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Final Global Conference

Common strategy of research of ME/CFS

Book of abstracts

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Rīga Stradiņš University, Riga, Latvia

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Epidemiology of ME/CFS in Europe: past, present and future

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In this keynote lecture, an overview of the epidemiology of ME/CFS in Europe will be provided. The aims of the lecture will be:

I. To summarise previous findings on the prevalence and incidence of ME/CFS in European countries (past).

Rationale: Previous systematic reviews on the prevalence and incidence of ME/CFS included studies from many parts of the world [1–4]. However, these previous reviews were conducted more than five years ago and either did not report the incidence of ME/CFS or did not include children or adolescents. Also, by having different inclusion criteria regarding the case definition of ME/CFS, previous reviews yielded highly variable and non-comparable findings. Thus, the EUROMENE working group 1, which focuses on epidemiology, led a systematic review to estimate the prevalence and incidence of ME/CFS in Europe [5].

II. To present and discuss the preliminary set of recommendations for standardised data collection for epidemiological research of ME/CFS in Europe (present).

Rationale: Currently, there is no single validated tool to measure all the different aspects of ME/CFS. Most researchers use a combination of various tools, without any real standardization, making it difficult to compare data and to replicate findings across studies. The issue of variability has prompted researchers from EUROMENE to consider the critical data that should be collected and to make recommendations that will facilitate consistency in methodologies and

interpretability of results. Led by the EUROMENE working group 1, a multidisciplinary team of epidemiologists, clinicians, statisticians, and researchers have provided preliminary recommendations to guide data acquisition for ME/CFS research, which will ultimately improve epidemiological research. In order to ensure scalability of the suggested assessments, including applicability in population-based studies, most of them are based on self-reports. In addition to questionnaires and when circumstances (both resources and needs) allow it, additional objective measurements are suggested in order to obtain a more comprehensive picture of ME/CFS. A discussion about this set of recommendations will be carried out.

III. To suggest future perspectives for epidemiological research of ME/CFS in Europe (future).

Rationale: It will be discussed how to implement the developments of EUROMENE (e.g., set of recommendations for standardised data collection for epidemiological research of ME/CFS in Europe) in order to overcome the current caveats in the field.

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What do young people find helpful in their management? Findings from a long-term follow up study of 784 young people

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Aim: The aim of the study is to seek feedback regarding the outpatient management of young people diagnosed with myalgic encepahalomyelitis/chronic fatigue syndrome (ME/CFS), and to determine the reported duration of illness, functional and educational long-term outcomes and predictive factors for recovery.
Method: Between 1991 and 2009, 784 young people, mean age 14.6 (6–18) years, were diagnosed with ME/CFS following referral to a specialised clinic at the Royal Children's Hospital, Melbourne, Australia. Baseline symptoms, history, depression and anxiety questionnaires were available from 418. The remaining 366, did not have similar standardised baseline information. Regular formal feedback occurred up to 7 occasions over a 14-year period with follow-up for a mean 8 (range 1–21) years after onset. Management included: symptom management and an overall plan where the young person decided how to apportion their energy use across social, educational and physical activities, including a pleasurable activity outside of home. This was adjusted by severity of illness, stage of education, family circumstances and life interests.
Results: Follow-up data were returned from 81.8 % (87.1 % of study group and 75.6 % of comparison group). There was no significant difference in functional rating or illness duration between the two groups. The mean duration of illness was 5 (range 1–15) years in the 50 % who reported recovery. By 5 years 38 % and by 10 years 68 % reported recovery. At 10 years the mean functional score was 8/10 (range 2–10) with 5 % scoring < 6. Depression, anxiety or severity of illness at diagnosis was not predictive of non-recovery. In addition, 1150 questionnaires (80 % of the cohort) provided qualitative data and feedback. Designing and monitoring their own management plan that included educational, social, physical and enjoyable activities, as well as having symptom management and understanding professionals were highly valued. However, remaining engaged in an education system that flexibly accommodated their illness and aspirations was consistently reported as crucial for long term functioning.
Conclusions: ME/CFS in young people has a mean duration of 5 years (1–15) with 68 % reporting recovery by 10 years. All improved functionally with 5 % remaining very unwell and a further 20 % significantly unwell. There were no obvious baseline predictors for recovery. However, depression, anxiety, orthostatic intolerance and to a lesser extent pain at follow up were identified as hampering recovery or function. Supportive professionals, remaining engaged in education and management strategies were identified as helpful. This included maintaining social contact and assistance to achieve educational or life goals.

Prevalence and characteristics of CFS/ME in Poland

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Diagnostics and treatment of chronic fatigue syndrome CFS/ME present a challenge to specialists as this syndrome is not clearly identified, uniform disease but a set of symptoms resembling those occurring in other diseases. In Poland CFS/ME is diagnosed very rarely which may be associated with the fact that etiology of the disease is still poorly known. The aim of this study was to summarise sociodemographic and illness characteristics in those reporting CFS/ME symptoms in a Polish population.

Recruitment was based on self-identification in response to an advertisement in CFS/ME community support networks across Poland, as well as a general advertisement on local radio and social media. In accordance with the Fukuda criteria for CFS, patients were eligible to enter the study if they were 1) age between 25 and 60 years, 2) fatigue more than 6 months 3) had at least four of additional symptoms: malaise after exertion, headache, impaired memory and/or concentration, unrefreshing sleep, sore throat, tender lymp nodes (cervical or axillary), muscle or joint pain, 4) the fatigue must not be the result of an organic disease. Those who fulfilled Fukuda criteria were invited to attend the research unit at the chronobiology laboratory. Pre-test health state assessment of subjects included: basic neurological, psychiatric, clinical examination. A consultant confirmed the inclusion and exclusion criteria and verified whether an extensive physical examination and laboratory research tests had been performed to exclude any underlying illness. Participants completed the following screening symptom assessment tools: Chalder fatigue scale, Epworth sleepiness scale, COMPASS 31, Quality of life scale (QOLS). Hemodynamic and autonomic parameters were automatically measured at rest with a Task Force Monitor.

In 1308 of 1400 (93 %) individuals who identified themselves as fatigued, recognised chronic conditions were identified e.g. neurological (n = 280, 21.5 %), neurodegenerative (n = 200, 15 %), psychiatric (n = 654, 50 %) and immunologic (n = 174, 13.5 %) disorders. The remaining 69 participants (mean age 38.3 ± 8.5) met the Fukuda definition for CFS/ME and had baseline objective assessment. Majority had experienced symptoms for over 2 years with 37 % having symptoms for 2–5 years and 21.7 % for more than 10 years. The C31 indicated that 50 % have symptoms consistent with orthostatic intolerance. 43/69 (62 %) had Epworth sleepiness scores ≥ 10 i.e. consistent with excessive daytime sleepiness. We classified the cohort according to predominance of sympathetic or parasympathetic function, 44/69 (64 %) were found to be sympathetic predominant and 25 parasympathetic. When we considered symptom burden between these two phenotypes, there were no significant differences in symptoms or impact upon quality of life between the groups

This is the first study to summarise illness characteristics of Polish CFS/ME patients. The study has confirmed that fatigue is a common and under-recognised symptom affecting the Polish population.

Considerations of ME/CFS biobanks and bio-repositories within EUROMENE

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Introduction: The ability to systematically collect high quality biological samples is essential for progression and advancement of ME/CFS research. Biobanks and bio-repositories, which collect, process, store, and distribute biological samples to support future scientific investigation, have become an important resource in medical research [1–3]. They provide the opportunity for biological samples and the data derived from those samples to be used by multiple researchers who cannot afford the significant expenses incurred by those procedures. In turn, the pooling of such data across multiple and international sites could provide a cost- and time- effective approach to maximise resources and increase sample sizes [4].
Aim: EUROMENE aimed to survey existing ME/CFS-related bio-resource throughout the participating countries; to appraise feasibility of building one common approach to achieve data comparability between countries; and to consider the challenges for establishing a common ethics, legal, and social (ELSI) framework [5; 6] for enabling the sharing of the samples.
Methods: Members representing a country currently hosting an ME/CFS bio-resources were asked to provide answers related to sample sizes and criteria of cases and any controls, quantity and type of samples allowed for storage, and whether an ELSI framework exists to give external researchers the ability to access their samples. These members were also asked to provide protocols related to recruitment and follow-up; informed consent; procedures for collecting, processing, storing, and sharing samples; access and sample sharing; and quality control, to consider potential synchronisation of procedures in order to maximise research efforts.
Results: The questionnaire was sent out to 32 EUROMENE members. Eight (25 %) members returned the questionnaire, representing Norway, Italy, UK, Latvia, France, Poland, Spain, and Germany. Five are ME/CFS-specific bio-resources, and three are a generic bio-resource with storage for ME/CFS-related research. ME/CFS cases are classified using the Fukuda CDC-1994 criteria in six countries, the 2003 CCC in three countries, the ICC in two countries, and the 2011 CCC in one country. Six countries include severely affected ME/CFS cases, and seven countries include healthy controls, although each classify these differently. Components of peripheral blood, serum, and plasma have been collected in six countries. Samples can be shared in all eight countries, although access is strict in Latvia and Italy. Some representatives provided a brief description of their protocols but many did not provide full protocols. In terms of ELSI frameworks in place, there is no coherent or linear way to share samples across sites, indicating a significant gap.
Conclusion: There are biological samples from ME/CFS cases that have been collected and stored by biobanks/bio-repositories in six of the eight EUROMENE countries that can be compared because they were recruited using the same case definition. However, whether there is enough information to guide systematic collection using standardised protocols across all participating countries is still unclear. Challenges are still to be overcome, especially in terms of ELSI; however, the groundwork has been laid for moving forward.

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HYPOTESIS: We underestimate the risk of chemicals in water and food in ME/CFS

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When conventional organisations of farmers and industry inform that the use of pesticides, chemicals and heavy metal are safe, they make an error. It is a statement that pesticides, chemicals as well heavy metals enter nerve tissue and gut and no doubt interfere with health negatively. What we need is to show the exact mechanism/relationships between specific diseases and "poison" involved. This statement may not be an excuse for politicians not to handle now. Data collected over the past many years shows a growing support that healthcare problems are growing secondary to exposure worldwide to these elements.

The Seveso disaster close to Milan in 1976 was one of the first accidents in industry which resulted in research in health risk secondary to chemicals. As a result, 2.5 kg dioxin was spread out in an area where many people lived, the understanding of this was not obvious, as information about chemicals used was not given prior to the two weeks had passed – after that the area was evacuated. A year later, 122 children were born with deformities, 450 children with chronic dermal diseases, and an increased occurrence of type 2 diabetes especially in women was observed.

Dioxin is only one example how damage can involve living organisms – Danes are daily exposed to drinking water and food. In 2019, it was found that two in three tests in water to drink were positive for smaller cocktails of pesticides. Dependent on how the cocktails are mixed – they invade the human organs. A lab-study from 2017 illustrates the example of 338 pesticides' penetration over membranes in the boiled egg model [1].

Today it is clearer that several diseases can result as a consequence of exposure to environmental factors – named *trigger points*. One factor of pesticides includes phthalate and chemicals in dress coats. Industrial air emission and proximity to emitters are associated with anti-citrullinated protein antibodies (ACPA) in a sample of 1586 unselected subjects [2].

In a controlled clinical study based on exposure to pesticides in tobacco field workers (n = 40) versus a control group in an office (n = 40), the groups were followed 360 hours in a period from June to September. All 80 tested subjects were non-smokers. In the exposed group blood concentration of aluminum, arsenic, chromium, copper, nickel, potassium, selenium and zinc were increased. Blood levels of antioxidants (e.g. B12–C vitamins) were increased but not sufficient to counterbalance the damage – mitochondrial damage/DNA damage [3].

From other designs GWI (Gulf War Veterans) [4], Alzheimer and Parkinson diseases [5], the evidence of pre- and post- natal exposures to environmental factors that predispose to the onset of neurodegenerative diseases later in life highlights the necessity to expand the research on identifying environmental risk factors to the development of neurodegenerative diseases (ME/CFS) – see reprogramming cells from Veterans [4].

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Biomarker in ME/CFS

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ME/CFS is a complex multifactorial syndrome in which dysregulations of the autonomic nervous, metabolic and immune system are evident. Biomarkers with sufficient sensitivity and specificity for diagnosing ME/CFS are not available yet. There are, however, a number of studies showing biomarkers characterising subgroups of patients. The most obvious clinical subtype is an acute infection-triggered onset in about 2/3 of patients while in 1/3 disease onset is not related to infection or gradual. There is first evidence of variants in autoimmune-related genes PTPN22 and CTLA4 being more frequent in patients with infectious disease onset. Further evidence for an autoimmune-related subgroup comes from studies showing dysfunctional ß2 adrenergic receptor antibodies in a subgroup of patients. Biomarker dysregulation was also found to be related to the presence of irritable bowel syndrome. Also, sex and disease duration were shown to influence alterations of biomarker. Therefore, when studying a biomarker, it is crucial to include clinical data which allows classifying subtypes of the disease.

Changed energy metabolism in patients with ME/CFS

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The study investigated whether impaired energy metabolism is involved in ME/CFS. Such knowledge could provide support for the development of new biomarkers and treatments. The research strategy was to build on the existing knowledge that has recently emerged regarding metabolic changes in ME/CFS, and to adopt new methods and strategies for studying mechanisms at the cellular level. This presentation will discuss the current approaches and the recent data.

Impaired regulation in the central energy pathways is likely to cause energy deficiency and excessive lactate production, which are hallmarks of fatigue and post-exertional malaise (PEM) associated with ME/CFS. Initially, it was found that altered regulation of the central enzyme pyruvate dehydrogenase (PDH) seems to play a role in patients with ME/CFS, based on changes in blood amino acid levels and gene regulation. Subsequently, extended analyses of the blood serum metabolome in ME/CFS patients were performed, using both untargeted and targeted analyses. Based on the findings, potential molecular mechanisms of metabolic regulation in cell culture studies were pursued. Blood signaling factors that were suspect to play a role were also measured, based on the observed changes in metabolite profiles. The reported changes in metabolism and immune system support the presence of an underlying immuno-metabolic pathomechanism in ME/CFS.

Marker for Autoimmunity in ME/CFS

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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a frequent and severe chronic disease significantly impairing life quality. The underlying pathomechanism is not well understood but there is convincing evidence, that at least a subset of ME/CFS patients has an autoimmune etiology (reviewed in [1]). ME/CFS disease onset is mostly reported to be triggered by an infection, and the link between infections and autoimmune diseases is well established. Further, comorbidity with autoimmune and autoimmune-related diseases including Hashimoto´s thyreoiditis, fibromyalgia, postural orthostatic tachycardia syndrome (POTS) were reported for ME/CFS patients.

Immune dysregulation including altered amounts of cytokines, immunoglobulins and other soluble markers, altered T- and B-cell phenotypes and a decrease of natural killer cell cytotoxicity has been frequently described in ME/CFS and in autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and primary Sjögren's syndrome. Furthermore, autoantibodies against various antigens were reported in ME/CFS. The role of antibodies against neurotransmitter receptors in ME/CFS is getting more and more interesting as functional adrenergic and muscarinic receptor antibodies may contribute to the dysregulation of autonomic nervous and immune system [2, 3]. The significance of autoantibodies in ME/CFS pathology is further strengthened by clinical trials targeting autoantibodies and show clinical benefits [4, 5]. In addition, evidence was provided for severe metabolic disturbances presumably mediated by serum in ME/CFS [6]. Moreover, single nucleotide polymorphisms (SNPs) in various genes are associated with the risk to develop autoimmune diseases. Mostly these genetic variants play a role in B and T cell activation and cytokine signaling mechanisms. Several SNPs in cytokines and human leukocyte antigen (HLA) associations were found in ME/CFS [7]. Recently we identify genetic variants in PTPN22 and CTLA4 being risk factors for infection-triggered ME/CFS [8].

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Chronic viral infections and ME/CFS

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disabling multisystem chronic disease with unknown etiology and pathogenesis. As in many patients, the disease starts suddenly with a “flu-like” illness, and it is also known that some viruses can produce a syndrome of post-infection fatigue. It was suggested that an infectious agent can trigger ME/CFS in at least a proportion of patients. In this presentation will be discussed currently available data on association of chronic viral infections with ME/CFS and possible mechanisms behind viral pathogenesis in ME/CFS.

Numerous viruses have been linked to ME/CFS including some herpesviruses (Epstein–Barr virus, cytomegalovirus, human herpes virus 6 and 7), enteroviruses, parvovirus B19, retroviruses, hepatitis C virus, Ross River virus [1]. Most of these viruses are able to produce a persistent infection and have also been shown to be neuropathogens. After an acute infection, they persist life-long in the body and may reactivate. Once reactivated, the viruses may contribute to the morbidity of ME/CFS via inflammation and immune dysregulation. Other possibility is that immunologic disturbance associated with ME/CFS may lead to reactivation of latent viruses. It is also suggested that viral infections can trigger the mitochondrial dysfunction and an autoimmune response [2], pathomechanisms that are crucial in current understanding of ME/CFS pathogenesis. At the same time, most of these viruses are ubiquitous in the general population, and, therefore, it is difficult to prove their causative roles. Despite multiple studies on association of viruses with ME/CFS, the data are not consistent and the role of viral infections in ME/CFS remains obscure.

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HHV-6 reactivation mimics mitochondrial fragmentation phenotype as seen in the serum of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients

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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a multi-factorial disorder with many triggers. Human herpesvirus 6 (HHV-6) and HHV-7 are two infectious triggers for which evidence has been growing. To understand possible causative role of HHV-6 in ME/CFS, latent HHV-6A was reactivated U2-OS cells and proteomic analysis was conducted by pulsed stable isotope labeling by amino acids in cell culture (pSILAC) analysis. Mitochondria were fragmented and 1-carbon metabolism, dUTPase, and thymidylate synthase were strongly induced by HHV-6 reactivation, while superoxide dismutase 2, mitochondrial oxidation of fatty acids, amino acids, and glucose via pyruvate dehydrogenase were strongly inhibited. Adoptive transfer of virus reactivated U2-OS cell supernatants led to an antiviral state in A549 cells that prevented superinfection with Influenza-A and HSV-1. Adoptive transfer of serum from ME/CFS patients produced a similar fragmentation of mitochondria and the associated antiviral state in the A549 cell assay. In conclusion, HHV-6 reactivation in ME/CFS patients activates a multisystem, proinflammatory, cell danger response that protects against certain RNA and DNA virus infections but comes at the cost of mitochondrial fragmentation and severely compromised energy metabolism.

Problems in determining the economic impact of ME/CFS in Europe

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This presentation will detail the problems impeding evaluation of the economic impact of ME/CFS which have been identified by the working group. Economic studies of ME/CFS, such as cost of illness analyses and economic evaluations of specific interventions, are problematic due to the use of different, arbitrary case definitions, as well as the unwillingness of many doctors to diagnose the condition. As a result, there is a lack of accurate incidence and prevalence data, and no obvious way to estimate costs incurred by undiagnosed patients. Other identified problems impeding economic studies of ME/CFS across Europe include, as for other conditions, difficulties in estimating direct and indirect costs incurred by healthcare systems, patients and families, as well as the heterogeneity of healthcare systems and patterns of economic development across countries.

Recommendations of the working group on the development of a Europe-wide consensus approach to the economic evaluation of ME/CFS; questions and answers

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This presentation will detail the progress of the Working Group in developing a Europe-wide approach to investigating the economic impact of ME/CFS. This approach will facilitate the acquisition of information on the economic burden of ME/CFS, and permit international comparisons of economic costs across European countries. Our recommendations. include the use of the Fukuda (CDC-1994) case definition and the Canadian Consensus Criteria (CCC), the development of a pan-European common symptom checklist, and the implementation of prevalence-based cost of illness studies in different countries on the basis of an agreed list of data items. The use of purchasing power parity (PPP) adjustments across countries has also been recommended to facilitate international comparisons, as well as the use of EuroQol-5D as a generic measure of health status and as a multi-attribute utility instrument to inform future economic evaluations in ME/CFS. We welcome the opportunity for the exchange of views on our recommendations.

Investigating the availability of data on ME/CFS patients in Latvia

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Research is performed in framework of COST (European Cooperation in Science and Technology) Action 15111 EUROMENE (European Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Network) to investigate the availability of data on ME/CFS patients in Latvia. There are no Europe-wide prevalence data, but it is assumed that more than two million people suffer by ME/CFS in Europe. The prevalence in developed countries appears to be within the range of 0.2–1 %, but this is dependent on case definition and criteria used by general practitioners (GP) and specialists to recognise ME/CFS. In accordance with the data from the Latvian Centre for Disease Prevention and Control (CDPC) and The National Health Service (NHS) of Latvia, the patient-related data are classified by ICD-10 code G93.3 (Postviral fatigue syndrome), R53 (Malaise and fatigue) and B94.8 (Sequelae of other specified infectious and parasitic diseases). CDCP data from primary care indicated that approximately 700 patients had ICD-10 code G93.3 assigned, while there were approximately 15,000 with ICD-10 code R53, and about 70 with code B94.8. In total, these constitute about 0.8 % of the Latvian population, which is considerably higher than the prevalence found in other comparable populations. Therefore, it is likely, though unconfirmed, that the category R53 includes a great many patients with illnesses other than ME/CFS. Category G93.3, by contrast, looks like a significant underestimate of the true population prevalence. A study was undertaken in Latvia to explore to what extent GPs manage ME/CFS disease. Data received by the GPs survey, with 91 responders, show that 13 responders use Fukuda definition and criteria, and mostly ICD-10 code R53 (Malaise and fatigue) is used by GPs to denote a diagnosis. GPs participated in the survey confirm that there are many undiagnosed patients, and the total number of CFS patients in their practices could be more than 10,000 patients. As a total number of GPs operated in Latvia currently is 1,340 practitioners, the received data demonstrate that the distinction between ICD-10 used diagnosis codes for ME/CFS is not clear. This produces inaccurate data on the true number of ME/CFS patients. Completive, in Latvia the patient-related data are dispersed between categories of G93.3, R53 and B94.8 of ICD-10, so the epidemiological data show the considerably higher prevalence of ME/CFS than found in other comparable populations. The situation may be supported by the intended implementation in 2022 of ICD-11, in which it is proposed to list “Postviral fatigue syndrome” in Chapter 08 (Diseases of the nervous system). Additionally, the disease register would be required for disease management, as the ME/CFS patients’ registries could facilitate the work of GPs, establish patients’ pathways and improve disease monitoring.

Incorporating the patient perspective when estimating the economic impact of ME/CFS

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This presentation discusses the importance of patient involvement in ME/CFS research and describes the development of a ME/CFS patient-academic partnership seeking to estimate the economic impact of ME/CFS under the Community Engaged Scholars Programme (CES-P). CES-P is an education and training initiative that aims to increase the capacity of community-academic partnerships to work together to conduct research that is underpinned by principles of public and patient involvement, with the goal of improving health and wellbeing of patients. We describe how CES-P is designed and operates and how it has been used to develop a collaborative patient-driven research agenda and approach that examines a range of economic issues faced by ME/CFS patients in Ireland.

Overview on works done during COST action and presentation of recommendations

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EUROMENE's working group #4 (WG4) "Clinical Research Enablers and Diagnostic Criteria" aims to determine (i) common strategy protocol for ME/CFS diagnosis; (ii) protocols and guidelines for ME/CFS subgroups detection according to the presence of symptoms and potential biomarkers variety; and (iii) synchronised guidelines for management/treatment of ME/CFS. A survey[1] conducted across EUROMENE's members pointed out disparities in diagnosis and treatment across 17 countries from the European Union: (i) 5/17 countries have guidelines for diagnosis: Fukuda criteria (4/5), Canadian Consensus criteria (1/5), the International Consensus Criteria (1/5) and the Oxford criteria (1/5); (ii) 5/17 have guidelines for clinical approaches, and many different questionnaires and tests were used for symptom registration and diagnostic investigation; (iii) 5/17 countries have guidelines for treatment. For symptom relief, pain killers (3/17) and anti-depressive (4/17) medication were most often recommended. Cognitive Behavioral Therapy and Graded Exercise Treatment were often recommended as disease management and rehabilitative/palliative strategies. For neuropsychological investigations, a literature's review included 52 articles from 553 published between 1988 and 2019, including 1849 ME/CFS patients and 1587 controls. This analysis led to propose a standardised neuropsychological assessment, providing a complete and detailed screening and short enough to avoid fatigue bias. This battery (duration: 75 minutes) includes: (i) Executive functions: Backward digit span, FCSRT, TMT A&B, Stroop, "P" fluency, Rey figure (copy), Zazzo's cancellation test; (ii) Memories: Forward digit span, FCSRT, Rey figure recall; (iii) Instrumental functions: praxies, DO80, "Animal" fluency; (iv) Dichotic listening test: word and sentences conditions; (v) Pain, fatigue, depression: BDI-II, VAS (pain), VAS (fatigue). Lastly, WG4 will provide recommendation for diagnosis, investigations and care/treatment of ME/CFS patients for European countries.

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Advances in Research on ME/CFS

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Significant progress is being made on many research fronts impacting individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Dr. Whittemore will highlight recent scientific findings from investigators supported by the National Institutes of Health (NIH), including the ME/CFS Collaborative Research Centers and the Data Coordinating Management Center. In addition, she will provide an update on NIH activities to support and advance research on ME/CFS including the ME/CFS NIH Intramural Research Study, ME/CFS stakeholder conference calls, activities of the Trans-NIH ME/CFS Working Group, and the Report from the National Advisory Council of NINDS Working Group on Research on ME/CFS.

Diagnostic criteria for Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS) – Recommendations from the EUROMENE's Clinical Working Group

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Introduction: The European Network on Myalgic Encephalomyelitis or Chronic fatigue syndrome (EUROMENE), aims to address the challenges related this disease, such as unknown aetiology, clinical variability, lack of diagnostic biomarkers, limited treatment options, and high associated economic burden. The network is organised into distinct working groups. The Clinical Working Group was set to survey and consider the existing procedures for diagnosis, management of symptoms and therapeutic approaches; and, to recommend a set of standardised procedures for the care of those with ME/CFS. The initial survey on clinical criteria used in European countries to diagnose ME/CFS [1] showed a paucity of standards and lack of integration of guidelines in European countries.

Aim: The aim of the study is to examine the main diagnostic criteria for ME/CFS, and to develop guidelines for standardising and optimising clinical diagnoses at both clinical and research settings.

Methods: The Clinical Working Group used a pragmatic strategy, working at face-to-face meetings complemented by remote communications to agree on key documents on clinical definitions of ME/CFS, and existing studies/guidelines for clinical assessments and care used in Europe and internationally. These documents were considered taking into account the WG members' experiences and expertise, for the recommended guidelines.

Results: The group agreed that the Institute of Medicine (currently, National Academy of Medicine) criteria [2] and the Canadian Consensus Criteria [3] should be recommended for diagnosing adults, in primary care and secondary care/research settings, respectively. The paediatric population should be assessed recommendations from Rowe et al [4],

Conclusions: Standardised procedures for ME/CFS clinical diagnosis and patient subgrouping can improve the clinical care and management of symptoms, while maximising research efforts for specific biomarker(s) finding and therapeutic approaches.

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Cardiopulmonary Exercise Test in ME/CFS: Why, How and When?

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In a cardiopulmonary exercise test (CPX), the energy production in the mitochondria in the muscle cells of the legs is stressed. The energy production depends on:

1. the number and quality of mitochondria influenced by the activity. Inactivity will result in a reduction of the mitochondria per cell [1];
2. whether the ovum contains a small percentage of low-quality mitochondria, thus making normal activity being possible. When the number of low-quality mitochondria increases faster than the normal ones, the percentage will increase, resulting in insufficient energy production later in life [2];
3. insufficiency of co-factors such as coenzyme Q10 and carnitine resulting in insufficient regeneration of Adenosine triphosphate (ATP) and insufficient energy [3, 4].
4. insufficiency of oxygen supply being well known in lung, heart and vascular disease. Less well known is a decreased energy production due to a carbohydrate and fatty acid supply to the mitochondria [5].

During the CPX, the response to increasing physical load was measured. The response aids to the differential diagnosis of the causes for physical impairment. The test is standardised and validated for almost any cause for physical impairment [6].

In ME/CFS, we are confronted with a large number of patients and a limited number of health care providers. Therefore, the selection of patients for referral to a centre for a CPX and other extensive tests must be agreed upon. The CPX test is too heavy a burden for some patients adding more to the need for a careful selection. A less demanding test that may present as an alternative became available recently [7, 8].

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How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS

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A framework has been proposed for understanding and interpreting the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) that considers the wider determinants of health and the long-term temporal variation in pathophysiological features and disease phenotype throughout the natural history of the disease.
As in other chronic diseases, ME/CFS evolves through different stages, from asymptomatic predisposition, progressing to a prodromal stage, and then to symptomatic disease. Disease incidence depends on genetic makeup[1–4], exposures to environment factors [5, 6], and the nature of the host response[7–9]. In people who develop ME/CFS, normal homeostatic processes in response to adverse insults may be replaced by aberrant responses leading to dysfunctional states[10, 11]. Thus, the predominantly neuro-immune manifestations that characterise early disease and are underlined by a hyper-metabolic state, may be followed by various processes leading to multi-systemic abnormalities and related symptoms[12–15]. This abnormal state and the effects of a range of mediators such as products of oxidative and nitrosamine stress, may lead to progressive cell and metabolic dysfunction culminating in a hypometabolic state with low energy production [16–18]. These processes do not seem to happen uniformly. Although a spiralling of progressive inter-related and self-sustaining abnormalities may ensue, reversion to states of milder abnormalities is possible if the host is able to restate responses to improve homeostatic equilibrium.
With time variation in disease presentation, no single ME/CFS case description, set of diagnostic criteria, or molecular feature is currently representative of all patients at different disease stages. While acknowledging its limitations due to the incomplete research evidence, we suggest the proposed framework may support future research design and health care interventions for people with ME/CFS.

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Patients from the French Chronic Fatigue Syndrome association fulfilled Systemic Exertion Intolerance Disease (SEID) criteria, but disagreed this new denomination

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Introduction: Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (CFS/ME) remains exclusively based on clinical examination after exclusion of other causes of fatigue, with various classifications published. In 2015, the American Institute of Medicine (IOM) proposed new diagnostic criteria for CFS/ME and a new name Systemic Exertion Intolerance Disease (SEID).
Aim and Methods: A questionnaire was sent to 494 adult members of the French Association of CFS/ME (ASFC) assessing the SEID criteria, and collecting their declared diagnosis of chronic fatigue (CFS/ME, or self-added proposals), their more disabling symptoms and their opinion about the new SEID terminology. French-translated questions from the IOM tool kit were used to assess each criterion of SEID. Subjects had to classify from the most to the least disabling six main symptoms (activities limitation, post-exertional malaise [PEM], unrefreshing sleep, cognitive impairment, orthostatic intolerance and pain) and to give their opinion on new denomination SEID.
Results: 227 (46 %) subjects responded. They declared one or more chronic fatigue diagnosis: 168 CFS (74 %), 44 ME (19 %) and 99 FM (44 %), 20 others (9 %); often in association: 108 subjects with CFS and/or ME without FM (CFS/ME, 48 %), 29 with FM alone (13 %) and 70 with CFS/ME and FM (CFS/ME+FM, 31 %). SEID criteria were found in 191/227 (84 %) of all subjects, 86/108 (80 %) of CFS/ME, 64/70 (91 %) of CFS/ME+FM and 25/29 (86 %) of FM groups. SEID and non-SEID patients were not different concerning age, sex, fatigue onset, trigger, fatigue diagnosis and other symptoms. PEM, unrefreshing sleep and cognitive impairment were more frequently reported in SEID than in non-SEID group ($p < 0.01$). Some questions of the IOM kit seemed to be more discriminant for PEM, unrefreshing sleep, and cognitive impairment. Activities limitation, pain and unrefreshing sleep ranked at the first place of most disabling symptoms for SEID patients, may be due to fibromyalgia comorbidity. Only 45 % of subjects declared that the "SEID" name was appropriate and 54 % thought it would convey a negative image of the disease with similar results in the different subgroups.
Conclusions: Most French patients from ASFC association with unexplained fatigue, currently related to CFS, ME, and/or FM fulfilled the SEID criteria. Some questions were identified as being more discriminant for some SEID criteria. Nevertheless, only a minority of the patients has accepted this new SEID terminology.

Phenotyping cognitive impairment in adult patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

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Aim: Cognitive complaints are one of the most common and disabling symptoms associated with ME/CFS [1]. In the present study, the results of the neuropsychological assessment performed in patients were retrospectively evaluated in our center with the aim to delineate the cognitive profiles associated with ME/CFS.

Material and Methods: 141 consecutive patients were included (sex ratio M/F: 36/105; age [mean ± SD]: 46 ± 13 yrs). Inclusion criteria were: (i) patient fulfilling CDC1994 criteria for CFS, (ii) presence of cognitive complaints, and (iii) neuropsychological evaluation performed in our center. A complete screening of all cognitive functions was carried out through an extensive battery of tests routinely used in clinical practice (duration: 75 minutes) and including: (i) Executive functions: Backward digit span, FCSRT, TMT A&B, Stroop, "P" fluency, Rey figure (copy), Zazzo's cancellation test; (ii) Memories: Forward digit span, FCSRT, Rey figure recall; (iii) Instrumental functions: praxies, DO80, "Animal" fluency; (iv) Dichotic listening test: word and sentences conditions; (v) Pain, fatigue, depression: BDI-II, VAS (pain), VAS (fatigue).

Results: Four cognitive profiles were identified: (i) patients (n = 12/141; age: 38 ± 13 yrs) with no cognitive impairment or weakness, except a specific slowing down of the reading speed in 1/3 of them; (ii) patients (n = 52/141; age: 48 ± 12 yrs) with significant weakness (test score <-1 SD) in selective visual attention and immediate visual memory, and a specific slowing down of reading speed; (iii) patients (n = 53/141; age: 46 ± 13 yrs) with a pathological score (< -1.65 SD) on tests evaluating selective visual attention, cognitive inhibition and reading speed as well as weakness (< -1 SD) in immediate visual memory and in mental flexibility. In this group, there was a correlation between the level of depression or fatigue, and deficits in flexibility or cognitive inhibition. These correlations were not found in other groups of patients. Finally, the last group (iv) of patients (n = 24/141; age: 46 ± 14 yrs) had episodic memory impairments (storage and consolidation), selective attention in visual input impairment and a specific slowdown in reading speed, with also a weakness (< -1 SD) in immediate visual memory, auditory attention, flexibility, cognitive inhibition and information generation.

Conclusion: From the obtained results, it appeared that cognitive impairment in ME/CFS patients fits into a semiological framework, characterised by a common backbone (slowing down of the speed of reading, disturbances in selective visual attention and immediate visual memory) possibly aggravated by the impairment of executive functions and episodic memories, instrumental functions remaining always spared.

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Including the housebound patient severely affected by ME/CFS in research: a compassionate approach

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Introduction: People with severe Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) are rarely included in research. Some may be alienated from all statutory medical services, and are therefore difficult to reach, but the CureME team has a broad experience of including these individuals in research. Investigators aiming to include people with severe ME/CFS need to consider the complexity of making an accurate diagnosis in the absence of any biomarker [1], the very real stigma associated with the diagnosis [2] and the many practical challenges around such inclusion.
Capitalising on qualitative and quantitative data collected by the UK ME/CFS Biobank, other ways have been explored to include those house- and bed-bound with ME/CFS in research to begin to address the inequities in care received by people with ME/CFS.
Methods: Qualitative and quantitative data of fifteen most commonly experienced symptoms reported by 80 SAPs were analysed.
Results: The results of the quantitative and qualitative data have been fully tabulated.
Discussion: ME/CFS is a low prestige disease with neither biomarker nor effective treatment and those who are severely affected are rarely included in research. It is believed that by responding to the needs of these individuals with pragmatism and compassion, their much-needed inclusion is studies can be facilitated to enhance their generalisability and to address inequity.
Conclusion: Despite the absence of curative treatments for SAPs, the researcher can include the housebound patient in research that is both effective and worthwhile. Affirming individual experience with compassion and competence, we can build on the body of knowledge around severe disease while learning much from the patient's narrative. Engaging in research can help to legitimise disease in the face of stigma and widespread disbelief.

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The impact of whole-body cryotherapy upon cognitive function in myalgic encephalomyelitis/chronic fatigue syndrome patients. Preliminary studies

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Introduction: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disorder characterised by symptoms including chronic fatigue, exercise intolerance, disordered cognitive functions, autonomic dysfunction, pain, and non–restorative sleep. To date, the specific aetiology of ME/CFS has not been determined [1, 2].
"Brain fog" belongs to one of the features of ME/CFS. These primarily include a general slowdown in response speed to tasks that require simple and complex information processing as well as the ability to focus on a task [3]. Studies also confirm that cognitive disturbances of ME/CFS patients are restricted to a decrease in basic processing speed and not related to depression severity [4, 5]. Moreover, autonomic nervous system functioning disturbances is one of the main symptoms of ME/CFS [6]. Moreover, autonomic nervous system is highly connected to central nervous system functioning [7]. Repeated Whole-Body Cryotherapy (WBC) exposures influence an increase in resting cardiac autonomic modulations that resemble the effects of a physical exercise program [8]. In the above study, the effects of WBC on cognitive function in ME/CFS patients were examined.
Material and Methods: 30 ME/CFS patients were included based on CDC criteria (mean age = 37.5) underwent 2-week whole body cryotherapy program. Trial Making Test part A (TMT A), Trial Making Test part B (TMT B) and Coding tests were used to examined cognitive function of participants. Normality assumption was tested with Shapiro-Wilk W test. In the case of meeting this assumption analysis was made with repeated measures ANOVA. Otherwise, Wilcoxon signed-rank test was used.
Results: ME/CFS patients significantly improved in TMT A (22.93 seconds pre vs 17.57 after, $F = 31.68$, $p < 0.0001$. Moreover, significant improvement in TMT B was also noted (50.5 seconds before vs 42.5 after, $F = 15.85$, $p = 0.001$). However, effect on difference between TMT B and A results was not significant. Performance of Coding significantly improved ($Z = 3.95$, $p < 0.001$).
Conclusions: Whole-body cryotherapy is a promising intervention aimed to improvement of processing speed of visual information in ME/CFS patients. Improved cognitive domain is the one in which ME/CFS patients subjectively feel disturbance in. However, further studies are needed to confirm these results.

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