The Charité Fatigue Center ME/CFS Research Conference 2023: Understand, Diagnosis, Treat 11 – 12 May 2023

Dr Katrina Pears attended the 2-day research conference for the ME Association and reports on a selection of the presentations. The conference programme can be accessed here. It included 28 short presentations and a poster session with 25 posters (that included Dr Karl Morten speaking about his Raman Spectrometry study).

Session 1- ME/CFS and Post-COVID Syndrome (PCS) I

1. Autoimmunity to the Autonomic Nervous System: The Mechanism to Many Common Clinical Conditions.

Yehuda Shoenfeld – Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel.

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2. ME/CFS as Part of the PCS Spectrum.

Carmen Scheibenbogen – Institute of Medical Immunology, Charité Fatigue Center (CFC).

Session 2- Diagnosis I

3. Diagnosing ME/CFS – State of the Art.

Uta Behrends – MRI Chronic Fatigue Center for Young People (MCFC), Children's Hospital, Munich Municipal Hospital Group and Technical University Munich, Munich, Germany.

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4. Autonomic Dysfunction in ME/CFS.

Paweł Zalewski – Ergonomics and Exercise Physiology, Nicolaus Copernicus University in Toruń, Toruń, Poland.

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5. Breathing and Muscular Dysfunction in ME/CFS.

Max Liebl- Physical Medicine, Charité, Universitätsmedizin Berlin, Germany.

Max Liebl discussed the role of physical and rehabilitation medicine in ME/CFS. For example, in his clinic PCD exercises are also given to ME/CFS (PCD = Primary Ciliary Dyskinesia, an inherited condition that affects the lungs and creates a mucus build up). The clinic also provides home exercises and manual therapy delivered by a physiotherapist to increase oxygen to tissues. An individual approach is needed to prevent PEM but also to manage kinesiophobia (the fear of movement).

Session 3- Diagnosis II

6. Brain Fog and Neurocognitive Assessment in ME/CFS.

Carsten Finke – Neurology and Experimental Neurology, Charité Universitätsmedizin Berlin, Germany.

Carsten Finke's talk had a Post-COVID Syndrome focus, where cognitive defects are at the centre of brain fog. He presented results from 2 studies that examined cognitive problems.

The results from the CAMINO study were based on 50 post-COVID patients who had subjective cognitive impairment and showed significantly worse cognitive performance when compared to controls.

Researchers used a range of measures, including psychosocial outcome via questionnaires and an examination of brain structure with MRIs. The scans showed reduced brain volumes and reduced microstructural integrity of the basal ganglia and thalamus. Furthermore, brain structure correlated with fatigue severity.

The second study (NAPKON) used data collected through a German network of 1,000 patients who were PCR positive for COVID-19 and compared those who recovered against those with lasting cognitive symptoms. It concentrated on post-COVID fatigue and cognitive deficits.

The study found a number of predictors for post-Covid fatigue, which was more likely in those who were female, younger, and also affected by the number of Covid symptoms, depressive disorder and neuropsychiatric disease. Whereas post-Covid cognitive defects were more likely in those who were older, male, had less education and without any neuropsychiatric disease. Significant improvements in fatigue and cognitive impairment were found in the one-year follow-up.

7. Sleep Disturbance in ME/CFS.

Christian Veauthier – Interdisciplinary Center of Sleep Medicine, Charité, Universitätsmedizin Berlin, Germany.

Christian Veauthier began by covering sleep disorders in the general population, which are more common in women and increase with age although not everyone develops a chronic disorder. There is a low prevalence in young women and in people under the age of 40.

Sleep disorders are common in ME/CFS. In this study 60 out of 64 people were found to have a sleep disorder, such as insomnia and sleep apnoea. Christian provided recommendations for doctors treating ME/CFS to not ignore conditions of delayed sleep phase syndrome (i.e., going to bed in the early morning), restless leg syndrome (RLS), and obstructive sleep apnoea (OSA). He is looking at treating sleep disorders in ME/CFS and hopes to come back next year to report on his discoveries and whether they can improve fatigue.

8. Hypermobility in ME/CFS.

Peter Rowe – Children's Center Chronic Fatigue Clinic, Johns Hopkins University, Baltimore, USA.

Peter Rowe talked about diagnosing hypermobility and previous studies in ME/CFS, including the fact that hypermobility is more common in females than males.

Previous research by Peter has looked into the overlap between EDS/ joint hypermobility, orthostatic intolerance and ME/CFS (Rowe *et al.*, 1999). Other studies have shown that joint hypermobility is more common in children with ME/CFS (Barron *et al.*, 2002).

Peter discussed the proposed mechanisms which have been suggested for the association between JH/EDS and OI, including effects of tissue laxity, physical inactivity and peripheral neuropathy. Other studies have shown that having joint hypermobility has not been seen to affect the onset of ME/CFS (Vogel et al., 2021) and brain blood flow has been found to be reduced in those with joint hypermobility and ME/CFS (van Campen *et al.*, 2021).

He finished with a summary explaining why EDS and joint hypermobility is important to look at in both clinical care and research studies.

Session 4- Understanding I

9. Assessing Endothelial Dysfunction.

Francisco Westermeier – Biomedical Analytics, FH Joanneum University of Applied Sciences, Graz, Austria.

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10. Optical Coherence Tomography Angiography and Cell Deformability in ME/CFS.

Bettina Hohberger – Ophthalmological Clinic, University of Erlangen – Nuremberg, Erlangen, Germany.

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11. Novel Biomarkers of Endothelial Dysfunction and Angiogenesis Alterations in PCS and ME/CFS.

Martina Seifert – Institute of Medical Immunology, Charité, Universitätsmedizin Berlin, Germany.

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12. Understanding Post-Exertional Malaise (PEM).

Christian Puta – Sports Medicine and Health Promotion, University of Jena, Jena, Germany.

Christian Puta looked at PEM and the understanding we have about it. He acknowledged that it was difficult to test for as testing tends to induce PEM. The teams work specifically looks at trying to study PEM without long recovery periods.

When PEM occurs peak oxygen uptake is reduced, systemic oxygen extraction to the tissues is reduced and this affects post-PEM recovery.

In ME/CFS patients, we need to be able to measure the anaerobic generation as patients do not have a big aerobic capacity. The study he conducted used a one-minute sit to stand test, which resulted in 56% of patients underperforming. After a second test, they found a 10–14-day recovery period, which was a big problem.

Hypoxia exists in ME/CFS where oxygen shortage in tissue causes more lactic acid. The study also found a low anaerobic threshold and low VO_2 (maximum oxygen consumption). This means there is inadequate energy production, with reduced peak VO_2, and ROS formation (no spare resources for daily living).

Morphological changes in red blood cells also exist in ME/CFS. Membranes are extended and enlarged, and this reduces O_2 extraction. It was proposed that this could be a diagnostic tool. Gene expression is also altered in post exercise in ME/CFS.

Rest and recovery are very important following exercise as it helps to protect against multi-systemic symptoms.

Session 5- ME/CFS and PCS II

13. Insights from ME/CFS May Help Unravel the Pathogenesis of PCS.

Anthony Komaroff – Brigham and Women's Hospital, Harvard Medical School, Boston, USA.

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14. Predictors of ME/CFS following EBV and implications for PCS.

Leonard A. Jason – Center for Community Research, DePaul University, Chicago, USA

Session 6- Understanding I

15. Immune Signature of ME/CFS.

Anna Aschenbrenner – Platform for Single Cell Genomics and Epigenomics (PRECISE), German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany.

Anna Aschenbrenner used system medical approaches, which are a combined approach involving machine learning and OMICS techniques. Her interest in this field started with the COVID pandemic, and she is still learning about ME/CFS. The study is called DeCOI (Deutsche Covid-19 Omics Initiative).

The team began by looking into the effects of a COVID-19 infection using scRNA-seq (RNA sequencing) which revealed deviations in the myeloid compartment (a major cellular compartment of the immune system comprising monocytes, dendritic cells, tissue macrophages, and granulocytes). They also found that severity and time affect alternations in monocytes, with significant transcriptional deviation in severe COVID-19.

Th researchers have become aware of the overlap in ME/CFS and trying to find a biomarker, but for the lap being their work focuses on post-COVID syndrome (PCS).

The study included 40 PCS and 20 controls (who had an infection but did not develop PCS). It was an RNA study that aimed to determine if there was any transcriptional changes months after a mild-infection of COVID-19.

The study looked at 233,000 cells, with the monocytes CD14+ and 16+ showing different gene sets. CD16+ T cell subset contributes to Endothelial damage and Cytotoxic CD16+ T cells are found to be more frequent in PCS patients.

They did not expect to find differences in cells months after an infection and were surprised they could still find signs of the virus. They found the disease can be found in the monocytes (pro-inflammatory program increases), NK cells (pro-inflammatory program and subpopulations increase) and T Cells (cytotoxic and CD16+ subpopulations increase).

16. Autoantibodies to Glial Cells.

Andreas Goebel – Pain Research Institute, Institute of Life Course and Medical Sciences, University of Liverpool; Walton Centre NHS Foundation Trust, Liverpool, UK.

This talk discussed some of the data from a very interesting study in 2021 that explored whether fibromyalgia (FMS) has an autoimmune component. We covered this in a research summary.

Andreas and his team have expanded their initial research. FMS patients have elevated levels of antisatellite glia cell immunoglobulin G antibodies.

The antibodies are found to be more in FM than healthy controls, and severe FMS is consistently associated with satellite glial cells (SGC – unique cells whose most

distinctive morphological feature is that they wrap around neuronal cell bodies, in most cases forming a complete envelope).

SGC might explain spontaneous pain in FMS. However, SGC has not been found to be associated with pain or fatigue in Long Covid.

17. EBV Mimicry in ME/CFS.

Nuno Sepúlveda – Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland.

The talk began by introducing the theories for autoimmune disease, focusing on the danger/damage theory.

The researchers focused on reanalysing data which had previously been collected by Carmen Scheibenbogen's group. They had examined 50 healthy controls and 92 ME/CFS patients, in which 54 had reported an infectious trigger (Loebel *et al.*, 2017).

This work used a mathematical approach and models to find answers. Through machine learning they have found different groups (technically speaking this is called classifiers which is a set of categories an observation belongs to). In ME/CFS they have identified 27 antibodies into different antibody classes which are important in the biology of the illness. Also, there is an increased antibody response in ME/CFS.

Nuno's results suggest that future research should not get too caught up on molecular mimicry (where foreign antigens shares sequence or structural similarities with self-antigens) or individual antibodies.

In terms of the cause of ME/CFS, he believes the cell danger hypothesis (CDR) is at play in the development of ME/CFS. CDR is an evolutionary cellular response to protect the cell from harm where it encounters a chemical, physical or microbial threat or stressor that could injure or kill the cell.

18. Mitochondrial Dysfunction and Herpesviruses in ME/CFS.

Bhupesh Prusty – Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany.

This work has been looking into the herpesvirus signature in ME/CFS and Long Covid. Bhupesh Prusty discussed mitochondrial dysfunction, herpesvirus and autoimmunity.

His team's research has found that an IgG antibody pattern is not associated with disease severity, but IgM against autoantigens is associated with ME/CFS disease severity.

They found that ME/CFS has overlapping properties/autoantibodies with MS and SLE (Multiple Sclerosis and Systemic Lupus Erythematosus), suggesting that ME/CFS has a strong autoimmune basis.

In ME/CFS there is an increased IgM response against common pathogenic antigens, which means that people with ME/CFS are more sensitive to common antigens, like cat hair. And immunoglobins from people with Severe ME/CFS can induce mitochondrial fragmentation in primary endothelial cells.

Results have also found that a subset of autoantibodies might be useful in providing a biomarker, these are antimitochondrial and anticytoskeletal antibodies. Another potential biomarker was Herpesviridae-derived dUDPase.

The final potential biomarker was Fibronectin, which is a multifunctional, adhesive glycoprotein that plays an important role in tissue repair, in regulating cell attachment and motility. In ME/CFS circulating immune complex alternations are found, with increased circulating fibronectin levels due to this not being incorporated into the proteins and remains in the serum. Furthermore, the Fibronectin levels are found to correlate with disease severity.

Finally, Bhupesh believes that ME/CFS only shares a few features with Long Covid, as it has been found to share less molecular signatures than previously thought.

Session 7- Treatment I

19. Treating ME/CFS – State of the Art.

Luis Nacul – Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK; Complex Chronic Diseases Program, British Columbia Women's Hospital and Health Centre, Vancouver, Canada; Faculty of Medicine, University of British Columbia, Vancouver, Canada.

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20. Multiprofessional Inpatient ME/CFS Treatment.

Johannes-Peter Haas – Pain Treatment Center for Young People (ZSTJM), Pediatric Rheumatology, Garmisch-Partenkirchen, Germany.

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21. Neuromodulation in ME/CFS.

Michael Stingl – Neurology, Vienna, Austria.

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22. Medical Care Situation and Stigma with ME/CFS.

Laura Froehlich – Center of Advanced Technology for Assisted Learning and Predictive Analytics (CATALPA), FernUniversität in Hagen, Hagen, Germany.

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23. Psychological Support in ME/CFS.

Bettina Grande – Psychotherapy, Heidelberg, Germany.

Bettina Grande's talk showed a good understand of ME/CFS and covered the dangers of PEM, which can be induced by physical or mental triggers, and how very

little exertion can cause a crash. The talk focused on how psychotherapy can be used to mange pacing and PEM.

The basis of pacing was covered and the importance of not pushing yourself. However, pacing was recognised to not come without problems, such as limitations, loneliness, anxiety, depression and the need for self-control.

Psychotherapy can be used to deal with PEM and help to manage pacing to avoid permeant damage. There was a clear recognition that pacing is challenging.

Session 8- Treatment II

24. B and Plasma Cell Targeting in ME/CFS.

Øystein Fluge – Department of Oncology and Medical Physics, University of Bergen, Haukeland University Hospital, Bergen, Norway.

Øystein Fluge covered data from clinical trials (Rituximab trials which started in 2008 (rituxME) and Cyclophosphamide trial (cyCloME)). The team began their research after seeing 12 cancer patients with a history of ME/CFS who reported benefits following treatment.

Despite very good clinical trials using Rituximab, the research failed to find any benefit from treatment against placebo in people with ME/CFS. A review of these studies and an ME Association statement from 2019 can be read here.

Øystein presented 6-year follow-up data of the two previous trials, which used SF-36 Physical Function scores and the DePaul Symptom Questionnaire.

- Rituximab is a B cell depleting antibody and selectively depletes B-cells expressing the protein CD20 on their surface).
- Cyclophosphamide is an alkylating cytotoxic drug affecting DNA. It may work in ME/CFS by inhibiting antibody secretion to B-cells.

In the follow up RituxME showed no significant differences over time (no difference versus placebo). CyCloME showed improvements from baseline to 18 months and then 18 months to 6 years, but there was a large variation among individual patients. Cyclophosphamide was shown to have more improvement, 18% got to a normal healthy level, but only around 8% in RituxME. Patients were not seen to get any worse with treatment.

It is difficult to know how research should proceed when there are no established pathomechanisms, and no approved outcome measures, e.g., how to symptoms naturally vary over time.

The team feel that ME/CFS is in most cases a reversible disease. There is usually no signs of organ damage and no evidence of histological inflammation in tissues.

The possible pathomechanisms of disease (which were in their latest paper) could include:

- an inadequate oxygen and nutrition supply, especially on exertion (working hypothesis).
- a disturbed immune system, leading to disturbed autoregulation of blood flow and hypoxia in tissues which causes changes in metabolism to compensate.

These are thought to be caused by three mechanisms: endothelial dysfunction, reduced venous return to the heart and reduced peripheral oxygen extraction. They think that ME/CFS is a variation of autoimmune disease with a role for B-cells/ plasma cells and autoantibodies.

They are now running a pilot study that will examine this hypothesis. The pilot is using injections of anti-CD38 antibody Daratumumab (a targeted cancer drug) in six patients to try and reset the immune system.

They are assessing the number of steps a patient can do in 24 hours as a way of measuring outcomes. An example of one patient was given, who had tried Rituximab previously with no improvement, but who now reported an increase in steps following treatment with Daratumumab.

25. Immunoadsorption in Severely Affected ME/CFS Patients.

Wolfgang Ries – Nephrology, Clinic for Internal Medicine, DIAKO Hospital Flensburg, Flensburg, Germany.

Wolfgang Ries talked about immunoadsorption (the removal of molecules from blood) and looked at the systems currently available, e.g., Immunosorba TR 350 Asahi, Globaffin and Ig Omni 5 Miltenyl.

He shared his views on apheresis (a process that removes disease-provoking elements from blood) as a potential treatment for people with Long Covid and in ME/CFS, and its safety when used in children and adolescents.

The theory surrounding the use of apheresis is that 'micro-clots' may be present in blood and could be causing persisting symptoms in both conditions. However, more research is needed before this invasive treatment can be recommended. There have been no clinical reports of clotting in ME/CFS. The ME Association's views of apheresis can be read here.

Wolfgang reported that there are complications of having apheresis, such as an adverse reaction, vascular access, bleeding, hypotension, hypocalcaemia, catheter infections, etc. although most are minor.

For people with ME/CFS, he said there are problems and difficulties attending clinics, especially for the severe, where separate rooms are needed and sensitivities to noise need to be managed, even the machine makes a noise.

Preliminary findings from study were covered, with improvement in 22 out of 31 patients, no change in 6 patients and another 5 ongoing. They use the BellScore to assess patients (see here), all had very low scores before treatment (i.e. high levels of

disability). (Please note that this is a very small study and not yet published, results need to be verified in further trials, so results need to be taken with caution).

26. Immunoadsorption in PCS and ME/CFS.

Elisa Stein – Institute of Medical Immunology, Charite Fatigue Center (CFC), Charité, Universitätsmedizin Berlin, Germany.

Elise Stein began by covering previous research on antibodies against GPCR in ME/CFS. Their research has focused on Post-Covid ME/CFS in 66 patients who have been coming to Charité for immunoadsorption (immunoadsorption is a selective apheresis method – a process that removes disease-provoking elements from blood).

The theory surrounding the use of apheresis is that 'micro-clots' may be present in blood and could be causing persisting symptoms in Long Covid and ME/CFS. However, more research is needed before this invasive treatment can be recommended. There have been no clinical reports of clotting in ME/CFS. The ME Association's views of apheresis can be read here.

Elise reported that the treatment was found to significantly lower IgG and they recorded outcomes such as clinical features, physical function, and symptom severity. Perhaps because the study contains such a small number of patients, they were unable to report statistically significant results.

She said that patients who respond positively to the initial treatment will be treated again if symptoms worsen. They are also looking at offering B-cell depleting CD19 or CD20 monoclonal antibodies. (Please note, I'm uncertain why they are looking at different treatments if apheresis does not sustain improvement, and speculation/ caution should be applied if improvements are not long lasting.)

27. Treating Orthostatic Intolerance and PoTS in ME/CFS.

Andrea Maier – Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany.

Andrea Maier began by talking about how they diagnosis orthostatic intolerance (OI), including the standing test they do which involves lying for 10 mins then standing for 10 mins. Orthostatic hypotension and Postural Orthostatic Tachycardia Syndrome (PoTS) were also covered.

The pain part of the talk was on therapy/treatment for PoTS. Which includes:

- Education – finding triggers (heat, long standing) and symptoms.
- Basic therapy – avoid lying in bed (hard in ME/CFS), slow standing up, small frequent meals, raise blood volume (drinking 2-3 liters per day), increase salt (8-12 g/day), compression stockings, abdominal binder, and treating related conditions (Ehlers-Danlos Syndromes, mast cell disorders, B12 depletion).
- Exercises – train calf and abdominal muscles, standing training, endurances training (hard in ME/CFS).

If these initial steps do not work (symptomatic therapy) then medications can be tried, at very low doses: saline capsules, midodrine, mestinone and fludrocortisone.

For hyperadrenergic PoTS, the medications are beta-blockers, cervedilole, ivabradine, clonidine, methyldopa, bupropione, escitaloprmae, desmopressine (drug doses were also suggested). A short-term course of Iv NaCl (intravenous sodium chloride) can also be tried.

In conclusion, PoTS is commonly seen in ME/CFS. There are many possible causes and cardiac disease needs ruling out first. In ME/CFS, PEM is a big challenge when trying to treat OI and PoTS. Patients with ME/CFS generally have the highest standing heart rate out of all the patients seen at her clinic.

28. Vascular Targeting in ME/CFS.

Klaus Wirth – Pharmacology, Goethe University Frankfurt, Frankfurt, Germany.

Klaus Wirth started his presentation by explaining that the vasodilator and vasoconstrictor balance is disturbed in ME/CFS.

Exertional intolerance is a hallmark of ME/CFS, and the main mechanisms are influenced by the skeletal muscles, brain and heart working as one unit. Furthermore, the β2-Adreneergic Receptors (β2AdR) are the exercise receptor, and dysfunction here impairs the ability to exercise.

The cardiovascular system is also disturbed in ME/CFS, which leads to problems such as orthostatic intolerance. Reduced blood flow and circulatory disturbances have also been found, including reduced cerebral flood flow (CBF), impaired neurovascular coupling and intracranial hypertension.

There are many potential causes of vascular dysfunction in ME/CFS, such as autoantibodies (e.g., AAB against β2AdR), autonomic dysfunction (e.g., sympathetic hyperactivity with increase vasoconstriction and decreased vasodilation), and blood vessels could also be affected (e.g., endothelial dysfunction). From looking at PoTS we can see what might be going wrong in the cardiovascular system in ME/CFS.

For therapeutic interventions, antisympathotonic drugs (which reduce the activity of the autonomic nervous system) such as Guanfacine and Clonidine might be considered. For treatment in ME/CFS, Klaus said that we need to dilate brain and skeletal blood vessels but not the intestinal blood vessels. However, selective dilution is currently not possible.

Vasoactive drugs have no effect on cerebral and skeletal muscle blood flow in healthy people. These drugs can raise CBF (cerebral blood flow) but can decrease vasoconstriction to skeletal muscles. Pyridostigmine and nicotine were given as examples for treating orthostatic hypotension and can help improve orthostatic regulation.

However, the drug of choice depends on the type of OI, with OI being present in at least 90% of ME/CFS and associated with decreased CBF.

There is hope for better treatment in the future, with new drug principles looking into stimulation of Na^+/K^+-ATPase in skeletal muscle, moderate stimulation of cerebral muscle blood flow with no fall in blood pressure as well as inhibition of microvascular leakage.

- Klaus published a review: ME/CFS and Comorbidities: Linked by Vascular Pathomechanisms and Vasoactive Mediators? | 18 May 2023.

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