained from the case histories and videotapes of the patients treated and followed-up in our centre. All the surgically resected masses and one case of prenatally diagnosed tumour, which resulted in a still birth were sent for histological examination. Postoperatively the patients were followed-up 9-72 months (medium 45+/-16, 8 months).

There was a total of 34,620 in-patient and out-patient echocardiograms (5942 of them fetal echocardiographies) performed in the time period from January 1, 2000 till December 31, 2006.

RESULTS

There were 17 cases of primary heart tumours diagnosed within the seven years of the research period, including three diagnosed prenatally between 24 and 36 (medium 27,3+/-3,5) weeks of gestation during routine fetal scan and been referred to the fetal cardiologist. Additional four cases were detected in the neonatal period, seven within the first year of life, at the age of 1 to 10 years in two cases and five at the age of 10 to17 years. From all 17 patients five of them were females (29%) and 12 (71%) were males.

There were 16 (94%) benign: Rhabdomyoma 8, Fibroma 2, Teratoma 1, Myxsoma 1, Lymfangioma1 and 3 unknown aetiology primary heart tumours and one (6 %) malignant: Mesotelioma.

Within the analyzed cases, the cardiac mass found posnatally by chance was in 5 cases (29%) and another five (29%) were found on echocardiography, having been referred because of a history of seizures and/or the diagnosis of the tuberous sclerosis. Eight patients (47%) had clinical symptoms of congestive heart failure or arrhythmia or abnormal chest x-ray, 6% (n=1) of patients were referred for cardiac examination due to abnormal findings on the chest x-ray performed as an out-patient, 24% (n=4) were referred for the cardiac examination due to a murmur of the heart and only 12% (n=2) were sent to the cardiologist due to symptoms such as cough, sweating, tachypnoe (patients 5 and 11 years old). In one case the manifestation of the tumour was cyanosis, respiratory distress and the signs of congestive heart failure in a newborn.

There are 3 unusual cases of the cardiac masses, all diagnosed prenatally, in the study group where the histology is unknown. We assume that they are benign nature because there are no hemodynamically relevant changes observed, the patients have no congestive heart failure and possible malignancy is not suspected clinically. All three patients were born in full term. In the first case the solid mass (7.5 x7.5 mm) obstructed the left ventricular outflow tract with maximum pressure gradient of 80 mmHg on continuous wave Doppler, but fortunately normal cardiac function on fetal echocardiogram at 30 weeks of gestation. The infant was asymptomatic postnatally even the cardiac mass remained the same size; the gradient subsequently had decreased until 16mm Hg at the age of four. In the second case the tumour was localized in the posterior wall of the right atrium and decreased in size significantly with the time. In the third patient a large firm tumour mass was found localized within the ventricular septum, but as it does not increase in size and is not obstructive, excision of the mass has been deferred. In case 2 and 3 the serum alpha-fetoprotein levels were controlled and they were elevated after the birth 844 and 44766 IU/ml respectively with a normal value up to 10 IU/ml, but decreased significantly to the normal values until the age of 6 months. As the nature of these three tumours is unknown the possibility of tuberous sclerosis was excluded by geneticist counselling and brain computed tomography.

Rhabdomyomas were diagnosed echocardiographically based on the characteristic findings and correlation with tuberous sclerosis. Rhabdomyomas comprise 50% (n=8) of all the benign tumors. There was tuberous sclerosis present in seven patients (88%) of the cases of rhabdomyomas. In one of them the patient deceased at the end of the operation due to acute cardiac insufficiency and critical dysfunction of the left ventricle after the extirpation of the tumour which was firmly connected to the posterior wall of the left ventricle. The indications for the surgery were severe compression of the left ventricle by the tumour. All the remaining patients with rhabdomyomas except the one who died at the end of surgery were followed-up for 3-84 months, there was no hemodynamically significant obstruction or resistant arrhythmias observed and therefore surgery was not indicated. There was one

death from an unrelated cause. There was a tendency for regression of the multiple rhabdomyomas but they are still detected echocardiographically in all the patients. The age of these patients at the end of the study (December 31.2006) ranged from 9 months – 15 years (medium 9, 4+/-6 years). These patients had mental retardation of variable degree, seizures, received anticonvulsive treatment and were followed-up by paediatric neurologists and psychiatrists. Most of the rhabdomyomas were observed to regress with a time in accordance with the literature (3, 4, 5, 6, 7, 10, and 11). Although none of the patients had complete regression of tumours. Only three of the patients from this group experienced congestive heart failure in neonatal period but none had serious arrhythmia and only one was in need of surgery. In the group of rhabdomyoma and all the benign primary cardiac tumours only one deaths due to the tumour occurred.

Over the time period there was an increasing rate of surgical intervention, which took place in 7(41%) cases, all the surgically treated cases are represented in Table 1. In 6 cases the operation was performed in our centre, but in one case abroad due to social reasons. Radical excision was performed in all cases of surgical treatment of primary heart tumour.

(Table 1).

In one case with a giant fibroma of the right ventricle the excellent surgical result was achieved by removing the mass following the principles of the Batista procedure to preserve the function of the left ventricle (19).

In one case from our operated patients group the heart tumour was found by chance as the patient was referred for follow up due to prenatally diagnosed muscular ventricular septal defect. The fetal echocardiogram was performed at 26 weeks of gestation and there were no signs of the cardiac mass at that time. At the age of three months the male infant presented asymptomatic but the echocardiogram showed typical appearance of myxoma in the right atrium, no ventricular septal defect was found. The nature of the tumour was confirmed after the mass was successfully removed by surgeon.

There was one malignant tumour detected. It was a malignant epitheloid mesothelioma which recurred 20 months following operation, the only case of recurrence of the tumour in our study. The patient has declined further palliative treatment.

In general the incidence of primary heart tumours in the paediatric age group was 0.049% in children referred for the cardiac examination with a prevalence of cardiac tumours in the paediatric population 3.92/100,000 in Latvia.

DISCUSSION

Primary heart tumours are a rare pathology in the paediatric age group (4, 6, 9, 10, and 15). The increase in the incidence of both neoplastic and nonneoplastic cardiac lesions detected annually has increased during the past two decades due to improved imaging techniques such as sonography, magnetic resonance and computed tomography. There are some limitations to our study. First of all, we have not examined entirely all paediatric patients with tuberous sclerosis in the country. Therefore the data about rhabdomyomas is not absolute. Secondly, the fact that specialized cardiac examination in the paediatric age group in our population is performed only in our centre explains the comparatively low incidence of primary cardiac tumours in the group of patients referred for the cardiac examination to a tertiary centre. The incidence of primary heart tumours in the paediatric population in Latvia is 2.4+/-1.4 cases per year or 0.049% in the children referred for cardiac examination. According to the international literature the incidence of the primary heart tumours in the paediatric age group varies from 0.003% to 0.08% (6,9,10,15) with a reported incidence up to 0.2% in children referred for the examination due to cardiac disease (4, 15) .

The possibility for antenatal diagnosis has improved during the past decade in our country. However, only three from seven neonatal cases were diagnosed in utero. Fetal cardiac tumours tend to appear between 20 and 30 weeks of gestation, therefore a second trimester fetal anomaly scan can not completely rule out a cardiac tumour (5, 8, 11, 13, and 14).

Absence of specific symptoms makes difficult to diagnose primary heart tumour early and sudden death could be the only presentation of the disease. Only 18% of our patients had signs of congestive heart failure clinically and/or there were parental complaints connected with clinical findings. There are no reported data of sudden death caused by primary heart tumour during this study period to our knowledge.

Although multiple rhabdomyoma was the most common primary cardiac tumour in the paediatric age group in Latvia, it constituted only 47% of all the primary heart tumours in paediatric age group whereas in the literature it accounts for up to 75% of the detected cardiac tumours in childhood (4, 6, 8, 9,10, 16). This discrepancy could be explained by the possible absence of existing cases among the neurological and psychiatric patients who are not yet diagnosed. There is a correlation between multiple cardiac rhabdomyomas and the diagnosis of tuberous sclerosis observed in 90-95% (1, 2, 3, 4, 5, 6, 10, 11), but in our study group 88 % of rhabdomyoma cases were associated with tuberous sclerosis. The second most common cardiac tumour was fibroma (12%), but it ranked first among the patients who underwent surgery for the heart tumour. We observed only a single case of each, teratoma, myxoma and lymphangioma, within the period covered by the study. In the case with a giant fibroma in the right ventricle the surgeon had preferred to use unique approach - principle that was proposed by R.Batista (1996) for critical patients with dilated cardiomyopathy - partial left ventriculectomy alternative to the heart transplantation (19). The case of myxoma at age of three months is extremely unusual as the myxoma it self is very rare in the paediatric age group. The myxoma is common cardiac mass in adults with female predominance and mostly located in the left atrium. In our case this all was opposite with no family history of myxomas. Only an accidental finding of muscular

ventricular septal defect on fetal echocardiogram at 26 weeks of gestation with subsequent follow up postnatally protected this infant from possible sudden death.

As previously described in literature, the malignant primary heart tumours in infancy are also very rare and carry a poor prognosis. Our study has demonstrated a dismal outcome in group of malignant primary heart tumour with tumour recurrence and multiple metastases 1 year 8 months after surgical tumour excision. The serum alpha-fetoprotein was used as the marker to predict the nature of the tumour in the group of clinically asymptomatic cardiac masses with unknown histology. However, the value of initial level of serum alpha-fetoprotein in judging the presence of possible immature or malignant elements is questionable. Two further elements can increase levels postnatally, specifically prematurity and the presence of tumour involving the germ cells. The presence perinatally of a tumour of the germ cells produces strongly elevated levels, albeit in most reported cases, the tumours either contained immature elements or malignant elements from the yolk sac (14). The serum alpha-fetoprotein decreases after an inverse logarithmic curve to approximately 100μg/L at 1 month of life, and then to a normal level at 1 year of age. It has been suggested that the rapidity of serum alpha-fetoprotein decrease is a more accurate prognostic factor than any isolated value (14).

CONCLUSIONS

Relatively often the primary cardiac tumour was an incidental finding. The localization, number and visual appearance of the tumour in echocardiography was indicative of the type of tumour and aided in planning management. Benign primary cardiac tumours were not the cause of death and with the exception of tuberous sclerosis there is good overall prognosis but every case is individual according to the localization, size and haemodynamic consequences. In the group of benign tumours congestive heart failure was observed only in one case following the successful operation, but 83% were free of congestive heart failure. The overall prognosis is good in this group.

ACKNOWLEDGEMENT

The authors wish to thank Professor Lindsey D Allan, Consultant Fetal Cardiologist at Harris Birthright Resarch Centre for fetal Medicine, King's College Hospital, London, UK, for the invaluable assistance.

Conflict of interest: None

REFERENCES

1. Allan L: Fetal cardiac tumors // In: Allan L, Hornberger L, Sharland G. Textbook of Fetal Cardiology. London: Greenwich Medical Media Limited; 2000; 358 – 365
2. Bader RS, Chitayat D, Kelly E, Ryan G, Smallhorn JF, Toi A, Hornberger LK. Fetal rhabdomyoma: prenatal diagnosis, clinical outcome, and incidence of associated tuberous sclerosis complex // J Pediatr, 2003; 143(5):620 – 4
3. Becker AE. Primary heart tumors in the pediatric age group: a review of salient pathologic features relevant for clinicians // Pediatr Cardiol, 2000; 21(4):317 – 23
4. Beghetti M, Gow RM, Haney I, Mawson J, Williams WG, Freedom RM. Pediatric primary benign cardiac tumors: a 15-year review // Am Heart J, 1997 ; 134(6):1107 – 14
5. Fesslova V, Villa L, Rizzuti T, Mastrangelo M, Mosca F. Natural history and long-term outcome of cardiac rhabdomyomas detected prenatally // Prenat Diagn, 2004; 24(4):241 – 8
6. Freedom RM, Lee KJ, MacDonald C, Taylor G. Selected aspects of cardiac tumors in infancy and childhood // Pediatr Cardiol , 2000; 21(4):299 – 316
7. Gamzu R, Achiron R, Hegesh J, Weiner E, Tepper R, Nir A, Rabinowitz R, Auslander R, Yagel S, Zalel Y, Zimmer E. Evaluating the risk of tuberous sclerosis in cases with prenatal diagnosis of cardiac rhabdomyoma // Prenat Diagn, 2002; 22(11): 1044 – 7
8. Hirakubo Y, Ichihashi K, Shiraishi H, Momoi MY. Ventricular tachycardia in a neonate with prenatally diagnosed cardiac tumors: a case with tuberous sclerosis // Pediatr Cardiol, 2005; 26(5):655 – 7
9. Holley DG, Martin GR, Brenner JI, Fyfe DA, Huhta JC, Kleinman CS, Ritter SB, Silverman NH. Diagnosis and management of fetal cardiac tumors: a multicenter experience and review of published reports // J Am Coll Cardiol, 1995; 26(2):516 – 20
10. Isaacs H Jr. Fetal and neonatal cardiac tumors // Pediatr Cardiol, 2004; 25(3):252 – 73
11. Jóźwiak S, Domańska-Pakieła D, Kwiatkowski DJ, Kotulska K. Multiple cardiac rhabdomyomas as a sole symptom of tuberous sclerosis complex: case report with molecular confirmation // J Child Neurol, 2005; 20(12):988 - 9
12. Jóźwiak S, Kotulska K, Kasprzyk-Obara J, Domańska-Pakieła D, Tomyn-Drabik M, Roberts P, Kwiatkowski D. Clinical and genotype studies of cardiac tumours in 154 patients with tuberous sclerosis complex // Pediatrics, 2006; 118(4): 1146 – 51
13. Lacey SR, Donofrio MT. Fetal cardiac tumors: prenatal diagnosis and outcome // Pediatr Cardiol, 2007; 28(1):61 - 7
14. Meuris B, Gewillig M, Meyns B. Extreme levels of alpha-fetoprotein in a newborn with a benign intrapericardial teratoma // Cardiol Young, 2006; 16:76 – 7
15. Padalino MA, Basso C, Milanesi O, Vida VL, Moreolo GS, Thiene G, Stellin G. Surgically treated primary cardiac tumours in early infancy and childhood // J Thorac Cardiovasc Surg, 2005; 129(6):1358 - 63
16. Thomas-de-Montpréville V, Nottin R, Dulmet E, Serraf A. Heart tumors in children and adults: clinicopathological study of 59 patients from a surgical center // Cardiovasc Pathol, 2007; 16(1): 22 – 8

17. The data of The Central Statistical Bureau of Latvia (2006): www.csb.gov.lv
18. Uzun O, Wilson DG, Vujanic GM, Parsons JM, De Giovanni JV. Cardiac tumours in children // Orphanet J Rare Dis, 2007; 1:2 – 11
19. Zidere V, Lubaua I, Lacis A. Giant fibroma of the right ventricle // Cardiol Young, 2002;12(6): 584 – 6

Address:
Elina Teivane
Children's Clinical University Hospital,
Department for Pediatric Cardiology and Cardiac Surgery
Vienibas gatve 45, Riga, LV-1004, Latvia
E-mail: eteivane@inbox.lv

Table 1. Characteristics of the operated patients

Case	*Gender*	*Age at diagnosis*	*Presenting symptoms and reason for referral*	*Hystology, size, localization and characteristics of the tumour*	*Outcome*
1	Female	13 month	Systolic heart murmur and premature atrial contractions	*Fibroma* 75 x 55 x 30 mm, within the myocardium of the right ventricle anterior wall; firm, circumscribed, not encapsulated with calcification islands	Total tumour excision (using the Batista procedure principles); alive and doing well
2	Male	5 years	Heart failure and systolic heart murmur	*Fibroma* 47 x 66 mm; in the right ventricle, firmly connected with its anterior wall	Operated abroad; alive, heart failure
3	Male	3 month	Muscular ventricular septal defect on fetal echocardiography at 26 weeks of gestation	*Myxoma* 20 x 30mm, pedunculated, with a stalk attached to the right atrium lateral wall; thin capsule, polycystic	Total tumour excision; alive and doing well
4	Male	11 years	Heart failure and abnormal chest X-ray (massive pericardial effusion)	*Epytheloid malignant mesotelioma* 200 x 100 x 80mm, polycystic, dense, encapsulated, firmly connected to the epicardium of the right ventricle with extension to the right atrium, aorta and pulmonary artery	Tumour excision; alive; tumour recurrence
5	Female	11 years	Abnormal chest X-ray	*Lymfangioma* 50 x 25 x 30 mm; polycystic, tight to the left ventricle, left diphragma, firmly connected to the pericardium	Total tumour excision; alive and doing well
6	Male	1day	Heart failure, cyanosis and abnormal chest x-ray (cardio/thoracic ratio of 0.8)	*Rhabdomyoma* 45 x 30mm; subepicardial, dense, without capsule, connected to the posterior wall of the left ventricle	Tumour excision; deceased at the end of operation due to heart failure and deficient left ventricular volume
7	Female	14 days	Heart failure, systolic heart murmur	*Teratoma* (immature grade I) 30mm x 28mm x 20mm; intrapericardial, multicystic, connected to the ascending aorta, compresses the right atrium and superior vena cava	Total tumour excision; alive and doing well

DOI: 10.2478/v10163-010-0017-2

ACTA CHIRURGICA LATVIENSIS • 2009 (9)

PROBLEM – SOLVING ARTICLE

Excessive Bleeding After Cardiac Surgery in Adults: Reasons and Management

Agnese Ozolina*, Eva Strike*,,Vladimirs Harlamovs*, Nora Porite***
*Pauls Stradins Clinical University Hospital, Department of Anesthesiology and Cardiothoracic Surgery, Riga, Latvia
**Riga Stradins University, Latvia

Summary
Postoperative bleeding is a concern for all patients undergoing cardiac surgery. In patients exposed to cardiopulmonary bypass, bleeding following surgery is excessive in up to twelve percent of patients in whom subsequent re-exploration is required. Several studies have evaluated main reasons, prevention of excessive postoperative bleeding and impact of patients outcomes. This article contains a literature review on excessive bleeding and re-exploration following cardiac surgery, main surgical and medical sources, prevention and management of bleeding.
Key words: re-exploration, bleeding, cardiac surgery.

INTRODUCTION

Excessive bleeding is common after cardiac surgery and it remains a major source of morbidity and mortality. There have been many studies analyzing the haemostatic derangements caused by cardiopulmonary bypass (CPB) and others have evaluated the various strategies of blood conservations. The incidence of re-exploration during early postoperative period after open heart surgery in the literature is ranging from 2% to 6% (31). The first cause for early mediastinal re-exploration after open heart surgery is the bleeding.

In studies held before 1990, re-exploration rates were as high as 14%, whereas they dropped down to 3% in recent studies. Reasons for this could be follows: shortening of the duration of the operations and more advanced technology, construction of extracorporeal circuatory and oxygenator lines that causes less heamatological trauma, better evaluation of patiens perioperatevly, transfusions of autologus blood components.

Excessive bleeding may result in patients receiving massive blood transfusions or suffering of life-threating complications such as miocardial infarction, low cardiac output sindrome, respiratory failure and pneumonia, severe arrhythmia, deep sternal wound infections, hepatic and renal insufficiency and need for hemofiltration, cardiac tamponade and increased mortality.

Mortality rates seen after revisions for bleeding are between 8–26% in literature, but incidence of wound infections after re-explorations is approximately 2% (15).

Major risks factors for bleeding are summarized in Table 1.

There have been several studies investigating genetic role of developing coagulopathy after cardiac surgery (14). Duggan and coworkers measured Plasminogen Activator inhibitor -1 (PAI-1) gene expression after cardiac surgery and its relation to perioperative morbidity. PAI-1 gene expression decreased after cardiopulmonary bypass in all patients. A larger reduction in PAI-1 gene expression was observed in homozygous carriers of the 5G allele. They are also more likely to receive transfusion of coagulation blood products.

Re-exploration rates due to bleeding

In literature need for re-exploration with bleeding revision was evaluated while investigating series of large numbers (Table 2).

Excessive bleeding reasons after cardiac operation in cardiopulmonary bypass

The main reasons are categorized as surgical or medical in nature.

Surgical: Excessive postoperative bleeding is from surgical sources in the majority of patients. In prior studies surgical causes of bleeding necessitating re-exploration were found to range from 35-100% (19,20,24).

It is usually related to: anastomotic sites (suture lines), side branches of arterial or venous conduits, substernal soft tissues, sternal suture sites, bone marrow, periosteum, raw surfaces caused by previous surgery, pericarditis.

Medical: That kind of bleeding usualy is persistent noted after complex operations frequently associated with abnormal coagulation. It is hard to diagnose if bleeding is due to coagulopathies. They have a greater extent, are exposed to greater amounts of inotropes with alpha effect and has greater incidence of low cardiac output syndrome. Also hospitaly stay and mortality rate in higher (19). Therefore for patients in the ICU with unexpected high chest tube output, the goal is to normalize the patients coagulation profiles within 4 hours (19).

There are many risk factors causing medical related bleeding. First of all these ar **preoperative factors** such as low body surface area with small blood circulation volume. It is significant risk factor for bleeding and masive blood transfusions because of greater hemodilution of using higher total volums in the CPB circuit (23).

Qualitative platelet defects are a major concern with the liberal use of antiplatelet medications in patients with acute coronary sindromes. Preoperative platelet dysfunction may result from antiplatelet medications. Most frequently used antiagregant is Aspirin. Clopidogrel also is significant risk factor who causes higher rate of re-exploration (9).

Preoperative trombocytopenia < 100 x 10^9L is a serious risk factor for bleeding and for masive blood transfusions in postoperative period (35). Be aware that reason for trombocytopenia also can be Heparin-induced trombocytopenia (HIT). Up to 8% of heparinized patients develop the antibody associated with HIT and approximately 1–5% of patients on heparin progress to develop HIT.

Patients with hepatic dysfunction, residual Warfarin effect, vitamin K-dependent clooting factors deficiencies, von Willebrand's disease and also thrombolytic therapy is more likely to have excessive bleeding after CPB.

Intraoperative factors

The main source for bleeding intraoperatively is CPB. Prolonged cardiopulmonary bypass period is an independent risk factor for higher mortality and morbidity rate after cardiac surgery and it is the best predictor of microvascular bleeding. The risk for bleeding increases if CPB period is more than 120 minutes (34).

Patients undergoing cardiac surgery in CPB acquire some degree of platelet dysfunction. Cardiopulmonaly bypass circuit induce platelet dysfunction because of release of alfa granule and alteration of platelet membrane receptors. How to predict excessive microvascular bleeding due to platelet dysfunction after CPB remains an elusive goal. More sensitive and specific compareble to routine laboratory coagulation tests in predicting blood loss are Thromboelastogram (TEG) and Platelet-Activated Clotting Test (PACT). However some authors report, that TEG have better predictive value than PACT (16).

Thrombocytopenia will be progressive as the duration of CBP lengthens. Also administration of Protamine transiently reduces the platelet count by about 30%.

Hemodilution on CPB reduces most factors by 35-50% and factor V by 80% (8). This is most pronounced in patients with small blood volume and they are more likely to have dilution coagulopathy thereby also higher risk for excessive bleeding (23). Loss of clotting factors also results from use of intraoperative cell-saving devices.Clotting factor degradation and platelet dysfunction causes also fibrinolysis due to plasminogen activation during CBP and heparinization itself induces a fibrinolytic state.

Hypothermia – it could reduce platelet and enzime function. Platelet agregation and adhesion decrease when body temperature is 33^0C and less.

Postoperative factors

The phenomen of „heparin rebound" has been considered to be the most common cause of bleeding in the postbypass period. The phenomen is the best defined as the reappearence of hypocoagulability of blood after adequate neutralization of heparin has been accomplished (30). This is more common in patients receiving large amounts of heparin, especially obese patients. The incidence of the „heparin-rebound prhenomen" have been investigated by many studies (29). Reappearence of heparin in circulation usually occur in 1-8 hours after neutralization with Protamine. Heparin effect was detected in 43% of patients studied at 2h, 31% at 4h, and 37% at 8h.

Number of reasons have been attributed to the appearence of heparine in the circulation. It may be either due to reabsorption of heparine into the blood stream from extravascular depots or it may be due to the faster degradation of Protamine. Also application of Cell saver system after Protamine administration may reintroduce unreversed heparine, but several studies have been reported that Cell saver system with separated red blood cells washed in physiological saline were totaly free of heparine, partly small remains of heparine could be found.

Anticoagulation for cardiopulmonary bypass

It is essential during CPB. The main anticoagulant is heparin. Its inhibits the coagulation system by binding to antithrombin III. Dose approximately is 3-4mg/kg of heparin prior to cannulation of CPB. Efficiency of heparin is performed in 3-5 minutes measuring active coagulation time (ACT). During cardiopulmonary bypass ACT must be maintained over 480 seconds. Because of individual patient respons to heparin and the effects of hemodilution and hypothermia on the ACT, anticoagulation can also be assessed by Medtronic Hepcon system. In few cases heparin resistance occure. It is present when heparine dose of 5 mg/kg fails to raise the ACT to an adequate level. More commonly it s noted in patients on preoperative heparin, IV nitroglycerin. It is usually related to antithrombin III deficiency.

Prevention of perioperative bleeding

Antifibrinolytic therapy have been demonstrated to reduce perioperative blood loss in cardiac operations. **Aprotinin**. It is serine protease inhibitor that has been demonstrated in numerous studies to be extremely effective in reducing perioperative bleeding and also in producing an antiinflammatory effect (32). In 2006 Mangano and coworkers (28) published an observational, multicenter, score adjusted study on 4,374 patiens. They demonstrated that patients receiving aprotinin had a double risk of acute renal failure, 55% increased risk of myocardial infarction and 181% increased risk of stroke. Aprotinin reduces bleeding but it is also a significant link to increased risk of morbidity and mortality. It has been stoped for using in many countries. But for example in Japan they continue to use it in cases of endocarditis because in this type of operations its efficiency is undisputable. Moreover the impact of patients morbidity and mortality using Aprotinin is still under discussion.

Tranexamic acid. During CPB releases plasmin and activates fibrinolysis. Tranexamic acid prevents plasmin formation and inhibits fibrinolysis**.** It has been shown to reduce perioperative blood loss in on-and off-pump surgery (3,6). Some studies have shown it to be as effective as aprotinin (7). Postoperative thrombotic

complications such as miocardal infarction, acute renal failure, stroke, pulmonary artery trombemboly where not founded when Tranexamic acid was administrated (26,27).

In several studies have shown topical use of tranexamic acid in the pericardial space to significantly reduce perioperative bleeding (1,2,12). Barica and coworkers (11) report of topical application of tranexamic acid in pericardial cavity. It was single-center prospective, randomized, double-blind trial, with 300 adult cardiac patients who were randomized into three groups. One group receive one million IU of Aprotinin, second group - 2.5 g of Tranexamic acid and third group - placebo topically before sternal closure. Bleeding rates values were significantly higher in placebo group. There were no found statistical differences between Tranexamic acid and Aprotinin groups. Also difference of blood product requirements was not statistically significant.

Autologus blood withdrawal – it has been shown to reduce allogen transfusion requirements and preserve red cells. However its efficacy in reducing perioperative bleeding is controversal (18).

Rewarming of patient till normothermia before the end of CPB. It could significantly improve coagulation function and prevent of postoperative bleeding.

Cardiopulmonary bypass consedirations

There are many factors for prevention of perioperative bleeding associated with cardiopulmonary bypass. One of that is using of heparin – coated circuit during bypass allows for a reduction in heparin dosing. It has been associated with reduced perioperative blood loss. Hematocrit level < 20% during CPB is a strong predictor of packed cell transfusions and higher mortality rate after surgery (22) however low intraoperative hematocrit levels dont predict excessive postoperative hemorrhage (13). In some studies retrograde autologus priming of the extracorporeal circuit has been shown to minimize hemodilution, thus maintaining a higher hematocrit and colloid oncotic pressure on pump (25).

Aviodance of cardiotomy suction also may reduce perioperative blood loss. Blood aspirated from the pericardial space has been in contact with tissue factor and contains high levels of factor VIIa, procoagulant particles and activated complement proteins and exhibits fibrinolytic activity. Blood aspirated from pericardial space consist very high concentration of inflalmmatory mediators, such as Il-6, however there were no data of Il-6 and TNF-alpha rising on patient's plazma after re-infusion.

It is unadvised to aspirante blood directly from pericardial space, it could be better to pump this blood via cell saver to wash it from activated components. Limitation of blood suction, reduces thrombin formation, platelet activation and sistemic inflammatory reaction.

Sirvinskas *et al.* (35) reports efficacy of collected and re-infused autologous shed mediastinal blood on a patient's in cardiac surgery. They concluded that re-infused shed mediastinal blood dont increase bleeding tendency and systemic inflammatory response. Conversely to this opinion there are also few studies reporting increased bleeding tendency after re-infusion of shed mediastinal blood.

Management of mediastinal bleeding in ICU

Excessive bleeding amount and time for re-operation in literature is defined variously. Excessive bleeding is defined as chest tube drainage greater that 3ml/kg/h in the first 3hours, continued bleeding of more that 200ml/h (10) or more that 200ml/h in the first 4 hours(19). Persistend bleeding must be treated immediately and agressively based on the suspected cause of hemorrhage. Management include:

1. Check of chest tube patency. Ongoing bleeding wihout drainage leads to tamponade.
2. Warm the patient to 37°C. Hypothermia produces a generalized suppression of the coagulation mechanism and also impairs platelet function.
3. Coagulation studies (PT, PTT, platelet count), ACT, also D-dimers, fibrinogen level, thromboelastography if necessary.
4. Maintenance of normothension and control agitation if the patient is awake and control shivering.
5. Increased level of positive and expiratory pressure (PEEP) to augment medistinal pressure has been shown to reduce bleeding.
6. Blood components should be based on suspection of the hemostatic defect, but transfuzion of allogeneic blood products is associated with many adverse affects. Patients needing surgical re-exploration have a significantly higher blood loss and need significantly higher amounts of fresh frozen plasma, packed red blood cells and platelet concentrates (31). **Fresh frozen plasm**a – contains all clotting factors except platelets. It is usefull if patient have hemodilution after CPB and there is progressive loss of coagulation factors during ongoing bleeding. Dose 10-15 ml/kg. **Cryoprecipitate** – it contains VIII and von Willebrand's factor and is also a source of fibrinogen (factor I) and XIII. It is usefull for patients with hypofibrinogenemia and von Willebrand's disease. **Platelets** – Should be given to the bleeding patient if the platelet count is less than 100,000/mkl. It is usefull when patient has platelet dysfunction after using of antiplatelet medications and IIb/IIIa inhibitors and following long duration of CPB. Platelet function is also impaired when hematocrit is less that 30%. **Packed red blood cells** – amount of packed red cell transfusion still is the main determinant of morbidity and mortality for patients requiring re-exploration due to bleeding. Hematocrit must be greater then 26-28% for patient who is bleeding to ensure tissue oxygen delivery. Dial and coworkers (13) found that strong predictor of packed red cell transfusion is severe intraoperative anemia (hematocrit < 19%). Blood transfusions more than 4 units increases risk of infections and operative mortality rate after on-pump surgery (15) and longer stay in ICU. Risk of development of infection is 3,9% in cases with 2 units whole blood transfused, 6,9% in cases with 3-5 units transfused and 22% in cases with 6 and more units of whole blood transfused.

Medical treatment in intensive care unit – include such kind of drugs: **Protamine**, should be given in a

dose 25-50 mg if the ACT is elevated. ACT should return in baseline after CPB but heparin rebound may occur in ICU and patient may start to bleed. ACT and rebound heparine can be assessed by Medtronic Hepcon system.
Desmopressine – Laupacis and coworkers (26) report that Desmopressine in dose 0,3mkg/kg i/v does not affect on bleeding rate and does not decrease rate of allogeneic transfusion rate as well, but it could be effective in patients who is taking Aspirin. Conversely to that in literature are few reports, that Demopressine should be given for patients who have tendency to bleed. It is usefull for patients with uremia and von Willebrand's disease as well. **Novoseven** – Recombinant Activated Factor VII. There are many studies approve its efficacy to decrease blood loos after on-pump cardiac surgery (21). But we should be also carefull with Novoseven because some of studies have been shown that Novoseven can increase risk of thrombosis. Therefore in cardiac surgery Novoseven could be recommended for patients with isolate VII factor deficiency. **Octoplex** – Prothrombin complex concentrate contains II, VII, IX, X factors and C and S proteins. It is efficacious and safe in immediate correction of dosage-dependent INR in patients who need rapid reversal of anticoagulant effect from the use of vitamin K antagonists (33). But we should be aware to use it on cardiac patients because Octoplex increases oncotic pressure and circulation volume and can produse heart failure.
Urgent re-exploration must be done when is presence of untapering mediastinal bleeding despite correction of coagulopathies, sudden massive bleeding, obvious signs of cardiac tamponade, cardiac arrest of a patient who continues to bleed urgent mediastinal reexploration must be done.
Re-exploration for bleeding is associated with increased operative mortality and morbidity. Ranucci and coworkers (31) demonstrated that patients who underwent a surgical reexploration had a higher moratlity rate 14,2% versus 3,4% who did not have re-exploration. The mean timing for surgical reexploration was 6,2 hours. Karthik and coworker (24) in 2004 published that patients needing re-exploration have a worse outcome in terms of morbidity but not a significantly higher mortality rate and the median time to reexploration was 8,5 hours.
Re-explorations very often is delay. Recently, Choong and coworkers (10) showed delaying surgical reexploration after 12 hours from the end of operation results in a longer stay in ICU, a higher need for intra-aortic balloon pump support, and increased mortality in a population of patients having undergone coronary revascularization. Conversely to this averment Ranucci and coworkers found that timing of the re-exploration was not associated with increased morbidity and mortality (31).

CONCLUSIONS

More aggresive management and early reexploration is one of the most important factor in cases of mediastinal bleeding. It may reduce the requirement for homologus transfusions, reduce the risk of respiratory and renal insufficiency and may also lower the wound infection rate associated with an undrained mediastinal hematoma (24,17). Eventually it may reduce rate of mortality.
Careful monitoring of mediastinal bleeding is essential in ICU in first 30 minutes, in each hour during first 4 hours as well as in 24 hours and 48 hours from the end of operation. Evaluation of coagulation studies and in some cases thromboelastography if necessary.
Cardiac off-pump surgery could be significant way how to decrease incidence of bleeding and re-exploration rate. Risk factors associated with CPB undergoing on-pump cardiac surgery should be minimized as possible. It is poosible to use smaller volumes for priming of the extracorporeal system and to use close system as well as circuit oxygenator lines that causes less heamatological trauma.
Cooperation, understanding and co-decision making between ICU staff, anaesthesiologists and surgeons is essential. Moreover, clinical protocol for mediastinal bleeding and re-exploration management in cardiac surgery must be formed.

Conflict of interest: None

REFERENCES

1. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis // Can J Anaesth, 2009; 56:202 – 12
2. Abul-Azm A, Abdullah KM. Effect of topical tranexamic acid in open heart surgery // Eur J Anaesthesiol, 2006; 23:380 – 4
3. Andreasen J, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary artery bypass surgery using cardiopulmonary bypass // Eur J Cardiothorac Surg, 2004; 26:311 - 7
4. Anthi A et al. Unexpected cardiac arrest after cardiac surgery: incidence, predisposing causes, and outcome of open chest cardiopulmonary resuscitation // Chest, 1998; 113:15 – 9
5. Balachandran S et al. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion after coronary artery surgery // Ann Thorac Surg, 2002; 73:1912 – 8
6. Casati V et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques // J Thorac Cardiovasc Surg, 2004; 128:83 – 91
7. Casati V et al. Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery // Ann Thorac Surg, 1999; 68:2252 - 6; discussion 2256 – 7
8. Chandler WL. Effects of hemodilution, blood loss, and consumption on hemostatic factor levels during cardiopulmonary bypass // J Cardiothorac Vasc Anesth, 2005; 19:459 – 67

9. Chen L et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting // J Thorac Cardiovasc Surg, 2004; 128:425 - 31
10. Choong CK et al. Delayed re-exploration for bleeding after coronary artery bypass surgery results in adverse outcomes // Eur J Cardiothorac Surg, 2007; 31:834 – 8
11. Barica D et al. Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective randomize study // Ann Thorac Surg, 2005; 27:592 – 598
12. De Bonis M et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study // J Thorac Cardiovasc Surg, 2000; 119:575 – 80
13. Dial S et al. Hemodilution and surgical hemostasis contribute significantly to transfusion requirements in patients undergoing coronary artery bypass // J Thorac Cardiovasc Surg, 2005; 130:654 - 61
14. Duggan E et al. Coagulopathy after cardiac surgery may be influenced by a functional plasminogen activator inhibitor polymorphism // Anesth Analg, 2007; 104:1343 – 7
15. Dunne JR et al. Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery // J Surg Res, 2002; 102:237 – 44
16. Ereth MH et al. Does the platelet-activated clotting test (HemoSTATUS) predict blood loss and platelet dysfunction associated with cardiopulmonary bypass // Anesth Analg, 1997; 85:259 - 64
17. Fiser SM et al. Cardiac reoperation in the intensive care unit // Ann Thorac Surg, 2001; 71(6):1888 - 92; discussion 1892 – 3
18. Flom-Halvorsen HI et al. Quality of intraoperative autologous blood withdrawal used for retransfusion after cardiopulmonary bypass // Ann Thorac Surg, 2003; 76:744 – 8; discussion 748
19. Hall TS et al. Re-exploration for hemorrhage following open heart surgery differentiation on the causes of bleeding and the impact on patient outcomes // Ann Thorac Cardiovasc Surg, 2001; 7:352 – 7
20. Hirose H, Takahashi A. Re-exploration for bleeding after coronary artery bypass grafting: what is the acceptable range of re-exploration rate // Ann Thorac Cardiovasc Surg, 2002; 8:248 - 9; author reply 249
21. Karkouti K et al. Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery // Circulation, 2008; 118: 331 – 8
22. Karkouti K et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery // Ann Thorac Surg, 2005; 80:1381 – 7
23. Karkouti K et al. Prediction of massive blood transfusion in cardiac surgery. Can J Anaesth, 2006; 53:781 – 94
24. Karthik S et al. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay // Ann Thorac Surg, 2004; 78:527 - 34; discussion 534
25. Kinduris S et al. Bleeding after cardiac surgery: risk factors, frequency, and outcomes // Medicina, 2006; 42:566 – 70
26. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators // Anesth Analg, 1997; 85:1258 – 67
27. Levi M et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints // Lancet, 1999; 354:1940 – 7
28. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery // N Engl J Med, 2006; 354:353 – 65
29. Pifarre R et al. Management of postoperative heparin rebound following cardiopulmonary bypass // J Thorac Cardiovasc Surg, 1981; 81:378 - 81
30. Purandare SV et al. Heparin rebound--a cause of bleeding following open heart surgery // J Postgrad Med, 1979; 25:70 – 4
31. Ranucci M et al. Surgical reexploration after cardiac operations: why a worse outcome // Ann Thorac Surg, 2008; 86:1557 – 62
32. Rich JB. The efficacy and safety of aprotinin use in cardiac surgery // Ann Thorac Surg, 1998; 66:S6 - 11; discussion S25 – 8
33. Riess HB et al. Prothrombin complex concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation // Thromb Res, 2007; 121: 9 – 16
34. Salis S et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery // J Cardiothorac Vasc Anesth, 2008; 22:814 – 22
35. Sirvinskas E et al. Influence of early re-infusion of autologous shed mediastinal blood on clinical outcome after cardiac surgery // Perfusion, 2007; 22:345 – 52
36. Wolfe R et al. Monitoring the rate of re-exploration for excessive bleeding after cardiac surgery in adults // Qual Saf Health Care, 2007; 16:192 - 6
37. Zabeeda D et al. Tranexamic acid reduces bleeding and the need for blood transfusion in primary myocardial revascularization // Ann Thorac Surg, 2002; 74:733 – 8

Address:
Agnese Ozolina
Pauls Stradins Clinical University Hospital,
Department of Anesthesiology and Cardiothoracic Surgery,
Pilsonu street 13, LV - 1002
Riga, Latvia
e-mail: Agnese_krauze@yahoo.com

Table 1. Major risk factors for bleeding requiring revision[a]

- Small body surface area
- Older patients
- Previous cardiac operations
- Previous cerebrovascular event
- Continuation of preoperative use of Aspirin, Clopidogrel and oral anticoagulants (Warfarin)
- Renal and/or hepatic insufficiency
- Prolonged cardiopulmonary bypass period
- Increased numbers of distal anastomoses and use of internal thoracic artery

[a] (10,13,31)

Table 2. Re-exploration rates

Author of study	**Re-exploration rate due to bleeding, reasons**
Choong, C.K., et al. Cambridge, United Kingdom[a]	Re-exploration rate – 5,9%
Hall, T.S., et al. Univeristy of California[b]	Re-exploration rate after coronary artery bypass grafting (CABG) – 3.6% • Surgical bleeding 66%: from the graft – 39% and from the chest wall – 34.5%. • Coagulopathic – 34%.
Hirose, H. and A. Takahashi Shin-Tokyo and Kobari General Hospital[c]	Re-exploration rate – 0.7% • Bleeding from the chest wall - 82.5%, bleeding, from the graft -17.6%
Karthik, S., et al. Liverpool, United Kingdom[d]	Re-exploration rate – 3,1%. • Graft anastomosis – 43%, sternal/left internal mammary artery – 26%, • Unspecified – 18%
Kinduris, S., et al. Kaunas University of Medicine, Lithuania[e]	Re-exploration rate – 4,3%
Ranucci, M., et al. Milan, Italy[f]	Re-exploration rate – 2,2%
Wolfe, R., et al. Monash University, Australia[g]	Re-exploration rate – 4,9%

[a] (10), [b] (19), [c] (20), [d (24), e (25), f (31), g (39)]

DOI: 10.2478/v10163-010-0018-1

ACTA CHIRURGICA LATVIENSIS • 2009 (9)

PROBLEM – SOLVING ARTICLE

The New Injury Severity Score: Availability in E valuation of Severity of Polytrauma Patients with Orthopaedic Injuries

Ruta Jakusonoka*, Andris Jumtins*, Zane Pavare**
*Department of Orthopaedic Surgery, Riga Stradins University/Centre of Disaster and Emergency Medicine, Riga, Latvia
**National Rehabilitation Centre Vaivari, Vaivari, Latvia

Summary
Significant number of patients with multiple injuries are registered every year in Latvia. In 2009 during seven months 298 patients with multiple trauma are registered. In the most of the cases cause of multiple injuries are road accidents (Health Statistics and Medical Technologies State Agency, Latvia).
Using of the simple modification of the Injury Severity Score (ISS) – the New Injury Severity Score (NISS) - makes possibility to better assess the patients with multiple injuries, particularly patients with orthopaedic injuries, predict resources for treatment, the outcome and functional results.
Key words: injury severity score; new injury severity score; polytrauma; damage control orthopaedics.

INTRODUCTION

Injury classification by type and severity is fundamental to the study of its magnitude, distribution and determinants. Since the late 1960s a number of scales assessing injury severity have been proposed. In 1971 by a joint committee comprising members of the American Medical Association, the Society of Automotive Engineers, the American Association for Automotive Medicine (now named Association for the Advancement of Automotive Medicine) the Abbreviated Injury Scale (AIS) was introduced. Now it is the most widely reported severity scale, used throughout in North America, Europe, Japan, Australia and New Zeland as a consensus derived anatomically based scale for rating the severity of injuries. The AIS was first published in 1976. Three revisions of the AIS have been published since than (1980, 1985, 1990) (19). The AIS is foundation for the ISS. Recently researchers proposed a simple modification of ISS – the NISS.
The overview provides insight in polytrauma definition based on Injury Severity Score and new concept of assessment of injury severity of polytrauma patients with orthopaedic injuries.

Definition of polytrauma

Severe trauma is one of the most frequent cause of death in people below 40. The successful management of polytrauma patients remains challenging despite of modern diagnostic and therapeutic approaches. Application of polytrauma concept to the multiply injured patient determines the treatment strategies and resources. The term „polytrauma" originates in the Greek words „poly" (multiple) and „trauma" (wounds) indicating a complex injury pattern of different anatomical regions. Many definitions of polytrauma have been described in literature. The modern definition of polytrauma as a syndrome of multiple injuries of defined severity (Injury Severity Score ≥16) with consecutive systemic reactions, wich may lead to disfunction of remote organs (definition according to Otmar Trentz), also comprises the complex host response to the injury (7).

The Injury Severity Score

The ISS was originally developed to predict survival after major trauma and has served as a standard summary measure of anatomic injury for more than 20 years. It is defined as the sum of the squares of the highest AIS code in each of the three most severely injured ISS body regions. The AIS was developed to be used by crash investigators to standardize data on the frequency and severity of motor vehicle related injuries. According to AIS each injury description has been assigned a seven digit numerical injury identifier. The single digit to the right of the decimal point is the AIS number according to the severity code ranging from 1 (minor injury) to 6 (maximum injury, possibly lethal). The six body regions of injuries used for ISS determination are: head or neck, face, chest, abdominal or pelvic contents, extremities or pelvic girdle, external injuries or burns. ISS scores range from 1-75. A score of 75 results in one of two ways: with three AIS 5 injuries or with at least one AIS 6 injury (2).

Table. Example of the ISS calculation of polytrauma patient with multiple orthopaedic injuries.

Table. Example of the ISS calculation of polytrauma patient with multiple orthopaedic injuries

ISS body region	Injury	AIS code	Highest AIS	AIS²
Head/neck	No injury	0		
Face	Skin abrasion	210202.1	1	1
Chest	Rib fractures 3-4, right side	450220.2	2	4
Abdomen/ pelvic contents	No injury	0		
Extremities/ pelvic girdle	Bilateral open fracture of femur Displaced fracture of left tibial shaft	851801.3 853405.3	3	9
External injuries/ burns	No injury	0		
ISS =14				

The ISS is a standard for trauma scoring and is based on patient mortality and outcome. The ISS is used for assessment of trauma patients, prediction survival probability, patient outcome evaluation, health care system research and to assess costs of trauma patients treatment.

The ISS makes possible a valid numerical description of the overall severity of injury in persons who have sustained injury to more than one area of body (3). Siegel JH et al. described using ISS for predicting of injury severity and death in blunt multiple trauma (18), Kluger Y et al. wrote about using ISS in assessment of injury severity in terrorist bombings (10).

Nevertheless ISS does not give very objective information of the amount of work and resources that the patient requires, if patient has serious multiple injuries in one of ISS anatomic regions. For example, ISS allows only one extremity injury to be considered. It means that patient with one long bone fracture could score the same as another with several such fractures and this underestimates the potential for functional difficulties in recovery. The example in table shows that patient who has many serious orthopaeadic injuries has ISS only 14 points. If the NISS is calculated the mentioned patient has 27 points (polytrauma). Thus the NISS avoids this shortcoming by including the most severe injuries, regardless of body region, and may allow more accurate prediction of functional outcome.

The New Injury Severity Score

The ISS has an idiosyncrasy that impairs its predictive power and complicates its calculation. Because of the mentioned problem a simple modification of the ISS called the NISS was presented. The NISS is defined as the sum of squares of the AIS severity scores of a casualty's three most severe injuries, regardless of body region in which they occur (13). Studies have reported that the NISS is more predictive of survival and performs better statistically than the ISS (5).

The NISS is a minor modification to the scoring of ISS and using both in parallel in monitoring trauma care can provide extra useful information for minimal extra effort. Lavoie et al. (2004, 2005) have found that the NISS is better choice in trauma research than ISS for predicting ICU admission, hospital lengh stay and of in-hospital mortality (11,12), Balogh Z et al. declared that NISS better predicted postinjury organ failure than ISS (4). Husum H et al. described that both the ISS and the NISS predicted short term mortality with accuracy for victims with penetrating trauma. According to their studies, the NISS predicted post injury complications significantly better than the ISS, but the accuracy of both tests was moderate and further studies are needed before the NISS should be adopted as a „golden standard" for severity scoring (9).

This enhanced trauma scoring may be useful in the assessment of trauma care delivery with the aim optimizing treatment of polytrauma patients with musculoskeletal trauma. The objective assessment of injury severity helps to choose the more appropriate method for management of polytrauma patients with long bone and unstable pelvic fractures. In recent time damage control orthopaedics (DCO) method has been accepted as a more appropriate tactic in the management of polytrauma patients with life threatening injuries and orthopaedic injuries. The approach of DCO takes the influence of postraumatic systemic inflammatory and metabolic reactions of the organism and is aimed at reducing both the primary and the secondary mortality in severaly injured patients. DCO appears to be an adequate alternative to early total care for patients at high risk of developing posttraumatic systemic complications such as acute respiratory distress syndrome, multiple organ failure (14,17) and systemic inflammatory response syndrome (SIRS). It provides the external fixation, which is effective, time saving and safe in patients with multiple injuries (8,15, 22).

Poole GV et al. studies show that although AIS and ISS appropriately reflect the impact of extraskeletal injuries, in patients with femur fractures they do not adequately reflect the increased morbidity associated with multiple lower extremity fractures. They suggest that AIS score counting for multiple long bone fractures of lower extremities may need to be upgrated (16).

A recent study by Sutherland et al. at the University of Aberdeen, Scotland, examined functional outcomes in a cohort of 200 patients with musculoskeletal trauma. This study showed that, while the differences were not large, the NISS provided better prediction of functional outcome than did ISS. Both scores are created from the same baseline information and use of both the traditional ISS and its modification, NISS, are recommended in studies assessing musculoskeletal trauma outcomes (20, 21).

Functional recovery after polytrauma is a long term process. Clinicians working in hospitals usually receive limited follow–up information about outcome such as functional results of musculoskeletal system, disability and quality of life (1, 6, 23).
The studies of the NISS using in predicting of functional results of polytrauma patients with orthopaedic injuries are supposed to help develop and improve the management of those patients.

CONCLUSIONS

Most of the studies show the usefulness of the NISS in assessment of injury severity, predicting resources and outcome of patients with multiple injuries. Particularly it refers to polytrauma patients with orthopaedic injuries. Use of both the ISS and its modification - NISS are recommended in studies for predicting and evaluation of functional results of those patients. Additional randomized studies are required in order to prove it convincingly.

Conflict of interest: None

REFERENCES

1. Anke AGW, Stanghelle JK, Finset A, Roaldsen KS, Pillgram-Larsen J, Fugl-Meyer AR. Long-term prevalence of impairments and disabilities after multiple trauma // J Trauma, 1997; 42:54 – 61
2. Association for the Advancement of Automotive Medicine. The Abbreviated injury scale.1990 Revision. Update 98 // Barrington, IL, USA; 2001; XVII–XIX
3. Baker SP, O'Neil B, Haddon W, et al. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care // J Trauma, 1974; 14: 187
4. Balogh Z, Offner PJ, Moore EE, Biffl W. NISS predicts postinjury organ failure better than the ISS // J Trauma, 2000; 48:624 – 627
5. Brenneman FD, Boulanger BR, McLellan BA, Redelmeier DA. Measuring Injury Severity: Time for a Change // The Journal of Trauma: Injury, Infection, and Critical Care, 1998; 44(4): 580 – 582
6. Butcher J, Laurence J, MacKenzie J, Cushing B, Jurkovich G, Morris J, Burgess A, McAndrew M. Long term outcomes after lower extremity trauma// J Trauma, 1996; 41:4–9.
7. Gebhard F, Huber-Lang M. Polytrauma - pathophysiology and management principles // Langenbecks Arch Surg, 2008; 393:825 – 831
8. Giannoudis PV, Pape HC. Damage control orthopaedics in unstable pelvic ring injuries // Injury, 2004; 35(7):671 – 677
9. Husum H, Strada G. Injury Severity Score vs. New Injury Severity Score for penetrating injuries // Prehosp Disast Med, 2002; 17(1):27 – 32
10. Kluger Y, Peleg K, Daniel-Aharonson L, Mayo A. The special injury pattern in terrorist bombings // Journal of the American College of Surgeons, 2004; 1996:875 – 879
11. Lavoie A, Moore L, LeSage N, Liberman M, Sampalis JS. The Injury Severity Score or the New Injury Severity Score for predicting intensive care unit admission and hospital length of stay? // Injury, 2005; 36(4):477 – 483
12. Lavoie A, Moore L, LeSage N, Liberman M, Sampalis J.S. The New Injury Severity Score: a more accurate predictor of in-hospital mortality than the Injury Severity Score // The Journal of Trauma, 2004; 56(6):1312 – 1320
13. Osler T, Baker SP, Long W. A modification of the Injury Severity Score that both improves accuracy and simplifies scoring // J Trauma, 1997; 43: 922 – 925
14. Pape HC, Hildebrand F, Pertschy S, et al. Changes in the management of femoral shaft fractures in polytrauma patients: from early total care to damage control orthopaedic surgery // J Trauma, 2002; 53:452 – 462
15. Philipson MR, Parker PJ. Damage control orthopaedics // J Trauma, 2007; 9(4):245 – 254
16. Poole GV, Tinsley M, Tsao AK, et al. Abbreviated Injury Scale does not reflect the added morbidity of multiple lower extremity fractures // J Trauma, 1996; 40:951 – 954
17. Stahel PF, Heyde CE, Ertel WW. Current concepts of polytrauma management // European Journal of Trauma, 2005; 31(3):200 – 211
18. Siegel JH, Rivkind A, Dalal S. Early physiologic predictors of injury severity and death in blunt multiple trauma // Arch Surg, 1990; 125:498 – 508
19. Stevenson M, Segui-Gomez M, Lescohier I, Scala C Di, McDonald-Smith G. An overview of the Injury Severity Score and the New Injury Severity Score // Injury Prevention, 2001; 7:10 – 13
20. Sutherland AG, Johnston AT, Hutchison JD. Giving musculoskeletal injuries more weight in assessing injury severity may better predict functional outcome // Value in Health, 2006; 9(1):24
21. Sutherland AG, Johnston AT, Hutchison JD. The New Injury Severity Score: better prediction of functional recovery after musculoskeletal injury // Value in Health, 2006; 9(1):24 – 27
22. Taeger G, Ruchholtz S, Waydhas C, Lewan U, Schmidt B, Nast-Kolb D. Damage control orthopaedics in patients with multiple injuries is effective, time saving and safe // J Trauma, 2005; 59(2):409 – 416
23. Zelle B, Lohse R, Hildebrand F, Krettek C, Panzica M, Duhme V, Sittaro NA. Evaluation and outcome of patients after polytrauma – can patients be recruited for long term follow up? // Injury, 2006; 37(12):1197 – 1203

Address:
Ruta Jakusonoka
Department of Orthopaedic Surgery
Riga Stradins University
12/22 Duntes Street,
Riga, Latvia, LV-1005
e-mail:ruta.jakusonoka@kmc.gov.lv

DOI: 10.2478/v10163-010-0019-0

PROBLEM – SOLVING ARTICLE

Biliary Cystic Tumours with Mesenchymal Stroma

Andrejs Vanags, Maris Pavars, Peteris Prieditis, Ilze Strumfa, Arvids Irmejs, Janis Gardovskis
Riga Stradins University, Riga, Latvia

Summary
Biliary cystadenoma and cystadenocarcinoma are rare cystic liver tumours arising from the bile ducts proximal to the hilum of the liver. The tumours have unique structure with ovarian-type mesenchymal stroma, leading to challenging considerations about their pathogenesis. The differential diagnosis is wide and further complicated by the lack of awareness about these neoplastic processes due to the rarity of the disease. Radical surgical treatment can be recommended whenever possible as it can result in prolonged survival.
Key words: biliary cystadenoma; biliary cystadenocarcinoma; mesenchymal stroma.

INTRODUCTION

Biliary cystadenocarcinoma (BCA) is an unusual cystic neoplasm of intrahepatic bile ducts. It is defined by cystic structure, composed of papillary epithelium with clear-cut signs of malignancy: cellular atypia, particularly nuclear polymorphism; mitotic activity and invasive growth. The benign counterpart of BCA is the biliary cystadenoma (BA), lacking the malignant features (4). The cystic biliary tumours (CBT) represent rare entities, with incidence of BCA approximately 1/10 million patients and of BA 1/20 000-1/100 000 (12).

CBT arise from bile ducts proximal to the hilum of the liver and share the cystic structure and presence of peculiar ovarian-type mesenchymal stroma with mucinous cystic tumours of the pancreas and retroperitoneum, leading to the hypothesis that ectopic ovarian stroma during embryogenesis can become incorporated along the biliary tree, in the pancreas and retroperitoneal space and cause the proliferation of the adjacent epithelium by production of hormones and growth factors (28). Origin from intrahepatic peribiliary glands (22), ectopic rests of primitive foregut sequestered in the liver (31) or pluripotential stem cells (3) has also been hypothesised. BCA without mesenchymal stroma more frequently arises in males and carries worse prognosis (22). There is evidence showing that at least some cases of BCA originate from BA. These data include the age difference between BCA and BA patients (18) as well as morphologic findings of malignant transformation in a lesion with focally innocuous structure (6).

BCA mostly develops intrahepatically (83%); however, origin from extrahepatic bile ducts (13%) or gall bladder (0.02%) is possible (18). BCA spreads within the liver as well as towards regional lymph nodes in the hepatoduodenal ligament. Distal metastases may develop in the lungs, the pleura or the peritoneum. TNM classification of liver tumours is applied for staging (4).

As was noted, the incidence of BCA is as low as one per 10 million patients (12). Due to the rarity of the disease, mostly case reports or small retrospective series are published, including 222 cases in the world medical literature, 1974-2008. Three (0.4%) cases of BCA were identified among 740 patients who underwent hepatic resection at the University Health Sciences Center of Colorado and the University of Pittsburgh Medical Center, 1964-1991 (14). In the same group, the frequency of BCA among the resected cystic lesions was 6.8% (3/44). BCA comprised 0.18% of all liver tumours registered by Japanese Liver Cancer Study Group (22). It has been estimated that 5-11% of patients with large liver cysts presenting for treatment or diagnosed in autopsy have BA (23), the benign counterpart of BCA and possible precursor of it. Other authors have cited that 5% of all hepatic cysts represent either benign or malignant CBT (17). However, such high frequency of CBT among all liver cysts would correspond to prevalence that is higher than of cholangiocarcinoma while even BA is rarer and BCA comprises 5.3-25% of both CBT (23). It has to be concluded that the early data are biased both by patient selection and also by diagnostic errors due to inferior material and methodology.

The average age of patients developing BCA is 50-60 years (4). The patients with benign CBT are younger than the patients with malignant CBT: mean age 40.6 (range 30-51) vs. 51.3 (range 41-63) years (18). Other authors have found that the mean age of BA patients is even 17 years less than for BCA (2, 25). CBT are more common in women: 80-100% of BA and 63-71.4% of BCA are described in female (18).

The most frequent clinical manifestation of CBT is the abdominal pain (23, 30), but abdominal distension, nausea (23), jaundice, cholangitis, tumour rupture, haemorrhage, compression of the portal or caval veins with possible subsequent ascites (30), hemobilia (14) and mucobilia (9) may occur. The most frequent physical finding is palpable abdominal mass (30); low location of lower liver margin can be found by percussion (31). The symptoms are non-specific and attributable to mass lesion as pain, tumour rupture (31), bleeding (11, 14), obstructive jaundice and ascites due to the compression of caval or hepatic vein (31) have been observed in the case of benign cystic lesions.

The development of CBT can last several years (2, 23). A case of biliary cystadenocarcinoma followed up as benign cystadenoma for 10 years has been described. The tumour still was resectable and the patient was free of any detectable recurrence for at least 4 years after the operation (13). Malignant transformation was observed in intrahepatic cystadenoma followed by serial biopsies (26). The long course is in accordance with the low grade of malignancy and gradual development of tumour through stages of increased epithelial proliferation, dysplasia, *in situ* cancer and, finally, invasive cancer. Thus, presence of cystic hepatic mass for several years does not exclude the possibility of malignant tumour and the need for careful follow-up if the cyst is not removed by operation.

Laboratory findings, including liver enzyme and bilirubin levels in blood, are abnormal if biliary tree is compressed (30). The serum carbohydrate antigen (CA19-9) and carcinoembryonic antigen (CEA) in BCA patients can be within the normal range (18); an abnormal level is not indicative of malignancy (31). Elevated levels of CEA and CA19-9 in the cyst fluid are reported in CBT but not in simple cysts (17).

The size of CBT varies from 1.5-30 cm (17) and is not helpful in the differential diagnostics between simple hepatic cyst and CBT as well as between BA and BCA. Grossly, BCA represents single multicystic lesion with internal mural nodules (fig. 1). Communication with the biliary tree has been reported by some and denied by other authors (18). Morphologically, BCA has cystic and papillary architecture (fig. 2). The cuboidal and non-ciliated columnar cells show atypia; invasion is the hallmark of malignant growth. The presence of mitoses is the third morphological diagnostic criterion of malignancy in a CBT (4). Oncocytic differentiation is described in at least 3 occasions (1). The BA is characterised by either mucinous or serous benign epithelium. The mesenchymal, ovarian–type stroma is present in benign and most malignant CBT.

Immunohistochemistry is of great importance in the differential diagnosis between primary and metastatic liver malignancies. There is lack of wide immunohistochemical studies of BCA; however, some case reports are available. Gradually increasing proliferative activity as characterised by Ki-67 as well as increasing p53 protein expression from adenoma to carcinoma was shown in BCA without ovarian-type stroma (7). Expression of cytokeratin (CK) 7 and absence of CK20, CEA, alpha-fetoprotein, calretinin, CD31 and chromogranin is described in biliary cystadenocarcinoma with oncocytic differentiation (1). However, presence of CK20, although highly typical for colorectal cancer, has been described also in cholangiocarcinoma, especially non-peripheral (20). It might be expected in BCA with growing awareness about this entity and, indeed, was reported by our group (24).

Although BCA is rare, liver cysts are frequent, being present in 2.5% of the population (16) or even 18% of asymptomatic patients (23). Because of the differences in the treatment, this differential diagnosis is of great importance. CA19-9 and CEA levels are not diagnostic for this purpose (18, 30). Fine needle aspiration or core biopsy is unlikely to yield sufficient tissue in case of simple cyst; it is also not suitable for the diagnostics of focal malignancy and rarely can lead to peritoneal carcinomatosis (15). Therefore radiological diagnostics, especially computed tomography (CT), is essential in the diagnostics (23). Transabdominal ultrasonography also is frequently used (23).

CBT characteristically are solitary large multilocular lesions (fig. 3). Presence of internal septations allows excluding a simple cyst. Vascularity of septa is characteristic for CBT (18) and is considered by some specialists to be more reliable in distinguishing BA from cyst than the simple presence of septations (23). Biliary cystadenoma is characterised by smooth and thin internal septa, but presence of enhanced mural nodules (18) in the outer wall or septa is the most important sign of malignancy. Calcification is not frequent but has been found specific for malignancy by some (18) but not all (16) authors as far as CBT are concerned. Size, number of septations or location of the neoplasm does not help to differentiate between benign or malignant CBT (18). Some authors have postulated that preoperative differentiation between BA and BCA by CT or magnetic resonance imaging (MRI) is not possible therefore liver resection should be performed for all CBT (17). This assumption is based on the experience that internal papillae with arterial enhancement may be present in both tumours so that CT and MRI yield overlapping data. Cholangiography is strongly advised by some specialists in order to detect communication between the cystic tumour and bile ducts (17, 23). However, contrary opinions are reported based on the finding that the communication with bile ducts can be appropriately treated during operation (23) without intraoperative cholangiography. However, cholangiography is described as the most accurate method for the diagnosis of extrahepatic biliary cystadenomas (2).

Cystic liver lesions, entering the differential diagnosis of BCA, include developmental, neoplastic, inflammatory and traumatic lesions as simple bile duct cyst, polycystic liver disease, biliary hamartoma, cystically degenerated cases of other primary or metastatic liver tumours, abscesses, hydatid cyst, extrapancreatic pseudocyst, hematoma and biloma (10, 16). The short characteristics of these lesions are following. Simple cysts are asymptomatic, solitary or multiple, possessing thin wall. They appear in the CT and MRI as non-enhancing, well circumscribed homogeneous lesions, filled with fluid. Multiple hepatic cysts can be the manifestation of autosomal dominant polycystic liver disease. In these patients, complications as intracystic haemorrhage are more common and can be evaluated by MRI. Bile duct hamartomas typically are multiple, measure less than 1.5 cm and are less smoothly contoured than simple cysts. The autosomal recessive Caroli disease represents the congenital cavernous ectasia of the biliary ducts, frequently complicated by stone formation. Communication with the biliary tract is diagnostically

important as well as the "central dot" sign by CT and bridges across the saccular dilatations by MRI. Both the aforementioned features result from the presence of portal vein branches within remaining connective tissue strands surrounded by dilated bile ducts. Embryonal sarcoma, rare and usually solid malignant tumour of adolescence, could seem cystic on CT and MRI due to myxoid stroma. The age and mostly solid appearance help to distinguish this tumour from BCT. Metastases can undergo cystic degeneration due to either necrosis or mucus secretion. Necrotic metastases by CT and MRI are revealed as multiple lesions with strong enhancement of peripheral viable tissue but irregular border. Mucinous metastases mostly are caused by disseminated colorectal or ovarian cancer; the latter can be recognised as mostly peripheral nodules due to transperitoneal implantation metastases in the capsule rather than intraparenchymal hematogenous spread (16). The multilayered wall and presence of multiple small hypoattenuating daughter cysts with thin eggshell calcifications allow recognising echinococcosis; if doubt exists, serologic assay must be applied (17, 19). Abscesses characteristically develop in the setting of sepsis or ascending cholangitis. Presence of air points towards gas-forming microbe. Acute abscess represents a cluster of small lesions that later converges into unilocular cystic lesion. Thick-walled lesion with enhancing wall develops and the "double target" sign can be observed due to increased peripheral rim enhancement secondary to increased capillary permeability. However, invasive malignancy can cause the same reaction (16). Presence of mobile debris at ultrasonography is characteristic of abscess (17). Biloma at CT and MRI appears as a well-defined cystic structure without septa, calcifications or pseudocapsule; history of trauma or operation also is helpful in order to suspect biloma or hematoma (16). In difficult cases, the diagnosis is made by histology (21).

To achieve long term cure, the ultimate goal of the surgical treatment of CBT is to remove all the neoplastic tissue. Treatment of CBT by marsupialization, internal Roux-en-Y drainage, aspiration, sclerosing or partial resection has high rate of complications – tumour recurrence and progression or sepsis. On the contrary, complete removal of the tumour can lead to prolonged survival (14, 29). However, there are different opinions towards the extent of operation in order to ensure radicality.

Definite operative intervention for CBT as tried in the Vanderbilt University School of Medicine on 2005, has included hepatic resection in 12/19 patients and enucleation in 6/19 patients. No perioperative deaths have occurred among these patients. Complications were limited to 1 biloma and 2 intraabdominal abscesses treated by percutaneous drainage; biliary leak treated by stenting, as well as non-surgical complications like atrial fibrillation, acute lung injury and pleural effusion. Fenestration and fulguration has been used in 2 patients with large cystic liver lesions. In one of these cases, laparoscopic fenestration and fulguration has been used as the main treatment. A satellite lesion adjacent to resected larger BCA mass also was fulgurated and the patient was free of disease 2142 days after operation (23). In the whole group of radically treated patients no recurrences have been observed after mean follow-up of 3.5 years with standard deviation 4.2 years (23).

Data confirming the safety of hepatic resection in specialized institutions are not confined to recent progress. For instance, results in patients operated between 1964 and 1991 are described (14). The relevant medical team has performed 44 hepatic resections for cystic liver lesions of different nature, having 1 operative death in a Jehovah's Witness and 9 major complications with complete recovery in all but 2 cases due to progression and spread of malignant tumour. The complications included 3 subphrenic abscesses, subarachnoid haemorrhage and 2 re-explorations for bleeding and pulmonary embolism. Authors suggested that resection due to its safety and efficacy is even better than aspiration, sclerotherapy, internal drainage, marsupialisation and fenestration for congenital hepatic cyst. The fact that none of the CBT was diagnosed correctly before the curative operation adds justification to recommend more aggressive surgical treatment for cystic liver lesion (14). Other groups have suggested that preoperative diagnosis of CBT can be reached in 95% although many patients have had wrong prior diagnosis and even operative treatment that was insufficient due to erroneous diagnosis and thus lead to recurrence (23). High level of awareness is a necessity in order to diagnose CBT.

In summary, enucleation or radical excision can be recommended for BA, but lobectomy or radical resection is recommended for BCA (18). In multiseptated cyst without definite preoperative diagnosis, the rate of malignancy is as high as 25-45%, therefore enucleation or complete resection is indicated (23).

Systemic chemotherapy including 5FU has been reported effective in a single patient with recurrence of BCA 41 month after surgery (8). Hepatic arterial infusion of cisplatin has been effective in another patient, decreasing tumour size from 12 to 2 cm in diameter (5).

If BA has been completely removed, the prognosis is excellent; otherwise malignant change may occur (26). The prognosis of BCA is significantly better than for other primary malignant liver tumours. Prolonged survival can be expected (14), even 156 months after radical surgery (29).

CONCLUSIONS

1. Increased awareness of biliary cystadenocarcinoma and cystadenoma could be helpful in recognising these rare primary intrahepatic tumours.
2. Due to the differences in the treatment and prognosis of different cystic liver lesions, as well as to lower informativity of other diagnostic methods, the radiological examination, especially CT, is important in the preoperative diagnostics. Presence of internal vascularised septa is characteristic for cystic biliary tumours but presence of mural nodules or calcifications should cause suspicion of malignancy.

3. The final diagnosis depends on histological findings. In a cystic liver tumour featuring ovarian-type stroma, the presence of nuclear atypia and mitoses in tumour cells and invasive growth proves biliary cystadenocarcinoma. Immunohistochemistry should be used to distinguish between metastasis and primary origin of the tumour from biliary epithelium. Staging by pTNM of liver tumours should be applied. Biliary cystadenoma is characterised by cystic structure, mesenchymal stroma and benign epithelium.
4. To achieve long term cure, the ultimate goal of the surgical treatment of biliary cystic neoplasms is to remove all the neoplastic tissue.
5. Appropriate surgical treatment of biliary cystadenocarcinoma may ensure prolonged survival.
6. The workup of cystic biliary tumour thus can be summarised as radiologic diagnostics including CT but possibly not limited by it; surgery and final pathological diagnosis. It represents a manageable challenge for modern medical team.

Conflict of interest: None

REFERENCES

1. Bardin RL, Trupiano JK, Howerton RM, Geisinger KR. Oncocytic biliary cystadenocarcinoma: a case report and review of the literature // Arch Pathol Lab Med, 2004; 128(2):25 – 28
2. Davies W, Chow M, Nagorney D. Extrahepatic biliary cystadenomas and cystadenocarcinoma // Ann Surg, 1995; 222(5):619 – 625
3. D'Errico A, Deleonardi G, Fiorentino M, Scoazek JY, Grigioni WF. Diagnostic implications of albumin messenger RNA detection and cytokeratin pattern in benign hepatic lesions and biliary cystadenocarcinoma // Diagn Mol Pathol, 1998; 76:289 – 294
4. Hamilton SR, Aaltonen LA (eds.) Pathology and genetics. Tumours of the digestive system. Lyon: IARC Press; 2000; 1-314
5. Hanazaki K, Yoshizawa K, Mori H. Hepatic arterial infusion chemotherapy of cisplatin for biliary cystadenocarcinoma // Hepatogastroenterology, 1999; 46(25):462 – 464
6. Ishak KG, Willis GW, Cummins SD, Bullock AA. Biliary cystadenoma and cystadenocarcinoma: report of 14 cases and review of the literature // Cancer, 1977; 38:322 – 338
7. Ishibashi Y, Ojima H, Hiraoka N, Sano T, Kosuge T, Kanai Y. Invasive biliary cystic tumour without ovarian-like stroma // Pathol Int, 2007; 57(12): 794 – 798
8. Iyama S, Takahashi Y, Shintani N, Fujikawa K, Ohkubo S, Sato Y, Sato T, Sato Y, Ohnuma K, Niitsu Y. [A case of recurrent biliary cystadenocarcinoma successfully treated with 5FU/CDDP systemic chemotherapy] // Nippon Shokakibyo Gakkai Zasshi, 2006; 103(10):1163 – 1168. [Pubmed abstract PMID 17023760]
9. Jan YY, Chen MF, Chen TJ. [Cholangiocarcinoma with mucobilia] // J Formos Med Assoc, 1994; 93, Suppl 3: S149 – 155. [Pubmed abstract PMID7606173]
10. Karahan OI, Kahriman G, Soyuer I, Ok E. Hepatic von Meyenburg complex simulating biliary cystadenocarcinoma // Clin Imaging, 2007; 31(1): 50 – 53
11. Kitajima Y, Okayama Y, Hirai M, Hayashi K, Imai H, Okamoto T, Aoki S, Akita S, Gotoh K, Ohara H, Nomura T, Joh T, Yokoyama Y, Itoh M. Intracystic hemorhage of a simple liver cyst mimicking a biliary cystadenocarcinoma. J Gastroenterol, 2003; 38(2):190 – 193
12. Koffron A, Rao S, Ferrario M, Abecassis M. Intrahepatic biliary cystadenoma: role of cyst fluid analysis and surgical management in the laparoscopic era // Surgery, 2004; 136:926 – 936
13. Kubota E, Katsumi K, Iida M, Kishimoto A, Ban Y, Nakata K, Takahashi N, Kobayashi K, Andoh K, Takamatsu S, Joh T. Biliary cystadenocarcinoma, followed up as benign cystadenoma for 10 years // J Gastroenterol, 2003; 38(3):278 – 282
14. Madariaga JR, Iwatsuki S, Starzi TE, Todo S, Selby R, Zetti G. Hepatic resection for cystic lesions of the liver // Ann Surg, 1993; 218(5):610 – 614
15. Manouras A., Markogiannis H, Lagoudianakis E, Katergiannakis V. Biliary cystadenoma with mesenchymal stroma: report of the case and review of the literature // World J Gastroenterol, 2006; 12(37):6062 – 6069
16. Mortele KJ, Ros PR. Cystic focal liver lesions in the adult: differential CT and MR imaging features // RadioGraphics 2001; 21:895 – 910
17. Poggio P, Buonocore M. Cystic tumours of the liver: A practical approach // World J Gastroenterol, 2008; 14(23):3616 – 3620
18. Pojchamarnwiputh S, Na Chiangmai W, Chotirosniramit A, Lertprasertsuke N. Computed tomography of biliary cystadenoma and biliary cystadenocarcinoma // Singapore Med J, 2008; 49(5):392 – 396
19. Proietti S, Abdelmoumene A, Genevay M, Denys A. Ecchinococcal Cyst // RadioGraphics, 2004; 24: 861 – 865
20. Rullier A, Le Bail B, Fawaz R, Blanc JF, Saric J, Bioulac-Sage P. Cytokeratin 7 and 20 expression in cholangiocarcinomas varies along the biliary tree but still differs from that in colorectal carcinoma metastasis // Am J Surg Pathol, 2000; 24(6): 870 – 876
21. Shrikhande S, Kleef J, Adyanthaya K, Zimmermann A, Shrikhande V. Management of hepatobiliary cystadenocarcinoma // Dig Surg, 2003; 20:60 – 63
22. Sudo Y, Harada K, Tsuneyama K, Katayanagi K, Zen Y, Nakanuma Y. Oncocytic biliary cystadenocarcinoma is a form of intraductal papillary neoplasm of the liver // Mod Pathol, 2001; 14(12):1304 – 1309
23. Thomas KT, Welch D, Trueblood A, Sulur P, Wise P, Gorden L, Chari RS, Wright JK, Washington

K, Pinson CW. Effective treatment of biliary cystadenoma // Ann Surg, 2005; 241:769 – 775
24. Vanags A, Pavars M, Prieditis P, Strumfa I, Irmejs A, Gardovskis J. Biliary cystadenocarcinoma: a case study of a rare tumour // Acta Chirurgica Latviensis, 2008; 8:90–93.
25. Wheeler DA, Edmondson HA. Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts // Cancer, 1985; 56(6):1434 – 1435
26. Woods G. Biliary cystadenoma: case report of hepatic malignancy originating in benign cystadenoma // Cancer, 1981; 47:2936 – 2940
27. Yu FC, Chen JH, Yang KC, Wu CC, Chou YY. Hepatobiliary cystadenoma: a report of two cases // J Gastrointestin Liver Dis, 2008:17(2):203 – 206
28. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini, Sessa F, Capella C, Solcia E, Rickaert F, Mariuzzi GM, Klopel G. Mucinous cystic tumors of the pancreas: clinicopathologic features, prognosis, and relationship to other mucinous cystic tumors // Am J Surg Pathol, 1999; 23:410 – 422
29. Zen Y, Fujii T, Itatsu K, Nakamura K, Konishi F, Masuda S, Mitsui T, Asada Y, Miura S, Miyayama S, Uehara T, Katsuyama T, Ohta T, Minato H, Nakanuma Y. Biliary cystic tumors with bile duct communication: a cystic variant of intraductal papillary neoplasm of the bile duct // Mod Pathol, 2006; 19:1243 – 1254
30. Zhang M, Yu J, Yan S, Zheng SS. Cystadenocarcinoma of the liver: a case report // Hepatobiliary Pancreat Dis Int, 2005; 4(3):464 – 467
31. Zhou JP, Dong M, Zhang Y, Kong FM, Guo KJ, Tian YL. Giant mucinous biliary cystadenoma: a case report // Hepatobiliary Pancreat Dis Int, 2007; 6(1):101 – 103

Address:
Andrejs Vanags,
Hereditary Cancer Institute,
Riga Stradins University,
Dzirciema Street 16, LV 1007,
Riga, Latvia
e-mail: vanags314@inbox.lv

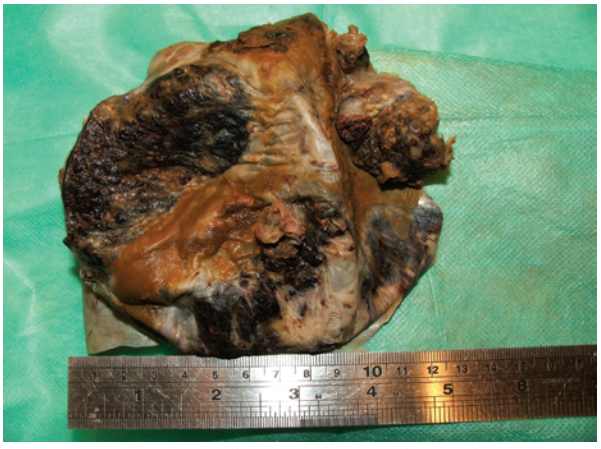


Fig. 1. Gross view of the inner surface of biliary cystadenocarcinoma in the formalin-fixed operation material. Note the marked, irregular nodularity

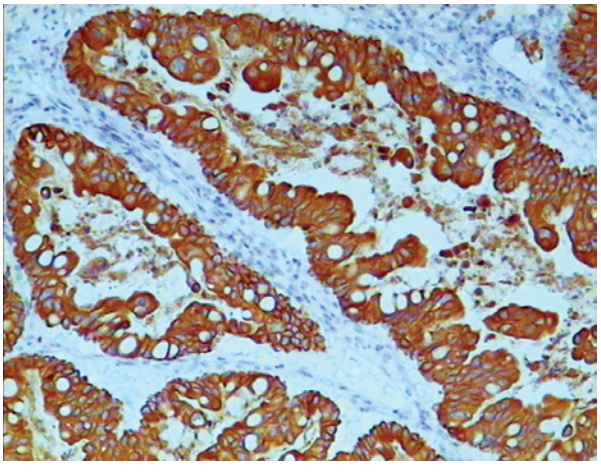


Fig. 2. Cystic and papillary architecture of biliary cystadenocarcinoma. Immunoperoxidase, anti-cytokeratin 7, original magnification 100x

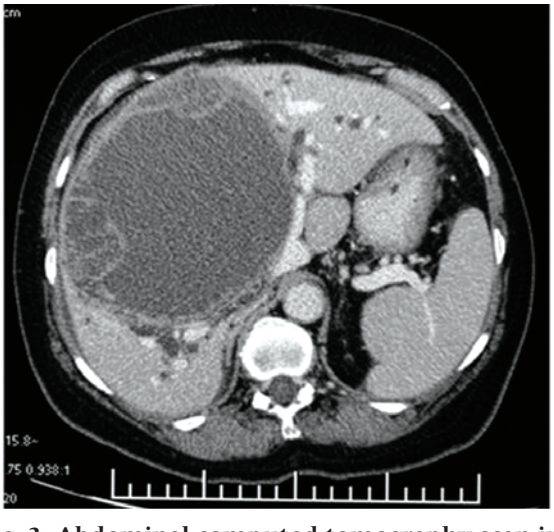


Fig. 3. Abdominal computed tomography scan in case of biliary cystadenocarcinoma

DOI: 10.2478/v10163-010-0020-7

ACTA CHIRURGICA LATVIENSIS • 2009 (9)

PROBLEM – SOLVING ARTICLE

Local Anaesthetics: What Can We Expect More than Pain Relief?

Iveta Golubovska*, Peteris Studers and Indulis Vanags*****
*Hospital of Traumatology and Orthopaedics, Riga, Latvia
**Riga Stradins Univesity, Research Laboratory of Traumatology and Orthopaedics, Latvia
***Riga Stradins University, Department of Anaesthesiology and Reanimatology, Latvia

Summary
This problem – solving article considers positive and negative non-analgesic actions of local anaesthetics, which may play a significant role in patient morbidity and mortality. Direct impact on inflammatory and immune substances and cells leads to antibacterial, anti-inflammatory, immunomodulating and systemic functions of numerous local anaesthetics. Local anaesthetics used perioperatively locally in continuous infusions or in systemic circulation reach and maintain safe and effective rates, but myotoxic and tissue growth inhibiting effect should be taken in account.
Key words: anti-inflammatory, immune response, local anaesthetics, systemic analgesia.
Abbreviations: CNS – central nervous system, BP – bupivacaine, hPMNs – human polymorphonuclear neutrophils, LA – local anaesthetics, LD – lidocaine, LP – lysophosphatide, LPA – lysophosphatidic acid, MP – mepivacaine, NK – natural killer cells, NSAID – non-steroidal anti-inflammatory drug, PG E2 – prostaglandin E2, RP – ropivacaine.

INTRODUCTION

Local anaesthetics (LA) are used widely in anaesthesiology and pain therapy–not only for acute pain, such as during surgery, but also for the management of postoperative and chronic pain. In patients with different (epidural, spinal, wound, plexus, nerve) catheter placement, regional anaesthetics provide a sufficient analgesic effect.

LA are used to facilitate analgesia through their inhibition of sensory nerve conduction. As sodium channel blockers, LA inhibit the propagation of action potentials along nerve axons participating in the transmission of pain signals through the peripheral and central nervous systems. Aside from sodium channel inhibition, it is now becoming clear that LA have actions on other important cellular components.

LA have antibacterial actions and beneficial effects on inflammatory responses such as inflammatory lung injury, increased microvascular permeability, and myocardial ischemia/reperfusion. Smaller concentrations of LA that is currently used may maintain anti-inflammatory effect with decreased risk of toxicity.

There is growing body of evidence that LA have immunological properties in addition to their direct anaesthetic activity, what could be very important in host defence reactions, and regional anaesthesia probably may stop metastatic dissemination after tumour surgery.

Antibacterial properties

Since the introduction of cocaine in 1884, LA have been used as a mainstay of pain relief. However, numerous studies over the past several decades have elucidated the supplemental role of LA as antimicrobial agents. In addition to their anaesthetic properties, medications such as bupivacaine (BP) and lidocaine (LD) have been shown to exhibit bacteriostatic, bactericidal, fungistatic, and fungicidal properties against a wide spectrum of microorganisms. We may found in the literature several studies with different LA used in different concentrations used for established pathogens.

Antimicrobial activity of BP against 10 microbial strains was studied. The strains tested were Escherichia Coli, Pseudomonas Aeruginosa, Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus Pneumoniae etc. It was found that BP at concentration of 0.25 % inhibited growth of the sensitive S. Epidermidis, S. Pyogenes, and S. pneumoniae and all the others at the concentration of 0.5 % (26).

It was investigated the antimicrobial effects of different concentrations of RP, BP, LD and prilocaine on Escherichia Coli, Staphylococcus Aureus, Pseudomonas Aeruginosa and Candida Albicans. Ropivacaine (RP) did not inhibit any of the microorganisms tested. BP reduced the viable cells of P. Aeruginosa at 0.5 % and 0.25 % solutions. LD 5 % and 2 % and prilocaine 2 % dilutions reduced the viable cells of all microorganisms tested (2).

It was hypothesized that LA have time-dependent effects on phagocytosis of S. Aureus, oxidative burst, and CD11b expression by human neutrophils (25). Host defence mechanisms are affected and the ability to eliminate bacteria might be reduced. LD and BP inhibited neutrophil functions in a time-dependent manner. Results indicate that in a whole blood model, time-dependent effects of local anaesthetics affect key neutrophil functions necessary for bacterial elimination. But these effects only occur at concentrations that are unlikely to be routinely attained in the clinical setting.

Review under antimicrobial properties of a LA (19) was conducted using MEDLINE. Studies testing the effect on microbial growth inhibition of LA alone and

in combination with other agents, such as preservatives and other medications, as well as the effect of conditions such as concentration and temperature, were included for review. Outcome measures included colony counts, area under the curve and time kill curve calculations, minimum inhibitory concentrations, and post-antibiotic effect. Multiple LA at the concentrations typically used in the clinical setting (e.g., BP 0.125%-0.75%; LD 1%-3%) inhibit the growth of numerous bacteria and fungi under various conditions. Different LA showed various degrees of antimicrobial capacity; BP and LD, for example, inhibit growth to a significantly greater extent than does RP. Greater concentrations, longer exposure, and higher temperature each correlate with a proportional increase in microbial growth inhibition.

Therefore LA may be weighted as adjunctive to traditional antimicrobial therapy. And also we should take in account a positive message of a relative safety of epidural, plexus and wound catheters.

Antiinflammatory properties

LA modulate inflammatory responses and may therefore be potentially useful in attenuating perioperative inflammatory injury (13). Clinically relevant concentrations of LA inhibit several actions of the phospholipid mediator lysophosphatidic acid (LPA) on human polymorphonuclear neutrophils (hPMNs). The selective inhibition of LPA-induced priming (15) is probably important, because the priming process is a critical component of hPMN mediated tissue injury both *in vitro* and *in vivo*. RP is a relatively new, long acting aminoamide local anaesthetic that is structurally similar to BP and has relatively low CNS and cardiotoxicity compared to BP. RP inhibits platelet-activating factor-induced priming of hPMNs (14). Local wound infiltration of RP results in a longer duration of action compared to BP, because of direct vasoconstrictive effect (29). The vasoconstrictive properties of RP are not unique, other amide local anaesthetic as LD, has similar properties. It is described that vasoactivity of RP could be reduced by using inhibitors of lipoxygenase and phospholipase A^2 (6).

Irrigation of a wounds or synovia with small concentrations of a LA maintains good anti-inflammatory effect due to preventing of neurogenic plasma extravasation (24). BP in clinically relevant concentrations inhibits of prostaglandin (PG) E2 receptor functioning in cultured cells (17). BP affects the membrane receptor itself and also the intracellular pathway. The effect is most likely due to modulation of G protein or phospholipase C function.

Accumulating data suggest however that LA posses a wide range of anti-inflammatory actions through their effects on cells of the immune system, as well as on other cells, e.g. microorganisms, thrombocytes and erythrocytes. The potent anti-inflammatory properties of LA, superior in several aspects to traditional anti-inflammatory agents of the NSAID and steroid groups and with fewer side-effects, would encourage clinicians to introduce them in the treatment of various inflammation-related conditions and diseases. They have proved successful in the treatment of burn injuries, interstitial cystitis, ulcerative proctitis, and arthritis and herpes simplex infections (5, 8).

Immunomodulating properties

Studies demonstrated that LA, such as mepivacaine (MP), BP, and LD, induce innate immune system dysfunction, as indicated by reduced chemotactic ability, phagocytic ability, and superoxide anion production by neutrophils. Furthermore, LA also impair the activity of natural killer **(**NK) cells. There have been several studies about the effects of LA on immune function. BP and LD have modulatory effects and depress neutrofil chemotaxis and phagocytosis (27). Mitogen induced lymphocyte proliferation is also inhibited (28). Lymphocytes are capable of killing of a variety infectious or tumour derived target cells *in vitro.* Cell responsible for this activity are called NK cells. They are arrived from conventional T cells, B cells and macrophages. LA like LD and procaine affect the function of plasma membrane of human NK cell function (30). Impaired cytolysis by LA may be partially explained by the inhibition of binding of NK cells to target cells.

The concentrations of LA in human plasma reach 2.2 μg/mL (lidocaine), 2.53 μg/mL (mepivacaine), and 0.73 μg/mL (bupivacaine) after their epidural administration. In this study, the concentrations of LD, MP, and BP that suppressed monocyte HLA-DR expression were 1, 1, and 0.25 μg/mL, respectively. These results suggest that LA suppress monocyte HLA-DR expression at clinically relevant concentrations. This suppressive effect might be stronger after local injection of these anaesthetics, because the local concentration might be larger than that in plasma. Careful attention must be paid to the effects of LA on the host-defense mechanisms in the clinical setting (21).

LD with epinephrine and prilocaine with felypressin were effective in significantly inhibiting adhesion, chemotaxis, phagocytosis, and the production of hydrogen peroxide by neutrophils and macrophages. Interestingly, LD with epinephrine potentiated the production of superoxide anion, whereas prilocaine with felypressine inhibited the production, irrespective of cells (3).

Antimetastatic properties

Experimental and clinical studies have shown that surgical trauma and stress affects the immune system including both the innate and adaptive immune responses. The break of immune homeostasis might enhance tumour growth and spread.

Investigations support idea that the using of intramuscular gene-gun therapy modified with BP can induce long-term antitumor immunity, and can provide the great advantage of inhibiting the disseminated tumour (1). Intramuscular administration of LA increases cell membrane permeability and enhance the expression of foreign genes in the muscles. Optimal interval after BP injection is 4 days after BP treatment into skeletal muscle. The other anaesthetic agents: LD and MP also enhance gene expression, but BP causes high membrane permeability. Innervation, blood supply and connective tissue are fully recovered after 7 days post BP treatment.

Retrospective analysis suggests that paravertebral anaesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up (9). There is ongoing research in Taiwan comparing local anaesthesia with general anaesthesia for breast cancer surgery and endometrial cancer surgery. Impaired cellular immunity after general anaesthesia has significant undesirable effects on tumour surveillance after breast surgery. The local block technique might avoid the surgery inducing neuroendocrine, metabolic, and cytokine responses, which will offer some advantages from better preservation of early postoperative cellular immune function and attenuate disturbance in the inflammatory mediators. Research focuses on the effects of regional anaesthesia on mediators that may be important in inflammatory response, tumour cell dissemination, deposition, and propagation in the early postoperative period.

Systemic analgesic properties

LA traditionally are administered for analgesia via epidural catheter, subcutaneous infiltration and regional nerve block procedures, but they have many potentially beneficial actions, especially when used as a continuous intravenous infusion. The use of intravenous LA infusions for postoperative pain control dates back to the 1940s when intravenous procaine was reported to provide analgesia for burns, abdominal surgery, and mastectomy. It was used in Stradins University Hospital during thoracic, abdominal and urological surgery. The use of parenteral LD for postoperative pain first was reported in 1961 by Bartlett (4).

Review briefly describes the anti-inflammatory properties of LA and discusses the benefits seen when used systemically for neuroprotection, postoperative ileus, decompression sickness, and glaucoma (31). There are only few studies dealing with systemic injection of LA. Therefore it is difficult to make a difference between the direct systemic effects of LA and the effects of epidural anaesthesia. There is a potential for an improved outcome after surgical procedures that is associated with significant perioperative stress reduction when LA are used. May be patients with contraindications to regional anaesthesia should receive LA intravenously for the surgical procedure. There is growing evidence that some patients would benefit from systemically administered LA (10).

LA infused intravenously to yield plasma concentrations far below those that block normal action potentials, yet that are frequently effective at reversing neuropathic pain. Thus, LA modify a variety of neuronal membrane channels and receptors, leading to what is probably a synergistic mixture of analgesic mechanisms to achieve effective clinical analgesia (32).

Group of Herroeder injected an intravenous LD bolus 1.5 mg/kg and followed by infusion 2 mg/min. Gastrointestinal motility, pain scores and length of hospital stay were studied. Results were very promising: perioperative intravenous LD not only improved gastrointestinal motility but also shortened length of hospital stay significantly. Anti-inflammatory activity modulating the surgery-induced stress response may be one potential mechanism. Systemic LD may thus provide an additional approach to improve outcome for patients not suitable for centroaxial anaesthesia (11, 12, and 16). Acute rehabilitation after laparoscopic colectomy using intravenous LD gives similar outcomes to those reported using epidural analgesia (20).

LD infusions given to patients undergoing total hip arthroplasty in a manner similar to infusions given in visceral studies produced no opioid-sparing, significant difference in pain ratings, tactile pain thresholds, or maximal degree of active hip-flexion, which raises questions about the effectiveness of LD infusions for somatic pain (22).

Many clinicians may hesitate to use intravenous LD, fearing adverse cardiac and neurologic effects. LD is contraindicated in patients with cardiovascular instability, those concomitantly using α-agonists or ß-blockers, and in patients with allergies to other amide LA (BP) (10). Perioperative intravenous administration of LD is an old technique that consistently has been shown to contribute to analgesia without respiratory depression, significant nausea, and other side effects common with opioid analgesics. A closer examination to determine an optimal regimen after visceral operations and its potential for use in other postoperative pain states is warranted.

But employing all positive properties of LA, we should take in account their general toxicity in large doses, and recently mentioned myotoxicity and effect on wound healing after local administration.

Myotoxicity of local anaesthetics

Clinically relevant skeletal muscle toxicity is probably a rare and rather unknown side effect of LA drugs. Nevertheless, skeletal muscle damage has to be considered a potentially serious complication of local and regional anaesthesia. Intramuscular injections of LA regularly result in striated muscle damage and myonecrosis, with a drug-specific and dose-dependent rate of toxicity (33). Subcellular pathomechanisms of LA myotoxicity are still not completely revealed. However, excessively increased intracellular Ca levels have been shown to have the key role in myocyte injury. Studying BP and RP both LA induced morphologically identical patterns of calcific myonecrosis, formation of scar tissue, and a marked rate of fiber regeneration. However, BP effects were constantly more pronounced than those of RP.

Active oxidative metabolism is a key determinant in BP toxicity, that BP myotoxicity is a relevant model of mitochondrial dysfunction involving the permeability transition pore and Ca dysregulation (18).

Wound healing impairing

LD and BP impair wound healing, but the mechanism of this side effect has not clearly understood. The phospholipid messenger lysophosphatide is released from activated platelets and induces fibroblast and smooth muscle proliferation. Lysophosphatide signalling was inhibited in the presence of LA and it may play a role in wound healing (23).

From other papers LA can adversely affect cell growth *in vitro*. Their effects on wound healing are controversial. Low concentrations of LD, as would be seen in plasma after spinal, epidural, or plexus anesthesia, do not significantly affect multiplication of fibroblasts. Higher doses of LD arrest cell multiplication at the S-phase of the growth cycle by an extremely potent inhibitor of cell multiplication. Higher concentrations, as would be seen after tissue infiltration, severely inhibit fibroblast multiplication and thus may impair wound healing (7).

CONCLUSIONS

New LA should offer, in addition to a potential decrease in cardiac toxicity and improved separation of motor and sensory blockade, further benefits because of its inflammatory and immune modulating action, as compared with racemic BP and other appropriate local anaesthetics. Further research should address the question of how much inflammatory or immune modulation is necessary to prevent inflammatory response with lack of the sodium channel-blocking property.

We stand up for extensive use of LA in abdominal surgery, oncologic surgery and taking an advantage from their systemic qualities avoiding local toxic effects.

Conflict of interest: None

REFERENCES

1. Ajiki T, Murakami T, Kobayashi Y, Hakamata Y, Wang J, Inoue S, Ohtsuki M, Nakagawa H, Kariya Y, Hoshino Y, Kobayashi E. Long-lasting gene expression by particle-mediated intramuscular transfection modified with bupivacaine: combinatorial gene therapy with IL-12 and IL-18 cDNA against rat sarcoma at a distant site // Cancer Gene Ther, 2003; 10:318 – 329
2. Aydin ON, Evigor M, Aydin M. Antimicrobial activity of ropivacaine and other local anaesthetics // Eur J Anaesth, 2001; 18:687 – 694
3. Azuma Y, Ohura K. Immunological modulation by lidocaine-epinephrine and prilocaine-felypressin on the functions related to natural immunity in neutrophils and macrophages // Curr Drug Targ Imm Endocr Metabol Disord, 2004; 4:29 – 36
4. Bartlett EE, Hutaserani O. Xylocaine for the relief of postoperative pain // Anesth Analg, 1961; 40: 296 – 304
5. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anaesthetics and their present and potential clinical implications // Acta Anaesth Scand, 2006; 50:265 – 282
6. Daisy TJ, Gail KW. Drug interactions: lipoxygenase inhibitors interfere with ropivacaine induced vasoconstriction // Can J Anesth, 2009; 56: 279 –283
7. Desai D, Kojima K, Vacanti CA, Kodama S. Lidocaine inhibits NIH-3T3 cell multiplication by increasing the expression of cyclin-dependent kinase inhibitor 1A (p21) // Anesth Analg, 2008; 107:1592 – 1597
8. Doran C, Ji X. The anti-inflammatory effect of local anaesthetics // The Pain Llinic, 2007; 19(5): 207 – 213
9. Exadaktylos AK, Buggy DJ, Moriarty, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? // Anesthesiology, 2006; 105(4):660 – 664
10. Gordon D, Schroeder M. Intravenous lidocaine for postoperative analgesia: renewed interest in an old strategy // APS Bulletin, 2008; 18(3)
11. Groudine SB, Fisher HAG, Kaufman RP. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy // Anesth Analg, 1998; 86:235 – 239
12. Herroeder S, Pecher S, Schönherr ME, Kaulitz G, Hahnenkamp K, Friess J, Böttiger BD, Bauer H, Dijkgraaf MGW, Durieux ME, Hollmann MW. Systemic Lidocaine shortens length of hospital stay after colorectal surgery // Ann Surg, 2007; 246(2):192 – 200
13. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response // Anesthesiology, 2000; 93:858 – 75
14. Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils // Anesthesiology, 2001; 95: 113 – 22
15. Hollmann MW, Kurz K, Herroeder S, Struemper D, Hahnenkamp K, Berkelmans N, den Bakker CG, Durieux ME. The Effects of S-, R-, and Racemic Bupivacaine on Lysophosphatidate-Induced Priming of Human Neutrophils // Anesth Analg, 2003; 97:1053 – 1058
16. Hollmann MW, Strumper D, Durieux ME. The poor man's epidural: systemic local anesthetics for improving postoperative outcomes // Med Hypotheses, 2004; 63:386 – 389
17. Honnemann CV, Heyse TJ, Mollhoff T, Hahnenkamp K, Berning S, Hinder F, Linck B, Schmitz W, van Aken, H. The inhibitory effect of bupivacaine on prostaglandin E (2) (EP (1)) receptor functionig: mechanism of action // Anesth Analg, 2001; 93: 628 – 634
18. Irwin W, Fontaine E, Agnolucci L, Penzo D, Betto R, Bortolotto S, Reggiani C, Salviati J, Bernardi P. Bupivacaine myotoxicity is mediated by mitochondria // J Biol Chem, 2002; 2779(14): 12221 – 12227
19. Johnson SM, Sain John BE, Dine AP. Local anaesthetics as antimicrobials agents: a review // Surg Infect (Larchmt), 2008; 9(2):205 – 213
20. Kaba A, Detroz BJ, Laurent SR. Acute rehabilitation program after laparoscopic colectomy using intravenous lidocaine // Acta Chir Belg, 2005; 105:53 – 58
21. Kawasaki T, Kawasaki C, Ogata M, Shimegatsu O. The effect of local anesthetics on monocyte mCD14 and human leukocyte antigen-DR expression // Anesth Analg, 2004; 98: 1024 – 1029
22. Martin F, Cherif K, Gentilli ME. Lack of impact of intravenous lidocaine on analgesia, functional

recovery, and nociceptive pain threshold after total hip arthroplasty // Anesth, 2008; 109:118 – 123
23. Nietgen GW, Chan CK, Durieux ME. Inhibition of Lysophosphatidate Signaling by Lidocaine and Bupivacaine // Anesthesiology, 1997; 86 (5): 1112–1119
24. Pietruck C, Grond S, Xie GX, Palmer P. Local anaethetics differentialy inhibit sympathetic Neuron mediated and C fiber mediated synovial plasma extravasation // Anesth Analg, 2003; 96: 1397 – 1402
25. Ploppa A, Kiefer RT, Krueger WA, Unertl KE, Durieux ME. Local anesthetics time-dependently inhibit Staphylococcus aureus phagocytosis, oxidative burst and CD11b expression by human Neutrophils // Reg Anesth Pain Med, 2008; 33(4):297–303
26. Rosenberg PH, Renkonen OV. Antimicrobial activity of bupivacaine and morphine // Anesthesiology, 1985; 62:178 – 179
27. Ramus GV, Cezano L, Barbalonga A. Different concentrations of local anaesthetics have different modes of action on human lymphocytes // Agents Actions, 1983; 13:333 - 341
28. Sinclair R, Ericcson AS, Greizer G. Inhibitory effects of amide local anaesthetics on stimulus-induced human leucocyte metabolic activation, LTB4 release and Il-1 secretion in vitro // Acta Anaest Scand, 1993; 37:159 – 165
29. Sung HJ, Sohn JT, Hwang EM. Direct effect of ropivacaine involves lipoxygenase pathway activation in rat aortic smooth muscle // Can J Anest, 2009; 56:4
30. Takagi S, Kitagawa S, Oshimi K, Takaku F, Miura Y. Effect of local anaesthetics on human natural cell activity // Clin Exp Immunol, 1983; 53:477 - 481
31. Wright JL, Durieux ME, Groves DS. A brief review of innovative uses for local anesthetics // Cur Op Anaesth, 2008; 21(5):651 – 656
32. Yanagidate F, Strichart GR. Analgesia // In: Handbook of experimental Pharmacology. Volume 177, Springer Berlin Heidelberg, 2007; 95–127
33. Zink W, Bohl JRE, Hacke N, Sinner B, Martin E, Graf B. The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blocks // Anesth Analg, 2005; 101:548 – 554

Address:
Iveta Golubovska
Hospital of Traumatology and Orthopaedics,
Duntes str. 12, Riga, LV1005, Latvia
Email: ivetagolubovska@gmail.com

DOI: 10.2478/v10163-010-0021-6

CASE REPORT

Intragastric Migration of Swedish Adjustible Gastric Band

Andrejs Vanags*,, Ilze Strumfa*,**, Maris Pavars*, Janis Gardovskis*,****
*Pauls Stradins Clinical University Hospital, Riga, Latvia
**Riga Stradins University, Latvia

Summary
Swedish adjustable gastric banding (SAGB) is an operative procedure meant for the treatment of morbid obesity. It is characterised by application of low-pressure, high-volume device upon the stomach. One of the major complications, currently described in 6% of patients, is the intragastric migration of the adjustable gastric band. The removal of the band is the gold standard in these cases and must be performed either urgently or as a scheduled manipulation according to the symptoms. We present a thoroughly documented case of surgical obesity treatment by SAGB complicated by intragastric band migration as well as our experience in settling the complication.
Key words: morbid obesity, bariatric surgery, Swedish adjustable gastric banding, migration.

AIM OF THE DEMONSTRATION

Here, we present a well-documented case of intragastric Swedish adjustable gastric band migration along with imaging studies and data of surgery in order to add our experience to the published evidence in the bariatric surgery.

CASE REPORT

Forty five-years-old female sought medical help because of morbid obesity. She weighted 124 kg and had body mass index (BMI) greater than 45 kg/m^2. As informed patient consent was received, she was included in the protocol for gastric band placement. The protocol consisted of the obesity evaluation, patient education in order to understand the medical condition and achieve weight loss of at least 10% and operative treatment after successful accomplishment of the prerequisites. The operative procedure was performed by laparoscopic approach in P. Stradin's Clinical University Hospital. During the following 8 months patient's weight reduced for about 50 kg and BMI decreased to 29 kg/m^2. However, the entire adjustable silicone gastric band device eroded inside the stomach. The complication was initially diagnosed by contrast X-ray surveillance 9 months after the operation. Tight feeling in the epigastrium and sense of fullness gradually appeared over the next 2 weeks. Gastroscopy was performed then and revealed granulation tissues in the dorsal wall of gastric subcardia and a silicone canule that had passed through the stomach wall and reached the prepyloric part of the stomach (figures 1-2). Patient was prepared for laparoscopic removal of the adjustable gastric band under endoscopic control on the next day. Due to the large size of the silicone gastric band exceeding the size of oesophageal lumen and thus precluding the endoscopic evacuation of the device, the attempt to remove the adjustable gastric band by endoscopic assistance was unsuccessful. Therefore an approximately 3 cm long incision in the gastric wall was done during the laparoscopy. The gastric band was removed then by endopouch assistance. The incision in the gastric wall and the fault were closed by separate sutures laparoscopically. There were no intraoperative and postoperative complications. The patients' general condition was good and she was discharged on 7th postoperative day in a good physical and mental condition. The laboratory investigation demonstrated no abnormalities.

Later, due to successful weight loss, a cosmetic abdominal wall defect manifested as a skin fold. Therefore an abdominal plastic operation was performed two months after the band removal. Simultaneously with the plastics, the patient benefited from herniorrhaphy in order to treat a concomitant postoperative hernia after the extirpation of uterus and adnexes performed due to uterine myoma one year prior to bariatric surgery. She was discharged in the 4th postoperative day in a good condition.

At present, 19 SAGB have been performed in P. Stradin's Clinical University Hospital, all of them by laparoscopic approach. We have had 2 major complications, but only one of them was associated with the band migration as described.

DISCUSSION

The Lap-Band system was first described in 1992 and clinically proved in 1994 in USA. Within the 15 years, laparoscopic adjustable banding was found an effective and safe treatment tool for morbid obesity (Forsell *et al.*, 1999; Chevallier *et al.*, 2004). More than 100.000 laparoscopic procedures have been performed since that (Blanco-Engert *et al.*, 2003). Nowadays laparoscopic adjustable gastric banding is the most frequently applied bariatric procedure in Europe (Weiss *et al.*, 2000). The advantages of laparoscopic gastric banding in contrast

to the gastric bypass or vertical banded gastroplasty consist in the reversibility of the laparoscopic procedure, minimal damage to the stomach and adjustable degree of restriction in every separate case (Langer *et al.*, 2004). Successful weight reduction depends more on the patient in contrast to the bypass malabsorptive procedure (Zehetner *et al.*, 2004). Short-term outcome of the SAGB, characterised by BMI dynamics, seems to be beneficial (Wong *et al.*, 2005). Experiences in other countries showed that SAGB can only restrict solid food, but is less effective if the patient use liquids or semi-solid food with high glucose content (Zehetner *et al.*, 2004). In our patient, SAGB ensured the weight loss. Thus, in our experience, SAGB is an effective method in bariatric surgery.

The reported rate of complications is low (Fried *et al.*, 2004; Zehetner *et al.*, 2004). One of the described complications is the gastric band migration through the gastric wall (Chevallier *et al.*, 2004). Other major complications like port-associated complications, oesophageal dilatation, and band slippage as well as pouch enlargement were observed in long-term studies (Stroh *et al.*, 2008). The band migration through the stomach wall happens mostly during the following two years after procedure (Weiss *et al.*, 2000, Langer *et al.*, 2004) at the rate 0.5% - 9% (Forsell *et al.*, 1999; Mittermair *et al.*, 2002; Nocca *et al.*, 2005). Several hypotheses have been proposed as band overfilling, rapid band filling and local infection caused by gastric wall trauma by the implanted band (Weiss *et al.*, 2000, Weiss *et al.*, 2004). Band migration usually is diagnosed by endoscopy or by contrast roentgenogram (Hainaux *et al.,* 2005).

Although our group of patients is still small, the rate of migration 1/19 (5.3%; 95% confidence interval 0.9 – 24.6%) is within the reported range. Routinely we perform follow-up by contrast roentgenogram as the migration can be asymptomatic. This approach is substantiated by published data and proved effective in the presented case.

Partial migration can be treated conservatively (Zehetner *et al.*, 2004) while the total migration should be treated operatively. Migration almost never requires urgent surgery (Mittermair *et al.*, 2002). Usually band removal is performed by laparoscopic approach, but there is another alternative published method of managing the band migration (Weiss *et al.*, 2000; Regusci *et al.*, 2003) as endoscopic band removal after cutting the band by the appropriate devise like scissor, laser etc.

Although complications may occur after bariatric surgery, adequate knowledge can help to plan the follow-up and to choose the best treatment options. Gastric band migration is a rare complication but it can be successfully managed.

In conclusion, intragastric Swedish adjustable band migration is one of the possible complications with rate of 5.3% in our cohort. However, long-term observation of the expanding group of patients may add new evidence. The laparoscopic approach can be used for bariatric surgery and for management of such complications as band migration if these occur. It allows early mobilisation, short hospital stay, early return to work and low risk of wound complications. Occurrence of the complications as described above generates necessity for individual follow-up as well as for the long-term evaluation of complication rate and the efficacy of SAGB.

Conflict of interest: None

REFERENCES

1. Blanco-Engert R, Weiner S, Pomhoff I, Matkowitz R, Weiner RA. Outcome after laparoscopic adjustable gastric banding, using the Lap-Band® and the Heliogast® band: a prospective randomised study // Obesity Surgery, 2003; 13:1 – 4
2. Chevallier JM, Zinzindohoue F, Douard R, Blanche JP, Berta JL, Altman JJ, Cugnenc PH. Complications after laparoscopic adjustable gastric banding for morbid obesity: experience with 1.000 patients over 7 years // Obesity Surgery, 2004; 14:407 – 414
3. Forsell P, Hallerback B, Glise H, Hellers G. Complications following Swedish adjustable gastric banding: a long-term follow-up // Obesity Surgery, 1999; 9:11 – 16
4. Fried M, Miller K, Kormanova K. Literature review of comparative studies of complications with Swedish band and Lap-Band® // Obesity Surgery, 2004; 14:256 – 260
5. Hainaux B, Agneessens E, Rubesova E, Muls V, Gaudissart Q, Moschopoulos C, Cadiere GB. Intragastric band erosion after laparoscopic adjustable gastric banding for morbid obesity: imaging characteristics of an underreported complication // ARJ, 2005; 184:109 – 112
6. Langer FB, Bohdjalian A, Hoda A, Silberhumer G, Felberbauer FX, Rasoul-Rockenschaub S, Zacherl J, Wenzl E, Prager G. Early results of laparoscopic adjustable gastric banding using the new low-pressure soft gastric band // Eur Surg, 2004; 36: 345 – 349
7. Mittermair RP, Weiss H, Nehoda H, Aigner F. Uncommon intragastric migration of the Swedish adjustable gastric band // Obesity Surgery, 2002; 12:372 – 375
8. Nocca D, Frering V, Gallix B, de Seguin, des Hons C, Noel P, Pierredon M. A, Millat B, Fabre JM. Migration of adjustable banding from a cohort study of 4.236 patients // Surg Endosc, 2005; 19:947 - 950
9. Regusci L, Groebli Y, Meyer JL, Walder J, Margalith D, Schneider R. Gastroscopic removal of an adjustable gastric band after partial intragastric migration // Obesity Surgery, 2003; 13:281 – 284
10. Stroh C, Hohmann U, Will U, Flade-Kuthe R, Herbig B, Höhne S, Köhler, Pick P, Horbach T, Weiner R, Wolff S, Lippert H, Wolf AM, Schmidt U, Meyer F, Manger T Experiences of two centers of bariatric surgery in the treatment of intragastral band migration after gastric banding – the importance of the German multicenter observational study

for quality assurance in obesity surgery // Int J Colorectal Dis, 2008, 23:901 – 908
11. Weiss H, Nehoda H, Labeck B, Peer R, Aigner F. Gastroscopic band removal after intragastric migration of adjustable gastric band: a new minimal invasive technique // Obesity Surgery, 2000; 10: 167 – 170
12. Wong SKH, So WY, Yau PYP, Chan AKL, Lee S, Chan PN, Chow FCC, Chung SSC. Laparoscopic adjustable gastric banding for the treatment of morbidity obese patients: early outcome in a Chinese cohort // Hong Kong Med J, 2005; 11:20 – 29
13. Zehetner J, Holzinger F, Triaca H, Klaiber Ch. A 6-year experience with the Swedish adjustable gastric band // Surg Endosc, 2005; 19:21 – 28

Address:
Andrejs Vanags,
Hereditary Cancer Institute,
Riga Stradins University,
Dzirciema Street 16, LV 1007,
Riga, Latvia,
e-mail: vanags314@inbox.lv

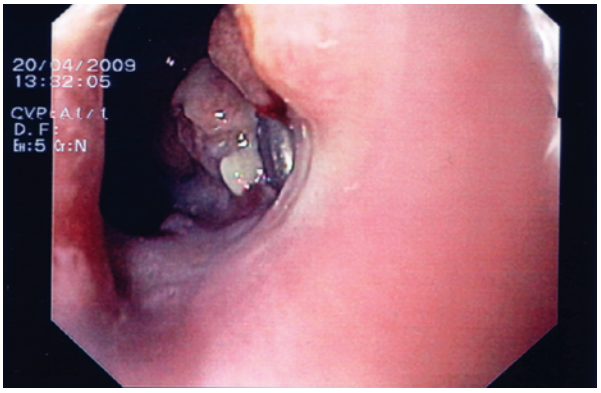


Fig. 1. Adjustable gastric band in the gastric wall

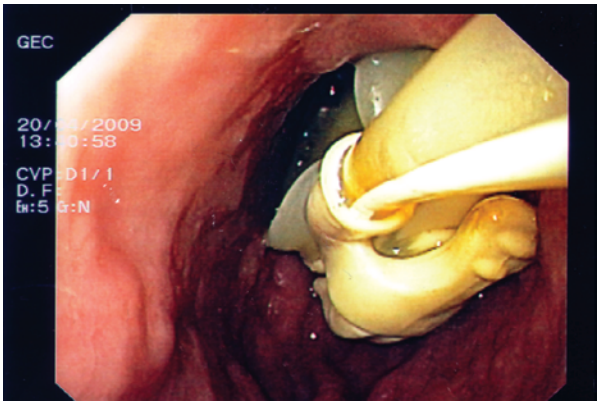


Fig. 2. Silicone adjustable band totally migrated through the stomach wall

DOI: 10.2478/v10163-011-0022-0

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

CASE REPORT

Malignant Peripheral Nerve Sheath Tumour of the Breast in Complex Clinical Background

Arnis Abolins*/, Andrejs Vanags*/**, Guna Volanska*/**, Inga Melbarde–Gorkusa*/**, Ilze Strumfa*, Genadijs Trofimovics*/**, Janis Gardovskis*/****

* Hereditary Cancer Institute, Riga Stradins University, Riga, Latvia

** Pauls Stradins Clinical University Hospital, Riga, Latvia

Summary

Here we describe a patient presenting with combination of three rare diseases, namely de novo malignant peripheral nerve sheath tumour of the breast, small cell variant of medullary thyroid carcinoma and multiple sclerosis. Although the combination by chance seems unlikely, the detailed history does not correspond to any of the known hereditary cancer syndromes and hypothetically may represent a new entity.

Key words: malignant peripheral nerve sheath, tumour, breast.

AIM OF THE DEMONSTRATION

Breast cancer is the most common cancer among women in European Union (5). The vast majority of breast malignancies are carcinomas, but non–epithelial malignancies may also involve the breast.

The aim of the case report is to demonstrate very rare oncological situation involving *de novo* malignant peripheral nerve sheath tumour (MPNST) of the breast associated with medullary thyroid cancer in the setting of multiple sclerosis.

CASE REPORT

A 46–year–old female, suffering from multiple sclerosis, was consulted in the Pauls Stradins Clinical University Hospital because of large breast tumour that has increased slowly during 5 years. The family history was unremarkable. By objective examination, firm tumour, measuring 15 cm, was palpable in the centre of the breast and 6 cm large, firm mass was palpable in right axilla. During extensive clinical evaluation, core biopsy was performed. It revealed solid, anaplastic tumour composed of giant spindle and polygonal cells with dark nuclei. By immunohistochemistry (IHC), the tumour cells intensively expressed S–100 protein and vimentin, but lacked melanosome protein HMB–45, pan–cytokeratin AE1/AE3 (CK), desmin as well as estrogen and progesterone receptors. Considering the immunophenotype and cellular atypia, malignant peripheral nerve sheath tumour of the breast was diagnosed. There were no subcutaneous nodules, *cafe au lait* spots, Lisch nodules or history of neurofibromas. Clinically, thyroid mass was also discovered during the diagnostic work–up. The thyroid core biopsy yielded overtly malignant tissue with different structure, composed of atypical small cells. By IHC, these cells expressed CK. Proliferation fraction by Ki–67 (clone MIB–1) was 87% of the tumour cells. The diagnosis of high–grade thyroid carcinoma was made. Total thyroidectomy was performed as recommended by oncological council. Grossly paradoxically circumscribed high–grade carcinoma, measuring 9x7x5.7cm and showing angioinvasion and capsule penetration, was found in the right side of the thyroid. The tumour showed small cell morphology as well as intense expression of CK and synaptophysin, focal expression of chromogranin A, nuclear p53 expression and high proliferation fraction (84%) by IHC (Figure 1). No evidence of multifocality was found. Metastases were present in cervical lymph nodes (2/4). The findings were consistent with medullary thyroid carcinoma, small cell variant, pT3N1M0. Right mastectomy with axillary lymph node dissection was performed 10 days after thyroidectomy. Grossly, 11x7x8 cm firm node was found in the breast, and 9.5x4x6cm – in axillary tissues. The tissue structure (Figure 2) was consistent with anaplastic sarcoma. By IHC, intense cytoplasmic and nuclear S–100 expression, nuclear p53 expression as well as low proliferation fraction (5%) was found. No metastases were found in 26 axillary lymph nodes. The diagnosis of breast MPNST, pT2aN1M0G1 was issued. The postoperative time was uneventful. The patient was discharged on the third postoperative day for out–patient radiation therapy. Nine months after the mastectomy, increased left cervical lymph nodes were found and removed. Metastases of thyroid carcinoma were detected. One month later the patient died of disseminated thyroid cancer.

DISCUSSION

Malignant peripheral nerve sheath tumour (MPNST), previously designated neurofibrosarcoma, is a rare tumour with an incidence of 1 per 100,000. It constitutes 5–10% of soft tissue sarcomas. Approximately half of these tumours in adults arise sporadically *de novo*. The other half occurs in patients suffering from neurofibromatosis, type I (NF1). The mean age at the

time of MPNST diagnosis is 37 years, but the patients with NF1 are 10 years younger. MPNST originates from a major or minor peripheral nerve sheath. The most common MPNST locations are the trunk (51%), the extremities (45%) and the head and neck in 4% of patients (1). Less than 10 *de novo* cases in breast are described (7).

The correct preoperative diagnosis of MPNST depends on biopsy in order to confirm the malignancy and to identify the histogenesis. The microscopic picture can be suggestive of MPNST but is not absolutely diagnostic. The IHC can be diagnostic or can exclude other malignant tumours (6).

The treatment of MPNST is complete surgical removal. There are no reports in the literature on the role of radiotherapy or chemotherapy for the treatment of MPNST of breast (7) but radiotherapy is recommended for high–grade tumours with negative histological resection margins and for intermediate–grade tumours with close or positive histological resection margins. Chemotherapy is recommended as treatment of metastatic disease and it may be helpful in preoperative settings to decrease unresectable primary tumours (4).

The patient had high–grade thyroid cancer consistent with the small cell variant of medullary carcinoma. However, there was no evidence of any multiple endocrine neoplasia (MEN) syndrome embarrassing both the final diagnosis and the etiologic considerations. The patient had combination of three rare diseases: multiple sclerosis (the incidence in the world 1.1–4/100 000) (2), primary MPNST of the breast (less than 10 cases described) and medullary carcinoma (0.03–0.5/100 000) (3). The association by chance only would be highly unlikely. However, the detailed history provides no evidence of the most likely syndromes like NF1, or MEN, or any familial cancer syndrome. Therefore we share our evidence with colleagues to demonstrate a possible new oncological syndrome.

Conflict of interest: None

REFERENCES

1. Anghileri M, Miceli R, Fiore M, Mariani L, Ferrari A, Mussi C, Lozza L, Collini P, Olmi P, Casali PG, Pilotti S, Gronchi A. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution // Cancer, 2006; 107: 1065 – 1074
2. Anonymous. Atlas multiple sclerosis resources in the world 2008. Geneva: WHO Press; 2008; 14
3. Chan JKC. Tumors of the thyroid and parathyroid glands // In: Fletcher CDM. Diagnostic Histopathology of Tumors. 3rd ed. Philadelphia: Churchill Livingstone Elsevier; 2007; 997 – 1097
4. Elsaify WM, Elsaify MM, Melek RK. De novo malignant peripheral nerve sheath tumor of the breast: case report number one // European Surgery, 2007; 39: 192 – 195
5. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006 // Annals of Oncology, 2007; 18: 581 – 592
6. Rosai J. Soft tissues // In: Rosai J. Rosai and Ackerman's Surgical Pathology. 9th ed. Edinburgh: Mosby; 2004. p. 2237 – 2371
7. Yi JM, Moon EJ, Oh SJ, Lee A, Suh YJ, Baek JM, Choi SH, Jung SS. Malignant peripheral nerve sheath tumor of the breast in a patient without neurofibromatosis: a case report // Journal of Breast Cancer, 2009; 12: 223 – 226

Acknowledgements
This work was supported by ESF project Nr. 2009/0230/1DP/1.1.1.2.0/09/APIA/VIAA/070.
A.V. was supported by ESF fellowship, project Nr. 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009.

Address:
Arnis Abolins
Hereditary Cancer Institute,
Riga Stradins University,
Dzirciema Street 16, LV-1007,
Riga, Latvia
E-mail: arnis.abolinsh@inbox.lv

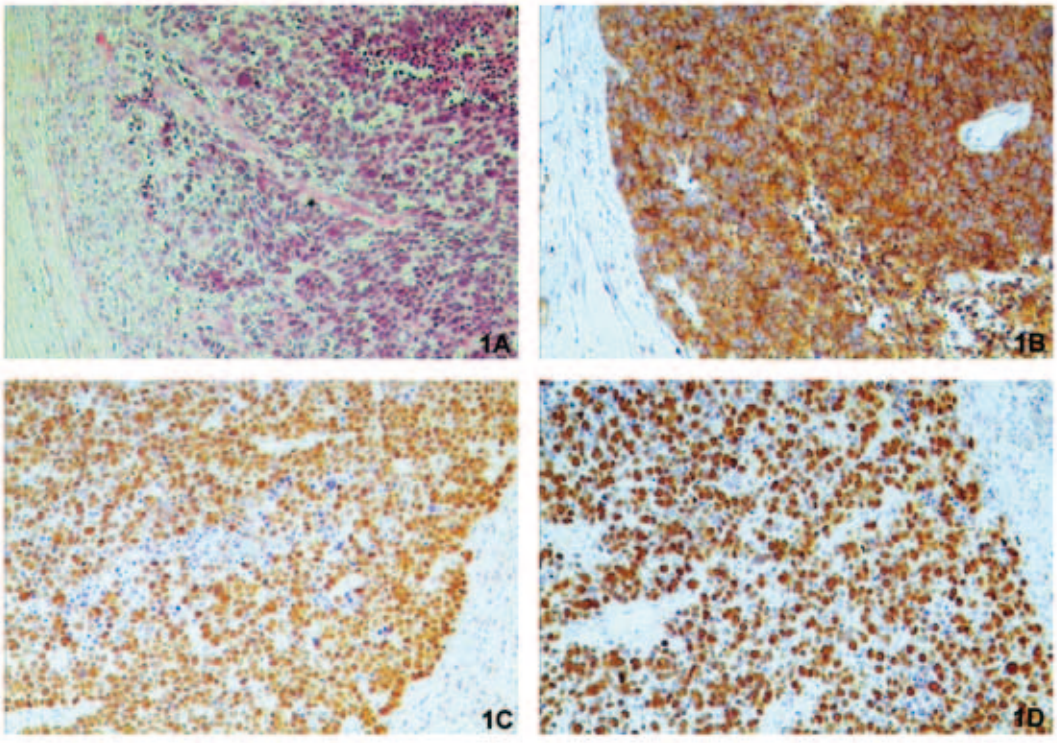


Fig. 1. Medullary thyroid cancer, small cell variant. A, Haematoxylin–eosin, original magnification (OM) x100. B, Synaptophysin, immunoperoxidase (IP), OM x100. C, Aberrant p53, IP, OM x100. D, Proliferation fraction by Ki–67, IP, OM x100

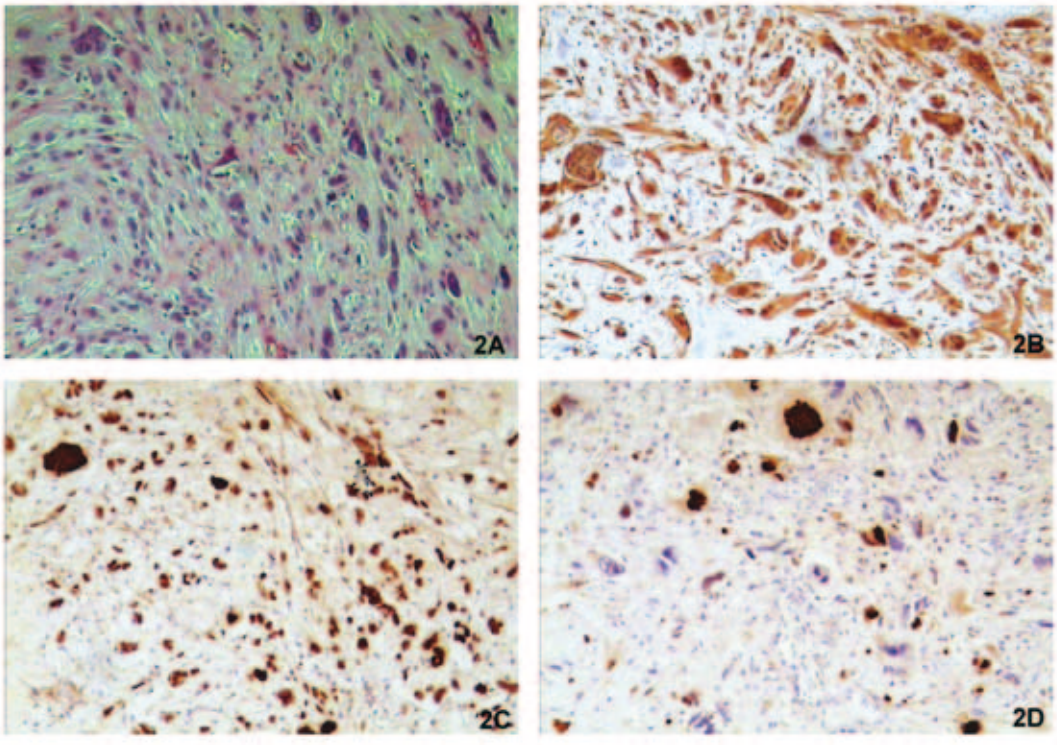


Fig. 2. Malignant peripheral nerve sheath tumour of the breast. A, Haematoxylin–eosin, original magnification (OM) x100. B, S–100 protein, immunoperoxidase (IP), OM x100. C, Aberrant p53, IP, OM x100. D, Proliferation fraction by Ki–67, IP, OM x100

DOI: 10.2478/v10163-010-0023-4

CASE REPORT

Congenital Long QT Syndrome in an Infant

Aris Lacis, Inga Lace, Elina Teivane, Vita Knauere, Inguna Lubaua, Inta Bergmane, Valts Ozolins, Lauris Smits, Normunds Sikora
University Hospital for Children, Riga, Latvia
Department for Pediatric Cardiology and Cardiac Surgery

Summary
Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by prolonged QT interval on ECG with prevalence close to 1/3000–1/5000. LQTS is characterized by the occurrence of syncopal episodes due to torsades de pointes ventricular tachycardia (VT) and by a high risk for sudden cardiac death among untreated patients (1, 2, 3). In 12% of patients with LQTS, sudden death is the first manifestation of the disease and only in 4% this happens in the first year of life (2). There is consensus that all symptomatic children with LQTS should be treated with β-blockers which are effective in preventing cardiac events and reducing mortality in 70%, but do not protect patients from sudden death completely (1,2,3,4). The prognosis is poor in untreated patients with annual mortality 20% and 10 year mortality up to 50% (1, 2). Here we present a case of relatively rare congenital heart rhythm disorders in an infant which required immediate treatment.
Key words: long QT syndrome; congenital arrhythmia.

AIM OF THE DEMONSTRATION

We present a case of congenital heart rhythm disorders in an infant which carry serious risk of sudden death if left untreated.

CASE REPORT

The child was sent to the hospital at the age of 21 days by the general practitioner due to bradycardia detected within a routine visit. The girl was born from the first pregnancy in urgent cesarean section due to fetal distress (umbilical cord wrapped around the neck) at 40 weeks of gestation, birth weight 3090g, height 54cm, Apgar score 7/9 and was discharged from the maternity hospital at the age of 4 days. The child received breastfeeding and parents did not have any complains about the newborn. The mother of the child is 21 years old and the father 23 years old, both completely healthy. The course of the pregnancy was uneventful. There were no cases of heart rhythm disorders or sudden death in the family history, no chronic illnesses in the family history. At the time of hospitalization (at the age of 21 days) the weight of the child was 3265g, bradycardia-heart rate 72 times per minute was detected, no heart murmurs, no hepatomegaly. Repeated electrocardiograms (ECG) showed first to second degree second type (Mobiz II) atrio-ventricular block and prolonged QT interval 0,52, cQT 0,54 as well as complete right and left anterior bundle branch block. Echocardiography was completely normal with LVDd 22mm, fractional shortening 37% and ejection fraction 61%. 24 hour ECG monitoring reveled first to second degree second type (Mobiz II) atrio-ventricular block and prolonged QT interval and repeated paroxysms of ventricular tachycardia with the ventricular rate up to 251 beats per minute (the longest one 49 seconds). No changes were found in thoracic x-ray, neurosonography and abdominal ultrasound. There were neither signs of acute infections nor TORCH infections present. There were no positive auto antibodies detected. At the age of 25 days epicardial pacemaker (DDD regimen) was implanted in the abdominal front wall and therapy with β-adrenoblocker Propranolol started. The postoperative period was uneventful and the girl was discharged at the seventh day after the operation. No prolongation of cQT was observed in family members of the girl. The hearing was detected to be normal. The analyses to detect the genetic background showed mutation characteristic for LQTS type 2 (mutation in gene HERG on chromosome7). The age of the girl is seven months now, she is followed up by pediatric cardiologist, receives Propranolol, no serious hearth rhythm disorders observed. The pacemaker regimen is DDD (lowest rate 90 beats per minute, upper track 200, AS-VS 69%, AS-VP 29%, AP-VS 1,5%, AP-VP 0,2%, threshold impedance A 0,375V, V 1,375V, impedance A 550Ω, V 439Ω). During the last check up the pacemaker diagnostic data and 24 hour ECG monitoring showed no runs of tachycardia.

DISCUSSION

QT prolongation may be congenital or acquired. Long QT syndrome is a genetic disease due to mutations of several genes all encoding ionic (potassium or sodium) channels involved in the control of ventricular repolarization. The characteristic ECG shows a prolonged QT interval (usually cQT greater than 0,46 seconds), abnormal T – wave morphology (bifid, biphasic or notched), 20% bradicardia due to second degree AV block, monomorphic or polymorphic ventricular tachycardia(present in 10-20%) (1,2,3). Based on genetic background, six types of Romano-Ward syndrome (LQTS 1-6, autosomal dominant, with normal hearing) and two types of Jervell and Lange-Nielsen syndrome (JLN 1-2, autosomal recessive, with deafness) are identified. Two additional syndromes (Andersen-Tawil and Timothy syndrome are

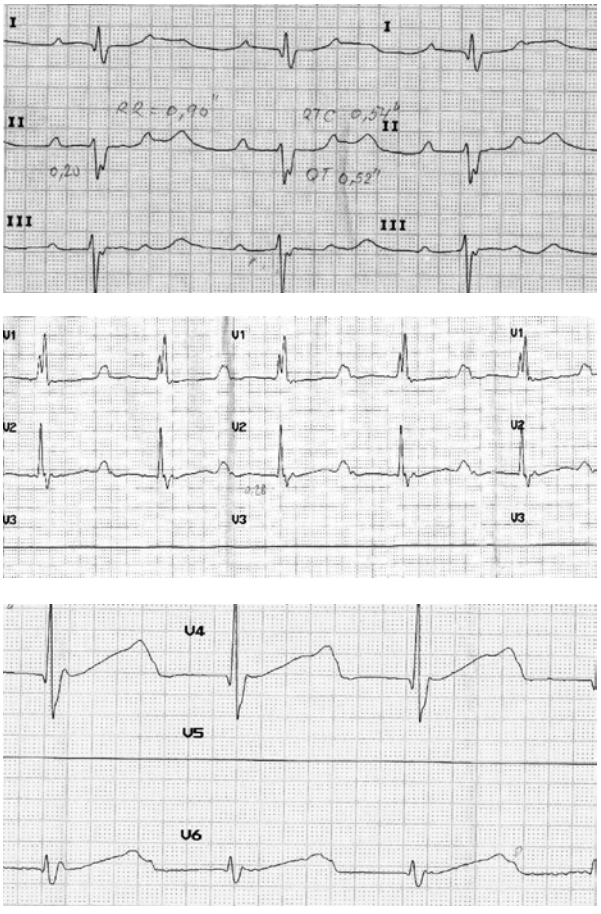
considered different subgroups (1,3). In our case there is evidence of characteristic genetic changes of LQTS 2. The LQT2 type is the second most common gene location that is affected in long QT syndrome, making up about 35 to 45 percent of all cases. This form of long QT syndrome most likely involves mutations of the *human ether-a-go-go related gene* (HERG) on chromosome 7. The HERG gene (also known as KCNH2) is part of the rapid component of the potassium rectifying current (I_{Kr}). (The I_{Kr} current is mainly responsible for the termination of the cardiac action potential, and therefore the length of the QT interval.) The normally functioning HERG gene allows protection against early after depolarizations (1, 3, 4). In most cases, several members of the same family are gene-carriers (family history positive in about 60% of cases). Low penetrance exists in LQTS, which means that gene-carriers may not show the clinical phenotype and may have a normal QT interval (2). Therefore a normal QT in the parents does not rule out familial LQTS. In addition, approximately 30% of cases are due to 'de novo' mutations which imply unaffected parents and no family history. 'De novo' LQTS mutations have been demonstrated in infant victims of cardiac arrest and sudden death diagnosed as Sudden Infant Death Syndrome (1,2). However, about 40% of the families with LQTS have not yet been linked to any of the known genes. Our patient showed serious hearth rhythm disorders already during the neonatal period. Relatively few LQTS patients have cardiac events during the first year of life, the vast majority become symptomatic later on, either during childhood or adolescence according to genetic subgroups (1,2,3). The acquired causes of LQT (including drugs, electrolyte imbalance, marked bradycardia, cocaine, organophosphorus compounds, subarachnoid hemorrhage, myocardial ischemia, protein sparing fasting, autonomic neuropathy, and human immunodeficiency virus disease) were excluded. Beta-blockers are the first choice therapy in LQTS and are effective in preventing recurrences in 80% of already symptomatic patients; different degrees of protection exist according to genetic subgroups. If beta-blockers are unable to prevent new cardiac events, additional drug therapy, left cardiac sympathetic denervation, pacemakers or the implantable cardioverter defibrillator should be considered based on evidence, with consideration for body size (1,2,3,4). In our case there were indications for both implantable pacemaker and the therapy with beta-blockers. Despite this combined therapy there is still risk for serious heart rhythm disorders but the risk for sudden death would be much higher if left untreated. With a prevalence 1/3000-1/5000 and a manifestation within the first month of life this case is a rarity in our small population but in the case of pathology with potentially life threatening consequences it is very important to diagnose it as early as possible.

Conflict of interest: None

REFERENCES

1. Allen HD, Driscoll DJ, Shaddy RE, Feltes TF. Disorders of Cardiac Rhythm and Conduction // In: Heart Disease in Infants, Children, and Adolescents. 7th Edition, USA: Moss and Adams, Lippincott Williams and Wilkins; 2008,Vol1, 328 – 331
2. Khan, Ijaz A. Long QT Syndrome: Diagnosis and Management // Am Heart J, 2002; 143(1):7 – 14
3. Park MK, Cardiac Arrhythmias // in: Pediatric Cardiology for Practitioners, 5th Edition, USA: Mosby Elsevier; 2008; 437 – 443
4. Schwartz PJ, Garson A, Paul T, et al. Guidelines for the interpretation of the neonatal electrocardiogram // Eur Heart J, 2002; 33:1329 – 1344

Address:
Elina Teivane
Children`s Clinical University Hospital,
Department for Pediatric Cardiology and Cardiac Surgery
Vienibas gatve 45, LV-1004,
Riga, Latvia
E-mail: eteivane@inbox.lv



The ECG of the 24 days old infant shows prolongation of cQT>500ms and atrio-ventricular block first to second degree Mobitz II

DOI: 10.2478/v10163-011-0024-y

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

CASE REPORT

Multislice Computed Tomography Imaging of Diverticultis Complication: Colovenous Fistula

Maija Radzina, Andris Laganovskis, Mara Tirane, Ligita Zvaigzne, Peteris Prieditis, Voldemars Bruns, Svetlana Lugovska
Pauls Stradins Clinical University Hospital, Riga, Latvia

SUMMARY
Acute colon pathology as diverticulitis is a frequent and important gastrointestinal disease, but the clinical diagnosis is often difficult to state. Several radiological studies have been used to assist in the diagnosis of acute diverticulitis (e.g. barium enema, ultrasound, and computed tomography (CT). Colovenous fistula is a rare complication of diverticulitis. We have analyzed MSCT imaging role in evaluation of such complicated form of diverticular disease.
Key words: multislice computed tomography, diverticulitis, colovenous fistula, hepatic portovenous gas.

AIM OF THE DEMONSTRATION

Europe is characterized by a high prevalence of the diverticular disease, which increases with age (prevalence of 8–12 cases per one million) (1). Lower gastrointestinal bleeding (occurring in about 5–15% of patients with colonic diverticula) and infection, resulting in abcesses, peritonitis and perforation (yearly incidence – 4 /100 000, occurring in about 15–20%), are the most frequent complications (1). Colovenous fistula is a rare complication of diverticulitis and only few case reports exist in literature. Several radiological studies have been used to assist in the diagnosis of acute diverticulitis (e.g. barium enema, ultrasound, and computed tomography (CT). We have analyzed MSCT imaging role in evaluation of such complicated forms of diverticular disease.

CASE REPORT

Here we describe a case of an 46–year old male patient, that was admitted to emergency room with progressive epigastric and left lower quadrant abdominal pain during last month, followed by diarrhea, weakness, fever for 7 days and progressive jaundice at admission. Due to recent chronic hip pain a regular NSAIDs treatment was received. Clinical findings revealed severe septic status with liver function impairment and possible diagnoses of toxic hepatitis or cholangitis.

MSCT of abdomen with oral and intravenous contrast media revealed multiple parenchymal lesions in the enlarged liver, suggestive of septic abscesses (Fig 1A). Portal venous gas and thrombotic changes of portal system were detected on CT post–contrast scan (Fig.1B).

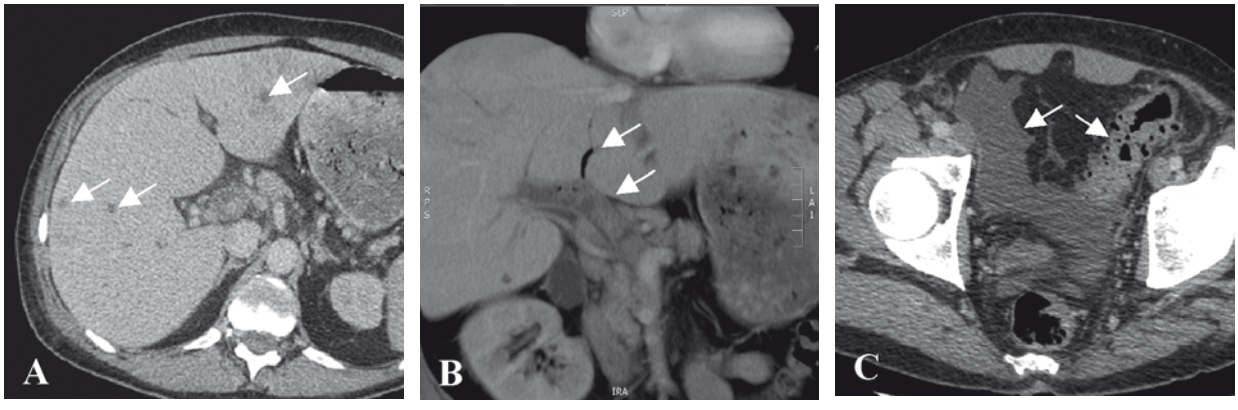


Fig. 1. A – CT, axial plane, post–contrast series – multiple, hypodense irregular lesions in the liver parenchyma – septic hepatic abscesses; B – CT reconstructions, coronal plane, post–contrast series – hepatic portovenous gas and inhomogenous, hypodense mass in the lumen of portal vein – thrombosis; C – CT, axial plane, post–contrast series – thickened wall and diverticula of sigmoid colon, pelvic free fluid – confirming diagnosis diverticulitis

There were also multiple left side colon diverticula, as well as irregular and thickened sigmoid colon wall, suggesting diagnosis of diverticulitis (Fig.1C).

Using multiplanar reconstructions an extra–anatomical formation – irregular, thickened wall, air filled channel (fistula) was revealed, it extended from sigmoid colon up to the epigastric region at the level of mesenteric and splenic vein junction (Fig.2).

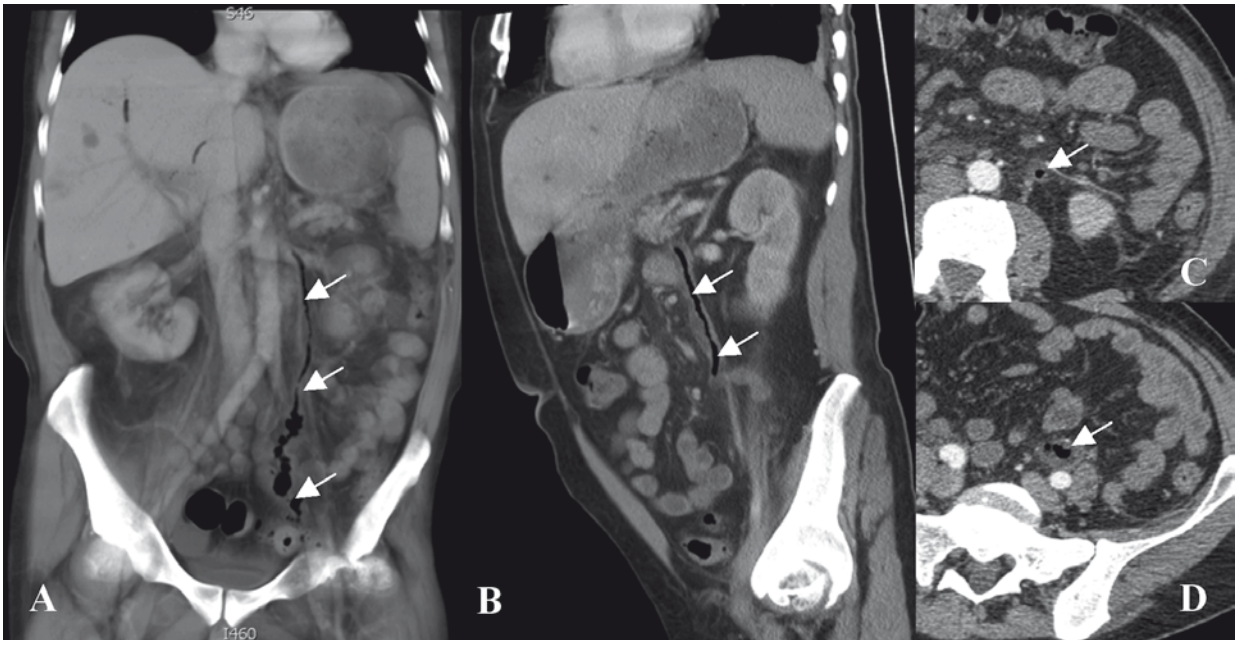


Fig. 2. CT reconstructions (A – coronal, B – sagittal, C, D – axial plane, post–contrast series show pathologic air–filled channel with well defined wall, extending from sigmoid colon up to epigastric region. Arterial branches along it's course and anatomical location suggest that inferior mesenteric vein is involved in colovenous fistula

Extensive peritoneal free fluid was noted (Fig.1C). A diagnosis of colovenous fistula (sigmoid colon to mesenteric vein) was proposed based on imaging findings and anatomy (Fig.3).

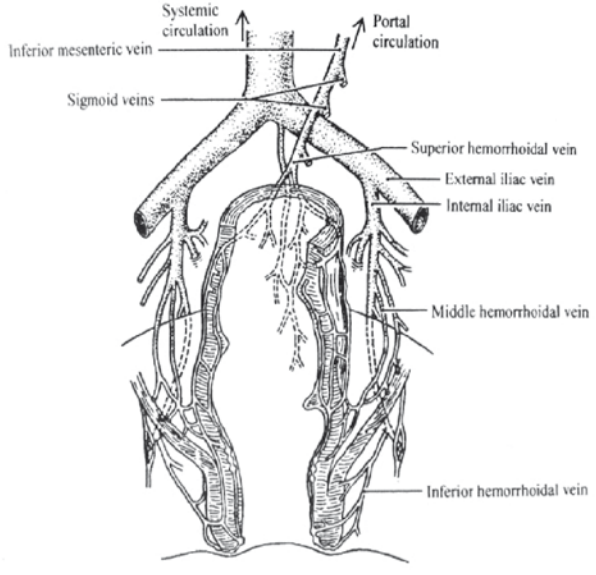


Fig.3. Anatomy of colon and hemorrhoidal veins (2)

Patient had surgery, but postoperative course was complicated with multiple laparatomies, drainage of liver and peritoneal abscesses. Follow–up CT demonstrated resolution of the portal vein gas and liver abscesses with persistent thrombotic changes in portal vein.

Cytology analysis revealed *Enterococcus* and *E.coli* presence in liver parenhchyma, peritoneal space and blood samples – confirming the diagnosis of colovenous fistula and sepsis.

After massive antibiotic treatment in ICU, during 6 weeks, eventually patient was discharged on 8th week with improvement and closure of the colovenous fistula.

DISCUSSION

Complication of diverticulitis includes abscess, phlegmona, and peritonitis in different stages of disease. Fistula and sinus tract formation may involve blood vessels, bladder, vagina, uterus, ureter, and adjacent large and small bowel or abdominal wall, which may be visible by CT. (3)

True enterovenous and colovenous fistulas are rare but potentially lethal entities. The most common reported causes of fistulas involving the mesenteric small bowel and the colon are Crohn disease and diverticulitis. Inflammatory involvement of the inferior mesenteric vein complicating diverticulitis of the sigmoid colon can result in septic thrombophlebitis and the presence of gas within the vein. Portomesenteric vein gas is a rare complication of colonic diverticulitis, but the combination of the two conditions can lead to hepatic abscess (4) as it was seen in this case.

Differential diagnosis of hepatic portovenous gas (HPVG) is bowel ischemia or infarction, which is the most

common cause of HPVG in adults and carries a mortality rate of 90% (5). Many other, nonischemic causes have been reported, such as intra–abdominal abscesses, bowel obstruction and distention, perforated gastric ulcer, gastric dilatation, gastrointestinal ileus, (acute hemorrhagic) pancreatitis, and ingestion of toxins. Less frequent are colon cancer, blunt abdominal trauma and hyperbaric decompression. Iatrogenic causes of HPVG can be barium enema, colonoscopy in patients with an inflammatory bowel disease or diverticulitis, endoscopic retrograde cholecystopancreatography with or without endoscopic sphincterectomy, and liver transplant (6).

Colovenous fistulas are often detected unexpectedly on barium studies by observing intravasation of the contrast agent. Substantial barium intravasation reportedly carries a high mortality rate (3). We haven't used the barium enema imaging in this case, because a number of studies over the past decade have shown CT to be the preferable initial examination, due to its ability to demonstrate not only the extent of intramural inflammation but also the degree of pericolic disease, including intraperitoneal inflammation, perforation, and abscess formation (7). In this case the fistula could be missed on axial scans, interpreting it as part of normal colon.

Additional benefits of MSCT imaging include detailed multiplanar peritoneal cavity examination, CT angiography of portomesenteric vein system (e.g. thrombus, HPVG) and parenchymal lesion detection.

As surgical treatment is probably essential for this condition, the possibility of colovenous fistula should be borne in mind in patients with HPVG, especially if they have bacteraemia.

In conclusion – septic complications with development of colovenous fistula formation in diverticulitis are rare. MSCT imaging made notable impact in diagnosis and subsequent treatment of this patient. CT, by virtue of its superior contrast resolution and anatomic detail, allows more complete assessment of diverticulitis complications, including fistula and it's possible causes and outcome with use of postprocessing multiplanar reconstructions, as shown in this case.

Conflict of interest: None

REFERENCES

1. Delvaux M. Diverticular disease of the colon in Europe: epidemiology, impact on citizen health and prevention // Aliment Pharmacol Ther 2003; 18 (Suppl. 3): 71–74
2. Takahashi M, Fukuda K, Ohkubo U, Tokuhiro N, Tsuchiya R, Yoshie M, Hirai Y. Nonfatal Barium Intravasation into the Portal Venous system during Barium Enema examination // Internal Medicine 2004; 43:1145 – 1150
3. Lawrimore T, Rhea JT.Computed Tomography Evaluation of Diverticulitis // J Intensive Care Med, 2006, 19(4): 194 – 204
4. Sebastià C, Quiroga S, Espin E, Boyé R, Alvarez–Castells A, Armengol M. Portomesenteric Vein Gas: Pathologic Mechanisms, CT Findings, and Prognosis // RadioGraphics 2000; 20:1213 – 1224
5. Pickhardt PJ, Bhalla S, Balfe DM. Acquired Gastrointestinal Fistulas: Classification, Etiologies, and Imaging Evaluation // Radiology 2002; 224: 9 – 23
6. Heye S, Ghijselings L, van Campenhoudt M. Hepatic portal venous gas as a complication of diverticulitis with colovenous fistula: a case report // Emergency Radiology, 2002; 9:234 – 236
7. Strålin K, Lindgren R, Birgersson C, Vikerfors T. Gas within the liver and polymicrobial bacteraemia due to colovenous fistula: two cases in one month // Scand J Infect Dis. 2006; 38(1):66 – 8

Address:
Maija Radzina
Institute of Diagnostic Radiology,
Pauls Stradins Clinical University Hospital
Pilsonu str. 13, Riga, LV-1002, Latvia
E-mail; maija@mailbox.riga.lv

CASE REPORT

Severe Deep Neck Space Infection and Bilateral Pneumonia of Odontogenic Origin: a Case Report

Ilze Dobele*, Gints Kragis, Girts Salms***, Peteris Apse****
*Department of Otolaryngology, Riga Stradiņš University, Latvia
**Department of Prosthetic Dentistry, Riga Stradiņš University, Latvia
***Department of Oral and Maxillofacial Surgery, Riga Stradiņš University, Latvia

Summary
Severe deep neck infections (DNIs) are potential complications of odontogenic pathology. DNIs affecting perimandibular space have a high prevalence and their etiologic and therapeutic aspects have been discussed. Early diagnosis and aggressive antimicrobial and surgical treatment are essential to successfully treat cervical abscesses and compromised upper airways of odontogenic origin. We report the case of life threatening pathology involving perimandibular, retropharyngeal spaces and bilateral pneumonia.
Key words: dental focal infection, abscess, difficult airway, deep neck infection, pneumonia.

AIM OF THE DEMONSTRATION

The aim of the article is to demonstrate a severe life–threatening pathology of dental origin and necessity of interdisciplinary collaboration for early diagnosis and appropriate management.

CASE REPORT

29 years old male was seeking for urgent help in the regional hospital regarding complaints about increasing breathing and swallowing difficulties and submandibular swelling lasting for 3 days. No dental pain was present. Dental and deep neck infection as well as laryngeal stenosis was diagnosed and patient urgently transported to the intensive care unit of the P. Stradiņš Clinical University hospital.

Clinical data: severe general status, conscious, hoarseness, stridorous breathing 28 times per minute, tachicardia 116 times per minute, forced posture – sitting, febrility 39,2°C, localised infiltration, redness and palpatory tenderness in the submandibular region. Oral status: restricted movements of tongue, tenderness and pain on percussion dd 22, 47, 48, 38. Laboratory data: white blood cell count 21.6 cells/mm³, C–reactive protein 319.4mg/l , K 4.5 mmol/l.
Radiological investigations:

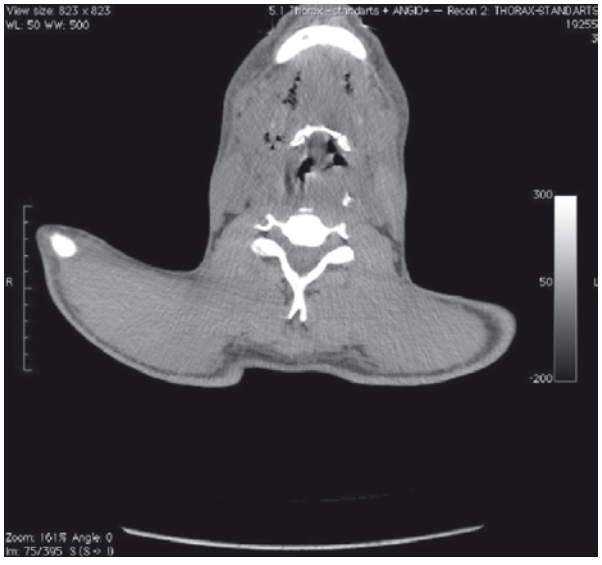


Fig. 1. Axial CT scan of the neck showing a bilateral perimandibular abscesses with compromised larynx

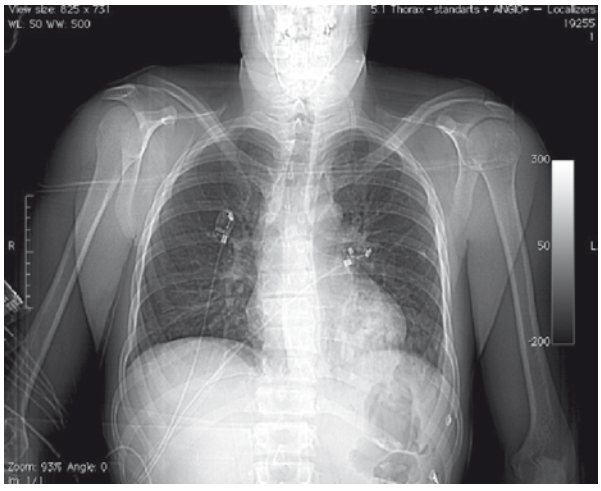


Fig. 2. CT of the chest showing alveolar infiltration in the lower left and middle right segment

Diagnosis: periapical abscesses of dd 22, 38, 47, 48, deep neck infection with laryngeal stenosis and bilateral pneumonia. Antibiotic therapy was begun empirically with Dalacin 600 mg IV 8 h and Metronidazole 100 mg IV 8 h. E/o (extraoral) incisions and drainage of the submandibular, retropharyngeal abscesses was performed. Tracheostomy done. dd 38, 48, 47 was extracted. Patient was sedated and ventilated (Fig. 3).

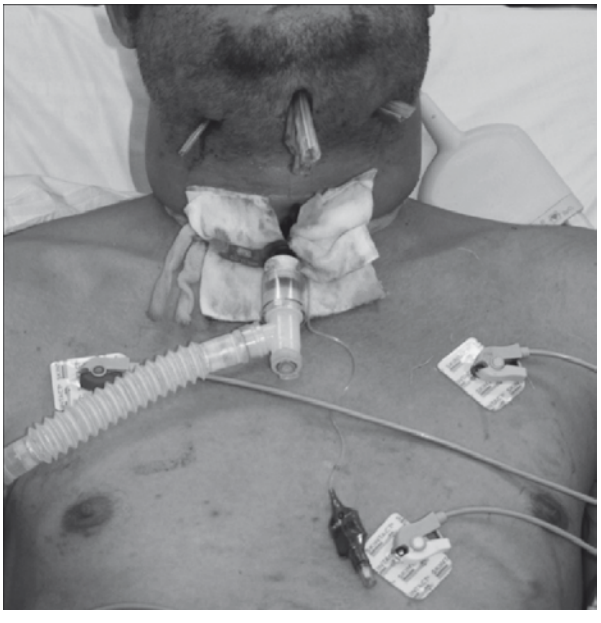


Fig. 3. Extraoral incisions for drainage of submandibular and retropharyngeal spaces. Tracheostomy tube

Next day patient breathes spontaneously through tracheostoma, eating soft food, temperature 36,3°C, WBC 12.8 cells/mm³, CRP 115.2 mg/l. Continuous antimicrobial therapy, wound dressing and drainage. 3rd day purulent discharges from drains observed and submandibular infiltration descending to the sternum, painful swallowing. Repeated surgical intervention done, i/v antimicrobial therapy Tazocine 4,5 mg IV 8 h added. 4 – 5th day infiltration of the neck decreasing , tracheostoma evacuated, patient breath spontaneously, light swallowing and speech difficulties. From intensive care unit transferred to the maxillofacial department for further treatment, p/o antimicrobial therapy continues no less than 3 weeks.

DISCUSSION

Odontogenic soft tissue infections may spred along the facial planes downwards and cause DNIs, which typically originate from the molar teeth of the mandible (3, 4, 6). There are two main factors that promote spreading of DNIs towards mediastinum: the cervical anatomy with an almost enclosed space along the facial planes of the neck and chest, and the effects of
gravity and reccurrent changes in the negative intrathoracic pressures that occur with inspiration (1). The reason for the high mortality of deep neck processes descending to the mediastinum is the difficulty in making the early clinical diagnosis (2). The typical signs of descending inflammation with thoracal involvement are reporeted to be pyrexia, dysphagia, swelling and induration of the neck and upper part of the chest, thoracic pain, dyspnea, hypoxia, and respiratory failure (10). However these symptoms are not always evident and often occurs late in the course of disease, therefore radiological assesment is the main non invasive diagnostic tool (3, 5). Post surgical follow–up CT examinations help to determine the adequacy of treatment and may indicate surgical revision. Besides sufficient surgical therapy, the adequate choice of antibiotics is of particular importance in the management of DNIs. DNIs most often frequently are polymicrobial processes with *Streptococcus* and *Staphylococcus species* as well as anaerobes playing the major pathogenic role (14). Most authors recommend an antibiotic therapy that primarily covers gram–positive, anaerobic as well as beta–lactamase producing bacteria. Commonly recommended choices for empiric antimicrobial therapy are penicillin alone or in combination with metronidazole and clindamicine (7, 14).
The surgical procedure of choice is determined by the goal of assure effective abscess drainage to prevent systemic toxicity and subsequent multiorgan failure (9, 12).
The prevalence of DNI is high in young and middle–aged adults with a preponderance of males aged 25–33 years. Reduced immune defence, high microbial virulence and smoking habits are predisposing factors (7). Complex head and neck anatomy often makes early DNIs challenging and suspicion is necessary to avoid delay in the treatment. Aggressive management and monitoring of the airways is the most urgent aspect of care as well as surgical drainage and appropriate antibiotic coverage (1, 3, 5, 9, 12). Interdisciplinary collaboration is essential for early diagnosis and appropriate management of severe pathologies of odontogenic origin (8, 11, 13).

Conflict of interest: None

REFERENCES

1. Fragiskos F.D. Odontogenic Infections // In: Fragiskos D. Fragiskos (Ed.) Oral Surgery. Berlin: Springer–Verlag; 2007: 205 – 241
2. Green A.W., Flower E.A., New N.E. Mortality associated with odontogenic infection! // Br Dent J 2001; 190: 529 – 530
3. Infections // In: Perry M. (ed). Head, Neck and Dental Emergencies, 1st ed. Oxford University Press; 2005: 62 – 75
4. Jacobson J.J., Silverman S. Bacterial Infections // In: Silverman S.S., Eversole L.R., Truelove E.L. Essentials of Oral Medicine. Hamilton, London: BC Decker Inc.; 2001: 159 – 169
5. Lee J.W., Immerman S.B., Morris L.G.T. Techniques for early diagnosis and management of cervicofacial necrotising fasciitis // J of Laryngol & Otology 2010; 124: 759 – 764
6. Li X., Kolltveit K., Tronstad L. et al. Systemic Diseases Caused by Oral Infection // Clin Microbiol Rev, 2000, 10:547 – 558
7. Meurman J.H., Lindqvist C. Livshotande odontogena infektioner. Tema Antibiotika // Tandläkartidningen 2002; 94(1): 18 – 22
8. Migliorati C.A., Madrid C. The inteface between oral and systemic health: the need for more collaboration // Clin Microbiol Infect 2007; 13(4): 11 – 6
9. Myers E.M. Pharynx and Larynx // In: Britt L.D. (ed) Acute Care Surgery: Principles and Practice. Springer Science+Business Media LLC; 2007; 277 – 304
10. Paju S., Scannapieco F.A. Oral biofilms, periodontitis, and pulmonary infections // Oral Dis 2007; 13(6):508 – 512
11. Rautemaa R., Lauhio A., Cullinan N.P. et al. Oral infections and systemic disease – an emerging problem in medicine // Clin Microbiol Infect 2007; 13(11): 1041 – 7
12. Submandibular – Submental Region (Robbins Level I) // In: Lucioni M. Practical Guide to Neck Dissection. Berlin: Springer–Verlag; 2007; 31 – 40
13. Vieira C.L., Caramelli B. The history of dentistry and medicine relationship: could the mouth finally return to the body? // Oral Dis 2009; 15(8):538 – 46
14. Vieira F., Allen S.M., Stocks R.M.S., Thompson J.W. Deep Neck Infection // Otolaryngol Clin N Am 2008; 41:459 – 483

Address:
Ilze Dobele
Department of Otolaryngology, Riga Stradins University
20 Dzirciema Street, LV-1007 Riga Latvia
E-mail: Ilze.Dobele@rsu.lv

DOI: 10.2478/v10163-011-0026-9

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

CASE REPORT

Neurogenic Thoracic Outlet Syndrome caused by Subacute Clavicle Osteomyelitis

Martins Kapickis
Centre of Microsurgery of Latvia, Riga East University Hospital, Riga, Latvia

Summary
A rare case of neurogenic thoracic outlet syndrome caused by subacute osteomyelitis (SOM) of clavicle is presented. It was treated by clavicle resection, I rib resection and scalenectomy followed by reconstruction of the clavicle by 6th rib vascularised bone transfer based on serratus anterior muscle as a rotational flap.
Key words: thoracic outlet syndrome, clavicle osteomyelitis, scalenectomy.

AIM OF THE DEMONSTRATION

According to Atasoy neurogenic thoracic outlet syndrome (TOS) is one of the most underrated, overlooked, and misdiagnosed conditions (1). It is estimated, that at least 0,1 % of the population are suffering from this condition(5). Unfortunately most clinicians are uncomfortable with the concept of the TOS. Not many physicians recognize this syndrome and even do not believe it exists, because frequently it is lacking any objective diagnostic criteria (8). It is considered to be a chameleon of syndromes, since it can imitate a number of pathologies, some of them very serious, thus correct differential diagnosis is of paramount importance (3). Most frequent cause of the TOS is trauma predisposed by soft tissue pathology which is followed by osseous pathology, such as cervical rib or elongated transverse process of C7 (9). Clavicle malunion and callus formation is a rare cause, but can produce compression of neurovascular structures with ease (6), (10).

Subacute osteomielitis of the calvicle is a rare condition. To our knowledge there are no reports of TOS being caused by subacute osteomyelitis of the clavicle in the English literature.

The following TOS case caused by SOM of the clavicle was treated completely with the clavicle resection, Ist rib resection, anterior and middle scalenectomy and reconstruction of the clavicle with vascularised ipsilateral 6th rib.

CASE REPORT

20 year old female music college student was seen in the outpatient clinic complaining of nocturnal aching pain and tingling in the right arm for 7 years. Pain and paresthesia along the medial aspect of her right arm and ulnar digits was exacerbated after intensive piano lessons for many weeks. There was difficulty to abduct the shoulder due to a pain and progressive weakness. Full passive range of motion in the arm was possible. She was also complaining of deformed right clavicle due to a hematogenous osteomyelitis in the childhood. History also revealed needle biopsy of the lesion four years ago and curettage in other hospital three years ago that was followed with postoperative antibiotic treatment for 6 weeks. There was no other treatment since.

On physical examination bulging deformity of the right mid–clavicular area was noted. Some localized tenderness over the clavicle that was not associated with warmth, redness, and soft–tissue swelling. Tinel sign was positive on the right carpal, cubital tunnel and supraclaviculary above the anterior scalene muscle. Tinel on the pronator tunnel and infraclaviculary (on the pectoralis minor) was negative. Phalen sign was inconclusive, but Roos (EAST) provocation test was positive at 1 minute. There was a strong trigger point irritation on the right trapecius muscle. There were no pulse changes performing the Adson test. Two point discrimination was normal in all fingers. Electromyography (EMG) and nerve conduction study finding was nonspecific.

Plain radiographs in anteroposterior view showed bulging deformity of the mid–clavicle and typical radiographic appearance of a single, central transparent zone of osteolysis, well–marked outlines, and a zone of sclerotic bone representing subacute osteomyelitis (Fig.1.). Magnetic resonance imaging in coronal T1–weighted magnetic resonance images of the right brachial plexus showed signs of compression by the bulging portion of the mid–clavicle (Fig.2).

5 months of physical therapy, suspension of piano playing was ineffective. Patient considered her life to be miserable. She was ready to undergo major surgical procedure.

A diagnosis of neurogenic TOS secondary to subacute OM of the clavicle was made based on the patient's history, physical examination, imaging studies. We planned to perform a clavicle resection, anterior and middle scalenectomy with transaxillary first rib resection, followed by clavicle reconstruction with vascularised VII rib transfer based on Serratus anterior muscle blood supply.

With the patient under general anesthesia, clavicle

resection was performed. Wound was packed and draped with Opsite (Smith and Nephew) dressing. Next, the patient is placed with hips in the straight lateral position and the thorax tilted posteriorly 60 degrees with sandbag support at the back as described by Roos (7). The forearm, arm, axilla and chest are prepared and draped into the surgical field so it may be freely manipulated during operation. Incision was modified so that we could get access to the axilla and harvest VII rib with 2 lower slips of Serratus anterior muscle. After the first rib resection, VII rib 12 cm long was harvested on the lateral thoracic artery. It was left in place and wound was packed with gauze dressing and covered with Opsite. The patient was placed supine again. Anterior and middle scalenectomy was performed via the supraclavicular approach. Both scalene muscles were sent for histological investigation.

The tunnel was made between axilla and supraclavicular wound. Flap was passed through the tunnel and transferred rib was fixed to the remaining sternal and acromial part of the clavicle with plates and screws 2,4 mm (Fig.3 A and B).

During harvesting of VII rib pneumothorax was encountered. It was uneventfully treated with Pleuracan (B.Braun) system.

Histology of the clavicle reveled subacute OM with mielofibrosis and atrophy with fibrosis in scalene muscles was diagnosed.

Immediately after surgery patient was taken to intensive care unit for 3 days. Patient was discharged on 10th postoperative day with arm sling. 6 weeks after the surgery, pain and paresthesia in the right upper extremity had improved considerably and patient returned to piano practice. The patient is asymptomatic 9 months after surgery.

DISCUSSION

Claviculectomy for Thoracic outlet treatment has been described by Enker and Murthy (1970) (4). It is not practiced for treatment of the thoracic outlet syndrome now days, because resection of the clavicle will cause some degree of instability and disfigured aesthetic appearance, particularly in women. Today there are few accepted methods for decompressing "thoracic outlet area" – first rib resection (supraclavicular or infraclavicular) alone or in combination with scalenectomy. There is no uniform agreement on which procedure or combination is more effective, but some authors state that for upper type of Thoracic Outlet syndrome scalenectomy alone will suffice. Others insist on doing complex approach to decompression of the area by removal of the first rib transaxillary and supraclavicular scalenectomy (2).

SOM is characterized by mild to moderate pain. Patient usually describes it as a persistent ache. Symptoms can be intermittent and onset is insidious. Often there is a long delay between the onset of pain and the diagnosis. Usually there are no constitutional symptoms. There may be many similarities between TOS and SOM of clavicle regarding pain: deep ache, night pain, insidious presentation and delay of diagnosis. In our case all symptoms were attributed to SOM and not TOS. Our patient was complaining of paresthesia and it is not a common symptom in SOM. Sometimes there are difficulties in differentiating subacute osteomyelitis from bone tumors such as osteoid osteoma, Ewing sarcoma or osteosarcoma, but in our case we were not having difficulty in diagnosis, since previous confirmatory biopsy have been performed.

Magnetic resonance imaging was helpful not only in differentiating SOM from tumors, but also in localizing compression area (Fig.2.). It is not uncommon for EMNG to be negative in cases with confirmed direct intra–operative observation or preoperative MRI conformation. For this reason EMNG should not be accepted a diagnostic tool. It has value only if it is positive.

In our case, an anterior and middle scalenectomy was performed including resection of the clavicle, first rib and reconstruction of clavicle with vascularised rib transfer. The patient obtained complete relief from her symptoms without major complications. Magnetic resonance imaging was not performed postoperatively to confirm straightening of distorted brachial plexus.

There are authors who are in favor of scalenectomies alone in cases of posttraumatic TOS due to a callus formation at the clavicle fracture site[7]. They are proposing that in clavicle fracture cases primary cause of TOS is scarring and contracture of scalene muscles and not a callus compression directly unto the underlying neurovascular structures in the costoclavicular space. In our case we were not able to resort to this advice since the clavicle itself has to be resected and reconstructed. At the same time scarred scalene muscles could not be left alone. To give even more space we decided to resect the Ist rib as well. It has been suggested by Atasoy that simultaneous transaxillary Ist rib resection and supraclavicular scalenectomy bears the best results in treatment of neurogenic TOS[10].

In this complex procedure full remission of symptoms were achieved by addressing both problems –TOS and SOM at the same time.

Conflict of interest: None

REFERENCES

1. Atasoy E. History of thoracic outlet syndrome // Hand Clin, 2004; 20:15 – 16
2. Atasoy E. Combined surgical treatment of thoracic outlet syndrome: transaxillary first rib resection and transcervical scalenectomy // Hand Clin, 2004; 20(1):71 – 82
3. Brantigan CO, Roos DB. Diagnosing thoracic outlet syndrome // Hand Clin, 2004;20(1):27 – 36
4. Enker SH, Murthy KK. Brachial plexus compression by excessive callus formation secondary to a fractured clavicle. A case report. Mt Sinai J Med, 1970;37(6):678– 82

5. Fugate MW, Rotellini–Coltvet L, Freischlag JA. Current management of thoracic outlet syndrome // Curr Treat Options Cardiovasc Med, 2009 Apr;11(2):176 – 83
6. Kitsis CK, Marino AJ, Krikler SJ, Birch R. Late complications following clavicular fractures and their operative management // Injury, 2003;34(1):69 – 74
7. Roos DB. Experience with First Rib Resection for Thoracic Outlet Syndrome // Annals of Surgery, 1971; 173 (3):429 – 442
8. Sanders JR, Shogan S. The controversies regarding thoracic outlet syndrome // In: Sanders JR. Thoracic Outlet Syndrome. A common sequela of neck injuries. Philadelphia: J.B. Lippincot Company, 1991; 2 – 3
9. Sanders RJ, Hammond SL. Etiology and pathology // Hand Clin, 2004; 20(1):23–26
10. Yoo et al. Thoracic Outlet Syndrome Secondary to Clavicular Malunion // Clin Orthop Surg, 2009;1(1):54 – 57

Address:
Martins Kapickis
Centre of Microsurgery of Latvia,
Riga East University Hospital,
Hipokrata str. 2, LV-1038
Riga, Latvia
E-mail: kapickis@dr.com

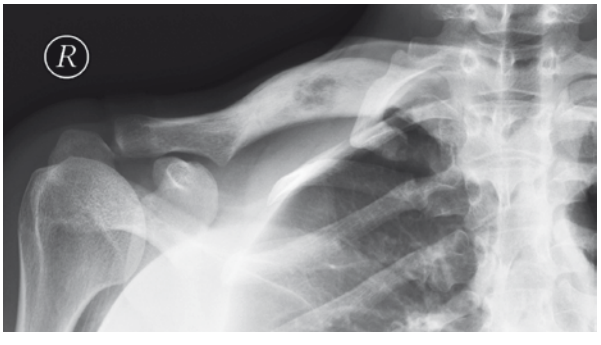


Fig. 1. Plain radiographs in anteroposterior view show bulging deformity of the mid–clavicle and typical radiographic appearance of a single, central transparent zone of osteolysis, well–marked outlines, and a zone of sclerotic bone representing subacute osteomyelitis

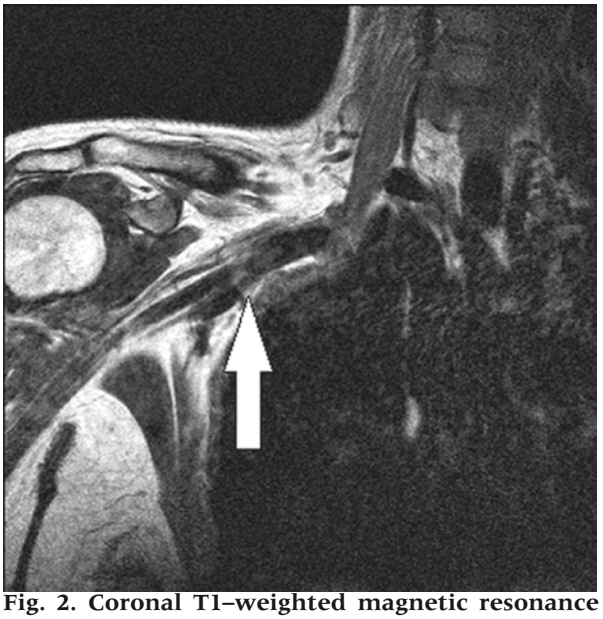


Fig. 2. Coronal T1–weighted magnetic resonance images of the right brachial plexus showed signs of compression (white arrow) by the bulging portion of the mid–clavicle

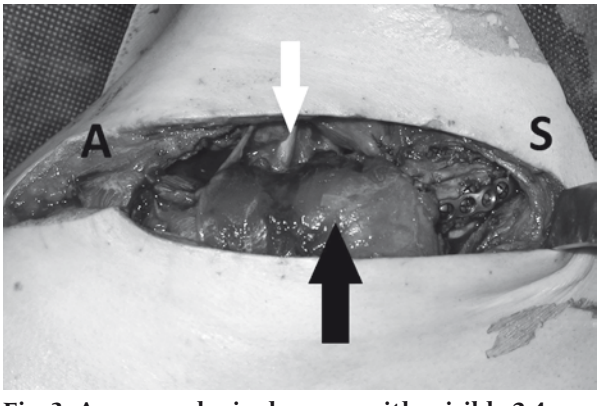


Fig. 3. A – supraclavicular area with wisible 2,4 mm titanium fixation plate. Black arrow – Serratus anterior muscle supplying vascularised rib transfer. White arrow – preserved supraclavicular nerves. S – steranal end, A – acromial end of the reconstructed clavicle

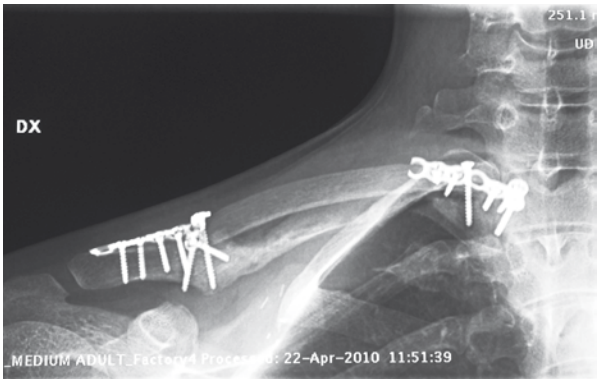


Fig. 3. B – Plain radiographs in anteroposterior view show reconstructed clavicle with vascularised rib transfer and 2,4 mm titanium fixation devices

CASE REPORT

Methicillin Susceptible Panton –Valentine Leukocidin Positive *S. Aureus* Pneumonia in a Child with Novel Influenza H1N1 Infection

Liene Cupane*/*, Nina Pugacova*, Girts Aleksejevs*, Dace Berzina**/***, Dace Gardovska*/***, Edvins Miklasevics**/*****
***Children`s Clinical University Hospital, Riga, Latvia**
****Pauls Stradins Clinical University Hospital, Riga, Latvia**
*****Riga Stradins University, Department of Paediatrics, Latvia**

Summary
The first case in Latvia of Panton – Valentine leukocidin (PVL) positive methicillin susceptible *Staphylococcus aureus* (MSSA) pneumonia in an adolescent with novel influenza A H1N1 is described.
A 15 year old boy was admitted to intensive care suffering from severe respiratory failure with bilateral necrotic pneumonia. The presence of influenza A H1N1 was confirmed by PCR. Invasive S. aureus was spa type t435 and Panton–Valentine leukocidin gene positive. He received therapy with ceftriaxone, oxacillin, clindamycin and oseltamivir phosphate and underwent two chest operations. He was discharged after 58 days in hospital.
Key words: H1N1, S. aureus, PVL; MSSA.

AIM OF THE DEMONSTRATION

Novel influenza type A (H1N1), or pandemic flu was first identified in April 2009 in Mexico and rapidly worldwide. On 11 June, 2009 the World Health Organization formally confirmed H1NI influenza pandemic. The course of illness was mild or moderate in most cases and hospitalization due to severe influenza was required mainly for persons from the following risk groups: children under 2, pregnant women those with underlying chronic disease and the immuno–compromised (14).

In Latvia the novel pandemic influenza A/ H1N1 virus was first identified in June 2009; and new cases appeared sporadically until November when more than 50 new cases of pandemic flu were identified per week (15). During the period 20 – 26 November, 2009, very high activity was reported in Europe including Latvia, with children up to 15 years of age affected to unusually high degrees(16).

Uncomplicated human influenza virus infection causes transient tracheo – bronchitis due as the virus attaches to tracheal and bronchial epithelial cells. The main complication is extension of viral infection to the alveoli often complicated with bacterial infection resulting in severe pneumonia. Necrotizing *S. aureus* pneumonia has long been recognized, but the association with PVL was made less than ten years ago. PVL positive *S. aureus* necrotising pneumonia is often lethal and can follow respiratory infections, especially influenza. Numerous cases since have been reported worldwide. Panton – Valentine Leukocidin is a bicomponent pore–forming *S. aureus* exotoxin which mainly acts on neutrophils. PVL producing *S. aureus* may be either methicilin sensitive or resistant, however mainly associated with community acquired methicilin resistant *S. aureus*.

Here, we report the first case in Latvia of methicillin susceptible Panton – Valentine leukocidin (PVL) positive *S. aureus* severe pneumonia in an adolescent with influenza A H1N1.

CASE REPORT

A 15 – year old boy was admitted to Daugavpils Regional Hospital on the evening 29 November 2009 with a 4 day history of low–grade to high fever, vomiting and a dry cough with haemoptysis and discomfort behind the sternum on the day of the hospitalization.

A chest X–ray, performed on admission, showed total right sided pneumonia, the patients' CRP (C– reactive protein) was 253,65 mg/l (N 0–7,9 mg/l) with other indicators as follows: HGB 15,8 g/dl, RBC – 5,56 $x10^6$ (N 4,5–5,3), WBC – 7,5$x10^3$ (N 4,5–13), PLT 160 $x10^3$ (N 181–521). A nasopharyngeal swab was taken to detect respiratory viruses. Empiric antibacterial therapy with ceftriaxone and metronidazole was commenced. After a few hours the patient was moved to the intensive care unit and subsequently to the main children's hospital due to his progressive respiratory insufficiency. On the morning of November 30 the patient was transferred to the Childrens Clinical University Hospital (CCUH) in Riga. On arrival at CCUH, Riga, the patient had difficulty breathing and had signs of severe respiratory failure; he was sitting in an enforced position, had tachypnea (35 – 40 times per min.) with loud, groaning breathing and intercostal retractions and his blood pressure was raised (200/87 mmHg). Auscultation of the lungs showed unilateral dullness on the right side.

The chest X–ray showed multiple focal shadows on both sides of the lungs and unilateral intensive infiltration in the middle part of the right lung that suggested severe bilateral pneumonia (Pict. 1). Laboratory findings showed significant changes in blood gases – decreased pO_2 – 70,6 mmHg (N 71–104 mmHg), increased pCO_2 – 78,6 mmHg (N 32–46 mmHg), base excess was 6 mmol/l (N –5 – 5), pH – 7,28 (N 7,37–7,45) and still elevated CRP – 261,65 mg/l, urea and creatinine levels were normal. His blood count at admission was normal except of "left shift" with 1% of metamyelocytes.

His history was unremarkable except miozitis after acute respiratory infection in January, 2008 and recurrent faringitis in the summer 2008.

He was admitted to the intensive care unit and empiric oral antiviral therapy with oseltamivir phosphate (75mg twice daily) and intravenous antibacterial therapy with ceftriaxone and oxacillin in additional to antihypertensives and symptomatic therapy were commenced. One day later clindamycin was added.

Novel influenza A H1N1 infection was confirmed by PCR and *S. aureus* isolated from blood and pleural fluid on the day of admission were methicillin susceptible, Panton – Valentine leukocidin producing and were *spa* type *t435.* Antibacterial susceptibility was determined according to CLSI standards (M2–A9, M100–S16). The *lukSF*–PV genes were detected by PCR (4). Chromatograms of the *spa* sequences were analysed by Ridom StaphType software (Ridom GmbH).

Blood analyses that were taken two days later showed elevated inflammatory markers interleukin 6 (Il6) was 172 pg/ml (N <10 pg/ml) and calcitonin prohormone procalcitonin (PCT) level 2– 10 ng/ml (N< 0,5 ng/ml).

Eleven hours after admission due to increasing respiratory insufficiency mechanical pulmonal ventilation was started and continued for 15 days. The general condition of the patient remained severe for more than five days.

On the 16th day the boy underwent operative therapy with a right side thoracotomy and resection of S4, S5 of the right lung (Pict.2) because of the severe condition due to pneumothorax and empyema. Further investigations of postoperative material revealed necrosis and inflamation of lung tissues. After the operation his general condition improved and it was decided to continue conservative therapy with antibiotics, but due to a post operative fistula of the right lung, the surgery was repeated after 3 weeks and the fistula was closed. The patient underwent repetitive bronhoscopies and antibacterial therapy with ceftriaxone (14 days), oxacillin (14 days), clindamycin (21 days) and oseltamivir phosphate (5 days). With this treatment blood cultures became negative on the 14th day of hospitalization. His general condition improved and after 58 days in hospital the patient was discharged.

DISCUSSION

Bacterial infection with *Staphylococcus aureus* is a known cause of severe illness often occurring after, and complicating, viral respiratory infection (9, 17). *In vitro S. aureus* will adhere mainly to poorly differentiated airway epithelial cells, confirming its tropism for injured and remodelled airway epithelium (7).

Panton – Valentine leukotoxin (PVL) is a pore forming staphylococcal γ toxin encoded by the *lukSF*–PV genes (10), and is associated with skin abscesses and necrotizing pneumonia (6). Pneumonia often arises from the blood born spread of organisms from infected tissues and can follow viral respiratory infections, especially influenza (8). From 2002–3 isolates it has been estimated that <2% of *S. aureus* in the UK were PVL positive, most were methicillin sensitive, with 65% of them associated with skin and soft tissue infections, 17% with pneumonia (3). Gillet *et al* (1) compared the clinical features of PVL positive and PVL negative pneumonias and found in contrast to PVL–negative pneuomonia patients, those with PVL–*S. aureus* were younger and mostly immunocompetent. They presented with influenza like symptoms, high fever, tachycardia, tachypnoe, heamoptysis and bilateral infiltrates, and pleural effusion more often. Other case series confirm the characteristics and severity of PVL – positive infections. (7,4,5,11). The symptoms of the described patient were equal with the described features.

Combined empirical antibacterial therapy of wide spectrum antibiotics is used in life–threating infections. We used ceftriaxone and oxacillin empirically to treat atypical pneumonia in addition to antiviral therapy with oselatamivir phosphate (12). Oseltamivir phosphate was started due to possibility of influenza infection and severe condition of patient (18). Due to a rapidly worsening general condition and changes in the chest X–ray which was similar to PVL caused pneumonia, clindamycin was added one day after the initial therapy. International guidelines not been published for the therapy of necrotising pneumonia caused by PVL positive *S. aureus*, however some local guidelines do exist (19), and mostly recommend the use of protein synthesis inhibiting antibiotics including clindamycin – when guided by in vitro susceptibility results. In addition, several publications recommend the addition of clindamycin in the treatment of toxin producing Gr+ bacteria as it may reduce toxin production (13).

Besides conservative therapy, surgery was also used due to the patients severe condition after two weeks, treatment with broad spectrum antibiotics and intensive care therapy. There is controversy over the indications and best timings for surgery in cases of pulmonary necrosis, especially in children. In our case the operation was done successfully despite the postoperative fistula, after the lobectomy, which prolonged the patients stay in hospital.

PVL positive *S. aureus* with *spa* type *t435* are mostly methicillin susceptible and are spread in Latvia with sporadic cases in Poland, Austria, Romania and Hungary (2). In Latvia PVL positive *S. aureus* with *spa* type *t435* is spread among children with purulent skin and soft tissues infections (Cupane, in preparation).

Our described case exposes that PVL – positive *S. aureus* with *spa* type *t435* can complicate influenza in otherwise healthy children, with rapid progression to

severe pneumonia that needs complicated and long management of the illness.

Conflict of interest: None

REFERENCES

1. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, et al. Association between Staphylococcus aureus strains carrying gene for Panton – Valentine leukkocidin and highly lethal necrotaising pneumonia in young immunocompetent patients // Lancet, 2002; 359: 753 – 759
2. Grundmann H, Aanensen DM, van den Wijngaard CC, Webster C, Tami A, Feil EJ, et al. // PLoS Med, 2010 ; 12: 7(1)
3. Holmes A, Ganner S, McGuane S, Pitt TL, Cookson BD, Kearns AM. Staphylococcus aureus isolates carrying Panton – Valentine leucocidin gene in England and Wales: frequency, characterization, and association with clinical disease // J Clin Microbiol, 2005; 5: 2384. – 2390
4. Hussain A, Robinson G, Malkin J, Duthie M, Kearns A, Perera N. Purpura fulminans in a child secondary to Panton – Valentine leukocidin – producing Staphylococcus aureus // J Med Microbiol, 2007; 56: 1407– 1409
5. Kravitz GR, Dries DJ, Peterson ML, Schlievert PM. Purpura fulminans due to Staphylococcus aureus // Clin Infec Dis, 2005; 40: 941–947
6. Lina G, Piemont Y, Godail–Gamot F, Bes M, Peter MO, Gauduchon V, et al. Involvment of Panton–Valentine leukocidin–producing Staphylococcus aureus in primary skin infections and pneumonia // Clin Infec Dis, 1999; 29:1128–1132
7. Mongodin E, Bajorel O, Hinnarsky J, Puchelle E, de Bentzmann S. Cell wall–associated protein A as a tool for immunocolonization of Staphylococcus aureus in infected airway epitelium // J Histochem Cytochem, 2000; 48: 523 – 534
8. Morgan M. Staphylococcus aureus, Panton – Valentine leukocidin, and necrotising pneumonia // BMJ, 2005; 331: 793 – 794
9. Peltola VT, McCullers JA. Respiratory viruses predisposing to bacterial infections: role of neuraminidase // Pediatr Infect Dis J, 2004; 23: 87– 97
10. Prevost G, Mourey L, Colin DA, Menestrina G. Staphylococcal pore – forming toxins // Microbiol Immunol, 2001; 257: 58 – 83
11. Roberts JC, Gulino SP, Peak KK, Luna VA, Sanderson R. Fatal necrotizing pneumonia due to a Panton – Valentine leukocidin positive community–associated methicillin – sensitive Staphylococcus aureus and Influenza co– infection: a case report // Ann of Clin Microbiol Antimocrob, 2008; 7: 5
12. Sectish TC, Prober CG. Chapter 397 – Pneumonia // In Kliegman RM, Behrman RE, Jenson HB,Stanton BF. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders Elsevier; 2007; 1795 – 1799
13. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallance RJ, Bryant AE. Impact of Antibiotics on Expresion of Virulence–Associated Exotoxin Genes in Methicillin–Sensitive and Methicillin–Resistant Staphylococcus aureus //J Infec Dis, 2007; 195: 202– 211
14. Who is more at risk of severe illness? What about other risks? [WHO web site] 24 February 2010. Available at: http://www.who.int/csr/disease/swineflu/frequently_asked_questions/risk/en/index.html Accesesed April 10, 2010
15. Results of laboratory confirmed cases of novel influenza A H1N1. [Infectology Center of Latvia web site] Available at: http://www.lic.gov.lv/docs/268/2010/jauna%20gripa_LIC_16012010.pdf Accessed April 16, 2010
16. High pandemic (H1N1) 2009 activity, particularly in children. WHO/Europe outbreak update, 30 November 2009. Available at: http://www.euro.who.int/influenza/AH1N1/20091202_1 . Accessed April 16, 2010
17. Surveillance for Pediatric Deaths Associated with 2009 Pandemic Influenza A (H1N1) Virus Infection – United States, April–August 2009, September 4, 2009 / Vol. 58 / No. 34 / Pg. 941 – 968 Morbidity and mortality weekly report, CDC
18. WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses [WHO web site]. February 2010. Available at: http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html Accesed April 16, 2010
19. Health Protection Agency. Revised guidance on the diagnosis and management of PVL–associated Staphylococcus aureus infections (PVL–SA) in the UK. [HPA web site] 2008 Available at: http://www.hpa.org.uk/PVL–SA_FinalGuidance.pdf

Address:
Liene Cupane,
Riga Stradins University, Department of Paediatrics
Vienibas gatve 45
LV-1004 Riga, Latvia
E-mail: lcupane@tvnet.lv

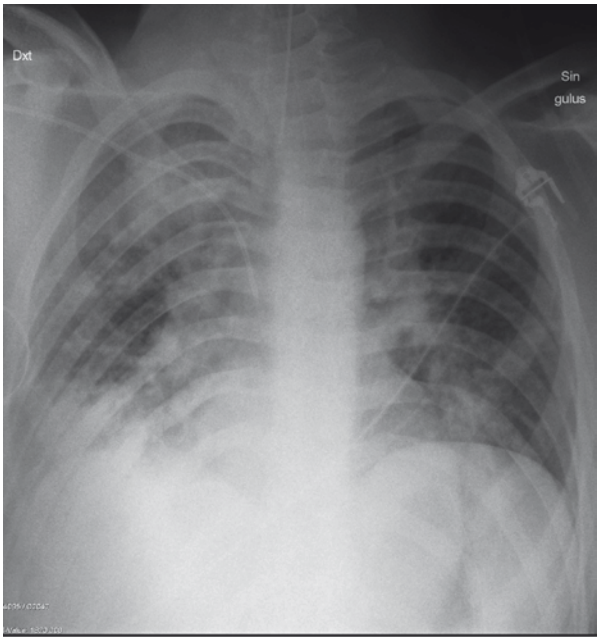


Fig. 1. Chest X–ray on admission with multiple focal shadows on the both sides of the lungs and unilateral intensive infiltration in the middle part of the right lung that suggested the severe bilateral pneumonia

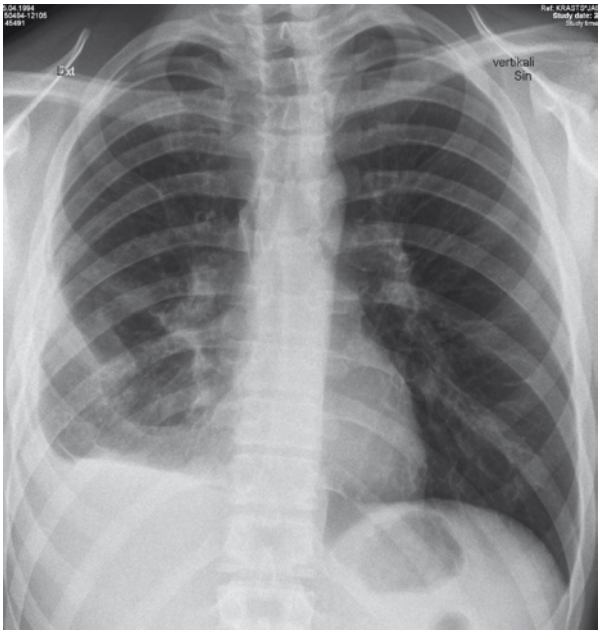


Fig. 2. Chest X–ray when the patient was discharged after resection of middle part of the right lung with clinical improvement

CASE REPORT

Patient with Syphilitic Thoracic and Abdominal Aortic Aneurysms

Kaspars Kisis*, Dainis Krievins*, Marcis Gedins*, Janis Savlovskis, Natalija Ezite**, Patricija Ivanova *****
*** Pauls Stradins Clinical University Hospital, Department of Vascular surgery, Latvia**
**** Pauls Stradins Clinical University Hospital, Institute of Radiology, Latvia**
***** University of Latvia**

SUMMARY
We are presenting a rare case of patient with two syphilitic aneurysms localized in thoracic and abdominal aorta. Routine lung computer tomography (CT) for the patient with complains about irritating and unclear ethiology cough revealed 10 cm diameter aneurysm of descending thoracic aorta (TAA) and additionally 4.8 cm aneurysm of abdominal aorta (AAA) just below the aortic hiatus. As there was no evidence of previous trauma, Marfan syndrome or connective tissue disease patient was screened for syphilis. Diagnosis of tertiary syphilis was confirmed and specific treatment started. As complains of irritating cough intensified – patients TAA was successfully treated endovascularly with thoracic stent graft (Valiant®Captivia, Medtronic Ltd.) on emergency basis. On control CT angiography 3 month after treatment there was no evidence of graft migration, endoleaks and aneurysmal sac was thrombosed. AAA has not increased in size, and open repair is planned.
Key words: syphilitic aneurysm, endovascular treatment.

AIM OF THE DEMONSTRATION

The aim of this article is to demonstrate a very rare condition – two syphilitic aortic aneurysms and successful treatment of TAA.

CASE REPORT

51 years old male with complains of chronic and increasing irritating cough underwent regular X–ray and CT exam of thorax. Performed lung CT scan was suspicious for thoracic aorta aneurysm. Patient was sent to P.Stradins Clinical University Hospital (CUH) department of vascular surgery for more extensive examination. CT angiography confirmed diagnosis of saccular TAA of 10 cm in diameter (picture 1) with an additional finding of 4.8 cm diameter aneurysm of abdominal aorta just below diaphragm (picture 2). As there was no evidence of previous trauma or connective tissue disease, patient was screened for syphilis and screening tests where positive. Final diagnosis tertiary syphilis was confirmed by *Treponema pallidum hemagglutination* assay (TPHA). Specific treatment was started with antibiotics – Penicillin G (for 1 month), but irritating cough became stronger indicating possible growth of TAA 3 weeks later. As growth of TAA could endanger patient's life due to rupture, decision to treat TAA endovascularly on emergency basis was made. The operation was performed in the vascular radiology laboratory under general anaesthesia. The right common iliac artery approach through the 5 cm incision parallel to the inguinal ligament was used to insert a stent graft delivery system. After applying 5000 units of heparin steerable 0.035 guidewire Back–Up Meier (*Boston Scientific Scimed. Natick, MA*) was inserted through a Pigtail catheter (*Merit Medical OEM, South Jordan, UT*) and positioned in the aortic arch. Percutaneous access to the left common femoral artery for angiographic control was gained through a 6 Fr sheath. The pig–tail catheter was inserted over a Hydrophilic 0.035 Terumo Glidewire (*Terumo Interventional Systems. Somerset, NJ*) and positioned in the aortic arch near the aortic valve. Over the Back–Up Meier guidewire 40×40×150 mm Valiant®Captivia Thoracic Stent graft (*Medtronic Ltd.*) delivery system was introduced and positioned in the aortic arch via 24 Fr sheath system (picture 3). An aortography of the arch was performed through the pig–tail catheter to ensure correct positioning and the stent graft was successfully deployed just distally from the origin of left subclavian artery (picture 4). The pig–tail catheter was removed and left common iliac artery was closed using Angio Seal (*St. Jude Medical. Minnetoka, MN*) vascular closure device. After the removal of the delivery system right common iliac artery was closed with a 6–0 Prolene interrupted suture. Abdominal aortic aneurysm was left untreated at this time.
The patient stayed for 24 hours in the intensive care unit ICU and was discharged from the hospital 4 days after the operation. Patient finished antibacterial treatment and a control CT angiography was performed after 3 months (picture 5). There were no signs of endoleak, stent graft migration, fracture or perfusion of the excluded aneurysmal sac.

DISCUSSION

Present days syphilitic aneurysms are rare pathology. Only some case reports have been published in literature over the last decade. We have not found any publication regarding double syphilitic aneurysm so far in English speaking literature (5, 8). Tertiary syphilis usually occurs 1–10 years after the initial infection, however in some cases it can take up to 50 years. This stage is characterized

by the formation of gummas, which are soft, tumor–like balls of inflammation known as granulomas. The more severe manifestations include neurosyphilis and cardiovascular syphilis. In a study of untreated syphilis, 10% of patients developed cardiovascular syphilis (7), 16% had gumma formation and 7% had neurosyphilis. Cardiovascular complications include syphilitic aortitis, aortic aneurysm, aneurysm of sinus of Valsalva and aortic regurgitation. Syphilis infects the ascending aorta causing aortic dilation and aortic regurgitation. Contraction of the tunica intima leads to a tree bark appearance that is wrinkly. The aortic valve dilation and subsequent insufficiency leads to diastolic regurgitation and causes hypertrophy of the left ventricle. The clinical course of these cardiovascular effects causes mediastinal encroachment and secondary respiratory difficulties (dyspnea), difficulty swallowing (dysphagia) and persistent cough because of pressure on the recurrent laryngeal nerve triggering the cough reflex, which was observed in our case. The aneurysm developed during the disease course may also rupture, leading to massive intrathoracic hemorrhage and likely death (2, 1), although the most likely cause of death is the heart failure resulting from aortic regurgitation. Syphilis screening tests, such as the Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests are not completely specific, as many other conditions can cause a positive result (4). False positives on the rapid tests can be seen in viral infections (Epstein–Barr, hepatitis, varicella, measles), lymphoma, tuberculosis, malaria, Chagas Disease, endocarditis, connective tissue disease, pregnancy, intravenous drug abuse. As a result, these two screening tests should always be followed up by a more specific treponemal test. Tests based on monoclonal antibodies and immunofluorescence, including TPHA and Fluorescent Treponemal Antibody Absorption (FTA–ABS) are more specific. Because the VDRL has a high sensitivity but low specificity, it is used as a screening test. Today, treponemal FTA–ABS TPHA tests are considered confirmatory assays with high specificity (98 %) and sensitivity (5).

In our case positive TPHA test and clinically saccular and irregular size of the anurysms helped to make proper diagnosis of syphilitic aneurysm.

Ascending aorta and aortic valve is the most common location of syphilitic aneurysms in most papers published. We could not find any report about simultaneously diagnosed syphilitic aneurysms of thoracic and abdominal aorta and treatment options in such case. Usual praxis is to treat acute infection of syphilis or other infection causing aneurismal disease and then proceed with open or endovascular treatment of aneurysm (3, 6). However, escalation of symptoms increased risk of rupture and in this case strategy of emergency aneurysm endovascular repair was important to save patients life.

Aneurysm of abdominal aorta at the time of repair of TAA was of relatively small size so it was left untreated. Patient also had no pain in abdomen or other complains related with. AAA was unchanged on 3 month follow CTA scans. Nevertheless, AAA has sacullar shape, there is still risk of rupture despite small aneurysm size. Unfortunately involvement of mesenterial vessels in aneurysm (*truncus coeliacus* and *superior mesenteric artery*) excludes possibility to treat patient endovascularly with currently availably endografts. Therefore we are planning open surgical repair of AAA for this patient.

Conflict of interest: None

REFERENCES

1. Bethany Goldstein, Alfio Carrocio et al. Combined open and endovascular repair of a syphilitic aortic aneurysm // J Vasc Surg 2003;38:1422–5
2. Eduard Kieffer, Laurent Chice, Fabien Kosltas, Amine Bahnini. Aneurysms of the innominate artery: Surgical treatment of 27 patients // J Vasc Surg 2001;34:222–8
3. G. Gilling–Smith. The evidence for endovascular aneurysm repair // In: J Earnshaw, John A Murie The evidence for vascular surgery. 2nd edition, Shrewsbury, tfm Publishing Limited, 2007; 145–153
4. Larsen SA, Steiner BM, Rudolph AH. // Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev 1995;8:1–21
5. Luis R. Leon, Joseph L. Mills. Diagnosis and management of mycotic aneurysms // vasc endovasc surg 2010 44:5
6. P. Allen Hartsell et al. Clinical manifestation and management of subclavian artery aneurysms. // perspect vasc surg endovasc ther 1999; 10: 69
7. Ravul Jindal, Michael Jeankins. Mycotic aneurysms // In: Sinmon D. Parvin, Jonothan J. Earnshaw Rare vascular disorders. 1st edition, Shrewsbury, tfm Publishing Limited, 2005; 237–245
8. Torsten Bossert, R.Battellini, V.Kotowitcz, V.Falk, J.F.Gummert, F.W.Mohr. Ruptured giant syphilitic aneurysm of the descending aorta in an octogenarian // J Card Surg 2004;19:356–357

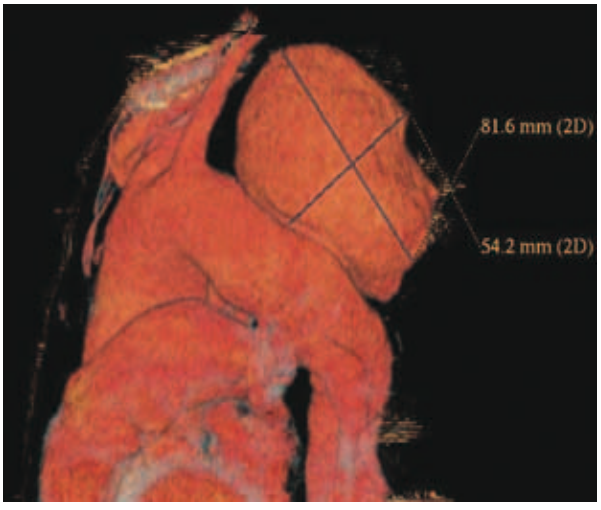


Fig. 1. Large aneurysm of descending thoracic aorta

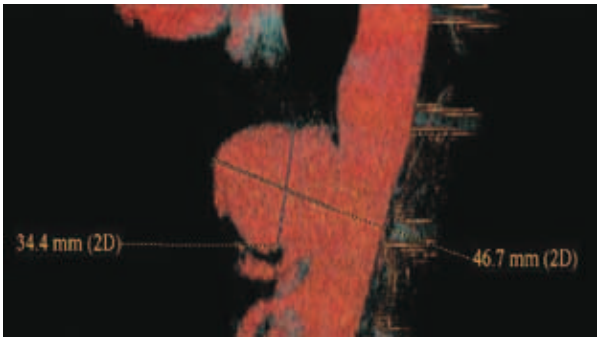


Fig. 2. Aneurysm of abdominal aorta

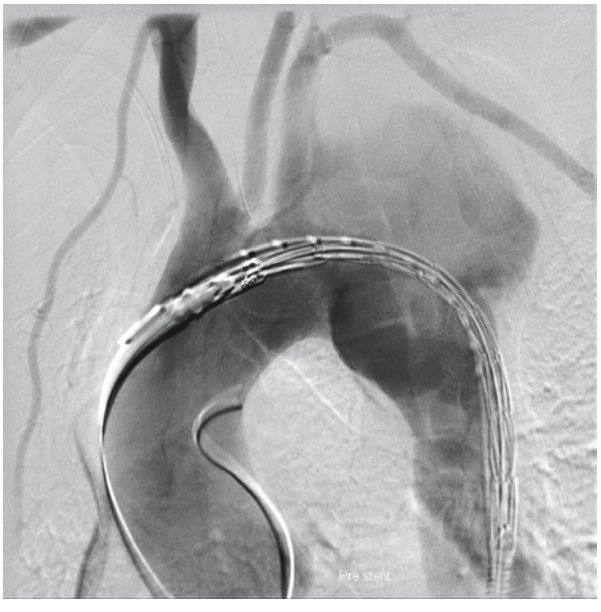


Fig. 3. Thoracic endograft placed in thoracic aorta

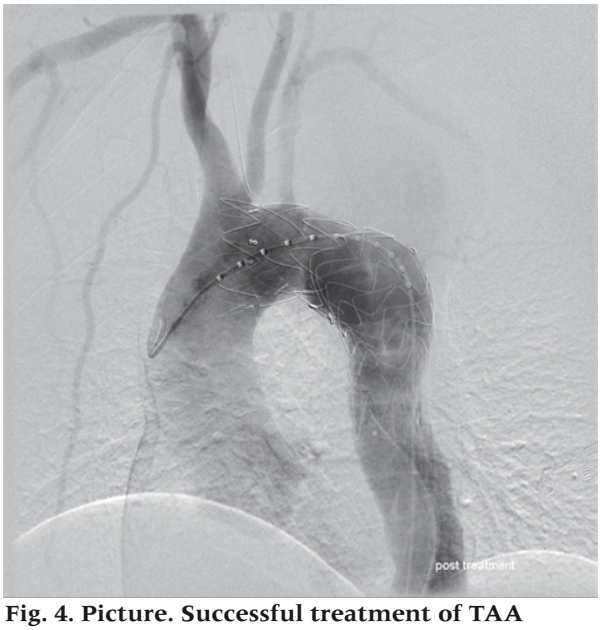


Fig. 4. Picture. Successful treatment of TAA

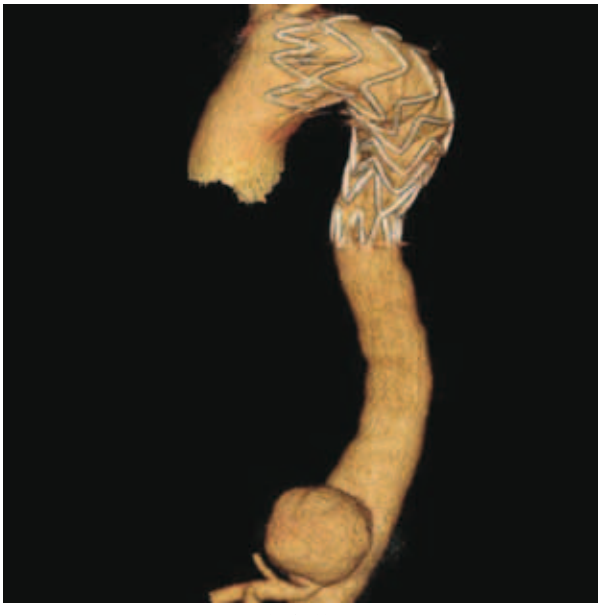


Fig. 5. Picture. 3 month follow up

Address:
Dainis Krievins
Pauls Stradins CUH, Department of Vascular surgery
Pilsonu Street 13
LV-1002, Riga, Latvia
E-mail: dainis.krievins@stradini.lv

DOI: 10.2478/v10163-011-0029-6

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

CASE REPORT

Management of a Patient with Double Aortic Arch and Severe Tracheal Compression

Aris Lacis, Inta Bergmane, Elina Ligere, Valts Ozolins, Lauris Smits, Normunds Sikora
Children`s University Hospital, Department of Pediatric Cardiology and Cardiac Surgery, Riga, Latvia

Summary
Vascular ring presents less than 1% of all congenital cardiovascular anomalies and may cause respiratory symptoms and feeding problems, double aortic arch (DAA) is the most common vascular ring (40%).The anomaly is due to a failure of regression of both the right and the left fourth branchial arches, resulting in right and left aortic arches which completely encircle and compress the trachea and esophagus, producing respiratory distress and feeding problems in early infancy (1, 2, 3, 4). The first post–mortem description of double aortic arch was in 1737 by Hommell. In 1945 Gross accomplished the first successful surgical intervention for a DAA (3). Double aortic arch is commonly an isolated anomaly but is occasionally associated with a variety of congenital heart defects (ventricular septal defect, transposition of the great arteries, tetrology of Fallot, coarctation of the aorta and chromosomal abnormalities as microdeletion of 22q11.2. The clinical course of the disease and its manifestation depends on the compression of the esophagus and trachea. The most common symptoms are persistent cough (78%), dyspnoe (75%), recurrent respiratory infections (56%), feeding problems (25–40%), and failure to thrive (5%). Symptomatic tracheobronchial compression varies inversely with the severity of compression. Tracheal compression causes airflow obstruction and decreased mucociliary clearance of secretions, leading to recurrent bronchopulmonary infections. Reflex apnoe is hypothesized to be a type of respiratory arrest that occurs when vagal afferent nerves are stimulated. Respiratory distress and a history of recurrent pulmonary infections and apneic spells are indications for surgical intervention (1, 2, 3). Division of the smaller of the two arches (usually the left) is performed through the left thoracotomy. There are three successful operations in the cases of vascular ring done in the Clinics for Pediatric cardiology and Cardiac surgery of University hospital for Children in Riga. We present the one of the cases with successful treatment of severe tracheal compression.
Key words: double aortic arch, vascular rings, congenital cardiac disease, cardiovascular surgery.

AIM OF THE DEMONSTRATION

Aim of the demonstration is to show the complete resolution of severe tracheal compression after the surgical treatment of double aortic arch.

CASE REPORT

The female patient N. was first hospitalized at the age of two months due to obstructive bronchitis, inspiratory and expiratory stridor. The child was born to healthy mother from the 5th pregnancy, 3rd delivery at the gestation age of 37 weeks, birth weight 2850g. She was breastfed for two weeks and afterwards received adapted formula. The child had frequent regurgitations, wheezing was observed following feeding. At the admission to the hospital at the age of two months weight was 5300g, some disembriogenic stigmata were observed– hypertelorism, small ears. The heart rate was 156 times per minute with systolic murmur grade 3/6 with maximum at the left 3rd intercostal space, normal femoral pulses, no hepatomegaly present. The child was breathing with a use of accessory muscles, prolonged expiration and dry crackles auscultated. The direct laryngoscopy showed the signs of acute laryngitis. The thoracic X–ray showed the small shadow of glandula thymus, no signs of congestion and the cardio–thoracic coefficient was 0,59. Electrocardiogram was consistent with the patient's age –synus rhythm 166 times per minute while baby crying. Echocardiography revealed perimembranous ventricular septal defect 5mm in size with a left to right shunt with pressure gradient 92mmHg, LVDd 22mm, fractional shortening (FS) 40%, ejection fraction >60%, aortic valve 8mm, pulmonary artery 10mm, patent foramen ovale 3mm. Neurosonography and abdominal ultrasound examination were without pathological changes. Clinical analyses were within the normal range. 24– Hour ph–metry showed 1, 5% total number of refluxes. The child had normal karyothype, microdeletion of chromosome 22q11.2 excluded. During the hospital stay she received inhalations with Salbutamol, Budesonide and Furosemide, Verospirone, Captopril as a treatment of cardio–vascular insufficiency. The baby was fed with formula Aptamil pepti with rice flour addition. The girl was discharged from the hospital with diagnoses: congenital heart disease, ventricular septal defect, cow's milk protein intolerance, gastro–esophageal reflux, reflux laryngitis, obstructive bronchitis. At home the baby received the same therapy of cardio–vascular insufficiency, inhalations, omeprazol. At the next visit to paediatric cardiologist mother complained that the child's condition has not improved and the wheezing is still observed. The child was admitted to the hospital for the further examination at the age of 4 months. The contrast x–ray of the esophagus showed slight compression of the esophagus

at the level of the 4th thoracic vertebra. The computed tomography with angiography due to double aortic arch suspected was performed. It revealed the double aortic arch with severe tracheal compression (the size of trachea at the narrowest point was 1,8mm), the size of both arches was 1:1. Because of the severe tracheal compression the bronchoscopy was performed which showed normal larynx and unchanged vocal cords, 2/3 of the upper tracheal lumen was free and the tracheal mucous tissues without the signs of inflammation. The tracheal lumen was fissure–like 2 cm above the bifurcation, compression from the outside suspected, the length of the compressed segment was 1,5 cm and it was possible to cross it with the bronchoscope. The operation: left thoracotomy, division of the double aortic arch (division of the left arch) was performed at the age of 5 months. The bronchoscopy following the operation showed the deformation of the tracheal lumen but it was easy to cross with the bronchoscope. Repeated computed tomography 6 months after the operation showed almost complete resolution of the tracheal compression. The child develops normally, no symptoms of wheezing observed, the ventricular septal defect closed spontaneously and the therapy was discontinued.

DISCUSSION

Double aortic arch is a rare congenital heart disease although the most frequently observed vascular ring that completely encircles trachea and esophagus. Remarkable history of respiratory distress, postprandial choking since birth, dysphagia and recurrent infections of lower respiratory tract are noted in majority of patients with double aortic arch (1,2). In every infant with wheezing, stridor and disphagia the presence of a double aortic arch should be carefully ruled out. Barium esophagogram is a valuable investigation which frequently shows indentation of the esophagus in the case of a vascular ring and can be safely and rapidly performed. Echocardiography is very useful to identify the associated congenital heart defects but the definite diagnosis of a double aortic arch is not easy because only subcostal and suprasternal views offer diagnostic windows for identifying a double aortic arch. For sufficient evaluation of the patient prior to surgery computed tomography (CT) or magnetic resonance imaging (MRI) is performed to improve the outcome through the ability to plan the operative strategy. Preoperative bronchoscopy can be performed to rule out associated tracheomalacia and bronchomalacia and is important for long and shot term prognosis. Outcomes are excellent after repair of double aortic arch, although persistent respiratory symptoms are frequent and probably associated with previous compression–related maldevelopment of the trachea and major airways.
Early diagnosis and surgery are important to reduce the long–term sequel of tracheobronchial compression in children.

Conflict of interest: None

REFERENCES

1. Alsenaidi K, Gurofsky R, Karamlou T, Williams WG, McCrindle BW. Management and Outcomes of Double Aortic Arch in 81 Patients// Pediatrics, 2006; 118:1336–1341
2. Park MK, Vascular Ring// In: Pediatric Cardiology for Practitioners. 5th ed. USA, Mosby Elsevier; 2008; 303–308
3. Shanmugam G, Macarthur K, Pollock J. Surgical Repair of Double Aortic Arch**:** 16–year Experience // Asian Cardiovasc Thorac Ann, 2005; 13:4–10
4. Weinberg PM, Aortic arch anomalies, Double Aortic Arch // In: Heart Disease in Infants, Children, and Adolescents. 7th ed. USA, Moss and Adams, Lippincott Williams and Wilkins, 2008, Volume 1, 749–752

Address:
Elina Ligere
Children`s University Hospital,
Department of Pediatric Cardiology and Cardiac Surgery
Vienības gatve 45, LV-1004,
Riga, Latvia
E-mail: eteivane@inbox.lv

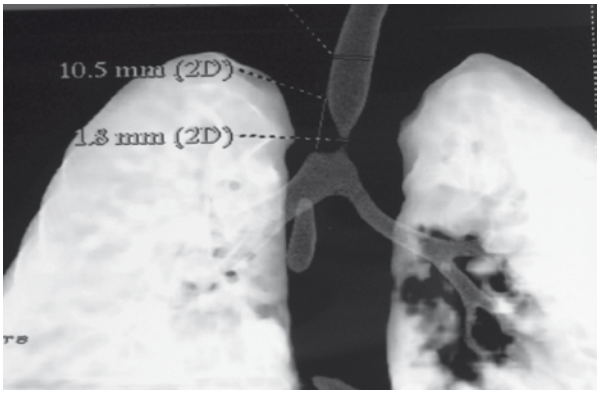


Fig. 1. Computed tomography at the age of 4 months: severe tracheal compression due to a double aortic arch

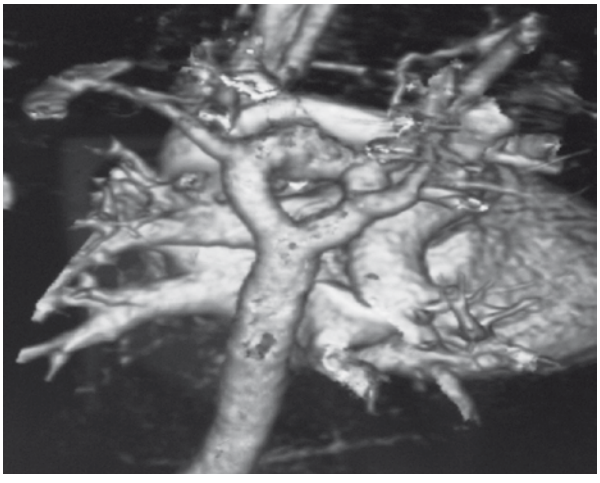


Fig. 2. CT: a double aortic arch (the size of both arches 1:1)

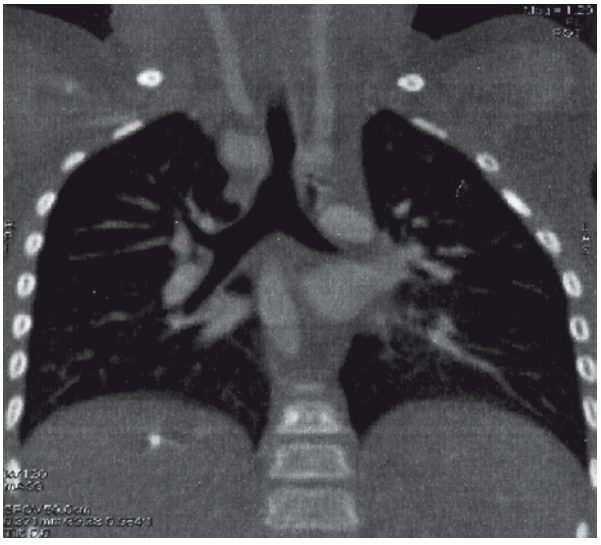


Fig. 3. Repeated computed tomography 6 months after the operation– almost complete resolution of the tracheal compression

CASE REPORT

Modified Senning Operation in the Treatment of Transposition of The Great Arteries

Aris Lacis *, Inguna Lubaua, Lauris Smits*, Valts Ozolins*, Normunds Sikora*, Zane Straume***
***Children's University Hospital, Clinic for Paediatric Cardiology and Cardiac Surgery**
****Riga Stradins University , Pediatric Chair, Riga, Latvia**

Summary
The arterial switch operation has become the procedure of choice for patients with transposition of the great arteries(TGA) in most medical centres. Although atrial switching may occasionally be employed in some centres in cases with delayed diagnosis, pulmonary hypertension and some other unusual entities. We preferred to use the atrial switch operation – modified Senning procedure for 6 years 6 months old boy with TGA , small atrial septal defect (ASD) and patent ductus arteriosus (PDA).
Key words: congenital heart disease, transposition of great arteries, modified Senning procedure, myocardial protection.

AIM OF THE DEMONSTRATION

The aim of this article is to demonstrate a case of successful repair of TGA in case of delayed diagnosis and complicated with high pulmonary hypertension.

CASE REPORT

On the 26 January 2009 a 6 years 6 months old boy with TGA , small ASD and PDA was repaired using the modified Senning procedure. His body weight was 12,5 kg (– 3 standart deviations). A patient was referred to us for progressively increasing cyanosis and dyspnoea on exertion. Clinical examination , chest radiography and echocardiography all comfirmed the diagnosis of the TGA with small ASD and PDA. The saturation of oxygen ranged between 51and 57%, hematocrit was 66,6%.

Surgical technique

The heart was exposed through a median sternotomy incision and purse– string sutures are placed in the ascending aorta for arterial cannulation and directly upon each vena cava for venous cannulation. Before cardiopulmonary bypass was established, the circumferences of the superior vena cava (SVC) and inferior vena cava (IVC) were measured and recorded. Marking sutures were placed on the interatrial groove to define the cephalic and caudal point extent of the left atriotomy. Cardiopulmoary bypass was established and patient's temperature was decreased to + 24° C. The aorta was cross –clamped, and cold blood cardioplegia was started. The right atrium was opened superiorly 1 cm anterior to the crista terminalis and the incision was extended anteriorly to the previously placed marking sutures near the junction of the IVC and right atrium. The atrial septum was inspected, and a flap was created from limbic tissue anteriorly toward the superior and inferior aspects each right pulmonary vein. The flap remains attached at the interatrial groove. A small patch of pericardium was sutured to the septal flap to make them adequate size for reconstruction the new septum. The hinged interatrial flap was then sewn along into place using longitudinal bites in the left atrial wall and horizontal bites in the atrial septal flap. The caval pathway was completed anteriorly by stitching (with continuous 5–0 Prolene sutures) the caudal extent of the right side of the free atrial wall to the atrial tissue about the IVC orifice and continuing to the coronary sinus. The coronary sinus was left to drain with pulmonary venous blood. A second suture was used to complete the superior attachment around the SVC.
The perimeter of the left atriotomy was extended by incising the tissues between both right pulmonary veins. The original right atrial incision was extended cephalic. The pulmonary venous atrium was constructed by using the autopericard flap in situ. The suture line was brought across the SVC that the suture line kept superior the area of the sinus node artery.(Figure 1).
Cardiopulmonary bypass was finished by using intra aortal "hot–shot" and rewarming.
Following the surgical procedure, repeated echocardiography demostrated good potency of tunnel between pulmonary veins and tricuspid valve and between the systemic veins and mitral valve.(Figure2). Postoperative period was uneventful. Saturation of oxygen increased until 97%. Electrocardiogramm shows no rhythm disturbances.

DISCUSSION

The arterial switch operation has become the procedure of choice for patients with TGA in most cardiac surgery centres (4,7). In cases of delayed diagnosis and complicated with high pulmonary hypertension, when arterial switch operation is contraindicated, only atrial switch is the best option for patient. Although atrial switching like Mustard or Senning procedures may occasionally be employed in some centres for this entity, its principal application is in the double switch operation for patients with congenitaly corrected tansposition and some other unusual entities, for example for patient older than 12 months to preserve left ventricular function (2,3,5).

Brom pioneered the revival of the original Senning operation, with some technical modifications, and this restored interest in this type of venous switching (8, 9). In our case the pulmonary venous atrium was completed by suturing the anterior component of the original right atrial wall to the pericardium in situ(1). The pericardium in situ technique for completing the pulmonary venous atrium is similar to the technique described by Lacour– Gayet and others for dealing with pulmonary vein stenosis (6).

Conflict of interest: None

REFERENCES

1. Castaneda AR, Jonas RA, Mayer IE. Cardiac surgery of the neonate and infant // Philadelphia, WB Saunders, 1994; 430
2. Hibino N, Imari Y, Aoki M. Double–switch operation for superior –inferior ventricles// Ann Thor Surg, 2001; 72: 2119–2121
3. Ilbawi MN, DeLeon SY, Backer CL. An alternative approach to the surgical management of physiologically corrected transposition with ventricular septal defect and pulmonary stenosis or atresia // J Thorac Cardiovasc Surg, 1990; 100: 410–415
4. Jonas RA, Laussen P. Transposition of the great arteries // In: Comprehensive surgical management of congenital heart disease. Hodder Arnold Publication, 2007; 256–279
5. Karl TR, Weintraub RG, Brizard CP. Senning plus arterial switch operation for discordant (congenitally corrected) transposition // Ann Thorac Surg, 1997; 64: 495–502
6. Lacour – Gauet F, Rey C, Planche C. Surgical obstruction after repair of total anomalous pulmonary venous connection // J Thorac Cardiovasc Surg, 1999; 117: 679–687
7. Mee LB. The arterial switch operation // In: surgery for congenital heart defects. 3 rd edition by Stark J, de Leval M, Tsang V. 2006, Jonh wiley and sons Ltd; 471–487
8. Pacifico AD. Senning operation// In: surgery for congenital heart defects. 3 rd edition by Stark J, de Leval M, Tsang V. 2006, Jonh wiley and sons Ltd; 451–457
9. Quaegebeur JM, Rahmer J, Brom AG. Revival of the Senning operation in the treatment of transposition of the great arteries // Thorax , 1977; 32: 517–524

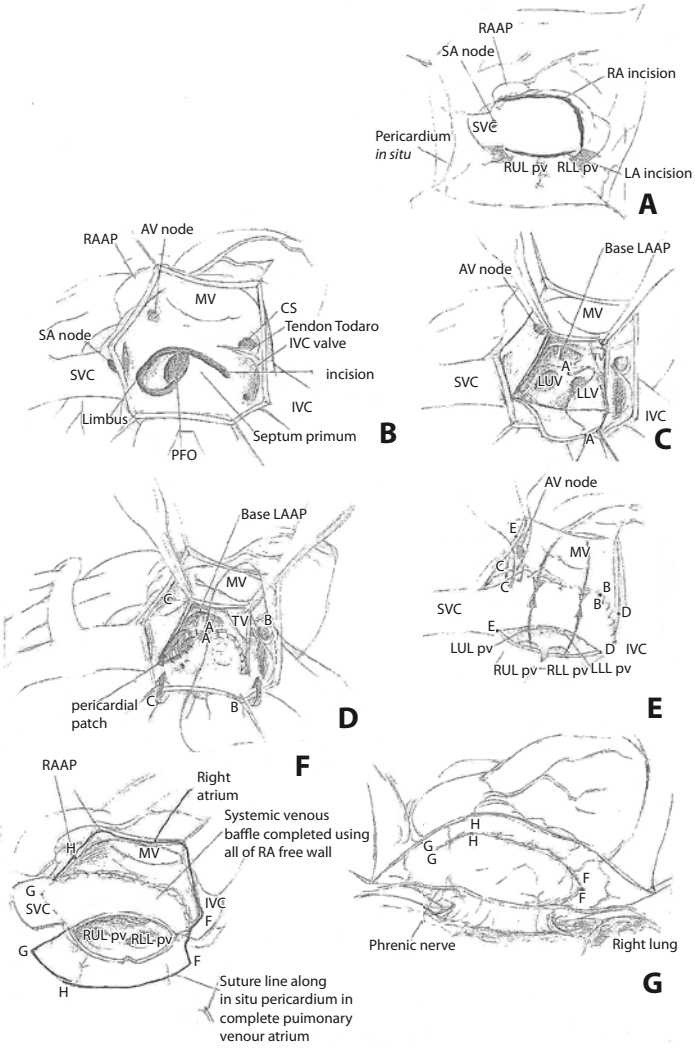


Fig. 1. Cartoons showing performing the modified Senning's procedure

A- right and left atrial incisions.

B- Inside view of the right atrium. Note the remant of septum in the area of fossae ovalis.

C- Construction of the roof of the pulmonary venous pathway. The hinged interatrial flap was sutured above the entrance site of the pulmonary veins and along the line leading to the posteriolateral angle of both the superior and inferior venae cavae and the remant of the interatrial groove.

D- Construction of the roof was finished with additional pericardial patch.

E- Completed systemic venous pathway. The lateral right atrial flap was sutured around the superior and inferior venae and along the ligament of Torado.The coronary sinus was left to drain into the neo– left atrium.

F- Constructions of the pulmonary venous pathway. The pericardial flap in situ was sutured first around the superior and inferior venae cavae and the right atrial wall.

G- The face edge of the medial right atrial flap was sutured to the free edge of the pericardium.

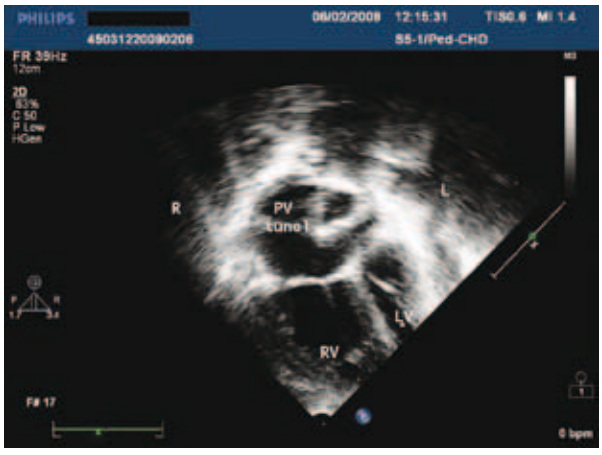


Fig. 2. Transthoracic echocardiography apical view demonstrate a tunnel from pulmonary veins to tricuspid valve. PV– pulmonary veins, RV– right ventricle, LV –left ventricle

Address:
Inguna Lubaua
Riga Stradins University, Latvia
Dzirciema street 16, Riga , LV-1007, Latvia
E-mail: inguna.lubaua@rsu.lv

DOI: 10.2478/v10163-011-0031-z

ACTA CHIRURGICA LATVIENSIS • 2010 (10/2)

CASE REPORT

Laparoscopic Repair of Paraesophageal Hiatal Hernia in a Newborn

Arnis Engelis */, Klaus Schaarschmidt***, Aigars Petersons */**, Astra Zviedre**, Mohit Kakar ****
*** Riga Stradins University, Latvia**
**** University Children`s Hospital, Riga Latvia**
***** Helios Clinic of Berlin-Buch, Berlin, Germany**

Summary
A 3-month old boy was hospitalized with the suspicion of right sided pneumonia. Examination revealed hiatal or paraesophageal hernia. Ultimately, a laparoscopic operation was performed. During the operation, PEHH of the transverse colon with displaced gastro esophageal junction was discovered. Laproscopic hiatal hernia repair with modified Thal fundoplication were performed. Recovery of child 2 years after surgery was uneventful.
Key words: hiatal hernia, paraesophageal hiatal hernia type IV, laparoscopy, laparoscopic Thal fundoplication.

AIM OF THE DEMONSTRATION

The aim of this article is to demonstrate a very rare pediatric surgical pathology, paraesophageal hiatal hernia (PEHH) type IV in a 3-month old boy.

CASE REPORT

A 3-month old boy, referred by pediatrician, to University Children's Hospital, Riga was hospitalized with high fever and suspected right-sided pneumonia. His birth weight was 3670 g, the weight at the time of hospitalization was 6165 g, the stool was regular and there was no bloating. Later on the mother confirmed that the child "ate with difficulty" ever since his birth. The baby had been ill for 4 days with a running nose, deep cough and a high fever, up to 38.1^{0}C, respiratory rate of 46 and hearth rate of 120 times per minute, slightly increased CRP (16.7 mg/l) and neutrophils count (70.3%) and had received inhalations and antibiotics. There were no pathologic respiratory sounds, merely a sharp breath. On the plain chest x-ray there was an unclear, hole-shaped shadow above the lower lobe of the right lung, which was interpreted as the above-mentioned right-side pneumonia with a possible abscess formation (Fig.1). Bronchoscopy revealed thick mucus in the lower lobes of both lungs with a growth of *Enterobacter Cloacae*, sensitive to most antibiotics. The pictures of the following gastro-intestinal barium contrast examination were interpreted as a sliding type I hiatal hernia with the cardia and fundus of the stomach above the diaphragm. Gastric evacuation was unimpeded. Topography of the duodenum was typical.
To exclude completely the congenital diaphragmatic hernia, computer tomography (CT) scan of the thorax was done. The imaging was interpreted as the *cardia* and *fundus* of the stomach and possibly the small intestinal loop located above the diaphragm, in the right side of the thorax (Fig.2). The 24-h pH-metry revealed an unanimously pathologic 11% acid reflux time below pH 4. On the basis of these findings, the working diagnosis of the hiatal or paraesophageal hernia was considered and a laparoscopic hiatus repair with Thal fundoplication was planned.
The operation was performed with 4 ports of 5-mm and an additional V-stitch for the liver retraction. Surgical exploration revealed the PEHH of the transverse colon and displaced gastro esophageal junction (PEHH type IV) (Fig.3). Puncturing of the distended colon loops and gas aspiration were performed to improve sight. The transverse colon and the stomach were carefully repositioned and a large congenital hiatal defect was revealed (Fig.4). The colonic wall did not show any signs of strangulation. After the repositioning the esophagophrenic and gastrophrenic ligaments appeared large and loose and were involved in the formation of the hernial sack. A hiatoplasty with modified Thal fundoplication were performed, and the hernia sack was partially removed. The operation lasted 3 hours 30 minutes. The postoperative course was uneventful.
The child is doing perfectly well 2 years after the operation and has normal 24-hour esophageal pH-metry results after 6 months and 2 years (we do a further control after 5 years routinely).

DISCUSSION

Statistically, hiatal hernia type I or the sliding hiatal hernia of the stomach has been estimated to form the largest incidence rate with 95% or more of all hiatal hernias in children, while types II, III and IV accounts for the rest of 5% of all paraesophageal hiatal hernias (PEHH). In contrast to sliding hiatal hernia, PEHH is a true hernia which usually contains the stomach or a part of it along with the small intestine, spleen, colon, or combinations of these organs (4,10). Transverse colon is the rarest content of PEHH and in children only very few cases have been reported so far, therefore differential diagnosis with congenital diaphragmatic

hernia can be difficult. The displaced transverse colon is usually symptomatic but not strangulated (3,4,6,9). PEHH generally requires surgical treatment (1,4,8,12).
PEHH is very rare in adults comprising less than 5% of all hiatal hernias together (5,11). In children it is an extremely rare condition and the exact incidence is not reported (2,7,10,13). Symptoms of PEHH vary considerably; from asymptomatic cases or cases with scarce, non-specific clinical picture to severe, sometimes even life-threatening conditions (5). Similar is the case with type IV PEHH in a infant which is exceedingly rare and has been mentioned in only a few publications (2,4,7,10,13). The symptoms and clinical course in our patient are similar to those reported in the literature. A suspected unclear pneumonia on the x-ray picture is a typical reason directing such patients to a pediatric surgeon. Transverse colon as content of PEHH has a rather protracted clinical course with chronic respiratory infection and disorders of defecation rather than acute complications as reported by others (4,7,10).
Surgical treatment in the case of PEHH is the single solution and should not be postponed unnecessarily. In case of severe symptoms an emergency operation is necessary. In most cases the conventional Nissen fundoplication has been suggested as an antireflux procedure, and during the open procedure the hernia sack has been fully or partially removed (1,8). Laproscopic operation in the case of PEHH has been mentioned in the literature, however it has been described as much more challenging compared with the laparoscopic antireflux procedure in gastro-esophageal reflux disease. We found one report of 2 cases, where open Thal fundoplication was performed in the PEHH type III (12). No reports have been found, where the laparoscopic Thal fundoplication would have been done in the PEHH type VI. In our case the reposition of the transverse colon, the stomach and esophagus was technically easy, therefore the partial excision of the hernia sack and the antireflux procedure took up most of the operation time. In our opinion, the modified laparoscopic Thal fundoplication in this case was very satisfactory from a technical point of view and so far successful in the long run. Therefore we use it as a standard procedure in all cases of gastroesophageal reflux, hiatus hernia and PEHH in infants.

Conflict of interest: None

REFERENCES

1. Al-Sahem AH. Congenital paraesophageal hernia in infancy and childhood // Saudi Med J, 2000; 21:164 -7
2. Chandrasekar S, Welch RJ, Watson H. Congenital mixed hiatus hernia in a neonate // Arc Dis Child Fetal Neonatal Ed, 2006; 91:F317
3. Hong JY, Song KY, Kim KW, Lee WK, Ha JG, Choi SO. Two cases of congenital paraesophageal hiatal hernia in infancy // J Korean Pediatr Soc, 2000; 43:1613 - 20
4. Imamoglu M, Cay A, Kosucu P, Ozdemir O, Cobanoglu U, Orhan F, Akyol A, Sarihan H. Congenital paraesophageal hiatal hernia: pitfalls in the diagnosis and treatment// J Pediatr Surg, 2005; 40:1128 - 33
5. Kahrilas PJ, Pandolfino JE. Hiatus hernia // GI Motility Online, 2006; doi:10.1038/gimo48.http://www.nature.com/gimo/contents/pt1/full/gimo48.html.
6. Karpelowsky JS, Wieselthaler N, Rode H. Primary paraesophageal hernia in children // J Pediatr Surg, 2006; 41:1588 - 93
7. Koulopoulos K, Kostelestos S, Christopoulos-Geroulanos G, Mauridis G, Kalantzi N, Condilis N, Plataras C, Skanavis K, Kerammidas D. Paraesophageal hernia in childhood// Ann Ital Chir, 2006; 77:57 - 8
8. Kundal AK, Zargar NU, Krishna A. Laparoscopic repair of paraesophageal hiatus hernia in infancy // J Indian Assoc Pediatr Surg, 2008; 13:142 - 143
9. Ozkan H, Nergul Y. A massive hiatal hernia that mimics a congenital diaphragmatic hernia. An unusual presentation of hiatal hernia in childhood. Case Report // Surgery Today, 2002; 32:1072 - 4
10. Samujh R, Kumar D, Rao KLN. Paraesophageal hernia in the neonatal period: suspicion on chest x-ray// Indian Pediatr, 2004; 41:189 - 91
11. Vandenplas Y, Hassal E. Mechanisms of gastro esophageal reflux and gastro esophageal reflux disease // J Pediatr Gastroenterol Nutr, 2002; 35:119 - 36
12. Van der Zee DC, Bax NM, Kramer WL, Mokhaberi B, Ure BM. Laparoscopic management of a paraesophageal hernia with intrathoracic stomach in infants// Eur J Pediatr Surg, 2001; 11:52 - 4
13. Yazici M, Karaca I, Etensel B, Temir G, Gunsar C, Guclu C, Mutaf O. Paraesophageal hiatal hernias in children // Dis Esophagus, 2003; 16:210 - 3

Address:
Arnis Engelis
Department of Pediatric Surgery
University Children's Hospital
Vienibas gatve 45, Riga, LV-1004, Latvia
E–mail: arengelis@yahoo.com

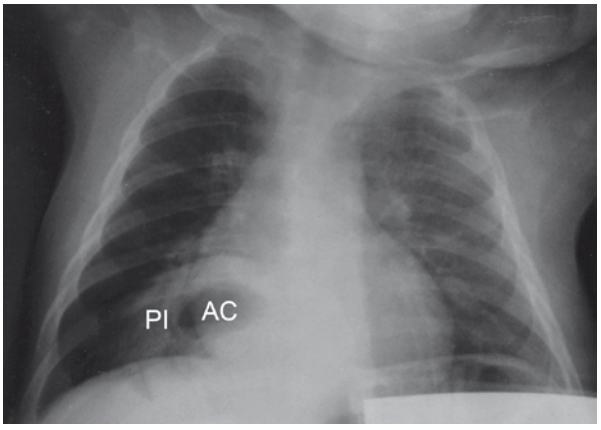


Fig. 1. Inicial thorax X-ray image. PI - suspected right side pneumonia infiltration; AC - suspected abscess cavity

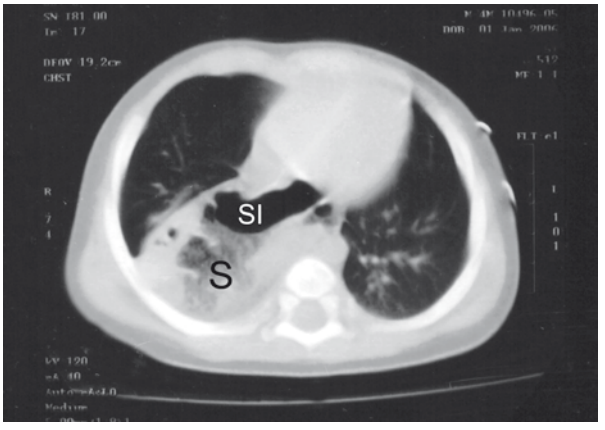


Fig. 2. Thorax computed tomography scan. S - stomach; SI – was interpreted as the small intestine in the right posterior part of the thorax

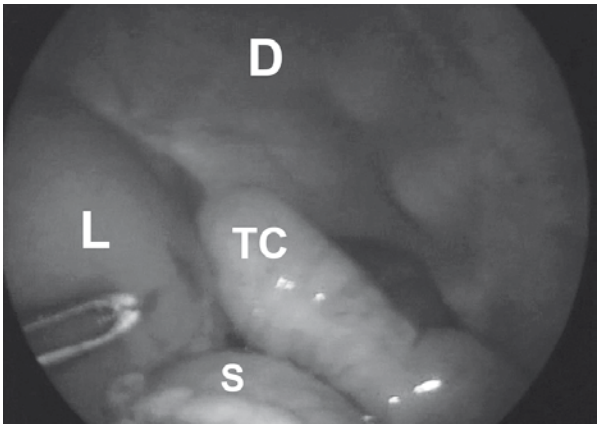


Fig. 3. Laparoscopic view. TC - transverse colon loop retreating through *hiatus esophagi* at the beginning of the procedure. L - liver; D - diaphragm; S - stomach

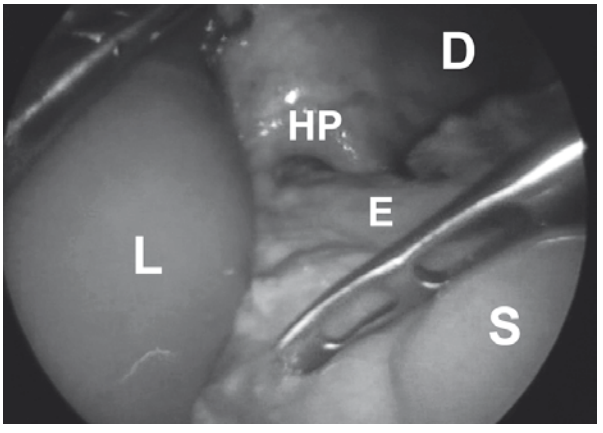


Fig. 4. Laparoscopic view. HP - paraesophageal hiatal hernia port; E - esophagus; S - stomach; L - liver; D - diaphragm