Liene Elsone

THE CLINICAL AND TREATMENT CHARACTERISTICS OF NEUROMYELITIS OPTICA

Summary of the Doctoral Thesis for obtaining the degree of a Doctor of Medicine

Specialty – Neurology

Riga, 2015
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Secretary of the Doctoral Committee of Medicine:

*Dr. med. Simona Doniņa*
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7.5 Presentation in the meetings arising from thesis (results of the thesis)

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ARR</td>
<td>Annual relapse rate</td>
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<tr>
<td>AQP4</td>
<td>Aquaporin 4</td>
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<td>AZA</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>b/l</td>
<td>Bilateral</td>
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<td>BUH</td>
<td>University Hospitals of Birmingham</td>
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<td>C</td>
<td>Cervical</td>
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<tr>
<td>CBA</td>
<td>Cell based assay</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CMJ</td>
<td>Cervicomedullary junction</td>
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<td>CS</td>
<td>Corticosteroids</td>
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<td>DD</td>
<td>Demyelinating disease</td>
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<td>EDSS</td>
<td>Expanded disability status scale</td>
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<td>F</td>
<td>Female</td>
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<td>FR-NMO</td>
<td>Frequently relapsing neuromyelitis optica</td>
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<tr>
<td>GAP</td>
<td>Gastrin releasing protein</td>
</tr>
<tr>
<td>IgG</td>
<td>Antibodies</td>
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<td>IVIG</td>
<td>Intravenous immunoglobulins</td>
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<td>IVMP</td>
<td>Intravenous methylprednisolone</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>TPMT</td>
<td>Thiopurine methyltransferase</td>
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<tr>
<td>LMMC</td>
<td>Latvian Maritime medicine centre</td>
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<tr>
<td>LETM</td>
<td>Longitudinally extensive transverse myelitis</td>
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<tr>
<td>M</td>
<td>Male</td>
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<td>MO</td>
<td>Medulla oblongata</td>
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<td>MOG</td>
<td>Myelin oligodendrocyte protein</td>
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<tr>
<td>MRC</td>
<td>Medical research council scale to assess muscle strength</td>
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<td>NP</td>
<td>Neuropathic pruritus</td>
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<td>OCB</td>
<td>Oligoclonal bands</td>
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<td>ON</td>
<td>Optic neuritis</td>
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<td>OA</td>
<td>Onset attack</td>
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<td>PLEX</td>
<td>Plasmapheresis</td>
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<td>p/o</td>
<td>Oral route</td>
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<tr>
<td>POL</td>
<td>Perception of light</td>
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<tr>
<td>PPMS</td>
<td>Primary progressive multiple sclerosis</td>
</tr>
<tr>
<td>PRES</td>
<td>Posterior reversible encephalopathy syndrome</td>
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<td>REUH</td>
<td>Riga Eastern university hospital “Gaiļezers”</td>
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<td>RRMS</td>
<td>Relapsing remitting multiple sclerosis</td>
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<td>JRH</td>
<td>John Radcliffe hospital</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SANMO</td>
<td>Severe attack neuromyelitis optica</td>
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<td>SP</td>
<td>Secondary progressive course</td>
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<tr>
<td>SPKPC</td>
<td>National centre for disease prevention and control</td>
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<td>SPMS</td>
<td>Secondary progressive multiple sclerosis</td>
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<td>SPNMO</td>
<td>Secondary progressive NMO</td>
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<tr>
<td>ICD-10</td>
<td>International classification of diseases, version 10</td>
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<td>Th</td>
<td>Thoracic</td>
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<td>TM</td>
<td>Transverse myelitis</td>
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<td>TS</td>
<td>Tonic spasms</td>
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<tr>
<td>UNK</td>
<td>Unknown</td>
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<tr>
<td>u/l</td>
<td>Unilateral</td>
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<td>UHW</td>
<td>University hospital of Wales</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MS</td>
<td>multiple sclerosis</td>
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<tr>
<td>NHS</td>
<td>national healthcare system in the UK</td>
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<tr>
<td>NMO</td>
<td>neuromyelitis optica</td>
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<tr>
<td>NMOS</td>
<td>neuromyelitis optica spectrum disorder</td>
</tr>
<tr>
<td>Non-FRNMO</td>
<td>non frequently relapsing neuromyelitis optica</td>
</tr>
<tr>
<td>No POL</td>
<td>blind, no perception of light</td>
</tr>
<tr>
<td>WNCC</td>
<td>The Walton Centre for Neurology and Neurosurgery</td>
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INTRODUCTION

Demyelinating diseases (DD) of the central nervous system presents with damage to myelin sheet and axonal loss. As a result of the pathological process they typically manifest with optic neuritis, cerebral involvement or myelopathy.

Although second commonest (after multiple sclerosis or MS) neuromyelitis optica (NMO) is a rare, demyelinating disease of the central nervous system. In high prevalence MS countries NMO: MS ratio varies between 1:40–1:100 (Wingerchuk, Lennon et al. 2006, Bichuetti, Rivero et al. 2008, Asgari, Lillevang et al. 2011). For many years, it was thought that NMO or Devic’s disease is a rare variant of MS. Since the discovery of specific pathogenetic antibodies (NMO-IgG or AQP4-IgG), which are positive in up to 70-90%, NMO is considered as a separate entity (Lennon, Wingerchuk et al. 2004). More recently, another specific (possibly pathogenetic) antibodies-MOG-IgG were detected in a proportion of AQP4-IgG negative patients, which by some researchers have been hypothesised being likely representative for a less severe and monophasic illness (Kitley, Woodhall et al. 2012, Kitley, Waters et al. 2014, Saadoun, Waters et al. 2014). Though, whether MOG-IgG similar to AQP4-IgG can be used as a prognostic marker for the disease, has yet to be clarified.

NMO is typically a relapsing condition accumulating disability with each relapse (Wingerchuk, Hogancamp et al. 1999, Wingerchuk and Weinshenker 2003). It is believed, that a progressive course, which is significantly contributing to a disability in patients with MS, is uncommon in NMO (Trojano, Avolio et al. 1995, Bergamaschi, Berzuini et al. 2001, Confavreux, Vukusic et al. 2003, Leray, Yaouanq et al. 2010). To date only a single report (8 years ago) has described secondary progressive disease course in NMO, which occurred in only 2% of cases (Wingerchuk, Pittock et al. 2007). A progressive onset of the disease (symptoms of the index event evolving over several months) has been also reported only in a single case (Woo, Chiu et al. 2014).

Several seasonal fluctuations was observed in the relapse activity among patients with MS, with activity peaks and increased hospitalisation rates occurring during “warmest” months (Bamford, Sibley et al. 1983, Jin, de Pedro-Cuesta et al. 2000, Koziol and Feng 2004, Ogawa, Mochizuki et al. 2004, Abella-Corral, Prieto et al. 2005, Fonseca, Costa et al. 2009, Balashov,
Whether disease activity in NMO, common with MS and other inflammatory CNS disorders, fluctuates over various seasons, remains unknown. To date there is only a single study looking at the seasonal variation of relapses in NMO, results of which are not convincing (Muto, Mori et al. 2013).

NMO, in common with opticospinal MS, typically presents with a decline of vision and myelitis; though over the past few years, several reports of brainstem involvement presenting with intractable hiccups or vomiting etc. have been reported (Kremer, Mealy et al. 2013). Several reports, often accidental case reports, on other NMO symptoms such as narcolepsy, hypothermia, hearing loss, severe pain, tonic spasms, neuropathic pruritus etc can also be found, thought whether they are characteristic for NMO is yet to be studied (Baba, Nakashima et al. 2009, Kanbayashi, Shimohata et al. 2009, Sato and Fujihara 2011, Iyer, Elsone et al. 2014, Suzuki, Nakamura et al. 2012, Nakano, Dei et al. 2014, Jarius, Lauda et al. 2013, Kremer, Mealy et al. 2013, Gratton, Amjad et al. 2014, Takanashi, Misu et al. 2014, El Otmani, Dany et al. 2015, Wang, Qi et al. 2015, Wingerchuk, Hogancamp et al. 1999, Kim, Go et al. 2012, Usmani, Bedi et al. 2012, Abaroa, Rodriguez-Quiroga et al. 2013).

It is important to note that many clinical, laboratory and radiological features of both, NMO and MS are similar; therefore it is often hard to distinguish NMO from MS. However, treatment in both is distinct. Better understanding and characterisation of common and unique features of NMO, should lead to an earlier recognition of the cases, and an earlier initiation of a treatment. An early and aggressive management of attacks is crucial in NMO. High doses of steroids, followed by plasma exchange, is typically used, although their efficacy is limited (Palace, Leite et al. 2012, Jacob, McKeon et al. 2013). In practice, to treat various immune-mediated acute conditions such as myasthenia, Guillain-Barré syndrome IVIG are also used. IVIG are also being used for prevention from future relapses in NMO (Bakker and Metz 2004, Okada, Tsuji et al. 2007, Magraner, Coret et al. 2013, Wingerchuk 2013) therefore IVIG may have a potential use in treatment of acute NMO relapses which has yet to be investigated (Jacob, McKeon et al. 2013, Mealy, Wingerchuk et al. 2014).

If NMO preventative treatment is delayed or immunomodulators typically used in MS are applied, relapses reoccur (Palace, Leite et al.
Treatment of the disease is based on anecdotal case reports. Due to severity and high disability of the disease, randomised placebo controlled treatment trials are unethical (Jacob, McKeon et al. 2013, Mealy, Wingerchuk et al. 2014). Among other drugs, azathioprine (AZA) due to its wide availability, low-cost and reasonably safe adverse effects profile, is one of the most commonly used immunosuppressant in the treatment of NMO. Despite clinical efficacy, AZA is often discontinued due to intolerance or on-going relapse activity (Mandler, Ahmed et al. 1998, Bichuetti, Lobato de Oliveira et al. 2010, Costanzi, Matiello et al. 2011). Neither efficacy of AZA in frequently relapsing or severe-attack NMO, nor retention to AZA, and the reasons for discontinuation in patients with NMO/NMOS, have previously been studied.

Several authors report retrospective identification of NMO cases using local or national MS/DD registers (Cossburn, Tackley et al. 2012, Pandit, Mustafa et al. 2013). Often MS and/or NMO registers also serve as a main source of material for various research projects (Collongues, Marignier et al. 2010, Cossburn, Tackley et al. 2012, Simon, Schmidt et al. 2014). National MS register exists in Latvia too. Whether it can be utilised for detection and identification of NMO cases in Latvia has yet to be explored.

**Purpose of work**

The purpose of this work was to analyse and characterise clinical features, efficacy of treatment of NMO / NMO spectrum, as well as to analyse the data entered into the Latvian MS register, for the purpose to improve diagnostic accuracy, treatment efficacy, and the outcomes of patients with NMO / NMOS.

**Objectives**

1. To analyse and characterise NMO / NMOS clinical characteristics:
   - Seasonal fluctuations of NMO relapses;
   - Frequency and characteristics of neuropathic pruritus and tonic spasms;
   - Frequency and characteristics of progressive disease course (progressive onset, secondary progressive course).
• Phenotype of NMO or suspected NMOS cases tested positive for MOG-IgG.

2. To analyse the treatment efficacy;
   • Efficacy of intravenous immunoglobulins (IVIG) in treatment of acute relapses.
   • Efficacy of azathioprine (AZA) in prevention of NMO / NMOS relapses, with different disease activity.

3. To analyse the quality and quantity of data entered into the Latvian DD/MS register in view of identifying NMO / NMOS cases.

Hypothesis

1. NMO / NMOS relapse activity, similar to MS, has seasonal variations.

2. Neuropathic pruritus and tonic spasms are frequent, unique and characteristic features of NMO / NMOS, in contrast to the progressive course, which is uncommon and non-characteristic.

3. Contrary to earlier reports, NMO patients tested positive for MOG-IgG can present with both, monophasic and relapsing disease, with a variable degree of loss of neurological function.

4. Intravenous immunoglobulins and azathioprine are both effective in treatment of NMO / NMOS relapses, however, the efficacy depends on the severity of disease, and how soon treatment commences.

5. Azathioprine is an effective drug in preventing NMO / NMOS relapses, however, less effective in frequently relapsing and severe-attack cases.

6. The quality and quantity of Latvian DS/MS register is insufficient for retrospective identification of NMO cases.

Scientific novelty and practical value

NMO is a rare disease of central nervous system, but if undiagnosed and untreated promptly and early, resulting in a high sequele and mortality. To avoid all the consequences, which may result from the disease, an early recognition of NMO symptoms and identification of potential effective treatments is crucial. It was particularly important to identify and characterise
the clinical features of NMO and their role in the diagnostic process of a disease, the information of which in current literature, is unavailable or limited. As a result of this work:

1. A several specific NMO / NMOS clinical characteristics were described for the first time, which may influence an earlier recognition and diagnostic process of the disease leading to an earlier initiation of treatment:
   - NMO/NMOS relapse seasonality have been studied in western populations for the first time;
   - an unique clinical feature – neuropathic pruritus have been identified and its characteristics and frequency explored;
   - a progressive onset of disease over several months and its frequency have been also identified and described for the first time;
   - a cases series of relapsing NMO with severe functional deficits tested positive for MOG-IgG1 have been reported for the first time;
   - the frequency and characteristics of tonic spasms and secondary progressive NMO have been explored and confirmed.

2. This is the largest study on the treatment of NMO so far and the largest case series describing AZA (commonly used immunosuppressant) efficacy in AQP4-IgG positive NMO / NMOS. Up to present day, the retention to AZA, and the factors associated to discontinuation of the drug, and its efficacy in frequently relapsing and severe-attack NMO / NMOS have not been studied.

3. The efficacy of intravenous immunoglobulins in management of acute relapses and potential associated risks with its use, have been studied and described for the first time, therefore widening a spectrum of potential treatments for the disease. In summary, the practical clinical guidelines to improve diagnostics and treatment of NMO / NMOS have been developed.

4. A study analysing a quality and quantity of data entered into the Latvian MS register in a view of potential identification of NMO / NMOS cases was performed for the first time; more importantly I have established a need to recognise NMO cases, and its been raised for the first time, a need to improve the MS register in Latvia; the guidelines to improve Latvian MS register have been developed.
Structure and content

The theses are written in Latvian on 131 pages (excluding bibliography and appendices) and consist of: Introduction, Purpose and Goals of the Work, Methodology, Results, Discussion, Main Conclusions arising from Thesis and Recommendations. Bibliography consists of 334 resources. The work includes 33 tables and 15 illustrations. Number of publications arising from thesis – 8, total number of publications related to the topic of work – 31.

Personal contributions

I have collected and summarised the data of patients with NMO, NMOS and suspected NMO and independently developed Liverpool’s NMO database (WCNN, United Kingdom). I have participated in the national NMO UK study and have been a collaborator in the several projects covering such major topics as clinical characteristics, laboratory findings and efficacy of treatment in patients with NMO / NMOS. I have also originated several sub studies, participated in the creation process of sub-study design, obtained, collected, systematised, processed and analysed the obtained study material.

I have independently analysed the Latvian MS register, as well as obtained, collected, summarised and analysed a clinical data of patients entered into the register, have been involved in the diagnostic process and decision making on treatments for several MS and also NMO / NMOS patients.

Ethical aspects

This work is not related to ethical issues. Patients were not exposed to the additional tests or experiments. Routine investigations and standard treatments which are important in improving diagnostic process and treatment outcomes were applied. The first part of this study (clinical characteristics and treatment of NMO) was completed as a part of the national NMO UK study which has been registered with the Regional Ethics Committee in 2003 (MREC02/8/082, Manchester, UK) and also the research governance committee of the WNNC (Liverpool, UK). The second part (analysis of Latvian DD/MS register) was performed as a part of the study “Epidemiological, clinical and laboratory characteristics of demyelinating diseases in Latvia” and
has been registered with a Rīga Stradiņš University Ethics Committee on 25\textsuperscript{th} October 2012.

Only the data of patients (for clinical and treatment characteristics of NMO) who have given a written consent have been included in the study. Only a single patient declined consent and her data were not included in a further analysis.
1. MATERIAL AND METHODS

1.1 Study design

The study consists of two parts. The first part is the analysis of clinical and treatment aspects of NMO (relapse seasonality, features of onset attack, neuropathic pruritus, tonic spasms, progressive disease course, phenotype of NMO / NMOS tested positive for MOG-IgG, efficacy of IVIG in treatment of acute relapses, efficacy of azathioprine in prevention of further relapses). This part was done at the WCNN (Liverpool, UK), as part of the national NMO study, and was done during a three-year fellowship (2011 to 2014). WCNN is a tertiary healthcare centre in the UK. The patients across the north and western parts of Great Britain, North Wales and Scotland have been referred to the WCNN, which provides a care for patients with NMO / NMOS at a national level. Some sub-studies (relapse seasonality, efficacy of azathioprine) have been done in collaboration with other tertiary centres: John Radcliffe Hospital (Oxford), University Hospital of Wales (Cardiff), University Hospitals of Birmingham (Birmingham).

The second part covers an analysis of the quality and quantity of the data entered into the Latvian MS register, and their potential role for retrospective identification of NMO / NMOS cases. The functionality of the register has been compared to other major MS registries worldwide. This study has been done in collaboration with the Riga Eastern clinical university hospital “Gailezers”— MS unit as a part of the project: “Epidemiological, clinical, laboratory characteristics of demyelinating diseases in Latvia”.

1.2 Study material

1.2.1 Study population and case selection

In the first part patients fullfilling the diagnostic criteria for NMO / NMOS (Wingerchuk, Lennon et al. 2006), and registered in any of the local (Liverpool, Oxford or Cardiff) NMO databases were analysed. Patient flow-chart is shown in Figure 1.1.
1.2.2 Data for the analysis of Latvian MS register

Patient inclusion criteria for each study objective were different; a detailed description can be seen in Table 1.1. Where patient data was merged from several centers/databases (relapse seasonality and treatment with azathioprine), medical case note review, and the neurological evaluation of patients was carried out at each center separately, the data was sent to Liverpool for further review and analysis.

1.2.2 Data for the analysis of Latvian MS register

The Latvian MS patient’s data proforma (Cabinet of Ministers, policy No 746, 15.09.2008. appendix 13), on the basis of which data is entered into the register, and also the personal experience I gained during my duties as a neurologist at the Latvian Maritime medicine centre (2003–2010) – which remains the only data operator, was used to analyse the information entered into Latvian MS register.
1.3 Methods
1.3.1 Data collection

Clinical (collection and analysis of medical records, neurological evaluation of patients) and laboratory methods were applied in this study. The following data were recorded for each patient: demographics, detailed medical history (dates and description of each attack, i.e. symptoms, severity, duration, attack treatment, neurological examination findings, outcomes (the dates of the onset attack and subsequent relapses were recorded and categorized as being accurate to within either a day, week, month, year or decade; only relapse dates accurate to within 30 days were included); additional data regarding specific symptoms, i.e. brainstem symptoms, neuropathic pruritus, tonic spasms etc., past medical history and co-autoimmunity; characteristics of pruritus (i.e. date of onset, description, localisation, association with other neurological symptoms, dermatological or systemic problems, findings on MRI, duration, intensity (according to numerological pain score, 0–10)); characteristics of tonic spasms, i.e. date of onset, description, localisation, association with other neurological symptoms, dermatological or systemic problems, findings on MRI, duration, intensity, accompanying symptoms, triggers, response to treatment etc.); treatment details (i.e. efficacy, start and stop dates, side effects, reasons for discontinuation etc, including for IVIG and azathioprine); laboratory results (i.e. AQP4-IgG, MOG-IgG results, CSF, haematological findings during treatment etc); investigation i.e. MRI results (reviewed with a neuroradiologist at WCNN).

All patient data was recorded retrospectively and/or prospectively during interviews using a structured proforma. Where necessary additional information was obtained from general practitioners, neurologists and other healthcare professionals involved in the patients’ care or during additional patients interviews (clinic or home visits, and phone interviews). All information was then compared with entries in the medical documentation, and entered into the NMO patient database (Liverpool).

A summary of study methodology is shown in Figure 1.2. Inclusion criteria and methods used for each study objective are different and therefore are best described separately and are summarised in Table1.1.
1.3.2 Neurological evaluation

- EDSS score used to describe an outcome on neurological examination (0 – normal, 10 – exitus letalis).
- MRC scale used to assess muscle strength (0 – plegic, 5 – normal strength).

![Diagram of study methodology]

**Figure 1.2. A summary of study methodology**

1.3.3. Assessment of the treatment efficacy

The effectiveness of treatment was evaluated using the parameters/indicators applied in other treatment studies: annualised relapse rates (ARR) pre and post treatment (total number of relapses divided by the duration of the disease in years), number (%) of relapse free patients, time to first and second relapse, EDSS pre and post treatment or at last follow-up, treatment discontinuation rate.)
1.3.4 Diagnostic criteria

1.3.4.1 Criteria for NMO

Internationally recognised and accepted diagnostic criteria for NMO / NMOS were used (Wingerchuk, Lennon et al. 2006). Criteria for NMO:

History of optic neuritis and longitudinally extensive myelitis and at least 2 of 3 supportive criteria:

- Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments;
- Brain MR not meeting diagnostic criteria for multiple sclerosis;
- NMO-IgG (or AQP4-IgG) seropositive status.

Criteria for NMO spectrum: optic neuritis OR longitudinally extensive myelitis and positive AQP4-IgG.

Suspected NMO / NMOS: idiopathic single or relapsing optic neuritis, brainstem involvement or myelitis not fulfilling the diagnostic criteria for NMO, MS or other diseases.

1.3.4.2 Criteria for SPNMO

To date only a single report is available about the secondary progressive course of NMO (Wingerchuk, Pittock et al. 2007). Criteria for SPNMO proposed in the previous study were also applied for this study and are as follows:

A gradual deterioration (visual, motor or sensory function) > 6 months and at least 1 of supporting criteria confirming progression:

1) drop of visual acuity by ≥ 2 points (0 – normal, 7 – blind),
2) deterioration of muscle strength ≥ 1 limb by 2 points (according to MRC scale) in ≥ 2 antigravity muscles (upper limb: deltoid, triceps, finger extensors, lower limb: hip flexors, posterior thigh muscles, plantar dorsal flexors),
3) increase of EDSS score by ≥ 2 points when compared to the last evaluation before progression (Wingerchuk, Pittock et al. 2007).
1.3.5 Definitions

- Relapse (exacerbation, attack) – acute development of a new or significant worsening of previous neurological deficit lasting for more than 24 hours in absence of active infection or fever, and is confirmed by neurologist. Relapses which developed within 30 days were counted as the same attack.
- Onset attack – the very first attack presenting with symptoms suggesting of optic nerve, brainstem or spinal cord damage. Nonspecific symptoms such as nausea, vomiting, dizziness not followed by other NMO typical neurological symptoms within next few days or weeks, were not counted as the onset attack.
- Clinical remission – a period between relapses, during which no neurological deterioration is observed (except for the cases where neurological deterioration is associated with infection and/or fever, etc.).
- Gradual onset- the onset of attack with characteristic NMO symptoms evolving gradually over at least 1 month (4 weeks or 28 days).
- Last relapse before the onset of SP – the last (acute or subacute – within few weeks) significant deterioration of neurological deficit or development of new symptoms in absence of recent infection, fever or reduction of steroids.
- SP onset – retrospectively identified time point of the onset of gradual progression of symptoms developed in a relation or not to the last relapse, which, despite a treatment received, continues to be able to satisfy criteria for SPNMO.
- Retention time – the time a patient continued on a drug, presumably a reflection of its efficacy and tolerability.
- FR-NMO – frequently relapsing NMO – a disease presenting with at least 2 relapses over the last 6 months or at least 3 relapses over the last 12 months (Pittock, Lennon et al. 2013).
- SANMO – severe attack NMO presenting with severe functional deficits within 6 months prior to starting a treatment: if presenting with myelitis – a maximal residual functional deficit or during peak – EDSS ≥ 6 (requires unilateral assistance) and if presenting with optic neuritis – EDSS ≥ 3 (blind in at least one eye or maximal visual score 6/36–6/60 in the worst eye).
1.3.6 Laboratory testing

Serum samples for AQP4-IgG and MOG-IgG were obtained at WNNC during routine clinic appointments and were tested at John Radcliff hospital neuroimmunology lab (Oxford) using the most sensitive method with the highest specificity (cell based assay) as described previously (Waters and Vincent 2008, Kitley, Woodhall et al. 2012, Woodhall, Coban et al. 2013, Kitley, Waters et al. 2014).

Serum samples were tested for AQP4-IgG for each patient. Only patients with negative AQP4-IgG and who attended NMO clinic at WCFT from 2012 until May 2014 were tested for MOG-IgG. MOG-IgG were tested in 98 patients: 21/24 AQP4-IgG negative NMO patients registered into database, 77 patients with suspected NMOS (AQP4-IgG negative idiopathic optic neuritis, myelitis, brainstem involvement or opticospinal demyelination not fulfilling the diagnostic criteria for NMO or MS). All MOG-IgG positive cases (NMO, optic neuritis, myelitis, brainstem involvement) were retested, using specified methodology and detecting MOG-IgG1. As a result, only patients tested positive for MOG-IgG1 were counted as positive.

1.3.7 Statistical analysis

A descriptive and analytical statistics were used to summarize results. Dates of the onset attack and all subsequent relapses were categorised as being accurate to within either day, week, months, year or decade). Only relapse dates accurate to within month (0-30 days) were included in the further analysis. Episodes occurring within 30 days of each other were considered to be part of the same relapse.

A continuous descriptive statistics are presented as median, mean and range or interquartile range (IQR) unless otherwise specified. ARR was calculated as a total number of relapses over number of years with NMO / NMOS. A categorical descriptives were reported as frequencies and percentages.

The Wilcoxon matched-pairs signed-rank test was used to compare different variables (i.e. ARR and EDSS scores pre- and post-treatment) and Mann–Whitney test – to compare two independent groups. Since patients inevitably had varying follow-up periods, ARR and EDSS were analysed in various subgroups of patients who satisfied various minimum follow-up
criteria. Kaplan-Meier curves were used to estimate the probability of patients remaining on treatment over time. Patients who died were treated as right-censored. However, a sensitivity analysis using the cumulative incidence (not shown) was found to be consistent with the Kaplan-Meier estimate.

For assessment of seasonal variations of relapses, statistical analysis (using R version 2.14.1) was carried out in two stages. Firstly, all data were included in a simple analysis (dividing the total number of exacerbations by 12 – the number of months per year) and Poisson regression (adjusted for month length) which examined variation in overall relapse counts per month. Subsequently a separate analysis was performed for relapses occurring between 01/01/2002 and 31/12/2011 in order to determine if data acquired more recently, and therefore less prone to recall bias, differed from more historical data. Patients contributed to the analysis for all months during this period in which they had disease and for which follow up data was available (or continued to the end of 2011 if followed up after this time). Finally, logistic regression was used to analyse the association of month with chance of relapse and corrected for age at onset and disease duration.

All statistical analyses were considered to be significant if \( p < 0.05 \); no corrections were made for multiple comparisons. Duplicate cases were excluded.

Study material and methodology used for the study are summarised in Table 1.1.
### Summary of methodology

<table>
<thead>
<tr>
<th>Study undertaken</th>
<th>Study population</th>
<th>Parameters analysed</th>
<th>Methods</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse seasonality</strong></td>
<td>165 AQP4-IgG positive NMO / NMOS patients with longitudinal follow-up who have been registered in NMO database at any of 4 centres (WNCC, JRH, WUS) from 01.06.2010 until 31.03.2012.</td>
<td>Demographics, detailed history (dates of the onset attack and subsequent relapses, categorised as being accurate to within either day, week, months, year or decade). Only relapse dates accurate to within month (0–30 days) were included in the further analysis.</td>
<td>Preliminary database, structured data proforma; systematic review of data base, medical records etc.; patients interviews (clinic or home visits, phone interviews); data comparison and quality inspection; exclusion of duplicates</td>
<td>Statistical modelling using R version 2.14.1 – 2 stages; Poisson regression (adjusted for month length) – examined variation in overall relapse count/month; Separate analysis for relapses occurring between 01/01/2002 and 31/12/2011 (less prone to call bias); logistic regression to analyse association of month with chance of relapse (corrected for age at onset and disease duration); descriptive statistics</td>
</tr>
<tr>
<td><strong>Features of onset attack</strong></td>
<td>All (n = 123) NMO / NMOS patients who were registered in NMO database at WCNN until 01.08.2014.</td>
<td>Demographics, detailed history of onset attack (including duration to peak of symptoms, severity of neurological deficits, treatment received for attack); MR findings</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS); data comparison and quality inspection</td>
<td>Descriptive statistics; continuous descriptive statistics are presented as median and range, categorical descriptives reported as frequencies and percentages</td>
</tr>
<tr>
<td><strong>Retrospective descriptive study</strong></td>
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<tr>
<td>(control group – historical data)</td>
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<tr>
<td>Study undertaken</td>
<td>Study population</td>
<td>Parameters analysed</td>
<td>Methods</td>
<td>Statistical analysis</td>
</tr>
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<td>-----------------------------------------</td>
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<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Neuropathic pruritus</strong></td>
<td>All (n=44) AQP4-IgG positive NMO / NMOS patients who attended NMO clinic at WCNN from 01.01.2011.–01.03.2012.</td>
<td>Demographics, detailed history of disease (i.e. relapses), MRI findings, characteristics of pruritus and its association with other neurological signs and MRI</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS), assessment of NP intensity with a numeric rating scale (0–10); data comparison and quality inspection</td>
<td></td>
</tr>
<tr>
<td>Retrospective descriptive study with longitudinal follow-up (control group – historical data)</td>
<td>All (n=44) AQP4-IgG positive NMO/NMOS patients who attended NMO clinic at WCNN from 01.01.2011.–01.03.2012.</td>
<td>Demographics, detailed history of disease (i.e. relapses), MRI findings, characteristics of tonic spasms and its association with other neurological signs and MRI</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS), assessment of tonic spasms; data comparison and quality inspection</td>
<td></td>
</tr>
<tr>
<td><strong>Tonic spasms</strong></td>
<td>All (n=44) AQP4-IgG positive NMO/NMOS patients who attended NMO clinic at WCNN from 01.01.2011.–01.03.2012.</td>
<td>Demographics, detailed history of disease (i.e. relapses), MRI findings, characteristics of tonic spasms and its association with other neurological signs and MRI</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS), assessment of tonic spasms; data comparison and quality inspection</td>
<td></td>
</tr>
<tr>
<td>Retrospective descriptive study with longitudinal follow-up (control group – historical data)</td>
<td>All (n=44) AQP4-IgG positive NMO/NMOS patients who attended NMO clinic at WCNN from 01.01.2011.–01.03.2012.</td>
<td>Demographics, detailed history of disease (i.e. relapses), MRI findings, characteristics of tonic spasms and its association with other neurological signs and MRI</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS), assessment of tonic spasms; data comparison and quality inspection</td>
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</table>
Continuation of Table 1.1

<table>
<thead>
<tr>
<th>Study undertaken</th>
<th>Study population</th>
<th>Parameters analysed</th>
<th>Methods</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary progressive course</strong></td>
<td>All (n = 123) NMO / NMOS patients who were registered in NMO database at WCNN until 01.08.2014.</td>
<td>Demographics, basic characteristics of disease, MRI findings, treatment details, characteristics of secondary progressive phase, findings on neurological examination (including EDSS, MRC)</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS, MRC, ambulatory index); data comparison and quality inspection; assessment of patients according to secondary progressive NMO criteria</td>
<td>Descriptive statistics; continuous descriptive statistics are presented as mean and standard deviations, categorical descriptives reported as frequencies and percentages</td>
</tr>
<tr>
<td>Retrospective descriptive study with longitudinal follow-up (control group – historical data)</td>
<td>All (n = 98) WCNN NMO / possible NMOS patients who were tested for MOG-IgG until 05/2014</td>
<td>Demographics, basic characteristics of disease (including phenotype of attacks, MRI findings, laboratory results, treatment details, findings on neurological examination)</td>
<td>Preliminary database, structured data proforma; systematic review of data base, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS); screening of laboratory data; repeat testing of all MOG-IgG positives and NMO negatives (AQP4-IgG) for MOG-IgG1; data comparison and quality inspection</td>
<td>Descriptive statistics; continuous descriptive statistics are presented as median and range, categorical descriptives reported as frequencies and percentages</td>
</tr>
<tr>
<td><strong>Phenotype of patients tested positive for MOG-IgG</strong></td>
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<td></td>
</tr>
<tr>
<td>Retrospective descriptive study with longitudinal follow-up (control group – historical data)</td>
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### Table 1.1

<table>
<thead>
<tr>
<th>Study undertaken</th>
<th>Study population</th>
<th>Parameters analysed</th>
<th>Methods</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with IVIG</td>
<td>All (n=93) WCNN NMO/NMOS patients from 08/2003–01/12/2012</td>
<td>Demographics, basic characteristics of disease, findings on neurological examination (EDSS), treatment details (i.e. IVIG); patients without acute deterioration during IVIG are not included in the analysis</td>
<td>Preliminary database, structured data proforma; systematic review of data base, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS); data comparison and quality inspection</td>
<td>Descriptive statistics; continuous descriptive statistics are presented as median and range, categorical descriptives reported as frequencies and percentages</td>
</tr>
<tr>
<td>Retrospective descriptive study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with azathioprine</td>
<td>All (n=103) NMO/NMOS patients who were followed-up at any of 4 centres (WCNN, JRH, WUH, BUH) and received AZA (until 05/2013); of those 72 with FU ≥ 6 months, 36 with ≥ 2 relapses within 6 months or ≥ 3 relapses within 12 months prior to starting AZA (FR-NMO), 62 with severe functional deficits (SA-NMO) i.e. EDSS ≥ 6 if presented with TM</td>
<td>Demographics, basic characteristics of disease, findings on neurological examination (EDSS), treatment details (i.e. efficacy, retention time, reasons for discontinuation, side effects)</td>
<td>Preliminary database, structured data proforma; systematic review of database, medical records etc.; patients interviews (clinic or home visits, phone interviews); neurological examination (EDSS);</td>
<td>Analytical and descriptive statistics; continuous descriptive statistics are presented as median and min-max range or inter quartile range (IQR), categorical descriptives reported as frequencies and percentages; Wilcoxon Signed Ranks Test was used to compare</td>
</tr>
</tbody>
</table>
### Continuation of Table 1.1

<table>
<thead>
<tr>
<th>Study undertaken</th>
<th>Study population</th>
<th>Parameters analysed</th>
<th>Methods</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective descriptive study with longitudinal follow-up (control group- historical data) and ≥3 (Visual Score ≥4 or maximum VA 6/36-6/60 in the worst eye) if presented with ON</td>
<td>–</td>
<td>data comparison and quality inspection</td>
<td>different variables and Mann-Whitney U test- for comparisons of 2 independent groups; Kaplan-Meier curves; patients who died were treated as right-censored</td>
<td></td>
</tr>
<tr>
<td><strong>Analysis of data entered into Latvian DD/MS register</strong></td>
<td>Latvian MS patient’s data proforma (Cabinet of Ministers, policy No 746, 15.09.2008. appendix 13)</td>
<td>Clinical history (PMH-including other autoimmune illnesses, clinical symptoms and their severity and recovery),test results, treatment details (i.e. efficacy), parameters characterising register (target population, minimal data set, technical support, data security &amp; confidentiality, reporting system and quality control, continuation, functionality)</td>
<td>Qualitative and quantitative data analysis using Latvian MS patient’s data proforma; evaluation of register’s potential role in retrospective identification of NMO/NMOS cases; functionality of register was compared to the literature data of major DD/MS registers worldwide</td>
<td>Descriptive statistics</td>
</tr>
<tr>
<td><strong>Descriptive study</strong></td>
<td>–</td>
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</table>

2. MAIN RESULTS

2.1 NMO clinical characteristics

2.1.1 Relapse seasonality

A total of 165 AQP4-IgG positive patients fulfilling a criteria for NMO/NMOS were identified within 3 centres. After excluding duplicates and patients with insufficient data (i.e. data are known only for the onset attack), 150 patients were eligible for a further analysis: 130 (86.7%) women and 20 (13.3%) men. Mean (SD) age at onset was 41.3 (± 17.12) and median duration of disease – 8.6 (0.3–37) years. During the observational period, a total of 772 relapses occurred, median – 4 (1–28) attacks/patient with an average annual relapse rate (ARR) – 0.59. 11% (17/150) patients had only one relapse but 77% (115/150) had 3 or more relapses.

An accurate date of onset (to within a month) was unknown for 80 (10%) attacks, therefore 692 relapses (150 patients) were included in a further analysis. A total of 57.6 (8.33%) attacks would be expected per month when a total number of relapses (100%) are divided by 12 (number of months per year). The number of relapses ranged between 46 or 6.6% (June) and 69 or 9.8% (January), and was equally distributed among all of the months of the year. There was no significant seasonal variation among genders or onset attack either. A Poisson regression (adjusted for length of the month) was used initially to analyse relapse counts per month and showed the lowest activity in June, however, the results were not statistically significant (2.1 Table).
Table 2.1

**Distribution of relapses using simple analysis and Poisson regression**

<table>
<thead>
<tr>
<th>Months</th>
<th>Simple analysis</th>
<th>Poisson regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total distribution of relapses per month (%)</td>
<td>Relapse rate ratio (95% CI)</td>
</tr>
<tr>
<td>January</td>
<td>69 (9.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>February</td>
<td>54 (7.8)</td>
<td>1.05 (0.70–1.59)</td>
</tr>
<tr>
<td>March</td>
<td>57 (8.2)</td>
<td>0.89 (0.59–1.36)</td>
</tr>
<tr>
<td>April</td>
<td>56 (8.1)</td>
<td>0.94 (0.62–1.43)</td>
</tr>
<tr>
<td>May</td>
<td>68 (9.8)</td>
<td>1.04 (0.70–1.56)</td>
</tr>
<tr>
<td>June</td>
<td>46 (6.6)</td>
<td>0.74 (0.47–1.16)</td>
</tr>
<tr>
<td>July</td>
<td>53 (7.7)</td>
<td>0.87 (0.57–1.33)</td>
</tr>
<tr>
<td>August</td>
<td>57 (8.2)</td>
<td>1.02 (0.68–1.53)</td>
</tr>
<tr>
<td>September</td>
<td>58 (8.4)</td>
<td>1.12 (0.75–1.68)</td>
</tr>
<tr>
<td>October</td>
<td>58 (8.4)</td>
<td>1.02 (0.68–1.53)</td>
</tr>
<tr>
<td>November</td>
<td>59 (8.5)</td>
<td>1.06 (0.70–1.59)</td>
</tr>
<tr>
<td>December</td>
<td>57 (8.2)</td>
<td>1.07 (0.71–1.59)</td>
</tr>
</tbody>
</table>

Subsequently, all relapses from 01/01/2002 to 31/12/2011 were analysed. Logistic regression was performed (corrected for age at onset and duration of disease) to analyse whether the month had an effect on the chance of having a relapse. Patients contributed to the analysis for all months during the period in which they had a disease and were followed up. The clustered logistic regression model takes into account the patients having multiple relapses, as well as the patients with a shorter follow-up period than the whole study duration, so if they only had an onset of the disease in 2005 they will contribute to the analysis between 2005 and 2011 but not earlier. The analysis showed a significant p value for November (p = 0.007) and October (p = 0.04) when compared to January.
Table 2.2

Clustered logistic regression model

<table>
<thead>
<tr>
<th>Month</th>
<th>Results</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>February</td>
<td>$1.5 \times 10^{-18}$</td>
<td>0.92</td>
</tr>
<tr>
<td>March</td>
<td>$2.0 \times 10^{-18}$</td>
<td>0.90</td>
</tr>
<tr>
<td>April</td>
<td>$1.5 \times 10^{-18}$</td>
<td>0.93</td>
</tr>
<tr>
<td>May</td>
<td>$2.6 \times 10^{-18}$</td>
<td>0.87</td>
</tr>
<tr>
<td>June</td>
<td>$2.4 \times 10^{-18}$</td>
<td>0.89</td>
</tr>
<tr>
<td>July</td>
<td>$2.1 \times 10^{-18}$</td>
<td>0.90</td>
</tr>
<tr>
<td>August</td>
<td>$1.8 \times 10^{-18}$</td>
<td>0.91</td>
</tr>
<tr>
<td>September</td>
<td>$3.3 \times 10^{-18}$</td>
<td>0.83</td>
</tr>
<tr>
<td>October</td>
<td>$3.3 \times 10^{-18}$</td>
<td>0.04</td>
</tr>
<tr>
<td>November</td>
<td>$4.4 \times 10^{-17}$</td>
<td>0.007</td>
</tr>
<tr>
<td>December</td>
<td>$1.0 \times 10^{-18}$</td>
<td>0.95</td>
</tr>
<tr>
<td>Disease duration</td>
<td>$8.6 \times 10^{-19}$</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at onset</td>
<td>$-1 \times 10^{-19}$</td>
<td>0.28</td>
</tr>
</tbody>
</table>

2.1.2 Features of the onset attack

Data for the onset attack was available for 121/123 (98%) patients (93 women, 94 AQP4-IgG positive). In a few cases an accurate duration from the onset of symptoms to their peak was unknown, also EDSS score, lesion location on MRI, treatment received for the onset attack or outcomes were unable to retrieve. Median age at disease onset was 40 (5–79) and disease duration – 6.8 (0.2–10.8) years. A clinical phenotype of the onset attack was: unilateral ON – 24% (n = 29), bilateral ON – 18.3% (n = 10), TM – 49.6% (n = 60), unilateral ON and TM – 5.8% (n = 7), bilateral ON and TM – 5% (n = 6). Symptoms evolved and reached their peak during the onset attack (known in 93 cases) median over 9 (1–168) days: within 1 day – 13% (n = 12), within few days (less than a week) – 27% (n = 25), within few weeks (less than a month) – 36.6% (n=34) or within several (1–18) months – 23.7% (n = 22). Data for AQP4-IgG positive and negative cases have been represented separately.
2.1.2.1 AQP4-IgG negative patients (n = 27)

Median age at disease onset for AQP4-IgG negative patients (15 women, 12 men) was 37.92 (5.08–61.33) and disease duration – 6.58 (0.17–26.58) years. A clinical phenotype of the onset attack was: unilateral ON – 15% (n = 4), bilateral ON – 15% (n = 4), TM – 40.7% (n = 11), unilateral ON and TM – 18.5% (n = 5), bilateral ON and TM – 11% (n = 3). Symptoms evolved and reached their peak during the onset attack (known in 19 cases) median over 12.5 (1–168) days: within 1 day – 5.3% (n = 1), within few days (less than a week) – 15.8% (n = 3), within few weeks (less than a month) – 42.1% (n = 8) or within several (1–18) months – 36.8% (n = 7).

Median EDSS score at peak of attack (known in 74% or 20/27 patients) was 5.75 (1.5–8). 80% (16/20) had severe neurological deficits (EDSS ≥ 3 when presented with ON and EDSS ≥ 6 when presented with myelitis). An acute treatment was received in 22 cases: 86.4% (n = 19) – steroids, 9.1% (n = 2) – steroids along with plasmapheresis, 4.5% (n = 1) – cyclophosphamide. At recovery (known in 24/27 patients) there were no significant neurological deficits in 33% (n = 8). The rest, had a significant residual deficits (n = 16). All patients relapsed, median after 5 (1–299) months.

2.1.2.2 AQP4-IgG positive patients (n = 94)

Median age at disease onset for AQP4-IgG positive patients (78 women, 16 men) was 40.6 (7.2–78.6) and disease duration – 6.58 (0.5–38.3) years. A clinical phenotype of the onset attack was: unilateral ON – 26.6% (n = 25), bilateral ON – 6.4% (n = 6), TM – 52.1% (n = 49), unilateral ON and TM – 2% (n = 2), bilateral ON and TM – 3.2% (n = 3), other syndrome – 9.6% (n = 9). Symptoms evolved and reached their peak during the onset attack (known in 74 cases) median over 7 (1–126) days: within 24 hours – 15.7% (N = 11), several days but less than a week – 29.7% (n = 22), one to 4 weeks-35.1% (n = 26), months (≥ 1) – 20.3% (n = 15). Median EDSS (known in 67/94 cases) was 4 (1–8). 77.6% (n = 52) of patients had a significant neurological deficits (EDSS ≥ 3 when presented with ON and EDSS ≥ 6 when with myelitis). Acute treatment was used in 61 (65%) cases (steroids – 56, steroids along with plasmapheresis – 3, plasmapheresis – 1, other – 1). Acute treatment was not given in 23 (24.5%). In 10 cases treatment details were unknown. A recovery from the attack (known in 90/94) was good in 52.2% (n = 47) and
insignificant in 15.5% (n = 14). The rest (n = 29), despite mild / moderate improvement following a treatment, were left with severe residual deficits. 91.4% (n = 86) had further relapses, median after 8 (1–278) months.

2.1.2.3 Patients with progressive onset (n = 22)

93 of 121 patients were able to report (and/or was recorded in the medical case notes) the duration from the onset to the peak of symptoms of their index event. During the index event, symptoms evolved and reached their peak (since onset) median over 7 or more days in 46.3% (56/121) cases; In 39% (22/56 or 17.3% of all NMO/NMOS cases) of those cases, symptoms evolved gradually over 4 weeks (median after 2.3 (1–18) months). AQP4-IgG antibodies were positive in 68.2% (15/22). Median age at disease onset was 42.5 (18.2–67.5) and disease duration at last follow-up was 5.38 (0.17–28.6) years. A clinical phenotype of the onset attack was: unilateral ON – 2, bilateral ON – 1, TM – 12, brainstem involvement – 3, unilateral ON and TM – 1, bilateral ON and TM – 3 cases. Acute treatment was received in 19/22 patients: steroids – 17, PLEX – 2, cyclophosphamide – 1. A recovery was good only in 41% (n = 9), though, 55% (n = 12) showed no recovery or it was insignificant; in a single case outcome was unknown. A further relapse occurred in 82% (18/22) of patients – median after 5 (2–299) months. 3/4 patients who presented with monophasic illness were followed up for less than a year and a single patient – for 5.1 years.

2.1.3 Secondary progressive course

A total of 123 patients data was analysed (95 women and 96 AQP4-IgG positive). Median age at onset of NMO/NMOS was 40 (5–79) and duration of the disease – 6.8 (0.2–38.3) years. From all the cases inspected, a total of 5/123 patients qualifyed for SPNMO criteria (2.3 Table), accounting for 4% of all NMO / NMOS cases. Initial brain MRI was normal in all except one case when a nonspecific white matter changes were shown. All patients had received immunosuppression: azathioprine – 4, prednisolone – 3, methotrexate – 2, IVIG – 1.
### Table 2.3

**Characteristics of SPNMO patients**

<table>
<thead>
<tr>
<th>No, gender</th>
<th>Age at NMO onset (at SP onset)</th>
<th>Diagnosis (lesion location on spinal MRI)</th>
<th>AQP4-IgG</th>
<th>OCBs</th>
<th>Total duration of NMO (duration from disease onset to SP), years</th>
<th>Duration of progressive neurological deficit, years</th>
<th>Total No of relapses (number of relapses before SP)*</th>
<th>EDSS before SP</th>
<th>EDSS at last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M</td>
<td>69 (71)</td>
<td>NMO (cervical LETM)</td>
<td>+</td>
<td>–</td>
<td>6.7 (2.7)</td>
<td>4</td>
<td>5 (5*)</td>
<td>6.5</td>
<td>8.5</td>
</tr>
<tr>
<td>2. M</td>
<td>55 (58)</td>
<td>NMO (cervical and thoracic LETM)</td>
<td>–</td>
<td>–</td>
<td>9.2 (3.9)</td>
<td>5</td>
<td>2 (2*)</td>
<td>4.0</td>
<td>6</td>
</tr>
<tr>
<td>3. M</td>
<td>32 (52)</td>
<td>NMO (cervical LETM)</td>
<td>+</td>
<td>+</td>
<td>30.4 (19)</td>
<td>3.4</td>
<td>2 (2*)</td>
<td>4.0</td>
<td>6</td>
</tr>
<tr>
<td>4. F</td>
<td>74 (76)</td>
<td>NMOS (thoracic LETM)</td>
<td>+</td>
<td>unk</td>
<td>8.6 (1.5)</td>
<td>7</td>
<td>3 (3*)</td>
<td>6.0/6.5</td>
<td>8</td>
</tr>
<tr>
<td>5. F</td>
<td>32 (50)</td>
<td>NMO (cervical LETM)</td>
<td>+</td>
<td>unk</td>
<td>12 (7)</td>
<td>5</td>
<td>1 (1)</td>
<td>4.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Mean</td>
<td>52.4 (61.4)</td>
<td></td>
<td></td>
<td></td>
<td>13.38 (6.82)</td>
<td>4.88</td>
<td>2.6 (2.6*)</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

* It is possible that the onset of the last relapse could be the onset of SP instead

2.1.4 Neuropathic pruritus

44 AQP4-IgG positive patients with a previous history of myelitis were included in the study and were interviewed median 64 (4–444) months after the onset of NMO. Neuropathic pruritus or pruritus without rash or other systemic symptoms was reported by 27.3% (12/44: 2 men and 10 women) of all NMO / NMOS patients. In 3 other cases, pruritus was associated with systemic symptoms (allergic reaction, hyperbilirubinaemia) or was not followed by other neurologic symptoms, therefore were not included in a further analysis. Median age of patients was 45 (33–77) years. Myelitis or brainstem involvement, confirmed on MRI, was present in all 12 patients. In 25% (3/12) NP was the first symptom of myelitis with other symptoms following (within the same distribution) median after 5 (2–28) days. In a single case NP was the very first symptom of onset attack. However, a majority (9/12) of patients reported NP median 7 (1–120) days after other sensory-motor symptoms. Areas affected by NP were similar to other symptoms of myelitis.

NP most frequently involved extremities (75%), trunk (67%) and occipital area (25%). 91.7% (11/12) of patients along with NP reported other associated sensory symptoms – median within 8.5 days: paraesthesia (n = 2), hiperesthesia (n = 1), numbness (n = 7), pain (n = 7). In 50% (6/12) of cases NP was paroxysmal and recurrent, and occurred median 1–5 times per day lasting for 240 (10–600) seconds each. However, in 41.67% (5/12) cases NP was reported as continuous- median over 3 (1–104) weeks, but in a single case it lasted for about 60 minutes. Median intensity of NP was 6/10 (2–9), and in almost half of the cases it was worsened by a touch, hot water or pain. In 3 cases NP was temporarily eased by scratching, though in one case a scratching made it even worse. Other focal signs i.e. hyperemia, sweating or temperature changes were reported by 2 patients.
### Characteristics of patients with neuropathic pruritus

<table>
<thead>
<tr>
<th>No., gender, age</th>
<th>TM with NN</th>
<th>Temporal relation between NP and myelitis</th>
<th>MRI lesion location</th>
<th>Location of NP</th>
<th>Severity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. F, 77</td>
<td>1, 4, 9</td>
<td>5 days before right arm numbness of first episode</td>
<td>C1-7</td>
<td>Right shoulder (details of only first episode available)</td>
<td>4</td>
<td>3 min each, lasted a few days</td>
</tr>
<tr>
<td>2. F, 54</td>
<td>1</td>
<td>4 days after right arm pain, hyperesthesia and paraesthesia</td>
<td>C2-4, Th2, Th8-9</td>
<td>Right arm, occipital area</td>
<td>5</td>
<td>3 min each; ‘on and off’ all day for 10 days</td>
</tr>
<tr>
<td>3. M, 74</td>
<td>1</td>
<td>4 months after pain, numbness and weakness in right-sided limbs</td>
<td>C4, C7</td>
<td>Nuchal area, over upper thoracic spine, right shoulder, right hip</td>
<td>5</td>
<td>10 min, max 1–2 times/day</td>
</tr>
<tr>
<td>4. F, 43</td>
<td>2</td>
<td>1 week after numbness of left arm and left side of trunk</td>
<td>CMJ-C7</td>
<td>Upper posterior trunk, across abdomen, both arms, left ear, neck</td>
<td>5</td>
<td>5 min, 5 times/day, for 1 month</td>
</tr>
<tr>
<td>5. F, 39</td>
<td>2</td>
<td>10 days after pain, tightness around left side of chest, paraparesis</td>
<td>CMJ – Th7</td>
<td>Upper anterior chest</td>
<td>8</td>
<td>4 min each, ‘on and off all day, for 6 months</td>
</tr>
<tr>
<td>6. M, 34</td>
<td>1</td>
<td>5 weeks after numbness on chest and legs</td>
<td>Th1-12</td>
<td>Both thighs</td>
<td>7</td>
<td>3 min, 1–2 times/day for 1 year</td>
</tr>
<tr>
<td>7. F, 33</td>
<td>2, 4</td>
<td>2 episodes associated with 2 relapses: 1) 2 weeks after TM; 2) 4 weeks before TM</td>
<td>MO-Th12</td>
<td>All 4 limbs and trunk (details of only first episode available)</td>
<td>8</td>
<td>Continuous for 1 month for 1st episode</td>
</tr>
<tr>
<td>8. F, 50</td>
<td>1</td>
<td>2 days after hiccups, vomiting, quadriplegia</td>
<td>MO – conus medullaris</td>
<td>Medial aspects of both arms</td>
<td>8</td>
<td>Continuous for 1 month</td>
</tr>
</tbody>
</table>
Continuation of Table 2.4

<table>
<thead>
<tr>
<th>No, gender, age</th>
<th>TM with NN</th>
<th>Temporal relation between NP and myelitis</th>
<th>MRI lesion location</th>
<th>Location of NP</th>
<th>Severity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. F, 54</td>
<td>1, 3</td>
<td>Few hours after double vision, vomiting, and right shoulder pain radiating down the arm</td>
<td>MO-C1</td>
<td>Right shoulder, upper arm, upper torso</td>
<td>7</td>
<td>Continuous for few weeks</td>
</tr>
<tr>
<td>10. F, 45</td>
<td>1</td>
<td>2 days before right-sided limb weakness, paraesthesia, pain, numbness</td>
<td>C3-C5</td>
<td>Right suprascapular</td>
<td>9</td>
<td>Continuous for 2 weeks</td>
</tr>
<tr>
<td>11. F, 45</td>
<td>1</td>
<td>Within 2 weeks after weakness, numbness in upper limbs</td>
<td>C2-5</td>
<td>Occipital area, neck, right upper arm</td>
<td>5</td>
<td>Continuous for 1 week</td>
</tr>
<tr>
<td>12. F, 36</td>
<td>1</td>
<td>2 days after weakness in right-sided limbs</td>
<td>From medulla to mid-thoracic cord</td>
<td>Right hand, left side of neck</td>
<td>2</td>
<td>1 hour each, 5 times/day for a week</td>
</tr>
</tbody>
</table>

F – female, M – male, LETM – longitudinally extensive myelitis, TM – transverse myelitis, NN – neuropathic pruritus, MRI – magnetic resonance imaging, CMJ – cervicomedullary junction, MO – medulla oblongata, C – cervical part of spinal cord, Th – thoracic part of spinal cord
2.1.5 Tonic spasms

44 AQP4-IgG positive patients with a previous history of myelitis were included in the study. 55% (24/44) of patients reported TS. In 2 cases the clinical information was insufficient, therefore those were not included in the further analysis. In total, 22 patients (20 women and 2 men) were interviewed in detail, median 64 (4–444) months after the onset of NMO. Median age of patients during the interview was 50 (14–76) and at NMO onset – 43 (7–69) years. Median disease duration was 79 (11–443) months and duration from the NMO onset to TM associated with TS – 14 (0–300) months. In 54.5% cases TS occurred during or following the onset attack: 40.1% (n = 9) within first month, 59.9% (n = 13) – median within first 8 (0.5–8) weeks. In a single case (4.5%) TS developed as the very first symptom of index attack followed by other sensory-motor symptoms of myelitis 2 weeks later.

TS frequency varied from 1 paroxysm/day to spasm episode occurring every 10 minutes. Median duration of each paroxysm was 40 (10–240) seconds. TS were reported at any time of the day, however in 54% of cases TS occurred only in the mornings or evenings. In a few cases, TS affected the quality of nocturnal sleep, but in 63.6% they were accompanied by pain. In 57% cases spasms were restricted to the lower limbs and in 4% to the upper limbs, though the rest (39%) had spasms in both-arms and legs. Distribution of TS is shown in the Figure 2.1. Exacerbating factors were noted in 63.6% (n = 14): mechanical pressure or touch – 4.5% (n = 1), change of posture, movement or other physical activity – 50% (n = 11), stress – 4.5% (n = 1), cold – 4.5% (n = 1).

Treatment details were available in 17 cases. 12/17 patients received carbamazepine, 9 (75%) of whom had moderate or good response. Baclofen was received in 6 cases but none of them resulted in a significant spasm control. Other drugs such as clonazepam, pregabalin, gabapentin, phenytoin, lamotrigine were also used and gave some symptom relief.
2.1.6 Phenotype of patients tested positive for MOG-IgG

In total, the results of 98 patients who were tested for MOG-IgG antibodies by 05/2014, were reviewed. Among those patients reviewed, 21 (87.5% of all AQP4-IgG negative NMO cases registered in the Liverpool NMO database) were AQP4-IgG negative NMO, and 77 suspected NMOS (i.e. idiopathic single or relapsing ON, TM or brainstem involvement negative for AQP4-IgG and not fulfilling the diagnostic criteria for NMO or MS).

MOG-IgG1 were tested positive in 11 of 98 patients (5 women and 6 men): 8 of 21 (38%) AQP4-IgG negative NMO, 1 single episode of opticospinal demyelination, 1 single TM, 1 relapsing TM and brainstem involvement. Relapsing course was observed in 7/11 or 64% (2.5 Table). In relapsing cases median age at onset of the disease was 20 ± 9, and median disease duration – 7.9 ± 5 years, but in monophasic cases – 29.5 ± 12 and 1.3 ± 0.7 years respectively. The initial brain MRI was normal in 9, showed nonspecific white matter changes in 1 and lesion located in the brainstem – in a single case.
### Characteristics of patients tested positive for MOG-IgG1

<table>
<thead>
<tr>
<th>No, gender, age at last FU</th>
<th>Disease duration, (total No of relapses)</th>
<th>Clinical phenotype (No of attacks)</th>
<th>First inter-attack interval (first ON and TM inter-attack interval)</th>
<th>Spinal MRI: (location of lesion)</th>
<th>CSF: OCBs (cells)</th>
<th>Outcomes after onset attack</th>
<th>EDSS (visual functional score) at last FU</th>
<th>Current treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. F, 26</td>
<td>12,6 years (13)</td>
<td>ON (13) and TM (1)</td>
<td>4 years (7 years)</td>
<td>LETM (CMJ-C7, Th2-8)</td>
<td>Negative (unk)</td>
<td>Full</td>
<td>4 (6)</td>
<td>IVIG 6-weekly and oral prednisolone</td>
</tr>
<tr>
<td>2. M, 19</td>
<td>3,9 years (7)</td>
<td>ON (&gt;7) and TM (2)</td>
<td>2 months (simultaneously)</td>
<td>LETM (Th4-11)</td>
<td>Unknown (14)</td>
<td>Almost full</td>
<td>3 (5)</td>
<td>Rituximab, IVIG 6-weekly and oral prednisolone</td>
</tr>
<tr>
<td>3. M, 26</td>
<td>7,4 years (3)</td>
<td>ON (2) and TM (1)</td>
<td>6 years (6 years)</td>
<td>LETM (C6 – conus medullaris)</td>
<td>Unknown (272)</td>
<td>Partial</td>
<td>4 (1)</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>4. F, 20</td>
<td>15,6 years (2)</td>
<td>ON (1) and TM (1)</td>
<td>4 years (4 years)</td>
<td>LETM (MO-C7)</td>
<td>Negative (13)</td>
<td>None</td>
<td>9 (1)</td>
<td>Azathioprine and oral prednisolone</td>
</tr>
<tr>
<td>5. F, 21</td>
<td>13,6 years (3)</td>
<td>ON (2), TM (2), cerebral (1)</td>
<td>1 year (1 year)</td>
<td>LETM (entire spinal cord)</td>
<td>Negative (264)</td>
<td>Almost full</td>
<td>6 (0)</td>
<td>Azathioprine and oral prednisolone</td>
</tr>
<tr>
<td>6. M, 22</td>
<td>6,1 years (2)</td>
<td>ON (1), TM (1), cerebral (1)</td>
<td>3 months (3 months)</td>
<td>LETM (Th3- 7, Th9-11)</td>
<td>Negative (unk)</td>
<td>Almost full</td>
<td>1 (1)</td>
<td>Azathioprine and oral prednisolone</td>
</tr>
<tr>
<td>No, gender, age at last FU</td>
<td>Disease duration, (total No of relapses)</td>
<td>Clinical phenotype (No of attacks)</td>
<td>First inter-attack interval (first ON and TM inter-attack interval)</td>
<td>Spinal MRI: (location of lesion)</td>
<td>CSF: OCBs (cells)</td>
<td>Outcomes after onset attack</td>
<td>EDSS (visual functional score) at last FU</td>
<td>Current treatment</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7. M, 42</td>
<td>2.3 years (1)</td>
<td>ON (1) and TM (1)</td>
<td>Only 1 attack (simultaneously)</td>
<td>LETM (C2-7, Th6, Th9- conus medullaris)</td>
<td>Negative (161)</td>
<td>Almost full</td>
<td>2 (1)</td>
<td>None</td>
</tr>
<tr>
<td>8. F, 41</td>
<td>1 (1)</td>
<td>ON (1) and TM (1)</td>
<td>Only 1 attack (simultaneously)</td>
<td>LETM (Th8-12)</td>
<td>Negative (189)</td>
<td>Partial</td>
<td>5.5 (2)</td>
<td>None</td>
</tr>
<tr>
<td>9. M, 20</td>
<td>1 (1)</td>
<td>ON (1) and TM (1)</td>
<td>Only 1 attack (simultaneously)</td>
<td>Short lesions (entire spinal cord)</td>
<td>Negative (140)</td>
<td>Almost full</td>
<td>1.5 (1)</td>
<td>None</td>
</tr>
<tr>
<td>10. M, 40</td>
<td>1.8 (2)</td>
<td>TM (1) and brain.st. (1)</td>
<td>2 months (has not had ON)</td>
<td>LETM (accurate location unknown)</td>
<td>Negative (35)</td>
<td>Full</td>
<td>6 (0)</td>
<td>Azathioprine and oral prednisolone</td>
</tr>
<tr>
<td>11. F, 19</td>
<td>0.8 (1)</td>
<td>TM (1)</td>
<td>Only 1 attack (only myelitis)</td>
<td>LETM (C2-Th12)</td>
<td>Unknown</td>
<td>Partial</td>
<td>6.5 (0)</td>
<td>Mycophenolate mofetil and oral prednisolone</td>
</tr>
</tbody>
</table>

2.2 NMO treatment characteristics

2.2.1 Acute treatment with IVIG

2.2.1.1 Characteristics of patients and indications for IVIG

Clinical data of 93 patients were reviewed. A total of 15 patients who received IVIG for treatment of acute relapses were identified. In 5 cases significant clinical details were missing; only patients with sufficient data (n = 10) were included in a further analysis: 8 women and 2 men, 8 AQP4-IgG positive (Table 2.6). Median age of patients at time of treatment was 41.9 (7.4–79.0) and disease duration – 3.3 (0.5–16.6) years.

IVIG was given 2g/kg body weight over 5 days in 10 NMO / NMOS patients for 11 relapses: 7 – TM and 4 – bilateral ON. Intravenous methylprednisolone over 3–5 days before IVIG was given in 10 and PLEX – in 5 cases. But despite treatment, a recovery from relapse was insufficient in all, except one patient and IVIG was started. A single patient received IVIG as a first-line treatment as was initially misdiagnosed with GBS (GBS is often treated with IVIG). In another case PLEX was not given as due to the potential side effects seemed unsafe. In the rest of the cases, the reasons why the priority was given to IVIG and not PLEX are unknown. Following an acute treatment with IVIG, all patients received a further treatment: 1 – IVIG 6–8 weekly, 9 –oral steroids.

2.2.1.2 Response to IVIG treatment and side effects

IVIG treatment was given median 0.5 (0–6) months after the onset of relapse. All patients had significant neurological deficits before treatment. However, at follow-up, median 2 (0-12) months after the treatment with IVIG, median EDSS score was improved by 0.5 points, from EDSS 7.0 (4–7.5) to EDSS 6.5 (3–9) respectively. In total, an improvement of neurological function was recorded in 45.5% (5/11).

In one of the cases which showed improvement (Table 2.6, case 1) IVIG was started early. Prior to the treatment she had severe neurological deficits (tetraplegic, respiratory insufficiency, EDSS 9), and was initially misdiagnosed as Guillain-Barre syndrome. She had positive AQP4-IgG antibodies and the diagnosis was corrected. She continued with oral steroids and at follow-up,
2 months after the treatment with IVIG, showed a significant improvement (EDSS 6.5). Another woman who was bedbound (EDSS 8.5), and had secondary respiratory failure (Table 2.6., case 4), was started on IVIG 14 days after the onset of relapse (4 months after the previous myelitis which left her behind with a significant disability, EDSS 6.5). There was a significant improvement noted following IVIG. Prior treatment with steroids was insufficient, however, 3 months after completing IVIG she was ambulant without any support (EDSS 4.5). Similar improvement was noted in 3 other cases (Table 2.6., cases 6, 7, 9), when IVIG was started within 7–9 days from the onset of relapse (after a failure of steroids).

A significant visual improvement (EDSS 3) was registered also in AQP4-IgG negative woman (Table 2.6., case 9) who initially presented with bilateral loss of vision (EDSS 4). In fact, she had been treated with plasmapheresis on a several occasions for her previous relapses, but without any improvement.

Side effects which could potentially be linked with a use of IVIG, were noted in 2 cases. A patient who presented with pneumonia and myocardial infarction (elevated troponin T) 7 days after her last IVIG infusion, improved within 3 weeks and was discharged home, however, died two months later from pneumonia. In fact, she already had a significant disability (quadriplegic) due to cervical cord relapse, and was unresponsive to steroids prior to IVIG, but PLEX deemed unsafe due to her old age and increased the risk of trombembolic complications.
### Characteristics of patients treated with IVIG

<table>
<thead>
<tr>
<th>No, age, gender</th>
<th>Diagnosis (clinical phenotype of attack treated with IVIG)</th>
<th>AQ P4-IgG</th>
<th>EDSS (resid. disab. from previous relapses)</th>
<th>IST (prior IVIG)</th>
<th>Tx for current attack (prior IVIG)</th>
<th>Indication for IVIG</th>
<th>Tx after IVIG for present relapse</th>
<th>EDSS before IVIG</th>
<th>EDSS after IVIG (before next relapse)</th>
<th>Obj. neurological impr.</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 43, F</td>
<td>NMO (cervical LETM, areflexia, respiratory failure)</td>
<td>+</td>
<td>3 (left eye no POL)</td>
<td>None</td>
<td>None</td>
<td>Misdx as Gullain-Barre syndrome</td>
<td>Oral pred</td>
<td>9</td>
<td>6.5 (2 months)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2. 38, F</td>
<td>NMO (bilateral ON, POL)</td>
<td>+</td>
<td>3 (exact visual acuity unk, able to read large print)</td>
<td>METX, oral steroids</td>
<td>PLEX, oral predn</td>
<td>No impr. from PLEX and pred</td>
<td>Oral pred</td>
<td>4</td>
<td>4 (0.5 months)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3. 49, F</td>
<td>NMO (thoracic LETM-power MRC 2-3/5 in legs)</td>
<td>+</td>
<td>Exact EDSS unknown (able to walk)</td>
<td>RTX, cyclophosphamide</td>
<td>IVMP</td>
<td>No impr. from IVMP, misdx as lupus</td>
<td>Unk</td>
<td>7</td>
<td>7 (5 months)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Continuation of Table 2.6

<table>
<thead>
<tr>
<th>No, age, gender</th>
<th>Diagnosis (clinical phenotype of attack treated with IVIG)</th>
<th>AQP 4-IgG</th>
<th>EDSS (resid. disab. from previous relapses)</th>
<th>IST (prior IVIG)</th>
<th>Tx for current attack (prior IVIG)</th>
<th>Indication for IVIG</th>
<th>Tx after IVIG for present relapse</th>
<th>EDSS before IVIG</th>
<th>EDSS after IVIG (before next relapse)</th>
<th>Obj. neurological impr.</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. 40, F</td>
<td>NMO (cervical LETM, respiratory failure, power MRC 2-4/5 arms and legs)</td>
<td>+</td>
<td>6.5 (ambulant with 2 crutches; was recovering from recent relapse)</td>
<td>None</td>
<td>IVMP followed by oral prednisol one</td>
<td>No impr. from IVMP and pred</td>
<td>Oral pred</td>
<td>8.5</td>
<td>4.5 (3 months)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. 79, F</td>
<td>NMO (cervical LETM, tetraparesis, power MRC 1-3/5 arms and legs)</td>
<td>+</td>
<td>7 (paraplegic, restricted to wheelchair)</td>
<td>Pred along with AZA</td>
<td>IVMP followed by oral pred</td>
<td>No impr. from IVMP, pred; not suitable for PLEX</td>
<td>Oral pred</td>
<td>8</td>
<td>8 (1 month)</td>
<td>No</td>
<td>MI (↑troponin T), pneumonía</td>
</tr>
<tr>
<td>6. 57, M</td>
<td>NMO (cervical and thoracic LETM, power MRC 0-3/5 arms and legs)</td>
<td>+</td>
<td>6.5 (ambulant with 2 crutches)</td>
<td>AZA</td>
<td>IVMP</td>
<td>No impr. from IVMP</td>
<td>Unk</td>
<td>7</td>
<td>6.5 (12 months)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Continuation of Table 2.6

<table>
<thead>
<tr>
<th>No, age, gender</th>
<th>Diagnosis (phenotype of attack treated with IVIG)</th>
<th>AQP 4-IgG</th>
<th>EDSS (resid. disab. from previous relapses)</th>
<th>IST (prior IVIG)</th>
<th>Tx for current attack (prior IVIG)</th>
<th>Indication for IVIG</th>
<th>Tx after IVIG for present relapse</th>
<th>EDSS after IVIG (before next relapse)</th>
<th>Obj. neurological impr.</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.38, F</td>
<td>NMOS (cervical LETM, power MRC 1-2/5 arms and legs)</td>
<td>+</td>
<td>7.5 (tetraparesis, was recovering from recent relapse)</td>
<td>None</td>
<td>IVMP, PLEX followed by oral pred</td>
<td>No impr. from IVMP, PLEX and pred</td>
<td>Oral pred</td>
<td>8.5</td>
<td>7.5 (3 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>8.55, M</td>
<td>NMO (bilateral ON, 1/60)</td>
<td>+</td>
<td>7 (restricted to wheelchair)</td>
<td>METX along with oral steroids</td>
<td>Oral pred</td>
<td>No impr. from pred</td>
<td>Oral pred</td>
<td>7</td>
<td>7 (0.5 months)</td>
<td>No</td>
</tr>
<tr>
<td>9.24, F</td>
<td>NMO (bilateral ON, POL)</td>
<td>–</td>
<td>3 (right eye POL, left 6/18)</td>
<td>Mitoxant rone, oral steroids</td>
<td>IVMP, PLEX</td>
<td>No impr. from IVMP, PLEX</td>
<td>Oral pred</td>
<td>4</td>
<td>3 (4 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>No, age, gender</td>
<td>Diagnosis (clinical phenotype of attack treated with IVIG)</td>
<td>EDSS (resid. disab. from previous relapses)</td>
<td>IST (prior IVIG)</td>
<td>Tx for current attack (prior IVIG)</td>
<td>Indication for IVIG</td>
<td>Tx after IVIG for present relapse</td>
<td>EDSS before IVIG</td>
<td>EDSS after IVIG (before next relapse)</td>
<td>Obj. neurological impr.</td>
<td>Side effects</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------</td>
<td>---------------------------------</td>
<td>------------------</td>
<td>-----------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------</td>
<td>---------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>10. 1* 7, F</td>
<td>NMO (bilateral ON, POL)</td>
<td>-</td>
<td>None (first attack)</td>
<td>PLEX 2 weekly for haemolytic uremic syndrome IVMP, PLEX</td>
<td>No impr. from IVMP, PLEX</td>
<td>Oral pred</td>
<td>4</td>
<td>4 (1 month)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10. 2* 7, F</td>
<td>NMO (cervical LETM, power MRC 0/5 arms and legs)</td>
<td>-</td>
<td>4 (POL bilaterally)</td>
<td>IVMP, followed by oral pred, PLEX</td>
<td>No impr. from IVMP, PLEX</td>
<td>Oral pred</td>
<td>9</td>
<td>9 (1 month)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

2.2.2 Preventative treatment with azathioprine

2.2.2.1 Overall characteristics of patients and treatment

AZA was given in 103 patients: 91 (88%) women and 12 (12%) men. 60 was diagnosed with NMO and 43 – NMOS. AZA was started median 2 (0–31) years after the onset of the disease and after 3 (0–22) relapses. In two cases AZA was started before the onset of NMO/NMOS: one patient was treated for lupus (1 month earlier) and another one – for myasthenia (2.5 years earlier). The median age of patients at start of AZA was 45.8 (3.7–79.0) and at last follow-up 50 (5–80) years; 8 patients were younger than 16 and 11 older than 65 years. Median disease duration at last follow-up was 6 (0.42–32.5) years.

Median duration of AZA was 18 (0.01–256) months. AZA as a first-line treatment (with or without prednisolone) was used in 91/103 (88%) patients, in 9 cases – after the failure of other immunosuppressants and median after 5 (3–10) relapses. Three patients were initially misdiagnosed MS, and were treated with beta interferon, glatiramer acetate or natalizumab. All drugs, except for prednisolone, were completely stopped before starting on AZA. In three cases AZA was initiated with a pulse of intravenous cyclophosphomide. At last follow-up, the median dose of AZA was 125 (25–275) mg; 63% (65/103) of patients received concomitant oral prednisolone, median 4.5 (1.25–45) mg/day.

2.2.2.2 Response to treatment: relapses

All patients \( (n = 103) \)

89% (92/103) of patients showed reduction of ARR, median from 1.5 (IQR, 0.6–4.0) before treatment to 0 (IQR, 0–0.27, \( p < 0.00005 \)) post-treatment. A clinical remission was achieved in 61% (63/103), and the rest or 39% (40/103) continued to relapse. Third of them (\( n = 12 \)) developed a new relapse within the first 3 months, others- median after 21 (4–83) months from starting AZA. However, despite further relapses a significant reduction of ARR was noted (median from 1.65 pre-treatment to 0.27 post-treatment). 65% (26/40) among those who relapsed and 62% (39/63) in clinical remission received concomittant prednisolone, median 4 (1.5–30) mg and 5 (1.25–45) mg.
respectively. Patients who failed previous immunosuppression, too showed improvement of ARR: median from 1.7 (0.9–3.6) to 0.27 (0–1.14).

24 patients discontinued AZA within the first 6 months, but 7 received AZA for less than 6 months. The rest (72 or 70%) continued AZA for at least 6 months. In patients with follow-up \( \geq 6 \) months, ARR \((n = 72)\) dropped from 1.6 (IQR 0.6–4) to 0.1 (IQR 0–0.5), \( p < 0.00005 \). A clinical remission was achieved in 49\% (35/72).

**Patients with \( \geq 2 \) relapses within 6 months or \( \geq 3 \) relapses within 12 months prior starting AZA \((n = 36)\)**

36 out of 103 cases (35\%) had a frequently-relapsing NMO (FR-NMO) i.e. experienced at least 2 relapses within 6 months or at least 3 relapses within 12 months prior starting AZA. Similar criteria were applied in the “eculizumab study” (a preventative drug used for the treatment of NMO with the highest efficacy so far), *(Pittock, Lennon et al. 2013)*. Patients’ characteristics are summarised in Table 3.7.

23/36 (64\%) patients were followed-up for longer than 1 year, i.e. median 37 (14–166) months. ARR reduced in 86\% (31/36) FR-NMO patients and clinical remission was achieved in 44\% (16/36). ARR was also reduced in 87\% (20/23) and remission achieved in 30.4\% (7/23) FR-NMO patients who were followed-up for longer than 1 year. 20 (56\%) FR-NMO patients developed a new relapse (total 69 relapses among them) median after 24 (IQR 5–83) months. 35\% (7/20) had a relapse within the first 4 months. AZA after the first relapse was continued in all, except one, cases and 63\% (12/19) of patients median after 84 (IQR 30–88) months from the start of AZA developed another relapse (Table 2.7., Figure 2.2.).

**Patients with \( \leq 2 \) relapses within 6 months or \( \leq 3 \) relapses within 12 months prior starting AZA \((n = 67)\)**

In total, 67/103 (65\%) patients had less than 2 relapses within 6 months or less than 3 relapses within 12 months prior starting or non-frequently relapsing disease (non FR-NMO). Characteristics of these patients \((n = 67)\) are summarised in Table 3.8. A reduction of ARR in this group was more significant than in patients with frequently – relapsing NMO \((p = 0.0025)\). Also, a median time to first \((p = 0.03)\) and second attack \((p = 0.0097)\)
was shorter, 52 and 176 in contrast to 24 and 84 months (Figure 2.2) respectively.

Table 2.7

Demographic and clinical characteristics of patients treated with AZA

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FR-NMO</th>
<th>Non FR-NMO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 36</td>
<td>N = 67</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>33 (92%)</td>
<td>58 (87%)</td>
</tr>
<tr>
<td>Men</td>
<td>3 (8%)</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Median age at start of AZA, years</td>
<td>39.9 (3.7–75.8)</td>
<td>50.1 (17.2–79)</td>
</tr>
<tr>
<td>Median age at last follow-up, years</td>
<td>45 (5–77)</td>
<td>52 (18–80)</td>
</tr>
<tr>
<td>Median disease duration at start of AZA, years</td>
<td>1 (0.08–14.42)</td>
<td>43 (0–31.47*)</td>
</tr>
<tr>
<td>AZA used as first line treatment</td>
<td>27/36 (75%)</td>
<td>63/67 (94%)</td>
</tr>
<tr>
<td>Median duration on AZA (months)</td>
<td>22 (0.03–256)</td>
<td>17 (0.01–254)</td>
</tr>
<tr>
<td>Median dose of AZA, mg/day</td>
<td>100 (25–250)</td>
<td>150 (25–275)</td>
</tr>
<tr>
<td>Median dose of oral prednisolone (mg)</td>
<td>5 (3.75–40)</td>
<td>2.5 (1.25–45)</td>
</tr>
<tr>
<td>Median number of total attacks before AZA</td>
<td>4 (2–12)</td>
<td>2 (0–22)*</td>
</tr>
<tr>
<td>Median number of attacks 12 months before AZA</td>
<td>3 (2–5)</td>
<td>1 (0–12)*</td>
</tr>
<tr>
<td>Median ARR before AZA, total</td>
<td>3.8 (0.28–12)</td>
<td>1 (0.06–25)</td>
</tr>
<tr>
<td>before AZA (with follow-up ≥12 months)</td>
<td>3.6 (0.28–8)</td>
<td>–</td>
</tr>
<tr>
<td>12 months before AZA</td>
<td>3 (0.6–6.9)</td>
<td>1 (0.2–12)</td>
</tr>
<tr>
<td>after AZA (in total)</td>
<td>0.21 (0–6.67)</td>
<td>–</td>
</tr>
<tr>
<td>after AZA (with follow-up ≥12 months)</td>
<td>0.27 (0–156; IQR 0.67)</td>
<td></td>
</tr>
<tr>
<td>Median EDSS before AZA</td>
<td>5.5</td>
<td>6</td>
</tr>
<tr>
<td>after AZA</td>
<td>4.5 (p = 0.35)</td>
<td>6 (p = 0.59)</td>
</tr>
<tr>
<td>Stabilisation or improvement of neurological function, %</td>
<td>86</td>
<td>75 (50/67)</td>
</tr>
<tr>
<td>Remission, %</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>Median time to first attack, months</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>Median time to second attack, months</td>
<td>84</td>
<td>176</td>
</tr>
</tbody>
</table>

*2 patients started AZA before the onset of NMO
AZA – azathioprine, EDSS – expanded disability status scale, FR-NMO – frequently relapsing NMO
Figure 2.2. Kaplan-Meyer curve. The probability of a patient developing first and second attack while on AZA at different time points

**Patients with severe functional deficits prior starting AZA (n = 63)**

A total of 62/103 (60.2%) of patients had severe functional deficits or severe-attack NMO (SA-NMO) within 6 months prior to starting AZA i.e. EDSS ≥6 (requires unilateral assistance) if presenting with myelitis or EDSS ≥3 (blind in at least one eye or maximal visual score 6/36-6/60 in the worst eye) if presenting with optic neuritis. 35/62 (57%) patients had NMO and others-
NMOS (mostly relapsing): 15 (23.8%) relapsing TM, 4 (6.3%) relapsing ON and 8 (12.7%) single TM. Median disease of duration was 20 and duration of AZA treatment – 17.5 (0.02–256) months. Median dose of AZA was 150 (25–275) mg/day. 39/63 (62%) received concomitant oral prednisolone – 5 (1.25–45) mg/day.

As a result of treatment, a remission was achieved in 66% (41/62). Median ARR reduced from 1.7 to 0. The rest of patients (n = 21) had 66 relapses among them. 15% (10/66) of all relapses on AZA (in 9 patients) occurred within the first 6 months of treatment. The first relapse developed median at 67 (IQR 17) months, however, none of those 21 patients discontinued treatment and 71% had another relapse median after 5 (2–172) months. In average, a neurological function (according to EDSS) remained unchanged.

2.2.2.3 Response to treatment: disability

EDSS scores were available for 96/103 patients. In 62% (59/96) cases EDSS remained unchanged, 23% (22/96) showed improvement by median 2 (1–4.5) points (p = 0.02), and 16% (15/96) – deteriorated. In total, an improvement of EDSS score was noted, median from 6 (IQR 3.5–6.5) to 5 (IQR 3.5–6.5). In all patients, except 2 (they had a significant decline in neurological function) who switched from other immunosupresants EDSS remained unchanged. After exclusion from the analysis patients who were ceased, at last follow-up (n = 9, EDSS = 10) a total EDSS score showed reduction from median 5.5 (IQR 3.5–6.5) to 4.0 (IQR 3.5–6.0), p = 0.03. EDSS remained stable or improved also in 86% (31/36) of patients with FR-NMO.

2.2.2.4 Retention to treatment

Accounting for all cases, median duration on AZA was 18 (0.01–256) months. At last follow-up the drug was continued in 54% (56/103) cases. 23% (n = 24) of patients discontinued treatment within the first 6 months, the rest (n = 72) – continued AZA for median 31.5 (7–256) months in total. Treatment was discontinued due to: 62% (n = 29) side effects, 19% (n = 9) death, 15% (n = 7) on-going relapses, 2% (n = 1) pregnancy. Reasons for discontinuation were unknown in a single case (2%). AZA due to side effects was discontinued earlier, median after 2 months, compared to 16 months due to on-going disease activity (median after 3 relapses). If comparing a discontinuation rates of AZA
among various subgroups (FR-NMO vs. non FR-NMO, SANMO vs. less severe NMO), no statistically significant changes were found (p = 0.48, p = 0.956). Among patients who received AZA for at least 6 months (after exclusion of those who discontinued AZA early or started the drug less than 6 months ago), a median duration on AZA was 31.5 (7–256) months.

Side effects occurred in 60% (62/103) and were the dominant reason (62%, 29/47) for discontinuation of AZA. Amongst side effects were: 24.3% (n = 25) gastrointestinal, 23.3% (n = 24) haematological, 5.8% (n = 6) cardiorespiratory, 2.9% (n = 3) infections and 7.8% (8) other disturbances. Due to gastrointestinal side effects AZA was discontinued in 72% (n = 18), due to haematological – 33% (n = 8), infections – 33% (n = 1), other side effects – in 75% (n = 6) of patients. Nine patients died whilst on AZA; all had a significant disability before starting AZA (median EDSS 7.5 (6–8). A median duration on AZA was 31 (2–256) months and disease duration – 6.25 (0.47–32.5) years. The cause of death was available for 5/9: 1 – sepsis, 1 – heart failure and pulmonary embolism, 3 – pneumonia, 1 – myocardial infarction.

Using Kaplan-Meier curve a probability of a patient remaining on AZA over time (Figure 2.3.) was estimated. Analysis showed, that the probability of remaining on AZA for at least 1 year was estimated to be 73% (95% CI: 63, 81), for at least 3 years – 58% (95% CI: 47.68), for at least 5 years – 47% (95% CI: 34.59) and for at least 10 years – 33% (95% CI: 19.48).

Figure 2.3. Kaplan-Meyer curve. The estimated probability of a patient remaining on AZA (with 95% confidence intervals)
## 2.3. Analysis of Latvian DD / MS register

### 2.3.1 Overall analysis of DD / MS register

<table>
<thead>
<tr>
<th>Parameters evaluated</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>National register. Initially was established (in 1997) as MS database with an access only within LMMC (national programme); patients were referred across from the entire country</td>
</tr>
<tr>
<td><strong>Minimal standardised data set</strong></td>
<td>Using MS proforma (Cabinet of Ministers, policy Nr 746, 15.09.2008. appendix 13); standardised parameters and international nomenclature is applied</td>
</tr>
<tr>
<td><strong>Data modules, general characteristics</strong></td>
<td>6 modules: demographics, family history (chronic illnesses-collagenosis, allergies etc. (according to ICD10) and MS history in family – mother, father, siblings, children), past medical history (vaccination, history of infectious illnesses – measles, mumps, varicella, rubella, last herpes, viral hepatitis; endocrine illnesses, gynecological history), MS history (symptoms of first, second and last relapse- as a free text, place of disease onset), neurological symptoms over time (some selected temporarily or permanent symptoms and their observational year have been recorded), findings at last follow-up (date, complains according to symptom group, findings on neurological examination as per EDSS, EDSS score; course of disease, classification according to anatomical distribution, MR dates; accounting group (A – confirmed MS, B – suspected or probable MS, C – best explained by other disease), date and conclusion on findings in neuroimmunological tests, date of completion of proforma. In a few modules- there is an option to add an additional data as a free text</td>
</tr>
<tr>
<td><strong>Data security, confidentiality</strong></td>
<td>Responsible institution- SPKC (normative justification is provided by Cabinet of Ministers, policy Nr 746, 15.09.2008. “The procedures for the establishment, updating and maintenance of registers for certain diseases”); data operator- continues to be LMMC. A person can gain privilege to enter the data if accepted by SPKC (written application process). Access is very restricted and well controlled; Confidentiality process determined by law and proceeded accordingly (Personal Data Protection Act). Individualized security access system, the amount of data according to each person's specifications.</td>
</tr>
<tr>
<td><strong>Maintenance of ethical principles</strong></td>
<td>The patient's written consent and information to the data input into the register is not required</td>
</tr>
</tbody>
</table>

Table 2.8
Data are entered into the electronic system using MS data proforma or directly.

Self-training of persons for data input using the MS patient card/proforma data input instructions. Data recording system takes place after the principle of good faith. Control mechanisms do not work in practice.

The registry is powered by a stable continuous funding.

Direct access to data provided to SPKC officers, as well as data operator-LMMC. Information about the application process for use of data for scientific purposes is not publicly available. At present, a valid MS card/proforma, which initially was made as far back as in 1997, has been approved by the Cabinet of Ministers in 2008. A revision of input modules and the update of the data proforma according to today’s needs has not been taken.

### 2.3.2 Possibility detecting NMO and variants of other rare demyelinating diseases or atypical symptoms

The data module of MS history lists various MS symptoms and includes disease classification according to the anatomical localisation (cerebral, cerebrospinal, spinal) and disease course.

The initial MS database (LMMC) and also the data proforma offered to include data on cases of other DD, i.e. group B (suspected MS) and group C (symptoms are best explained by other disease), though, in real practice this approach was not followed systematically. An analysis of the Latvian MS register was conducted, which involved filtering for specific clinical, laboratory or MRI parameters (features), with a view to retrospectively identify potential NMO cases. A summary of the analysis is shown in Table 2.9.
## Analysis of MS register: screening by specific NMO characteristics

<table>
<thead>
<tr>
<th>Main parameters</th>
<th>Screening by features</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of disease</td>
<td>able to detect</td>
<td></td>
</tr>
<tr>
<td>Characteristics of relapses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinical site involved</td>
<td>partially able to detect</td>
<td></td>
</tr>
<tr>
<td>severity</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>Presence/absence of specific/unique/rare clinical features</td>
<td>potentially available to list</td>
<td></td>
</tr>
<tr>
<td>Efficacy of treatment (stabilisation/deterioration/unchanged)</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>Other illnesses (co-autoimmunity)</td>
<td>potentially available to list</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>Co-autoimmunity</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localisation of brain lesions</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>Localisation of spinal cord lesions</td>
<td>unable to detect</td>
<td></td>
</tr>
<tr>
<td>Characteristics of spinal cord lesions (i.e. length of lesion)</td>
<td>unable to detect</td>
<td></td>
</tr>
</tbody>
</table>
3. DISCUSSION

3.1 NMO clinical characteristics

3.1.1 Relapse seasonality

NMO is typically a relapsing condition accumulating disability with each relapse. An average annual relapse rate is 0.82 (Kitley, Leite et al. 2012). Putative triggers of immune system activation are unknown, though, NMO / NMOS relapses likely occur following an initiation of an immune cascade resulting in neuroinflammation and clinical deterioration. The role of environmental factors in pathogenesis of MS and other inflammatory disorders have been studied for at least several decades. Observations have shown a rise of MS activity and prevalence further from the equator. This phenomenon has been explained by solar activity and the role of vitamin D synthesis in the etiopathogenesis of MS (Handel, Giovannoni et al. 2010, Handel, Handunnetthi et al. 2010, Spelman, Gray et al. 2014). Interestingly, that despite an immunosuppressive effect of UV radiation, in the Northern hemisphere, amongst the individuals of MS or ON, the highest incidence and disease activity was observed during the “warmest” months (with a few variations among different years). Some authors report the activity peaks occurring in both, “colder” and “warmer” months (Bamford, Sibley et al. 1983, Jin, de Pedro-Cuesta et al. 2000, Koziol and Feng 2004, Ogawa, Mochizuki et al. 2004, Abella-Corral, Prieto et al. 2005, Fonseca, Costa et al. 2009, Balashov, Pal et al. 2010, Meier, Balashov et al. 2010, Salvi, Bartolomei et al. 2010, Handel, Disanto et al. 2011, Damasceno, Von Glehn et al. 2012, Iuliano 2012, Hart and Gorman 2013, Muto, Mori et al. 2013, Spelman, Gray et al. 2014).

Whether NMO, common with MS and other inflammatory CNS disorders, in which seasonal patterns of relapses have been noted, results from an interaction between environmental and genetic factors, remains unknown. To date there is only a single study looking at the seasonal variation of relapses in NMO – amongst Japanese, but none in western populations. The study mentioned above showed negative results. That study included both, AQP4-IgG seropositive and seronegative cases, which could have had an impact on the results (Muto, Mori et al. 2013). In fact, opticospinal MS, which is often hard to distinguish from NMO, is common in Asian countries.
This is the only study reporting seasonality data in western populations of NMO so far and is representative of the cohort of patients from the United Kingdom. To avoid any diagnostic uncertainties only data of AQP4-IgG positive patients were analysed.

A total of 57.6 relapses would be expected to occur each month of the year, which would be equal to 8.33% (100% divided by 12 months). The real number of relapses was lowest in June (46 or 6.6% vs. expected 8.33%, relapse rate ratio – 0.74), and possibly in July (53 or 7.7%, relapse rate ratio 0.87), although this did not show a statistical significance (p = 0.19 un 0.52). It is possibly explained by a slightly higher number of relapses in adjacent months (May and August). However, after logistic regression was performed, a slight raise of relapses in October (p = 0.04) and November (p = 0.007) was observed. Interesting is the fact that the results of this study, demonstrating an increased disease activity during the “cold months”, shows the opposite trend observed amongst Western MS patients (Koziol and Feng 2004, Fonseca, Costa et al. 2009, Handel, Disanto et al. 2011, Damasceno, Von Glehn et al. 2012).

Although the p value indicates a statistically reliable result the analysed group of patients is relatively small and therefore the results should be evaluated with caution. At the same time we should bear in mind that the data from Japan showed no seasonal variation in NMO. This, in turn, leads to the thinking that external factors in the NMO pathogenesis, if contributing at all, are distinct from those involved in MS. It is also possible that during the stage of NMO when the disease is already established, the ethiopathogenic mechanisms are not sensitive to the seasonal fluctuations or external factors. In overall, the results of this study, similar to those from the other studies on clinical, laboratory (cytokines, etc.) and radiological features, support the hypothesis that NMO and MS are two separate entities.

This study has several limitations. Although each of the study centres corresponds to the national referral centre for patients with NMO, this was not a population-based study and therefore a risk of referral bias can not be fully excluded. Also, a retrospective design may introduce some types of bias. Only clinically evident relapses were counted and radiological approval was not required. Also accurate dates were not available for 10% of the cases. Relapses before and after the initiation of immunosuppression were not separated either. It is also possible that some of the adequate exacerbations were not counted; as if 2 relapses occurred very close together i.e. within 30–60 days, they were considered as one instead of 2 separate ones.
In view of the significant clinical sequel of NMO relapses, a future studies using prospective data, are needed to help to elucidate the mechanisms underlying a relapse initiation and inform a potential new therapeutic approaches.

3.1.2 Features of the onset attack

Until recent history, only few NMO cases were described in the literature. A knowledge and understanding of the disease changed dramatically in 1999 after the proposal of diagnostic criteria of NMO (Wingerchuk, Hogancamp et al. 1999) and a further characterisation of the cases, and repeatedly – in 2004 after a discovery of specific and unique antibodies NMO-IgG in a sera of a number of these patients (Lennon, Wingerchuk et al. 2004). NMO onset is at the age of 40–50, though a late onset – over 50 is not uncommon (Collongues, Marignier et al. 2013). In an initial study analysing NMO clinical features of 71 patients, a unilateral ON during the onset attack occurred in 26% of patients with monophasic and 48% of patients with a relapsing disease, bilateral ON – 17% of monophasic and 8% of relapsing NMO, but TM – in 22% of those with monophasic and 48% with a relapsing course (Wingerchuk, Hogancamp et al. 1999).

A number of NMO/NMOS patients described in this study is one of the largest encountered in the literature. The phenotype and severity of the onset attack (the majority of patients manifested as myelitis), and the duration of first inter-attack interval did not differ from the earlier reports by other authors (Bichuetti, Oliveira et al. 2009, Cabrera-Gomez, Bonnan et al. 2009, Collongues, Marignier et al. 2010, Jarius, Ruprecht et al. 2012),Wingerchuk, Hogancamp et al. 1999, Bichuetti, Oliveira et al. 2009, Bizzoco, Lolli et al. 2009, Collongues, Marignier et al. 2010, Asgari, Lillevang et al. 2011). Simultaneous involvement of the optic nerves and spinal cord, similar to the earlier reports, was more common among patients tested negative for AQP4-IgG (29% vs. 5%) (Jarius, Ruprecht et al. 2012). In a single case report the patient tested positive for AQP4-IgG with symptoms of the index event (myelitis) evolving gradually over several months has been described (Woo, Chiu et al. 2014); no other similar reports can be found in the current literature. A frequency of progressive onset attack in NMO is unknown.

This is the first study describing the time interval from the onset to the peak of the symptoms of the very index event. The study revealed that the
development of the initial symptoms (onset attack) within a few hours to days was observed in only about half of the patients, in other cases developing gradually over several months, defining a subacute or progressive onset of NMO. In a single case, the initial symptoms evolved progressively over approximately 18 months. Clinically and radiologically the diagnostic criteria for NMO were met (Wingerchuk, Lennon et al. 2006), however a seronegativity for AQP4-IgG antibodies makes a diagnosis of MS still possible. Perhaps, progressive onset NMO/NMOS are more common than recognised with many cases still being masqueraded by a progressive myelopathy, MS etc. Pathogenic processes of such progressive cases are difficult to explain, but possibly, in the pathogenesis of NMO, like in MS, both – inflammatory and degenerative processes play a significant role. One can argue that these progressive patients are not entirely NMO; however, AQP4-IgG antibodies that are highly specific biomarker for NMO were detectable in 68% (15/22) of these cases.

This study has several limitations: a retrospective design (often the information was obtained several years after the onset of the disease) and other limitations that are common in observational studies of case series with a small number of patients such as selection bias, a chance of random coincidence, absence of a comparative control group etc.

### 3.1.3 Neuropathic pruritus

Itching (pruritus) is “an unpleasant skin sensation with an irresistible urge to scratch” and is the characteristic symptom of various dermatological diseases, but may also occur in systemic, including neurological diseases. NP is a rare but well defined neurological symptom that occurs as a result of a disturbances of synaptic conduction within the central or peripheral nervous system in the absence of pruritogen (Twycross, Greaves et al. 2003, Oaklander 2011, Oaklander 2014). NP may occur in post-herpetic neuralgia, both mono- and poly-neuropathy, trigeminal neuralgia, traumatic nerve damage, complex regional pain syndrome, multiple sclerosis, Creutzfeldt-Jakob disease, stroke and even NMO cases (Osterman 1976, Osterman 1979, Yamamoto, Yabuki et al. 1981, Yamamoto, Kawazawa et al. 1989, Koeppel, Bramont et al. 1993, Binder, Koroschetz et al. 2008, Alai, Skinner et al. 2010) (Oaklander 2012). NP is not uncommon in patients with NMO/NMOS, however, only a few cases have been described (El Otmani, Dany et al. 2015, Wang, Qi et al. 2015). Incidence of NP and characteristics were not described in detail so far.
A pathogenic mechanisms of pruritoceptive itching are induced by skin irritation by pruritogens that causes the stimulation of the free nerve endings of the specialized C-fibers. Impulses are transmitted to the ganglia of the posterior spinal root. In the spinal cord, pruritus seems to be mediated by both, histaminergic and non-histaminergic neurons (Oaklander 2011, Oaklander 2014). The dorsal root ganglia contains the neurons which express the gastrin-releasing protein (GAP), neuromedin B etc. and other subtype of neurons that mediate an itching (Sun and Chen 2007, Sun, Zhao et al. 2009, Su and Ko 2011). The afferent impulses are then transmitted through the spinothalamic tract and thalamus to the primary somatosensory cortex. Similar pathways exist within the trigeminal sensory system. It is believed that the pain has inhibitory effect on itching; therefore a scratching can bring a relief. Although the physiological processes of neuropathic itch are not fully understood, researchers believe that the itching can be caused by a failure at any point along the sensory pathways of the nervous system (Binder, Koroschetz et al. 2008, Jeffry, Kim et al. 2011, Oaklander 2011, Mochizuki and Kakigi 2014, Mochizuki, Papoiu et al. 2014, Oaklander 2014).

In MS, neuropathic pruritus has been associated with brain and spinal cord lesions (Ostermann and Westerberg 1975, Yamamoto, Yabuki et al. 1981, Yamamoto, Kawazawa et al. 1989, Sandyk 1994, Oaklander 2012). In transverse myelitis associated with NMO, NP is likely caused by inflammation and demyelination along the neurons in the dorsal horn of the spinal cord or while in brainstem, lesions of the spinal nucleus of the trigeminal nerve or periaqueductal pathways (Mochizuki, Tashiro et al. 2003, Liu, Berta et al. 2012, Mochizuki, Papoiu et al. 2014). Interesting is the fact that NP was more common in NMO (27.3%) than MS (4.5%). NP occurred as the first neurological symptom in 6% of MS cases (Matthews 1975). In contrast, 25% (3/12) of the patients from this study described NP as the first symptom of myelitis.

Perhaps, that the relatively high incidence of NP in NMO patients is associated with a different distribution of spinal lesions, which in NMO patients are predominantly localised centrally, whereas MS has typically peripherally-placed spinal cord lesions. As already known, the posterior horns of the spinal cord are rich in GAP and neuromedin B receptor-bearing neurons that are involved in the physiological processes of itch (Su and Ko 2011). It is also possible, that neurons involved in the generation of NP, are richer in AQP4, the role of which in the pathogenesis of NMO is well studied. However,
comparative, prospective studies of NP in NMO and MS would be needed to confirm this hypothesis.

NP described earlier in MS patients, started suddenly and was lasting from a few seconds to a few minutes, was distributed within well-demarcated area of the skin and accompanied by other sensory disturbances or pain (Matthews 1975, Yamamoto, Yabuki et al. 1981). Paroxysmal pruritus in this study presented similarly.

This study has several limitations. Retrospective design and recall bias (data obtained median 64 (4–444) months after the onset of NP) are one of them. It is also possible that the NP as a neurological symptom is under recognised. However, the fact that a large proportion of NMO patients reported itching themselves, could suggest that there is a true association between NP and NMO. Other limitations – limitations that are common in observational studies of case series with a small number of patients: selection bias, a chance of random coincidence, absence of comparative control group.

It should be emphasised that the NMO, if untreated, is a rapidly debilitating illness with a high disability and mortality risk, therefore, any sign that could indicate an early disease activity has the potential to reduce these risks. It is essential to remember that an unexplained itching in some cases may be the first warning of upcoming NMO relapse.

3.1.4 Tonic spasms

TS, sometimes referred to as paroxysmal dystonia, are sudden, involuntary, paroxysmal, and brief and stereotyped movements that result in dystonic, most often unilateral, posturing of the limb, but without a permanent functional deficit. TS can be very disabling and painful, but often easily relieved with a membrane-stabilising medications such as carbamazepine. To improve the quality of life of these patients, it is very important to recognise this clinical syndrome early. TS occur with damage along the movement pathways at any level of the CNS, but most commonly – as a result of spinal cord injury. TS, just like other paroxysmal phenomena in demyelinating disease, are thought to result from an excessive axonal excitability generating ectopic impulse activity (Matthews 1958) (Ostermann and Westerberg 1975).

TS can be triggered by voluntary movement, emotion or hyper-ventilation; are often accompanied by other sensory or motor disturbances. TS have been noted in demyelinating diseases, sometimes presenting as initial

The results of this study confirm that TS is a common (> 55%) disabling residual symptom of myelitis in patients with NMO/NMOS. In fact, the frequency of TS is higher in prospective (patient interview) than retrospective (review of medical records) studies (Wingerchuk, Hogancamp et al. 1999, Kim, Go et al. 2012, Usmani, Bedi et al. 2012, Abaroa, Rodriguez Quiroga et al. 2013), and amongst AQP4-IgG-positive than negative (38% vs. 5%) patients (Iorio, Damato et al. 2013); TS is a characteristic feature of NMO / NMOS.

In rare cases (4.5% in this study) TS may occur as the first symptom of myelitis, but most commonly- during a recovery phase of the first TM. This suggests a partial role of remyelination in the development of TS (Kim, Go et al. 2012). Therefore, unless a spasm is the first clinical manifestation of myelitis, treatment with corticosteroids is likely to be ineffective. In line with earlier reports, TS best responded to carbamazepine (also were treated with gabapentin, phenytoin or baclofen) indicating a transient ion channel dysfunction as a primary pathogenic mechanism of TS in patients with active demyelination (Waubant, Alize et al. 2001).

This study has several limitations. One of those – a retrospective study design. In a recent literature frequency of TS in patients with MS has not been reported, therefore to assess the differences between these two diseases, a comparative prospective studies are needed. Other limitations – limitations that are common in observational studies of case series with a small number of patients: selection bias, a chance of random coincidence, and an absence of a comparative control group.

### 3.1.5 Secondary progressive course

80–90% of NMO has a relapsing-remitting course. A disease outcome depends on the number of exacerbations, and a neurological deficit accrues with each relapse. Only 10-20% of patients have monophasic disease and achieve full clinical remission.
There is only a single study (8 years ago) reporting frequency of SPNMO; it occurred in 2% (2 out of 95) of cases (Wingerchuk, Pittock et al. 2007). In this study, the proportion of patients fulfilling the criteria for SPNMO (4%) was similar to that in the earlier report. A low number of NMO patients with SP course is probably explained by older age at onset and worse lifespan, which is often much shorter than the mean duration from onset to SP in patients with MS (16 years). Interestingly that, a SP course of disease, despite more frequent exacerbations and more severe axonal loss, is rare in NMO unlike in MS (65% within 16 years) (Leray, Yaouanq et al. 2010). The age at onset of the study population varied from 32 to 74 years, though a SP course was clearly observed after the 50-year threshold in all cases. Overall, a duration from the disease onset to SP was shorter (mean 6.8 ± 7 years) than one reported in MS (average 16 years). Younger patients at disease onset (32 years) had relatively longer duration to SP (19 and 7 years), compared with 69, 55 and 74-year-old patients (2.7, 3.9 and 1.5 years). Perhaps, processes of the NMO/NMOS pathogenesis, like MS, involves two stages – inflammatory and degenerative; and a secondary disease progression likely develops irrespective of the degree of axonal loss or number of earlier exacerbations (Wingerchuk, Pittock et al. 2007)(Confavreux, Vukusic et al. 2000, Scalfari, Neuhaus et al. 2011).

This study has several limitations: a retrospective study design and limitations that are common in observational studies of case series with a small number of patients – selection bias, a chance of random coincidence, absence of a comparative control group, and the literature data used as a control group.

3.1.6 Phenotype of patients tested positive for MOG-IgG

It is well known that NMO patients with positive AQP4-IgG (up to 90%) are at increased risk of further exacerbations (Matiello, Lennon et al. 2008, Weinstock-Guttman, Miller et al. 2008, Akman-Demir, Tuzun et al. 2011, Etemadifar, Mollabashi et al. 2012). To prevent them from further relapses and disability, an early long-term immunosuppressive therapy is crucial. Seronegative NMO cases (10‒30%) for both, clinicians and researchers are often at a mystery.

Relatively recent anti-MOG antibodies (MOG-IgG) which bind to the specific myelin oligodendrocyte protein were found in sera from patients with AQP4-IgG negative ON, TM and NMO. The sensitivity and specificity of assay depends on the applied methodology. In one study, in the majority (3/4) of
MOG-IgG positive (AQP4-IgG negative) NMO patients, a monophasic disease course was observed, characterized by a less pronounced loss of neurological function. As a result, the researchers concluded that the MOG-IgG antibodies represent ADEM type disease and a relatively favourable outcome (Kitley, Woodhall et al. 2012, Kitley, Waters et al. 2014). In another laboratory study, a MOG-IgG mediated demyelination (followed by remyelination) in mice was observed, though without characteristic astrocytic damage, complement activation or severe inflammatory reaction which typically occurs in AQP4-IgG positive NMO, and no significant clinical deficits were noted confirming the hypothesis suggested by the previous group (Saadoun, Waters et al. 2014). However, despite earlier reports a relapsing disease in patients tested positive for MOG-IgG is being increasingly reported (Rostasy, Mader et al. 2012, Ramanathan, Reddel et al. 2014, Tsuburaya, Miki et al. 2015). Interestingly, in a recent study of relapsing MOG-IgG positive ON patients, a median annual relapse rate (0.5) was not significantly different from that one seen in AQP4-IgG positive (0.7) or AQP4-IgG negative (0.9) NMO cases (Sato, Callegaro et al. 2014). Similarly, in this study – a significant number of exacerbations was recorded in 4/11 patients who were followed-up for more than 3 years. In four patients who had only 1 clinical attack, disease duration was less than 2 years. It should be emphasised that this study only presents data on relapses approved by neurological and/or radiological evaluation of patients. In two cases (Table 2.5, cases 2 and 9) transient disturbances were observed while reducing the dose of steroids, or in presence of an active infection, therefore those were not counted as exacerbations.

This study describes 6 MOG-IgG (MOG-IgG1 subtype) positive (AQP4-IgG negative) relapsing NMO cases, thereby not validating the hypothesis of MOG-IgG as a biomarker for ADEM type or monophasic NMO and less pronounced neurological deficit. Overall, this work describes 11 MOG-IgG1 positive NMO or suspected NMOS cases (8 AQP4-IgG negative NMO and 3 patients with clinically limited form). The available data leads to conclude that MOG-IgG antibodies are not a unique biomarker for monophasic disease or clinically non-severe deficit and can also be present in patients with relapsing NMO and cases with severe disability. At last follow-up a severe visual or motor dysfunction was noted in more than a half of the patients. Moreover, despite the fact that a recovery from the onset attack was relatively good.
Simultaneous optic neuritis and myelitis preceding a prodrom, was observed in both, monophasic and relapsing NMO cases. Interestingly, the mean age at disease onset was higher in patients with monophasic disease (29.5 ± 12 vs. 20 ± 9, p < 0.05). According to the literature data, oligoclonal bands in the majority of patients with NMO, unlike MS, are negative; cell count is often higher than 50. This study showed similar results: oligoclonal bands were negative in 8/8 cases, while pleocytosis >100 was reported in 71% (5/7) of cases.

To avoid false-positive cases, the positive samples were retested repeatedly, using currently the best available methodology for MOG-IgG1 (cell-based assay).

It is crucial to treat a relapsing NMO (including AQP4-IgG negative patients) already preventively with immunosuppression (Jacob, McKeon et al. 2013). Despite earlier reports, this study did not convince that a loss of neurological function in MOG-IgG positive cases is milder and that the presence of antibodies indicates a monophasic illness. Role of the MOG-IgG still has to be clarified and the guidance of the management of patients based on the MOG-IgG seropositivity alone would not be ethical. In one report, immunosuppressive therapy – oral steroids (9) with/without azathioprine (4) or mitoxantrone (1) was given in more than a half (10/16) of patients, 70% (7/10) of whom remained in remission (Sato, Callegaro et al. 2014).

This study has several limitations: a retrospective study design and limitations that are common in observational studies of case series with a small number of patients – selection bias, a chance of random coincidence, absence of a comparative control group, the literature data used as a control group. Also, among various studies a methodology with variable assay sensitivity and specificity was used to detect MOG-IgG.

### 3.2 NMO treatment characteristics

#### 3.2.1 Acute treatment with intravenous immunoglobulins

Deficits in NMO / NMOS patients accumulate with each relapse, resulting in permanent disability; therefore an early and aggressive management of attacks is crucial. Although there are several medications available to treat NMO, most of them are effective only in prevention and treatment of acute exacerbations is restricted to the use of corticosteroids.
with/without plasmapheresis (PLEX). In practice, IVIG are used to treat various immune-mediated acute conditions such as myasthenia, Guillain-Barré syndrome (GBS) and also being used for prevention from future relapses in NMO (Bakker and Metz 2004, Okada, Tsuji et al. 2007, Magraner, Coret et al. 2013, Wingerchuk 2013). Their potential use in treatment of acute NMO relapses has not been investigated so far. This is the first report describing efficacy and safety of IVIG in the acute treatment of NMO relapses.

This study showed a significant improvement in neurological function following IVIG in almost half (5/11 or 45.5%) of the patients. Most of those (4/5) that showed a significant clinical benefit were AQP4-IgG positive. In the remaining cases (6/11) a stabilisation of neurological function was observed.

While it is inevitably difficult to separate out the efficacy of IVIG treatment from the potential late effect of steroids and PLEX given before or after IVIG (typically prednisolone is continued for several months after an acute pulse), improvement was observed in cases when IVIG treatment was started earlier: median within 1 (0–2) weeks from the onset of symptoms compared to median 3.5 (0.5 to 6) months in the rest of the cases. All patients (except one), who did not show a significant improvement, had severe irreversible residual deficits from their previous attacks, and no significant improvement was expected.

It seems that a use of IVIG in treatment of acute NMO relapses is relatively safe and a risk of serious adverse reactions is relatively low. In a single case, elderly woman, following a course of IVIG, a myocardial infarction and pneumonia developed, most likely of multifactorial etiology. In fact, she already had an increased risk of complications due to her old age and a significant prior disability (tetraparesis, secondary hypoventilation); also IVIG was started simultaneously with azathioprine.

This study has several limitations: retrospective design, small number of cases, very variable time range between treatment and the evaluation of neurological function (0-12 months), also the use of other medications while on IVIG. Therefore the results should be interpreted with a caution. Other limitations: selection bias, a chance of random coincidence, absence of a comparative control group, the literature data used as a control group. In order to be fully confident of clinical efficacy of IVIG, the results of this study need to be approved in a randomised study with a larger number of patients.
3.2.2 Preventative treatment with azathioprine

Randomised studies on the treatment of NMO have not been done so far, and the evidence of treatment is empirical and based on anecdotal case reports. Most of the immunosuppressants used in the NMO/NMOS shows a reduction of annualised relapse rates from 1.48–2.8 to 0–0.93 with a remission being achieved in up to 37–74% (Mandler, Ahmed et al. 1998, Cree, Lamb et al. 2005, Weinstock-Guttman, Ramanathan et al. 2006, Watanabe, Misu et al. 2007, Jacob, Weinshenker et al. 2008, Jacob, Matiello et al. 2009, Bichuetti, Lobato de Oliveira et al. 2010, Bedi, Brown et al. 2011, Costanzi, Matiello et al. 2011, Kim, Kim et al. 2011, Pellkofer, Krumbholz et al. 2011, Cabre, Olindo et al. 2013, Ip, Lau et al. 2013, Kim, Huh et al. 2013, Kitley, Elsone et al. 2013, Pittock, Lennon et al. 2013, Elsone, Kitley et al. 2014, Huh, Kim et al. 2014). Among other drugs, azathioprine (AZA) due to its wide availability, low-cost and reasonably safe adverse effects profile, is one of the most commonly used immunosuppressants. AZA is thiopurine and exerts its immunosuppressive effect as an antagonist of endogenous purines that are components of DNA, RNA and certain enzymes (Sahasranaman, Howard et al. 2008). AZA is metabolized by the enzyme called thiopurine methyltransferase (TPMT); therefore patients with low TPMT activity (about 11% of the population) are at increased risk of AZA toxicity, i.e. myelotoxicity. In NMO, AZA is usually started with 25 mg/day and increased gradually over several weeks up to 2.5–3 mg/kg/day. Often, it is initiated along with prednisolone 0.5–1 mg/kg/day, which can be tapered down once AZA has reached a therapeutic dose (mostly over 6 months) (Palace, Leite et al. 2012, Jacob, McKeon et al. 2013). Despite clinical efficacy, AZA is often discontinued due to intolerance or on-going relapse activity. An efficacy of AZA in frequently relapsing (FR-NMO) or severe-attack NMO (SA-NMO), nor the retention to AZA, and the reasons for discontinuation in patients with NMO/NMOS have not previously been studied.

This is the largest treatment study of AQP4-IgG positive NMO patients so far and the first report on the effectiveness of AZA in patients with FR-NMO and SA-NMO. To avoid potential diagnostic errors only AQP4-IgG positive cases were included. AZA was started median 2 years after the onset of the disease and 3 exacerbations.

The results showed that 89% of all patients had a reduction of relapse activity (median ARR decreased from 1.6 to 0.1), which is similar to the earlier
reports (Costanzi et al. – 76%, Bichuetti et al. – 70%, Mandler – 100%). A significant reduction of relapses was also observed in 86% of FR-NMO (median ARR decreased from 3.8 to 0.21). A complete clinical remission was observed in 61% out of all study patients, and in 44% of those with FR-NMO; neurological function improved or stabilized in 78% of all patients. When analysing only patients with a follow-up >6 months (after exclusion of those who started AZA relatively recently or stopped early), the number of patients who achieved complete clinical remission decreased to 49%. Also the results indicate a proportional reduction in efficacy of AZA in patients with higher disease activity pre-treatment, and a longer follow-up period. It is important to note that, despite the significant reduction of ARR and the fact that the majority of patients achieved a remission, this study clearly demonstrates that in patients with frequently relapsing disease (FR-NMO) AZA was less effective than in those with non FR-NMO.

Interestingly, almost a third (12/40 or 30% of the total group and 7/20 or 35% of FR-NMO) of patients had a new exacerbation within the first 3–4 months, which is probably due to the slow titration of the medication and therefore a delayed efficacy. Although, a duration to the first relapse was shorter (24 vs. 52 months) in patients with FR-NMO. Perhaps this is partly affected by a lower dose of the medication in patients with FR-NMO. Though, only one patient with FR-NMO stopped AZA following the first relapse and 12 out of 19 cases developed further relapses. Median duration to the second attack (176 vs. 84 months) was also longer in patients with lower pre-treatment disease activity.

A significant number of patients whilst on AZA developed at least one side effect resulting in treatment discontinuation in 47% (29/62) of patients. Side effects were the commonest reason for discontinuation of the drug – 62% (29/47), in contrast to 15% (7/47) due to on-going relapses, 2% (1/47) – pregnancy and 2% (1/47) – unspecified reason. Another 9 patients died whilst on AZA, likely due to terminal stage of the illness rather than a use of the product (a significant disability prior starting AZA was registered in all cases). Interestingly, a discontinuation due to adverse reactions was also in 38% (24/63) of patients who were in a remission. In this study, a drop out rate due to adverse events (58%) was comparable to that one in other reports on NMO, but higher than the withdrawal rates of AZA in other diseases (up to 22%) (Pinto, Chebli et al. 2009, Prefontaine, Macdonald et al. 2010, Costanzi, Matiello et al. 2011, Timmer, McDonald et al. 2012, Chaparro, Ordas et al. 2013,
Haematological side effects (lymphopenia, neutropenia or pancytopenia) were one of the most common side effects which lead to discontinuation of AZA (one third of cases). As lymphopenia along with macrocytosis are often used as one of the goals of treatment, higher thresholds may reduce withdrawal rate. Similarly, deranged liver enzymes are often only temporary and are normalised after a reduction in dose. Discontinuation or continuation of AZA in such circumstances is often associated with the clinician's experience of treatment. It is possible that physician thresholds to risk aversion also played a role. Majority of study patients alongside AZA also received other treatment, such as steroids, painkillers, treatment for bladder dysfunction, spasticity, etc., which may have contributed to some of the side effects. Of all the side effects that were identified, the haematological and gastrointestinal are ones which are likely directly attributable to AZA. Haematological changes lead to AZA withdrawal in 8% (8/103), and gastrointestinal symptoms – 18% (18/103) of the study patients. These results are comparable to another study with the next largest study on AZA in NMO/NMOS: 9% (6/70) and at least 14% (10/70) (Costanzi, Matiello et al. 2011). In another randomised, controlled studies on AZA used for other conditions, haematological side effects were noted in 6–50%, gastrointestinal – 3–21% and infections – in 42% of patients (Chaparro, Ordas et al. 2013). The study results confirmed that AZA along with a low dose prednisolone is effective in a significant proportion of NMO/NMOS patients. However, regards to FR-NMO, it seems that it would be reasonable starting on more aggressive treatments already at an early stage of the disease.

This study has several limitations. One of them – a retrospective study design. There is also a possibility that less severe side effects were not documented. At the same time, an accurate body weight during the treatment period for each individual patient was unknown; therefore AZA dose based on body weight could not be calculated. Also the accurate dose of medications, MCV (mean corpuscular volume- often used as a biomarker for AZA effectiveness), duration of prednisolone during relapse were not known (Costanzi, Matiello et al. 2011). Other limitations: selection bias, a chance of random coincidence, absence of comparative control group, the literature data used as a control group.
3.3 Analysis of Latvian DD/MS register

It is well known that many of NMO cases are initially misdiagnosed as MS. Until December 2009, more than 1,600 cases with a confirmed diagnosis of MS (Group A) and at least similar number of cases with suspected MS or other unspecified DD (Group B) were included in the Latvian DD/MS register. Assuming that 1 per each of 40–100 MS patients is unrecognized case of NMO, in total, at least 40 to 160 NMO patients should be registered in Latvia (Wingerchuk, Lennon et al. 2006, Asgari, Lillevang et al. 2011).

Based on the literature data on the prevalence of NMO (0.32–4.40 per 100,000), the minimum expected number of NMO cases in Latvia (according to the data of Statistics Bureau, a population of Latvia at the beginning of 2014 was 2,001,500) varies between 6 and 88. Interestingly, despite the fact that until year 2012 all patients across the whole country were referred to a single MS centre (LJMC), during the period between September 2003 to December 2009, none of the patients had confirmed a diagnosis of NMO, and there were only 2 cases with suspected NMO. Perhaps, this is due to the lack of recognition of the disease and the fact that a detection of NMO specific antibodies (AQP4-IgG or NMO-IgG) during this period was not available on site, but costs to analyse a sera outside the country had to be covered by patient itself.

Latvian MS patient proforma covers a large part of the internationally commonly used modules and data which are required to estimate a prevalence and incidence of MS. Additionally, data for patients with group B (suspected MS) and group C (other illness, which explains the symptoms better has been confirmed) can be added i.e. for patients with clinically isolated syndrome, suspected MS, NMO, etc. similar to the other registers for demyelinating diseases i.e. Denmark, Sweden, Italy, Lyon (EDMUS), etc. However, only data of patients with confirmed diagnosis of MS are currently being entered into the Latvian DD/MS register. In some countries, such as Denmark, France, Korea, India, etc., using DD/MS register and retrospectively searching by various characteristics i.e. NMO clinical and radiological features followed by further diagnostic evaluation, several patients with NMO have been identified (Cossburn, Tackley et al. 2012, Pandit, Mustafa et al. 2013, Viswanathan, Arip et al. 2014).

NMO is clinically characterised by optic neuritis with severe unilateral or bilateral visual loss and longitudinally extensive myelitis (more than 3 vertebral segments in length) causing severe motor, sensory, bladder and
bowel dysfunction; recovery of neurological function is often incomplete, regardless of the treatment acutely received. Often these are accompanied by intractable vomiting, nausea, hiccup, itching, and pain or tonic spasms. Initial brain MRI is typically normal or may show some nonspecific white matter changes, oligoclonal bands are negative. Treatment with beta interferons, natalizumab, fingolimod, etc. typically used for MS, may result in a significant deterioration of neurological function. In contrast, MS typically presents with mild to moderate unilateral optic neuritis, short myelitis (does not exceed one-two segments of length) with good recovery, regardless of whether an acute treatment was received, and positive oligoclonal bands in the cerebrospinal fluid.

A medical and MS history module in Latvian MS patients proforma is quite detailed, although the criteria according to which the parameters/symptoms have been selected for inclusion remains unclear (not all the essential ones have been included, and neither a severity of symptoms). Also, investigations and treatment received are only very vaguely covered and the results of a number of important ones are not even included. This in fact, can result in irreversible consequences (overlap treatment, significant side effects etc.), and therefore also automatically excludes the possibility of data quality control and monitoring of registered MS cases, or retrospective identification of other diseases, i.e. NMO. Automatized or manual review of the data compliance with the international diagnostic criteria, definitions, etc. after completing data proforma or entering into the register is not performed, which increases a risk of input errors. A number of other significant uncertainties concerning the data entered into MS proforma and therefore into the register were observed and are further described in the full version of thesis.

In order to identify and select NMO and other DD cases (often initially misdiagnosed as MS), significant modifications of the register have to be implemented. It is important not only mentioning the date of the first two attacks (like it is currently), but also the consecutive ones; that would enable the calculations of annualised relapse rates, treatment affectivity, etc., and therefore selection of the best available treatment for an individual case. Also, a monitoring of steps of the ambulatory index (unilateral or bilateral support, restriction to wheelchair, bed-bound etc.) and EDSS over time are currently not required.

There are several limitations for use of the register data for research, both, technical and ethical, which are described in the full version of thesis.
This study has several limitations: only MS patient data proforma was used for analysis, as access to the register itself was not possible, therefore there is a chance that data modules (and data within each module) between proforma and register are distinct; at the same time, a literature data for DD/MS registers from other countries for comparison are also limited. An analysis of other medical resources such as inpatient or outpatient medical records, or other potential methods for case identification in this study was not carried out.
4. CONCLUSIONS

1. When comparing the seasonal activity of NMO / NMOS relapses across the whole year, unlike MS, it appears to be slightly lower in June and higher in October and November, although prospective studies are needed to confirm these results.

2. A significant proportion of patients (18%), presents with a progressive disease onset with symptoms evolving gradually over 4 or more weeks. Progressive disease onset in AQP4-IgG negative patients occurs more often than in AQP4-IgG positive patients. However, a SP course of the disease is rare, and not characteristic in patients with NMO/NMOS (in only up to 4%).

3. Neuropathic itch is a common and characteristic feature of NMO-presented by at least one third of NMO/NMOS patients with transverse myelitis; in up to a quarter of patients it may occur as the first symptom of an upcoming relapse. Tonic spasms are frequent (in up to 55%), and characteristic symptom of NMO/NMOS patients with transverse myelitis, but is mostly seen during a recovery phase. Only a small percentage (4.5%) of patients develops TS as their first manifestation of myelitis.

4. Contrary to an earlier hypothesis, NMO / NMOS patients tested positive for MOG-IgG antibodies can present with a relapsing course and severe neurological deficits too.

5. Intravenous immunoglobulins started early, are effective in acute treatment of NMO/NMOS relapses in almost half of the patients.

6. Azathioprine is an effective drug to prevent relapses in NMO / NMOS, reducing annual relapse rate in up to 89% of patients, and providing a complete clinical remission in up to 61%, though its efficacy in patients with frequently relapsing disease is significantly lower.

7. The quality and quantity of the data entered into the Latvian DD/MS register is not sufficient to retrospectively identify NMO / NMOS cases.
5. RECOMMENDATIONS

5.1 Clinical practical recommendations to improve diagnostics, and the treatment of patients with NMO / NMOS

1. In all cases, with a characteristic clinical syndrome (ON, TM), even with a progressive disease course (either the onset of the disease or at a later stage); it is important to consider a diagnosis of NMO / NMOS, and arrange further investigations.

2. An unexplained itching in some cases may be the first warning sign of upcoming NMO relapse. Therefore in patients with previous symptoms suggestive of demyelination who presents with an unexplained itching, localized within dermatomes, it is important to look for other neurological signs suggestive of brainstem lesion or myelitis, and act accordingly if they evolve – starting a treatment with corticosteroids early.

3. It is recommended to treat TS early, as they can be very painful and disabling. Treatment initiation is typically recommended with carbamazepine (membrane stabilising medication), switching to other medications only in cases of inefficacy or intolerance.

4. In MOG-IgG positive cases it is recommended to use similar principles as with conventional NMO, i.e. an early initiation of immunosuppressive therapy in all relapsing cases.

5. Additional IVIG therapy to treat NMO / NMOS relapses can be offered in cases of insufficient efficacy of corticosteroids and plasmapheresis.

6. In patients with frequently relapsing NMO, and patients with ongoing relapses, it is recommended switching to an alternative drug despite the severity of the attack.

7. Given the fact, that a significant proportion of patients developed their first relapse after starting AZA within the first 3-4 months, if tolerated, a more rapid dose titration of AZA, along with high-dose corticosteroids is recommended.
5.2 Recommendations to improve the quality of Latvian DD/MS register

In view of specificity of the DD, and care required for the patients with DD, often including a high cost for the treatment, any information entered into the Latvian MS register should be able to serve as a source of information for the continued care of patients with DD i.e. monitoring an efficacy of the treatment, disability, progression of disease course, and identification of different subtypes of MS and cases with other DD of the central nervous system (including NMO). A substantial amount of work regarding the data input within the MS proforma, in view of the clinical and scientific value of data, and their role in planning financial resources has to be conducted. To ensure this, the required data has to be simplified and facilitated in the majority of the modules. They must be easy to understand, easy-to-use, and have future value. From an ethical point of view, it would be recommended to develop and implement in practice an approach whereby patient informed consent is obtained prior to entering their data into the register for the potential use for research.
6. BIBLIOGRAPHY


7. PUBLICATIONS AND PRESENTATIONS

7.1 International peer-reviewed publications (papers) arising from thesis


7.2 International peer-reviewed publications (conference proceedings) arising from thesis


• Elsone L., Townsend T., Mutch K., Das K., Boggild M., Jacob A. Tonic spasms in neuromyelitis optica. 16th Congress of the European Federation of Neurological Societies – EFNS (Stockholm, Sweden, 09/2012), conference proceedings.

7.3 International publications on the topic of work (thesis)


7.4 Conference preceedings on the topic of work (thesis)

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**7.5 Presentations in the meetings arising from thesis (results of the thesis)**

- **Elsone L.**, Kitley J., Luppe S., et al. Long term efficacy, adherence and reasons for discontinuation in 103 cases of neuromyelitis optica treated with azathioprine: a multicentre study from the United Kingdom. ECTRIMS (poster presentation, Copenhagen, Denmark, 10/2013).
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• Elsone L., Waters P., Woodhall M., Jacob A. Relapsing AQP4 antibody negative NMO with MOG antibodies. ABN (poster presentation, Cardiff, UK, 05/2014).
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