European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (*EUROMENE*) - CA15111

Deliverable 16

Programme, book/abstract book and overview of final global conference and conclusions

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1. **Programme: http://euromene.eu/conference/programme.html**
2. **Book of abstracts: http://euromene.eu/conference/book_of_abstracts.html**
3. **Overview of final global conference**
4. **Conclusions**

OVERVIEW

Final Global Conference "Common strategy of research of ME/CFS"

Rīga Stradiņš University, Riga, Latvia, March 12–13, 2020

The work of the conference was organized in 4 sessions with 7 presentations in person and 9 via Zoom system with following questions and discussion.

SESSION 1 - ME/CFS epidemiology:

In the first session, 5 reports were presented - two in person and 3 in the Zoom system. The report „Epidemiology of ME/CFS in Europe: past, present and future" was the WG1 overview of on ME/CFS epidemiology. Dr Fernando Estévez-López summarized previous findings on the prevalence and incidence of ME/CFS in European countries and presented the preliminary set of recommendations for standardized data collection for epidemiological research of ME/CFS in Europe. To ensure scalability most of suggested assessments are based on self-reports. Also additional objective measurements are suggested in order to obtain a more comprehensive picture of ME/CFS. The implementation of recommendations

to standardize data collection for epidemiological research of ME/CFS in Europe had been discussed to overcome the current gaps in the field.

The report on ME/CFS prevalence in young people had been presented by invited expert Prof Katherine Sylvia Rowe from the Department of General Medicine, Royal Children's Hospital, Murdoch Children's Research Institute (Melbourne, Australia). She presented the feedback data regarding the outpatient management of young people diagnosed with ME/CFS allowing determine the duration of illness, functional and educational long-term outcomes and predictive factors for recovery. It is shown that ME/CFS in young people has a mean duration of 5 years 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 were identified as helpful. This included maintaining social contact and assistance to achieve educational or life goals.

The report "Prevalence and characteristics of ME/CFS in Poland" had been presented by Dr Pawel Zalewski from the Nicolaus Copernicus University in Toruń, Poland. In Poland ME/CFS is diagnosed very rarely which may be associated with the fact that etiology of the disease is still poorly known. The socio-demographic and illness characteristics in those reporting CFS/ME symptoms in a Polish population were presented. In 1308 of 1400 (93%) individuals who identified themselves as fatigued, recognized chronic conditions were identified e.g. neurological (21.5%), neurodegenerative (15%), psychiatric (50%) and immunologic (13.5%) disorders. The remaining 69 participants met the Fukuda definition for CFS/ME and had baseline objective assessment. The cohort was classified according to predominance of sympathetic or parasympathetic function. No significant differences in symptoms or impact upon quality of life between the groups had been identified. The study has confirmed that fatigue is a common and under-recognized symptom affecting the Polish population.

The report "Considerations of ME/CFS bio-banks and bio-repositories within EUROMENE" was presented by Dr Kathleen Mudie from the London School of Hygiene & Tropical Medicine, United Kingdom. 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 for

enabling the sharing of the samples. The questionnaire was sent out to 32 EUROMENE members, of them 8 (25%) 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. In terms of ELSI frameworks in place, there is no coherent or linear way to share samples across sites, indicating a significant gap. Challenges are still to be overcome, especially in terms of ELSI; however, the groundwork has been laid for moving forward.

Dr Henrik Nielsen, Privat Hospitalet Danmark presented the "HYPOTESIS: We underestimate the risk of chemicals in water and food in ME/CFS". When conventional organizations 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. Data collected over the past many years shows a growing support that healthcare problems are growing secondary to exposure worldwide to these elements (dioxin, pesticides etc.).

SESSION 2 - ME/CFS biomarkers

In the second session, 4 reports were presented - one in person and 3 in the Zoom system. Report on "Biomarker in ME/CFS" was presented by WG2 Leader, Prof Carmen Scheibenbogen, Institute of Medical Immunology, Charité, Germany via Zoom system. 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; however, there are a number of studies showing biomarkers characterizing 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 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.

Dr Franziska Sotzny, Charité - Universitätsmedizn Berlin, Germany via Zoom system presented report "Marker for Autoimmunity in ME/CFS". The underlying pathomechanism of ME/CFS is not well understood but there is convincing evidence, that at least a subset of ME/CFS patients has an autoimmune etiology. 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, co-morbidity with autoimmune and autoimmune-related diseases including Hashimoto´s thyreoiditis, fibromyalgia, postural orthostatic tachycardia syndrome (POTS) had been 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 and 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. The significance of autoantibodies in ME/CFS is further strengthened by clinical trials targeting autoantibodies and showing clinical benefits. Evidence was provided for severe metabolic disturbances presumably mediated by serum in ME/CFS; 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. Recently we identify genetic variants in PTPN22 and CTLA4 being risk factors for infection-triggered ME/CFS.

The report "Chronic viral infections and ME/CFS" was presented by Prof Evelina Shikova-Lekova, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria. In this presentation the currently available data on association of chronic viral infections with ME/CFS and possible mechanisms behind viral pathogenesis in ME/CFS had been discussed. Numerous viruses have been linked to ME/CFS and most of them 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, pathomechanisms that are crucial in current understanding of ME/CFS pathogenesis. 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.

Dr Bhupesh Prusty, Institute for Virology and Immunobiology, Julius-Maximilians-Universität Würzburg, Germany via Zoom system presented the report "HHV-6 reactivation mimics mitochondrial fragmentation phenotype as seen in the serum of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients". Human herpesvirus 6 (HHV-6) and HHV-7 are two infectious triggers of ME/CFS 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 super-infection 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. 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.

SESSION 3 - ME/CFS socio-economics

In the third session, 3 reports were presented – all three in person. Report "Problems in determining the economic impact of ME/CFS in Europe" was presented by Prof Uldis Berkis, Rīga Stradiņš University. He detailed the problems impeding evaluation of the economic impact of ME/CFS which have been identified by the WG3. 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.

Prof Uldis Berkis presented also the report "Recommendations of the working group on the development of a Europe-wide consensus approach to the economic evaluation of ME/CFS; questions and answers" showing the progress of WG3 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. The 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.

Dr Diana Arana, Raga Stradiņš University presented the report "Investigating 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 recognize 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 (Post-viral 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. A study was undertaken 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. 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.

SESSION 4 - ME/CFS clinical research

In the fourth session, 4 reports were presented – one in person and 3 via Zoom system. Dr Eliana Mattos Lacerda, London School of Hygiene & Tropical Medicine, United Kingdom presented the report "Diagnostic criteria for Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS) – Recommendations from the EUROMENE's Clinical Working Group".

The study aims to examine the main diagnostic criteria for ME/CFS, and to develop guidelines for standardizing and optimizing clinical diagnoses at both clinical and research settings. By working at face-to-face meetings complemented by remote communications the group agreed that the Institute of Medicine (currently, National Academy of Medicine) criteria and the Canadian Consensus Criteria should be recommended for diagnosing adults, in primary care and secondary care/research settings, respectively. The paediatric population should be assessed by recommendations from Rowe et al. Standardized procedures for ME/CFS clinical diagnosis and patient sub-grouping can improve the clinical care and management of symptoms, while maximizing research efforts for specific biomarker(s) finding - therapeutic approaches.

Ms Shennae O'Boyle, London School of Hygiene & Tropical Medicine, United Kingdom via Zoom system presented report "How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS". 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, exposures to environment factors, and the nature of the host response. In people who develop ME/CFS, normal homeostatic processes in response to adverse insults may be replaced by aberrant responses leading to dysfunctional states. Thus, the predominantly neuro-immune manifestations that characterize early disease and are underlined by a hyper-metabolic state, may be followed by various processes leading to multi-systemic abnormalities and related symptoms. 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. 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.

The report “Including the housebound patient severely affected by ME/CFS in research: a compassionate approach” was presented Zoom system by Ms Caroline Kingdon, London School of Hygiene and Tropical Medicine, United Kingdom. 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. Qualitative and quantitative data of fifteen most commonly experienced symptoms reported by 80 SAPs were analyzed. 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 legitimize disease in the face of stigma and widespread disbelief.

Dr Sławomir Kujawski, Nicolaus Copernicus University in Toruń, Poland via Zoom system presented the report “The impact of whole-body cryotherapy upon cognitive function in myalgic encephalomyelitis/chronic fatigue syndrome patients: Preliminary studies”. Autonomic nervous system functioning disturbances is one of the main symptoms of ME/CFS. Moreover, autonomic nervous system is highly connected to central nervous system functioning. Repeated Whole-Body Cryotherapy (WBC) exposures influence an increase in resting cardiac autonomic modulations that resemble the effects of a physical exercise program. 30 ME/CFS patients based on CDC criteria were included in 2-week whole body cryotherapy program and the effects of WBC on cognitive function in ME/CFS patients were examined. Trial Making Test part A (TMT A), Trial Making Test part B (TMT B) and Coding tests were used to examine cognitive function of participants. ME/CFS patients significantly improved in TMT A; moreover, significant improvement in TMT B was also noted t on difference between TMT B and A results was not significant. Performance of Coding significantly improved ($Z = 3.95$, $p < 0.001$). WBC is a promising intervention aimed to improve of visual information processing speed in ME/CFS patients.

Improved cognitive domain is the one in which ME/CFS patients subjectively feel disturbance in.

CONCLUSIONS

The Recommendations/position paper should be prepared for health professionals and health policy makers, healthcare services providers, research community and research policy makers, patient organizations and others NGOs.

Long-term impact of CA1511 should be ensured via sustainable integrated network of researchers in Europe working in the field of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.