Report on IACFS conference August 2021

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Speaker List

DAY ONE 20/8/21

Introduction

This virtual conference opened with a welcome by the president of IACFS, **Fred Friedberg** (Stoneybrook, USA). The conference had been preceded by an excellent set of clinical workshops and a one-day patient conference.

Keynote Speaker

Avindra Nath – NINDS

ME/CFS and Long-Covid: overlapping or distinct entities?

COVID-19 infection is known to cause neurological symptoms. There are multiple reported symptoms related to acute SARS co-V2 infection including anosmia, encephalopathy, strokes, meningitis/ encephalitis, seizures, leukoencephalopathy, and sudden death from brain stem abnormalities. 1/3 of patients that are hospitalised with COVID have an altered mental state, on average spending 3x longer in hospital. 2/3 of these patients are unable to manage ADL's on discharge from hospital. There is also an increased mortality rate in patients with acute COVID encephalopathy.

Data from UK shows that there are a lot of neurological manifestations after COVID compared to other viral illnesses including intracranial haemorrhage, ischaemic stroke, dementia, and psychiatric illnesses. Long-Covid is only one manifestation. Long-Covid patients fall into 4 groups (with some overlapping symptoms)

1) Exercise intolerance and fatigue
2) Brain fog- particularly word finding difficulty
3) Autonomic dysfunction including tachycardia/ POTS variants, low blood pressure, temperature dysregulation, gastrointestinal symptoms, and peripheral vasoconstriction (often presenting as tingling in hands and feet)
4) Myalgias including joint, muscle and chest symptoms

There is phenotypic overlap between ME/ CFS and Long-Covid

Two pathophysiological mechanisms are proposed – persistent infection and / or persistent immune activation. There is evidence from studies to support both mechanisms.

CSF shows T cell exhaustion and dedifferentiated monocytes consistent with immune response to infection suggesting immune dysregulation of the innate immune system.

Autopsy study results of COVID-19 cases showed inflammatory infiltrates in all parts of the brain but with more involvement of the brain stem.

There was vascular leakage and leukocyte infiltration of the olfactory bulb however no virus or spike protein detected.

Increased activation of platelets in blood vessels, but particularly around the endothelial cells possibly suggesting this is the site of injury.

Post-mortem MRI scans show macro and microvascular injury and neuronal injury in the brain stem.

Treatment possibilities included antiviral agents (if there is persistent viral infection), immune modulatory agents and treatments that could reverse T-cell exhaustion. Clinical trials are needed.

Q&A session: Some people appear to recover after COVID but 2-3 weeks later start developing new symptoms. This may be due to persistent infection driving the immune system or a gradual increase in the immune response leading to an autoimmune response.

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Infectious Diseases

Covid-19 infection in patients with myalgic encephalitis/chronic fatigue syndrome (ME/CFS) – a preliminary study.

John Chia (MD) from Lomita,CA, USA looked at Covid-19 infection in patients with ME/CFS. Acute infection with Covid-19 is often followed by long lasting debilitating symptoms, known now a Long-Haul Covid. This study looked at whether those with pre-existing ME/CFS would get a more severe illness if they contracted Covid-19. 26 ME/CFS patients were studied and they also had enterovirus infection (EV). Prior EV was diagnosed using stomach biopsies.

Patients who developed Covid-19 were followed over 3-6 months. 15 had mild symptoms, and 11 were bedridden with flu-like symptoms, fatigue and brain fog for 2-4 weeks. 14 of the 26 felt worse ME/CFS symptoms for months after the acute infection. 4 of the 11 were hospitalised. One had perforated sigmoid diverticulitis, 3 had pneumonia (treated with off-label use of remdesivir and steroids). Recovery took up to 3 months for the latter.

During follow-up, enteroviral proteins were detected in peripheral blood leucocytes in 13 patients, but none had ongoing Covid-19 proteins.

He concluded that Covid-19 infection had caused significant worsening on ME/CFS symptoms in half the patients and 4 required hospitalisation. Remdesivir had led to marked improvement of ME/CFS symptoms and needs further study.

COVID-19 Symptoms Over Time: Comparing Long-Haulers to ME/CFS

Leonard Jason,(PhD) from Chicago, Illinois, USA told us that in previous pandemics, 10-20% patients do not recover. He had then studied long-haul Covid patients over time and compared these patients to those with ME/CFS. The objective was to determine which symptoms among 278 long-hauler COVID-19 patients changed over time, and how their symptoms compare to another chronic illness group: 502 patients with ME/CFS.

A standard symptom questionnaire was used and included a list of covid-19 symptoms.

Over time, the Long Haulers reported an overall reduction in most symptoms, including unrefreshing sleep and post-exertional malaise, but worsening of neurocognitive symptoms.

When compared to ME/CFS, the COVID-19 patients were initially more symptomatic for the immune and orthostatic domains. ME/CFS patients were more impaired in the gastro-

intestinal and neurocognitive domains. But over time, the long-haulers evidenced significantly less severe symptoms than those with ME/CFS, except in the orthostatic domain. Among the COVID-19 long haulers, several neurocognitive symptoms got worse over time, whereas improvements occurred in most other areas.

It is probable that these studies of the differential patterns of symptoms may lead to better understanding of the pathophysiology of both illnesses.

Pathogenesis of ME/CFS is associated with enterovirus infection of brain neurons, immune activation and apoptosis.

John Chia (MD) from Lomita, CA, USA discussed the pathogenesis of ME/CFS and its association with enterovirus (EV) infection of brain neurons, immune activation and apoptosis. He has maintained for a long time that enteroviruses are implicated in ME/CFS. He cited studies done in 1994 and 2001 and on a patient of his in 2004. In animals, EVs can cause persistent infection in brain neurons.

In this study, brain samples were taken from 6 different brain areas. Viral capsid protein 1 was shown in neurons of different brain areas, and most prominently in the Purkinje cells of the cerebellum.

In this study there was evidence for chronic EV infection of brain neurons without excessive inflammatory cells or glial activation. A number of neurons were undergoing apoptosis.

The study provides an immunopathological explanation for the debilitating neurological symptoms in ME/CFS.

Provocation Studies 1

ME/CFS Have an Altered Resting State in Functional Magnetic Resonance Imaging (fMRI) After Exercise in a Model of Postexertional Malaise

The work of **Rakib Rayhan** (MD) from Washington, DC, USA was presented by James N Baraniuk. The subject of the talk was that ME/CFS patients have an altered resting state in functional magnetic resonance imaging (fMRI) after exercise in a model of post-exertional malaise (PEM). He cited earlier studies when it was shown that comparisons between ME/CFS, Gulf war Illness (GWI) and controls had significant differences during a cognitive task at baseline, but postexercise ME/CFS had significantly elevated blood oxygenation level dependent (BOLD) brain activation compared to GWI.

He first asked the question of why we should do MRIs. He then went on to describe meshes of brain networks. He described default mode networks and task networks. The objective therefore was to see if there were differences in resting state brain activation between ME/CFS and controls before exercise or after exercise provocation.

The results indicated that the ME/CFS patients had reduced functional connectivity between the 29 nodes before and after exercise compared to controls, indicating impaired function at rest. Exercise caused significant activation of the anterior default mode network node that is

associated with mind wandering or internal focus. These exercise-induced changes may be considered objective markers of PEM. PEM symptom exacerbation and cognitive dysfunction may be related to post-exertional uncoupling of the anterior DMN.

A Cardiopulmonary Exercise Challenge changes the Extracellular Vesicles Proteome in ME/CFS

Ludovic Giloteaux, (PhD) from Ithaca, NY, USA had looked at whether a cardiopulmonary exercise challenge would be likely to change the extracellular vesicle proteome in ME/CFS. Extracellular vesicles (EVs) bind from plasma membrane and carry nucleotides such as RNA. They are known to be released during exercise.

18 ME/CFS patients and 18 controls were studied. All had regular blood tests and EVs were isolated. There was no significant difference in vesicle size, but there was a significant increase of EVs in controls, not observed in CFS. A proteomic run was then done, and changes in response to exercise were measured in both groups. Measurements were taken at baseline, after 15 minutes and then 24 hours after a cardiopulmonary exercise test.

Proteomic analysis identified 886 proteins, including 164 and 95 unique to ME/CFS patients and controls respectively. 61% pertained to the immune system. 163 proteins are dysregulated in ME/CFS at the 3 time points, with the majority being downregulated. 91 were only dysregulated during recovery.

The conclusion was that there are EV proteome changes post-exercise . This study may thus lead to development of biomarkers and therapies.

Ventilatory Functioning During Serial Cardiopulmonary Exercise Testing in People With and Without Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Todd Davenport (DPT) from Stockton, CA, USA looked at quantifying ventilatory functioning at rest and during activity in those with and without ME/CFS. Subjects received 2 maximal CPETs on a braked bicycle ergometer, administered 24 hours apart. Throughout each test, measurements of breath-by-breath gas samples, workload, heart rate, breathing rate, tidal volume, end tidal oxygen, and end tidal carbon dioxide were taken at rest, ventilatory anaerobic threshold (VAT), and peak exertion.

The subjects were matched and included 37 females with ME/CFS and 38 healthy sedentary women.

There was a significantly blunted rise in VO2 max (volume of oxygen consumed) in ME/CFS which was functionally disabling. The ME/CFS patients experienced overall lowered performance. The heart rate showed a blunted rise in ME/CFS patients associated with exercise, and the respiratory rate increased markedly in the second test. Minute ventilation and tidal volume were lower in the ME/CFS group at VAT and peak exertion.

He concluded that those with ME/CFS demonstrate abnormal pulmonary measurements on CPET that may correlate with abnormal metabolic and cardiac functioning. Potential effects on pulmonary function of short-term PEM induced by CPET remain unclear.

CPET Findings in Post-Acute Sequelae of COVID-19

Donna Mancini (MD) from New York, NY,USA had looked at the CPET findings in the post-acute sequelae (PACS) of 41 Covid-19 patients. They underwent cardiopulmonary exercise testing and a targeted interview. 46% of these patients fitted the criteria for a diagnosis of ME/CFS. 59% had a reduced peak oxygen consumption, all from a circulatory impairment. 88% of patients had an abnormal ventilatory response to exercise with either dysfunctional breathing (irregular rapid breaths), elevated ventilatory equivalent for CO2 or reduced end tidal CO2.

She concluded that most patients with PACS have circulatory impairment with exercise. But dysfunctional breathing and chronic hyperventilation may underlie some of the symptoms of PACS. Circulatory impairment, abnormal ventilatory pattern and ME/CFS are common in patients with persistent symptoms post-COVID-19

Use of CPET may be effective in objectively identifying abnormalities associated with PACS which could be targeted for treatment.

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Biomarkers

Circulatory Micro-RNA-374b-5p and PHB2 as biomarkers to distinguish ME from fibromyalgia

Evguenia Nepotchatykh (PhD) from University of Montreal presented finding from a study on a specific circulatory mRNA. Previous studies identified mRNA 374b-5p to be associated to fibromyalgia, leading to a replication study recruiting more patients. Plasma prohibitin 2 (PHB2) is a target molecule of mRNA-374b-5p. PHB2 has a role in bioenergetics and cell regulation.

In this study miRNA-374b-5p and PHB2 were measured in ME, FM, and healthy controls

Results showed that mRNA-374b-5p was over expressed in ME/CFS compared to controls and conversely it was severely downregulated in fibromyalgia. This replicated previous study results and confirmed a significant difference between ME/CFS and FM. PHB2 levels were higher in FM compared to the ME/CFS group and healthy controls.

It is proposed that mrR-374b-5p and PHB2 could be biomarkers to aid in distinguishing ME/CFS from FM.

Circulating Irisin levels in ME/CFS are associated with Disease Severity

Dr Wesam Elremaly (PhD) from University of Montreal, Canada presented study findings on Irisin, which is a newly discovered myokine hormone related to muscle function. It has been suggested that Irisin mediates the beneficial effects of exercise. A study has been done of 92 ME/CFS patients

and 40 healthy controls to compare plasma irisin levels and to see if levels correlate with disease severity. Blood samples were tested for Irisin before and after exercise testing, along with a questionnaire of health status.

Results showed that plasma Irisin levels were lower compared to the healthy control group at baseline. After stress exercise testing Irisin levels were higher in the patient group with more severe physical fatigue and PEM scores. This may be a potential biomarker for ME/CFS severity and could also be studied as a further treatment option.

Sex-specific Plasma Lipid profiles of ME/CFS patients and their association with pain, fatigue and cognitive symptoms

Dr Laila Abdullah (PhD) from Rosekamp Institute (USA) looked at plasma lipid profiles in patients with ME/CFS. Previous studies have shown lipid abnormalities affecting mitochondrial function resulting in an increased inflammatory response causing fatigue, cognitive impairment, and pain. Dr Abullah's study was a cross sectional design of 50 healthy controls and 50 ME/CFS patients. Plasma phosopholipids, neutral lipids and bioactive lipids were examined. Results showed in ME/CFS lipid profiles are different according to gender. In females with ME/CFS there was more upregulation of lipids associated with inflammation and oxidative stress whereas in males there was upregulation of lipids associated with metabolic dysfunction.

Omega-3 and Omega-6 fatty acids were correlated with more fatigue symptoms. Other lipid species were correlated with pain, headache, and cognitive impairment. Further validation and studies would be useful to better understand ME/CFS pathogenesis.

Neurology

Differential effects of Exercise on fMRI of the midbrain ascending arousal network nuclei in ME/CFS and Gulf War in a model of PEM

Dr James Baranuik, (MD) Georgetown University, Washington discussed study findings of functional MRI scans after submaximal exercise provocation. In particular he looked at which specific midbrain nuclei were affected by exercise in CFS and GWI. Overall findings found that there were no net changes in controls pre and post exercise. Before exercise ME/CFS patients had lower brain activation in the midbrain compared to controls and GWI, consistent with reduced cerebral blood flow. Post exercise ME/CFS patients showed all positive changes to the identified midbrain nuclei whereas GWI patients had the opposite effects of decreased BOLD activation. These opposite dynamic effects imply different pathological mechanisms in ME/CFS and GWI. These findings suggest hypothesis for further study that the ascending arousal network nuclei in the midbrain contribute to PEM in ME/CFS.

A case-controlled study of Brain White matter integrity and its association with fatigue and cognition in adolescents with ME/CFS

Elisha Josev, (PhD) from Murdoch Children's Research Institute in Melbourne, Australia has investigated the brain white matter microstructure in adolescents with a new diagnosis of ME/CFS to

see if there was a difference with healthy controls and whether changes correlate with cognitive function and fatigue.

25 ME/CFS patients and 23 healthy controls with a mean age of 16 years underwent a diffusion-weighted MRI brain scan. Analysis was done to evaluate macrostructure and microstructural white matter changes, along with symptom questionnaires.

Results showed that ME/CFS subjects had greater fatigue with decreased quality of life scores along with poorer cognitive performance. MRI results showed greater white matter fibre cross-section of the left inferior longitudinal fasciculus; however, this was unrelated to ME/CFS symptoms. There were no other differences between patients and controls in macrostructural or microstructural white matter properties.

Literature in adults suggests disturbances in the integrity of brain white matter structure which was not seen in this study. This may suggest that longer illness duration or older age influence changes in the brain structure.

DAY TWO 21/8/21

Immunology

Development of blood biomarker using deviated B cell receptor repertoire in ME/CFS

Wakiro Sato, (MD) speaking from Tokyo, Japan discussed the development of a blood biomarker using deviated B cell receptor (BCR) repertoire in ME/CFS.

BCR repertoire was analysed by next generation sequencing and the bioinformatics tool.

ROC analysis indicated the possibility of distinguishing patients from healthy controls. B cell clones using IGHV3-30 and IGHV3-30-3genes were more frequent in patients with an obvious infectious related episode at onset, negatively correlated with disease duration and correlated to expression levels of interferon response genes in plasmablasts. Analysis of CDR3 length distribution of IGHV3-30/3-30-3 revealed significantly higher frequencies at specific lengths from patients. Measurement of antibodies demonstrated a significantly increased frequency of anti-b1/2 adrenergic receptor in antibody-positive ME/CFS patients. The frequency of IGHV3-30 and IGHV3-30-3 genes are more frequent in these antibody-positive patients. Finally, a new patient group data suggested reproducibility of the BCR repertoire analysis.

He concluded that BCR repertoire analysis could be developed as a valuable tool to help diagnose ME/CFS

Immune dysregulation in myalgic encephalomyelitis/chronic fatigue (ME/CFS) and long COVID-19 syndromes: CD8 T-cell over activation and exhaustion, increased CD4+CD8+ T-cells and aberrant cytokines.

Anna Gil (MD) from Worcester, Mass, USA presented her work and she questioned whether these were the same or related diseases. The reaction to infection was a dysregulated immune response leading to overaction of T cells. The CD8 T cells become active, exhausted, cease

to function properly and then die. The activated CD4:CD8 ratio is increased in both diseases, but less so in long covid.

The possibility of viral persistence and viral protein-mediated immune response both need to be explored. Clinical trials for early interventions that modulate the immune system are needed. The possibility that anti-virals may help was also discussed as therapy.

These studies may identify potential biomarkers and mechanisms driving the immunopathogenesis.

Predictors for Developing Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Following Infectious Mononucleosis

Leonard Jason (PhD) from Chicago, Illinois, USA discussed the predictors for developing severe ME/CFS following infectious mononucleosis (IM). He noted that 5% of college students get IM, and of these 8% go on to have a diagnosis of ME/CFS. Using the DSQ, there are pre-illness changes and therefore one can possibly predict a diagnosis of ME/CFS. Particularly there were significant differences in gastro-intestinal symptoms.

A prediction index had been crafted for 4 groups: Recovered, implied recovered, ME/CFS and severe ME/CFS. The differences predicted the likelihood of severe illnesses. A 6 year follow-up is planned. All this may be relevant for Long-Covid.

Because of the issue of the gastro-intestinal tract in these studies, Jason et al plan to look further at John Chia's work on enteroviruses.

Neurology and Epidemiology

No signs of neuroinflammation in CFS of QFS

Ruud Raijmakers, (MD) Gelderland, Netherlands reported on Q fever syndrome (QFS) and possible neuro-inflammation compared to ME/CFS. Neuroinflammation is driven by activation of microglia. He compared 9 ME/CFS patients with 10 QFS patients and 9 healthy controls. All were female. All were carefully evaluated for confusing variables.

PET scans were performed and the [11C]-PK11195 binding potential (BPND) was calculated.

BPND of [11C]-PK11195 positively correlated with symptom severity scores in QFS patients but a negative correlation was found in CFS patients.

However, because symptoms of neuro-inflammation seem likely in long-lasting ME/CFS and QFS, longitudinal investigation in all post-infectious fatigue patients should be followed.

Cognitive Assessment in Patients with and without Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Gudrun Lange, (PhD) New York, USA discussed cognitive assessment of patients with and without ME/CFS. The objective of their study was to demonstrate the utility of PROsetta Stone's linking metrics (legacy and PROMIS) in ME/CFS.

Both legacy and PROMIS were found to be highly correlated. Linking metrics allow for cross-talking between the two, and if there is a need to change instruments during longitudinal studies, there is consistency.

These measuring instruments were used to measure cognitive function before and after exercise, looking at the effects of post-exertional malaise (PEM). The ME/CFS patients were found to be significantly slower on all measures after exercise.

ME/CFS patients with combined cognition and exercise testing had slower reaction time than those with cognitive testing only. It took up to 15 days to get back to their usual level of function.

The measures used avoided costly and lengthy neuropsychological tests.

Severe and very severe ME/CFS in Norway

Kristian Sommerfelt (MD) from Bergen, Norway, looked at severe and very severe ME/CFS in Norway. This was done using an internet-based survey targeting those with severe and very severe ME/CFS and their carers. 491 patients, of which 47 were classified as very severe were included.

Disease onset was before 15 years of age for 45% of the very severe group, and 32% in the severe group. Disease duration was more than 15 years for 19% in the very severe and 27% in the severe group. The very severe were generally younger. Most common symptoms were fatigue and muscle and joint pain. Sensory intolerance was frequently reported.

The most severely affected were totally bedbound, unable to talk and with dramatic worsening of symptoms after just minimal activity or sensory stimuli. Care and assistance from the health care providers, social services and municipal authorities was often assessed as inadequate, often worsening symptom load and burden of care. Substantial lack of disease knowledge among healthcare providers was reported from patients, while 52% were satisfied with their general practitioner, but few with specialist/ hospital health care. Carers described an extensive burden of care with inadequate help from healthcare providers or municipal authorities. More than 40 hours a week, or a full-time job, was spent among 71% of the carers. They described a large negative impact on their work and financial situation, and mental wellbeing.

He concluded that childhood onset was common in these groups of patients, and there was a dramatic burden of care with little external support for carers. Little social support was available.

A Descriptive Study of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome in the Vaccine Safety Datalink

Elizabeth Unger (MD) from the CDC in Atlanta, GA,USA focussed her talk on a Descriptive Study of ME/CFS in the Vaccine Safety Datalink, within the Kaiser Permanente NW Health System (KPNW). The main aim was to determine the accuracy of ME/CFS diagnosis and to describe the characteristics of the illness. The time frame was 2006-2017.

522 cases were selected, and 73% were female. 200 were randomly selected for further study. Of those reviewed only 3% met the IOM (2015) case definition for ME/CFS. 12% were classified as probable cases. 20% were classified as possible cases.

Mean duration of time between onset and diagnosis in the definite and probable cases was 5 years. In these groups a positive family history was identified in 10% of cases.

The conclusion was that Automated ICD diagnosis codes do not accurately identify ME/CFS cases. Manual chart abstraction is required to confirm accuracy of diagnosis, which is time consuming and requires substantial training.

Clinical cases

Case Presentation: Treating ME/CFS with Aripiprazole

Hector Bonilla (MD), Associate Professor from Stanford University presented a case of a 65-year-old male with a history of ME/CFS for 14 years. This case had severe symptoms with significant functional impairment. He had received an extensive workup and tried many treatments with mild of no improvement in symptoms. He was treated with aripiprazole with a dramatic response after only 2 weeks. He reported that he “felt like a new man” with resolution of non-epileptic seizures, better thought clarity and concentration and decreased fatigue. Dose was gradually up titrated to 2mg daily with sustained response reported over 1 year.

Dr Bonilla then presented a study of 100 ME/CFS patients, with a mean duration of illness of 13 years. They were treated with a mean dose of aripiprazole of 1.2mg (dose range 0.25-2mg). 74.3% of participants showed a response to treatment with aripiprazole, particularly improved fatigue, brain fog and unrefreshing sleep.

Possible mechanisms of action of aripiprazole include decrease in inflammatory cytokines, decreased microglial cell inflammation, immunomodulator function and dopamine mediated mechanisms.

Case Presentation: An unusual case of Mast Cell Activation Syndrome presenting as ME/CFS and pericarditis.

Dr Tania Dempsey (MD) from AIM Centre for Personalised Medicine, New York presented a case of a 63-year-old female with years of progressive allergic-type symptoms and symptoms suggestive of ME/CFS. She subsequently developed pericarditis after treatment with an antibiotic. Symptoms improved with uses of H1 and H2 blockers. Her work up included raised plasma histamine and plasma heparin levels. Diagnosis of Mast Cell Activation Syndrome was made using the Consensus 2 criteria.

Dr Dempsey discussed diagnosis of MCAS which should be considered in anyone whose prior evaluations fail to find any evidence of disease better explaining the full range of findings. MCAS occurs when mast cells “inappropriately” and excessively release chemical mediators that affect the

surrounding tissue. MCAS can overlap with the constellation of symptoms that many patients with ME/CFS suffer from. She proposed further study to evaluate the link between MCAS and ME/CFS.

Case Presentation: ME/CFS and Cranio-cervical Instability

Peter Rowe (MD) from Johns Hopkins University presented a case of a 24-year-old nurse with symptoms of Hypermobile EDS, ME/ CFS, POTS, MCAS and neurogenic thoracic outlet syndrome. Symptoms may have been triggered after a motor vehicle accident or rock climbing. She had a large number of symptoms which included headaches, light-headedness, crepitus in the neck and a feeling of her head feeling unsupported. Symptoms resolved with use of a hard cervical collar.
MRI imaging identified cranio-cervical instability. Subsequent fusion resulted in marked improvement in her symptoms.

Dr Rowe discussed the symptoms and examination findings of cranio-cervical instability, which should be considered in patients with hypermobile EDS, which can cause ligament instability at the base of the skull leading to neck pain exacerbated on flexion, visual changes, fatigue, and autonomic dysfunction. Patients often report that their head feels heavy and unsupported. Neck muscle strengthening is first line treatment with fusion only required for severe and refractory symptoms.

Case Presentation: Oxaloacetate Supplementation provides hope of fatigue amelioration in ME/ CFS

Dr David Kaufman (MD) from Centre for Complex Diseases presented a preliminary pilot study on the use of oxaloacetate for symptom relief in ME/CFS. A previous study in 2017 showed a depletion in oxaloacetate in ME/CFS. Oxaloacetate is known to have widespread functions in normal metabolism.

Dr Kaufman has done an initial study of 41 ME/CFS patients. 20 patients received 500mg oxaloacetate twice daily and 21 patients received 1000mg twice daily. Patients were surveyed using 3 different fatigue scores before, during and after treatment at 6 weeks. Results showed a significant reduction in fatigue within 2 weeks with a further drop in fatigue after 6 weeks. 80.8% of patients in the case study had a decrease in fatigue greater than historic fatigue levels. Patients have continued to feel better with ongoing use over 6-8 months. Use of higher doses gave even better results. The medication was very well tolerated with minimal side effects of mild GORD and insomnia. The medication has been shown to be safe at levels to 1000mg twice daily in multiple clinical trials for other conditions. Oxaloacetate is classified in the US as a medical food and is available online. Cost at higher doses may be prohibitive for many patients.

This exciting pilot study needs to be validated with a gold standard trial. The main challenge is obtaining funding for such a study.

Provocation studies 2

Two symptoms accurately identify PEM in ME/CFS

Todd Davenport (DPT) from the University of the South Pacific discussed his group's study findings that help to diagnose post exertional malaise more accurately. This is important as prior studies have found that people who did not recover from cardiopulmonary exercise testing (CPET) are >11 times more likely to have ME/CFS. PEM can be difficult to diagnose by practitioners and therefore identifying a simplified clinical prediction tool may lead to improved diagnostic accuracy of PEM and ME/CFS.

In the study, 49 ME/CFS patients and 10 controls underwent 2 CPET 24 hours apart. The participants then completed open ended symptom questionnaires on 5 different occasions. Results of analysis found that only 2-4 symptom categories were needed to make an accurate diagnosis of PEM. There were two symptoms that were identified, post-exertional decrease in function and lack of positive feelings or mood in response to exercise, that consistently identify people with ME/CFS compared to controls.

Progression of PEM in ME/CFS patients from a Plasma Metabolomics Perspective

Dr Arnaud Germain (PhD) from Cornell University presented his study of 60 ME/CFS patients and 45 controls. Study participants undertook cardiopulmonary exercise testing and had longitudinal blood sampling done. Plasma was analysed by Metabolon using a global metabolomics panel including 1157 compounds.

Results showed different metabolic response to exercise between controls and ME/CFS patients. There were also differences between males and female ME/CFS patients. The majority of the significantly different metabolites were lower than in control subjects, supporting the possible theory that ME/CFS is a hypometabolic (hibernation) condition. There was also over representation of currently unknown metabolites in the ME/CFS group, possibly suggesting that currently unidentified/ unknown metabolites may have a role in ME/CFS.

Physiological effects of a repeated 5-minute exercise challenge in individuals with ME/CFS

Lynette Hodges (PhD) from Massey university in New Zealand presented the findings of her study of 11 ME/CFS patients. Study participants completed three testing sessions including CPET and two 5-minute exercise challenges at aerobic threshold., measuring heart rate variability. Her findings showed that ME/CFS patients were only able to achieve 84% of age-predicted maximal heart rate response and BP response. Repeated exercise challenge did not change heart rate variability. Completing CPET and also 5-minute exercise challenges showed that both resulted in a prolonged recovery phase. Providing an exercise prescription to patients with ME/CFS needs to very cautious as exercising at higher heart rates based on usual age-predicted heart rate calculations are more likely to lead to PEM. Heart rate would be more accurately calculated from a CPET.

Conclusion

The conference was wrapped up by **Dr Lily Chu**, vice-president of IACFS, who thanked everyone for helping to make this conference such a success. She was ably assisted by a team of over 100, and there had been 380 attendees from all around the world at this conference. The enormous amount of work involved in hosting such an event (without a hitch) is to be applauded. Lily was hopeful that the next IACFS conference planned for New York in 2022 will allow live attendance, so that the ever-growing team of ME/CFS scientists, clinicians and their patients can meet up again and revive many old friendships.

We would like to thank the IACFS and their team of organisers for the opportunity to participate in this global event. We would also like to thank ANZMES for funding our attendance.

Sarah Dalziel (Rotorua) and Rosamund Vallings (Auckland), New Zealand

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