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Understanding, diagnosing, and treating Myalgic encephalomyelitis/chronic fatigue syndrome – State of the art: Report of the 2nd international meeting at the Charité Fatigue Center

Sophie Steiner [a,1], Annick Fehrer [a,1], Friederike Hoheisel [a,1,*], Simon Schoening [b,1], Anna Aschenbrenner [c], Nina Babel [a,d,e], Judith Bellmann-Strobl [f,g,h,i], Carsten Finke [f], Øystein Fluge [j,k], Laura Froehlich [l], Andreas Goebel [m], Bettina Grande [n], Johannes-Peter Haas [o], Bettina Hohberger [p], Leonard A. Jason [q], Anthony L. Komaroff [r], Eliana Lacerda [s], Max Liebl [t], Andrea Maier [u], Olav Mella [j,k], Luis Nacul [s,v,w], Friedemann Paul [g,h,i], Bhupesh K. Prusty [x], Christian Puta [y,z,aa], Gabriela Riemekasten [ab], Wolfgang Ries [ac], Peter C. Rowe [ad], Birgit Sawitzki [ae], Yehuda Shoenfeld [af], Joachim L. Schultze [c,ag,ah], Martina Seifert [a,e,ai], Nuno Sepúlveda [aj,ak], Franziska Sotzny [a], Elisa Stein [a], Michael Stingl [al], Friederike Ufer [am], Christian Veauthier [an], Francisco Westermeier [ao,aw], Klaus Wirth [ap], Bernd Wolfarth [aq], Pawel Zalewski [ar,as], Uta Behrends [at,au,av,2], Carmen Scheibenbogen [a,2]

[a] Institute of Medical Immunology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin and Berlin Institute of Health (BIH), Berlin, Germany
[b] ME/CFS Research Foundation, Hamburg, Germany
[c] Systems Medicine, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn, Germany
[d] Center for Translational Medicine and Immune Diagnostics Laboratory, Medical Department I, Ruhr-University Bochum, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Herne, Germany
[e] Berlin Institute of Health at Charité-Universitätsmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), Charitéplatz 1, Berlin, Germany
[f] Department of Neurology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[g] Experimental and Clinical Research Center, A Cooperation Between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité-Universitätsmedizin Berlin, Berlin, Germany
[h] Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
[i] NeuroCure Clinical Research Center, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, and Max Delbrück Center for Molecular Medicine, Berlin, Germany
[j] Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway
[k] Department of Clinical Sciences, University of Bergen, Bergen, Norway
[l] Center of Advanced Technology for Assisted Learning and Predictive Analytics (CATALPA), FernUniversität in Hagen, Germany.
[m] Pain Research Institute, Institute of Life Course and Medical Sciences, University of Liverpool, and Walton Centre NHS Foundation Trust, Liverpool, UK
[n] Psychotherapy and Psychoanalysis, Heidelberg, Germany
[o] Deutsches Zentrum für Kinder- und Jugendrheumatologie, Zentrum für Schmerztherapie junger Menschen, Garmisch-Partenkirchen, Germany
[p] Department of Ophthalmology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[q] Center for Community Research, DePaul University, Chicago, IL, USA
[r] Division of General Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[s] Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
[t] Department of Physical Medicine, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany
[u] Department of Neurology, Medical Faculty RWTH Aachen University, Aachen, Germany
[v] Women's Health Research Institute, British Columbia Women's Hospital, Vancouver, BC, Canada
[w] Department of Family Practice, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[x] Institute for Virology and Immunobiology, Julius-Maximilians University Würzburg, Würzburg, Germany
[y] Department of Sports Medicine and Health Promotion, Friedrich-Schiller-University Jena, Jena, Germany
[z] Center for Interdisciplinary Prevention of Diseases Related to Professional Activities, Friedrich-Schiller-University Jena, Jena, Germany
[aa] Center for Sepsis Control and Care (CSCC), Jena University Hospital/Friedrich-Schiller-University Jena, Jena, Germany

* Corresponding author at: Charité - Universitätsmedizin Berlin, Institute of Medical Immunology, Campus Virchow Klinikum, Augustenburger Platz 1/Südstraße 2, 13353 Berlin, Germany.
E-mail address: friederike.hoheisel@charite.de (F. Hoheisel).

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[ab] Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany
[ac] Internal Medicine, Department of Nephrology, Diakonissenkrankenhaus, Flensburg, Germany
[ad] Department of Pediatrics, Division of Adolescent and Young Adult Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[ae] Translational Immunology, Berlin Institute of Health (BIH) & Charité University Medicine, Berlin, Germany.
[af] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Reichman University Herzelia, Israel
[ag] Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany
[ah] PRECISE Platform for Single Cell Genomics and Epigenomics, DZNE und Universität Bonn, Bonn, Germany
[ai] DZHK (German Center for Cardiovascular Research), Partner Site, 10785 Berlin, Germany
[aj] Department of Mathematics & Information Science, Warsaw University of Technology, Warsaw, Poland.
[ak] CEAUL - Centro de Estatística e Aplicações da Universidade de Lisboa, Lisbon, Portugal
[al] Department of Neurology, Zentrum Votivpark, Vienna, Austria.
[am] Institute of Neuroimmunology and Multiple Sclerosis, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[an] Interdisciplinary Center of Sleep Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany
[ao] Institute of Biomedical Science, Department of Health Studies, FH, Joanneum University of Applied Sciences, Graz, Austria
[ap] Institute of General Pharmacology and Toxicology, University Hospital Frankfurt, Goethe-University, Frankfurt, Germany
[aq] Department of Sports Medicine, Charité-Universitätsmedizin Berlin, Humboldt University of Berlin, Germany
[ar] Department of Exercise Physiology and Functional Anatomy, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University Toruń, Toruń, Poland
[as] Department of Experimental and Clinical Physiology, Warsaw Medical University, Stefana Banacha 2a, Warszawa 02-097, Poland
[at] Children's Hospital, School of Medicine, Technical University of Munich, Munich, Germany
[au] German Center for Infection Research (DZIF), Berlin, Germany
[av] AGV Research Unit Gene Vectors, Helmholtz Munich (HMGU), Munich, Germany
[aw] Centro Integrativo de Biología y Química Aplicada (CIBQA), Universidad Bernardo O'Higgins, Santiago, Chile

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ABSTRACT

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a devastating disease affecting millions of people worldwide. Due to the 2019 pandemic of coronavirus disease (COVID-19), we are facing a significant increase of ME/CFS prevalence. On May 11th to 12th, 2023, the second international ME/CFS conference of the Charité Fatigue Center was held in Berlin, Germany, focusing on pathomechanisms, diagnosis, and treatment. During the two-day conference, more than 100 researchers from various research fields met on-site and over 700 attendees participated online to discuss the state of the art and novel findings in this field. Key topics from the conference included: the role of the immune system, dysfunction of endothelial and autonomic nervous system, and viral reactivation. Furthermore, there were presentations on innovative diagnostic measures and assessments for this complex disease, cutting-edge treatment approaches, and clinical studies. Despite the increased public attention due to the COVID-19 pandemic, the subsequent rise of Long COVID-19 cases, and the rise of funding opportunities to unravel the pathomechanisms underlying ME/CFS, this severe disease remains highly under-researched. Future adequately funded research efforts are needed to further explore the disease etiology and to identify diagnostic markers and targeted therapies.

1. Introduction

ME/CFS is a frequent and complex disease triggered by various, mostly viral infections [1]. Despite being a severe and common illness, ME/CFS is part of a spectrum of post-infectious diseases that has received little attention from medicine and research for decades. The pandemic has led with Long COVID-19 to a dramatic increase in post-infectious syndromes. It was shown that severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) can trigger ME/CFS in a subset of patients [2,3]. Before the emergence of SARS-CoV-2, already an estimated three million people in Europe suffered from ME/CFS, and as a result of the COVID-19 pandemic, many millions more were hit by this devastating disease [4–6]. The most relevant symptoms include mental and physical fatigue, exertional intolerance with post-exertional malaise (PEM), cognitive impairment, orthostatic intolerance, and pain, which often severely interfere with daily life. As of now, the knowledge of pathomechanisms underlying ME/CFS is fragmented, no diagnostic markers have been established, and there is still no approved treatment. The role of immune, vascular, metabolic, and/or autonomic nervous system dysfunction in disease pathogenesis is under intensive investigation [7]. Furthermore, a significant overlap with mechanisms identified in post-COVID syndrome (PCS) has been demonstrated [8–10]. The research initiated worldwide on PCS is bearing great hope for elucidation of ME/CFS pathomechanisms and the development of diagnostic markers and targeted therapies.

2. ME/CFS belongs to the spectrum of post-COVID syndrome

Yehuda Shoenfeld opened the meeting by giving an expert overview on autoimmunity with regard to the autonomic nervous system focusing on the role of G-protein coupled receptors (GPCR) autoantibodies (AAbs), a topic that has been intensively researched recently [11]. Several studies provide evidence that anti-GPCR AAbs targeting adrenergic and acetylcholine receptors play a role in ME/CFS, PCS, and postural tachycardia syndrome (POTS) in which autonomic dysregulation is a prominent feature [12,13].

Carmen Scheibenbogen presented the results of an ongoing observational study on the clinical presentation and disease course of ME/CFS triggered by SARS-CoV-2. Of PCS patients presenting with moderate to severe fatigue and exertion intolerance approximately one half fulfilled the Canadian Consensus Criteria (CCC) [14] for the diagnosis of ME/CFS and most patients remained severely affected beyond 18 months of disease onset [2,3]. Furthermore, studies on the association of anti-GPCR AAbs with the severity of symptoms, endothelial dysfunction, and candidate biomarkers [9,15] were shown, and an outlook on clinical trials targeting these mechanisms was given.

ME/CFS and PCS share a range of underlying potential abnormalities as outlined in an extensive review by **Anthony L. Komaroff**, including abnormalities pertaining to the central and autonomic nervous system, the immune system, energy metabolism, oxidative stress, cardiopulmonary exercise capacity and the cardiovascular system [16]. Of the identified disease mechanisms, many interact with one another, such as potential viral replication and reactivation, which may lead to oxidative

[1] These authors contributed equally to this work and share the first authorship.
[2] Joint senior authors.

and nitrosative stress, in turn leading to cellular senescence. Oxidative stress can also induce mitochondrial dysfunction, which in interaction with viral replication and reactivation results in nitric oxide dioxygenase (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3)- inflammasome activation, giving rise to chronic inflammation [17]. Multiple recent findings also provide evidence for the persistence of SARS-CoV-2 RNA and antigen as potential culprits for chronic low-grade systemic inflammation in PCS [18,19].

Studies presented by **Leonard A. Jason** provide insights into potential predisposing factors for ME/CFS and PCS via analyses of immune profiles prior to infection with Epstein-Barr-Virus (EBV) [20]. Data from 4501 healthy students were collected and followed up for the occurrence of ME/CFS. Among the participants, 5% of those who developed infectious mononucleosis (IM) were later diagnosed with ME/CFS. Individuals with deficiencies in Interleukin-5 (IL-5) and Interleukin-13 (IL-13) production were more likely to develop severe ME/CFS after EBV infection possibly due to immune dysregulation. Cytokine network analysis revealed more densely interconnected cytokine networks at least six weeks before IM in ME/CFS patients. Those with preceding severe gastrointestinal symptoms and low IL-5/IL-13 blood levels had a nearly 80% likelihood of developing severe ME/CFS. Moreover, ME/CFS patients showed dysregulated metabolic pathways essential for cell proliferation, particularly during pro-inflammatory immune responses [21]. Implications for the identification of predisposing factors can also be drawn from findings on PCS, where Jason and Dorri found cognitive and autonomic dysfunction to be predictors of SARS-CoV-2 infection associated with ME/CFS [21].

3. Diagnosing ME/CFS

Due to the complexity of symptoms, limited education and acceptance of the disease as well as poor access to medical care for severely affected patients, the diagnosis and treatment of ME/CFS can be difficult, and a high number of undiagnosed patients is presumed [22,23]. **Uta Behrends** presented the state-of-the-art diagnostic approach involving a comprehensive medical history, the evaluation of diagnostic criteria via appropriate questionnaires, physical examination, functional tests, routine laboratory analyses, and imaging as required for appropriate differential diagnostics. In the course of this, the newly developed Munich-Berlin Symptom Questionnaire (MBSQ) [24] was presented, which combines the CCC [14] and Institute of Medicine (IOM) criteria [25] and allows for a quantitation of symptoms. Such diagnostic assessments should be offered in specialized centers to achieve timely diagnosis and care for affected patients. Regular reassessments should be provided to evaluate the individual courses of disease, including partial or complete remissions, especially in children and adolescents [26,27].

Further lectures focused on the diagnosis and potential role of autonomous and skeletal muscle dysfunction, sleep disturbance, cognitive symptoms, and hypermobility. Symptoms of a dysfunctional autonomic nervous system in ME/CFS are complex and entail the involvement of the parasympathetic and sympathetic system. A sympathetic noradrenergic failure can manifest by orthostatic, exercise, and temperature intolerance. In contrast, patients with hyperactivity of the autonomic system show symptoms such as paleness, higher blood pressure, trembling, bristling hair, or sweating. **Pawel Zalewski** presented different phenotypes of autonomic dysfunction in ME/CFS, which emerged from a study of his research group [28]. Correct phenotyping is crucial in providing personalized therapy for affected individuals. This can be achieved through various examinations including blood pressure determination, monitoring of heart rate variability, and laboratory tests for neurotransmitters. Physical abilities should also be assessed through examinations like handgrip strength [29], and a NASA 10-min Lean Test. These tests serve as a basis for creating an individual treatment plan.

Physical and rehabilitation medicine can offer function-centered diagnostics and therapy for ME/CFS patients, enabling an individual approach. **Max Liebl** presented findings of muscular dysfunction and abnormalities, with a focus on respiration, by conducting function-centered diagnostics in ME/CFS patients analyzed within the CFS_CARE study of the Charité [30]. Methods used for this purpose include measuring thoracic respiratory excursion and conducting manual diaphragm as well as cervical and thoracic spine examinations. These diagnostic tools provide a basis for individual physical therapy. Reflective respiratory therapy, which is a combination of thermal stimuli with special massage grip techniques for increased thoracic flexibility and harmonized breathing patterns, was particularly highlighted in this context [31]. Furthermore, the importance of home exercises for ME/CFS and PCS patients combining mobility and breathing exercises with self-applied relaxation strategies was emphasized.

In the cognition and magnetic resonance imaging (MRI) in post-COVID (CAMINO) study, characteristics of white matter and subcortical brain structures in patients with PCS-associated fatigue and cognitive impairment were examined [32]. **Carsten Finke** presented the results of this study unveiling that PCS is linked with deficits of attention, memory (learning, long-term, and working memory), and executive function (semantic fluency, dual-task). Structural MRI showed a reduced volume and impaired microstructural integrity of basal ganglia and the thalamus in association with PCS fatigue [32]. Analyses of a population-based sample of the German National Pandemic Cohort Network (NAPKON) study COVIDOM identified older age, shorter education, male gender, and history of neuropsychiatric disease as predictors for cognitive deficits as well as younger age, female gender, number of acute COVID symptoms and depression as predictors of fatigue in PCS [33]. Similar studies are ongoing in ME/CFS patients within the National Clinical Study Group (NKSG) an interdisciplinary network of physicians and scientists to develop translational research and therapeutic trials for the treatment of ME/CFS and PCS [34].

One in three persons in Germany describes sleep disturbances, but only every fifth suffers from sleep disturbances at least three nights per week [35]. Obstructive sleep apnea (OSA) is more frequent in men than in women and its prevalence increases with age [36]. Sleep disturbances are described as obligatory ME/CFS symptom in current case definitions as defined by the IOM criteria [25], the CCC [14], and the National Institute for Health and Care Excellence (NICE) guidelines [37]. The CCC recommends the exclusion of restless legs syndrome and OSA in every CFS patient [14]. Affected people diagnosed within the ongoing CFS_CARE study at Charité [30], revealed a high prevalence of at least one sleep disorder (60 of 64 ME/CFS patients) as presented by **Christian Veauthier**. Hence, sleep disorders seem to be very common in ME/CFS and physicians are advised not to overlook them. Therefore, home sleep testing should be performed on every ME/CFS patient. Diagnosing and treating them according to official guidelines could result in improvement of fatigue and cognitive symptoms.

Peter Rowe highlighted the importance of diagnosing joint hypermobility (JH) and hypermobile Ehlers-Danlos syndrome (hEDS) as potential comorbidities of ME/CFS with, an increased prevalence in ME/CFS patients, as shown by various studies [38–40]. Often, hypermobility is accompanied by orthostatic intolerance (OI). Mechanisms of the association between OI and JH/hEDS are not fully understood, but there is evidence for connective tissue laxity in blood vessels [38], peripheral neuropathy [41], and mast cell activation syndrome [42]. Affected ME/CFS patients can benefit from the diagnosis of hypermobility syndromes in terms of appropriate clinical management [43].

4. Understanding ME/CFS

4.1. Endothelial dysfunction

Impaired blood flow and endothelial biomarkers were an important topic at the meeting. **Francisco Westermeier** elaborated on the importance of nitric oxide (NO) and the NO-forming enzyme endothelial

nitric oxide synthase (eNOS) for cardiovascular tissue and endothelial homeostasis. In the presented work conducted by Blauensteiner et al. [44], the Sirtuin 1 (SIRT1) – eNOS axis in ME/CFS was investigated and revealed an increased level of selected microRNAs associated with endothelial dysfunction. Additionally, Francisco Westermeier showed data that indicated an inhibitory phosphorylation effect of eNOS, which leads to a reduced NO production of endothelial cells (EC) incubated with plasma from ME/CFS patients [45]. Furthermore, preliminary data on L-arginine metabolites, which are essential for NO production, hint towards dysregulation in ME/CFS patients, with contrary patterns in males and females.

Martina Seifert investigated the functional effects of serum factors on ECs in vitro from PCS patients of which a subset had ME/CFS. Differences in the secretion of selected small molecules (e.g., Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Myeloperoxidase (MPO), myeloid-related protein (MRP) 8/14, and others) were found between PCS and PCS ME/CFS patients and healthy individuals after serum treatment of human EC [46], which may be related to a different pro-angiogenic potential. Interestingly, anti-EC-AAbs (AECA) were more abundant in the sera of PCS/CFS patients [46]. Finally, plasma extracellular vesicles were discussed as potential biomarkers of altered endothelial function in PCS/CFS and ME/CFS, as preliminary data showed a markedly different phenotype and proteome compared with vesicles from healthy individuals.

As emphasized by **Christian Puta**, understanding PEM is crucial and requires analysis of exercise-induced responses. PEM is defined as an intolerance of mild to moderate mental and physical exertion with an aggravation of symptoms, which usually last longer than 14 h and can persist for several days or weeks with dysregulated acute exercise tolerance [47] and dysregulated recovery processes [2]. PCS and ME/CFS patients have a low aerobic capacity [16,17], and therefore anaerobic capacity should be considered in diagnostics. It was hypothesized that immunological and metabolic dysregulations, hypoxia, as well as dysfunctional microcirculation, and morphological changes in red blood cells leading to inadequate tissue perfusion might be causative for PEM. More generally, it is crucial that strategies to avoid PEM are considered in rehabilitation therapies for ME/CFS patients.

4.2. Immune dysregulation

The utilization of omics technologies has been instrumental in the characterization of immune dysregulation ongoing in severe acute COVID-19 [48] and led to the identification of substantial transcriptional deviations in immune cell subsets of the myeloid compartment and T cells [49]. **Anna Aschenbrenner** presented the first results from a study on a well-defined cohort of PCS patients including a subset fulfilling the CCC for ME/CFS using single-cell RNA sequencing for the analysis of circulating peripheral immune cells. In comparison to fully recovered healthy individuals 5–12 months after SARS-CoV-2 infection, those PCS patients showed a pro-inflammatory monocyte profile, pro-inflammatory NK cell subpopulations, and an increase in the number of cytotoxic $CD16^+$ T cells.

Andreas Goebel presented research jointly conducted with Camilla Svensson (Karolinska Institute), David Andersson, and Stuart Bevan (Kings College London) [50] on findings of AAbs to satellite glia cells (SGC). Injection of isolated immunoglobulin G (IgG) fractions from fibromyalgia syndrome (FMS) patients led to reduced locomotion, decreased skin innervation as well as hypersensitivities against mechanical and cold stimuli in mice. The binding of IgGs to SGC and neurons could be shown. Hence, anti-SGC AAbs might explain the spontaneous pain described as a symptom in FMS patients. In preliminary studies on PCS, there was no clear evidence that pain was associated with anti-SGC AAbs. Future efforts are needed to better understand whether PCS-associated pain can be passively transferred to mice.

Bettina Hohberger presented the impact of functional AAb (fAAb) targeting GPCR (GPCR-fAAb) on capillary microcirculation in patients with PCS, quantified in the macula by optical coherence tomography angiography (OCT-A) [51,52]. Hohberger reported on an experimental therapy of a patient with PCS and glaucoma, being seropositive for GPCR-fAAbs, who was treated with the DNA aptamer BC007 for neutralization of the GPCR-fAAbs. After this experimental treatment, the patient's PCS symptoms improved. This was accompanied by an improvement in capillary macular microcirculation, measured by OCT-A, and a decrease in intraocular pressure. Using a cardiomyocyte beat rate test system several GPCR-fAAbs were observed in sera of patients with PCS, or glaucoma [53,54].

4.3. Viral reactivation

Nuno Sepúlveda presented a re-analysis of published data on IgG responses to over 3000 peptides derived from 14 EBV proteins in 92 ME/CFS patients and 50 healthy controls [55]. The study had the objective of investigating the potential role of EBV mimicry in triggering autoimmunity. A machine learning approach revealed stronger antibody responses against two peptides from EBNA4 and EBNA6 in ME/CFS patients with a putative infection in their disease onset compared to controls indicated that using these antibody responses together with age and gender the final classification model had good diagnostic sensitivity and specificity [56]. In a consecutive study, two peptides derived from EBNA6 were identified with high sequence homologies with different human proteins encoding by the following genes CCCTC-binding factor (CTCF, a master genomic regulator), adipocyte enhancer-binding protein 1 (AEBP1, associated with Ehlers-Danlos Syndrome), homebox A9 (HOXA-9), and adrenergic receptor alpha 1B. Strikingly, these human genes and the respective coding proteins may play a role in ME/CFS pathology, via a putative EBV molecular mimicry.

The presentation given by **Bhupesh Prusty** dealt with the coherency of viral antibodies, autoimmunity, and mitochondrial dysfunction in ME/CFS pathogenesis. Patients with ME/CFS, PCS, and/or post-COVID fatigue showed high antibody responses against the deoxyuridine triphosphatase (dUTPase) of EBV, herpes simplex virus 1 (HSV-1), and human herpes virus type 6 (HHV-6), indicating a possible role of herpesvirus reactivation. Evidently, these specific dUTPases can induce mitochondrial damage. The second focus of the lecture was on a protein microarray analysis, which revealed a correlation between IgM antibodies (e.g., house dust mites, cat/dog hair) and ME/CFS disease severity, suggesting increased responsiveness to foreign antigens. Furthermore, ME/CFS patients in this study exhibit higher circulating fibronectin levels compared to controls, which may be associated with chronic inflammation and disruption of clot homeostasis. Additionally, presented data indicate that IgG fractions from patients with severe ME/CFS can induce mitochondrial fragmentation in ECs in vitro. These findings suggest that virus reactivation in localized tissues may contribute to mitochondrial dysfunction and tissue inflammation in ME/CFS.

5. Treatment of ME/CFS

5.1. State of the art and off-label therapies

Luis Nacul introduced the third theme of the conference, which addressed the treatment options for ME/CFS currently applied in practice and under clinical investigation. Patient care, including pharmacological and non-pharmacological treatment options, should be based on consented guidelines like the NICE guideline on ME/CFS (NG206) or the Expert Consensus of the European Network on ME/CFS (EUROMENE) [6,37]. Specific treatment options should be agreed upon patient and health professional, following transparent discussions concerning existing evidence, the balance between potential benefits and risks, and patient preferences. Non-pharmacological interventions, like pacing,

highly personalized and specialized outpatient care as well as further aid in reducing symptom burden can improve the long-term prognosis of ME/CFS [6,57,58]. It is important to consider opportunities for early recognition and treatment of patients at all levels of health services. Training and education of health professionals, including in primary care, are important to enable better coverage and care of patients, particularly at early stages of the disease, when therapeutic interventions will likely be more beneficial [59].

Based on his broad clinical experience, **Michael Stingl** presented a range of neuromodulating drugs that can be helpful in ME/CFS. Short-time usage of benzodiazepines can be beneficial in lowering the symptom burden of PEM, sleep disturbances, or sensory overload due to their sedative/anxiolytic properties [60]. Anticonvulsants can suppress the excessive firing of neurons, reduce neuropathic pain, and counteract potential neuroinflammation [61]. Furthermore, antidepressants and antipsychotics with anti-inflammatory and neuromodulator properties can be administered to improve cognition and endothelial function [62–70]. Based on first clinical studies cholinesterase inhibitor pyridostigmine, used for myasthenia gravis therapy, is promising for treating vascular dysfunction, hypoperfusion, and muscle fatigue in ME/CFS [71]. OI in ME/CFS may manifest as POTS, orthostatic hypotension (OH), or even postural symptoms without tachycardia (PSWT). Non-invasive interventions for the treatment of all forms of OI are centered on identifying and avoiding individual triggers of symptom exacerbation (e.g. volume depletion, long standing, heat exposure), applying compression garments, pacing when strengthening leg and abdominal muscles, and increasing fluid and sodium intake [72]. Additionally to the non-pharmacological basis therapy, pharmacological treatments for POTS and OH entail a range of centrally and peripherally acting substances, including ivabradine, propranolol, midodrine, pyridostigmine, and fludrocortisone as presented by **Andrea Maier** and **Luis Nacul** [67,69,73]. Initial low-dose administration is not only recommended in patients with OI to provide better tolerability, but possible side effects have to be carefully monitored.

Johannes-Peter Haas introduced an interdisciplinary, multi-professional, multimodal approach for young patients with ME/CFS at the German Center for Pediatric and Adolescent Rheumatology in Garmisch-Partenkirchen. The main goals are to increase patients' ability to apply individual pacing efforts and to provide knowledge on how to improve blood circulation, implement sleep hygiene, and manage pain. The components of the therapy are fixed within a weekly schedule not exceeding 30 min each, whilst allowing for individual adaptations on a daily basis. Follow-up data after four months suggest lasting improvements in certain domains, including physical functioning.

Laura Froehlich presented a survey about the medical care situation in ME/CFS in Germany indicating that patients were severely medically underserved. Their overall satisfaction with the care provided by general practitioners was low and only one-third were being treated by physicians specializing in ME/CFS [74]. Findings from the same survey also point towards a high degree of stigmatization perceived by ME/CFS patients, resulting probably in lower functional status and satisfaction with social roles [75]. **Bettina Grande** emphasized that although psychotherapy and psychosomatic rehabilitation have no proven curative effect in ME/CFS, there is an important role for psychotherapeutic support. Whilst acknowledging the limitations of psychotherapy in the care of ME/CFS patients, psychotherapists can improve patients' ability to handle their individual energy levels, loneliness, and frustration to improve general well-being [76,77].

5.2. Clinical trials

Results of ongoing clinical trials and current perspectives on targeting endothelial dysfunction and hypoperfusion were presented. **Elisa Stein** and **Wolfgang Ries** both showed results of clinical trials on immunoadsorption, which had previously shown to be effective in subgroups of ME/CFS patients [78,79]. **Elisa Stein** presented the interim results from an observational trial of immunoadsorption in patients with SARS-CoV-2-triggered ME/CFS. The study aims to investigate the effectiveness in improving physical functioning and reducing symptom burden, as well as tolerability of the treatment [80]. Preliminary data provide first evidence of efficacy in two-thirds of the patients. Effective depletion of total IgG, IgA, IgM, and anti-β2 adrenergic receptor AAb levels was shown. **Wolfgang Ries** pointed out that immunoadsorption is a feasible treatment approach with good efficacy in severely affected ME/CFS patients. However, individualized measures have to be taken in order to prevent PEM, including specialized transport and the reduction of audio-visual stimuli. Preliminary data from 31 severely affected PCS and ME/CFS patients indicate a response rate of 70% after five treatment sessions.

Øystein Fluge provided an overview of the clinical trials investigating the B cell-depleting monoclonal antibody Rituximab (RituxME) and the alkylating cytotoxic agent Cyclophosphamide (CycloME) in ME/CFS [81,82]. Preliminary findings from a six-year follow-up indicated a more beneficial outcome in patients enrolled in the CycloME trial, compared to patients in the RituxME trial. Fluge et al. hypothesized that ongoing immune responses in ME/CFS may be characterized by a persisting pattern of IgG AAbs that emerge after systemic infection. Those antibodies originate from mature plasma cells (PC) and possibly target ECs, neurons in the autonomous nervous system as well as GPCRs, resulting in disturbed vascular function and blood flow regulation [83]. Since Rituximab showed limited efficacy possibly due to its inability to target mature PC, and considering the cytotoxicity of Cyclophosphamide, a small trial is currently investigating the feasibility of the anti-CD38 antibody Daratumumab targeting long-lived PC, and first evidence for efficacy was shown [84].

Finally, **Klaus Wirth** presented the mechanisms possibly underlying the disturbed balance of vasoconstriction and vasodilation, which results in hypoperfusion and impaired mitochondrial function. This might be triggered by AAbs targeting e.g., anti-β2 adrenergic receptor, stress responses, or vascular damage following infection [85,86]. Potential treatment options should focus on the preferential vasodilation of blood vessels in the brain via soluble guanylate cyclase stimulators, phosphodiesterase type 5 (PDE5) inhibitors, autoantibody targeting, and stimulators of endothelial acetylcholine receptors [71,87–89]. Moreover, further novel therapeutics could direct the preferential vasodilation of skeletal muscle blood vessels.

6. Conclusions

In summary, recent advances in ME/CFS research, diagnosis, and treatment were discussed at this two-day meeting. Several innovative diagnostic and therapeutic approaches provided promising concepts of care for ME/CFS patients. The importance of translating research findings into therapeutic strategies was highlighted to improve the clinical outcomes of ME/CFS patients.

Authorship

SSt, AF, FH, and SSc wrote the manuscript draft. All other authors made substantial scientific contributions during the conference by presenting and discussing their research, which is now summarized here in this report. Moreover, all authors reviewed the manuscript critically for important intellectual content and have given final approval for the version to be submitted.

Submission declaration

This work has not been previously published and is not under consideration for publication elsewhere. If accepted, this work will not be published elsewhere in the same form, in English, or any other language, including electronically without the written consent of the copyright holder.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors did not use generative AI and AI-assisted technologies in the writing process, which go beyond improving readability and language.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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