

IACFS Conference, New York 2022

Report by Drs Sarah Dalziel and Rosamund Vallings

DAY 1

Two Workshops were presented:

CARING FOR LONG COVID PATIENTS

Hector Bonilla (Stanford University, USA) and R.Jane McKay (University of BC, Canada).

In British Columbia, Patients were followed up for 18 months. There were 5 multidisciplinary clinics involved in care, education and research. Patients had many symptoms. 10% of the Long Covid patients were diagnosed with ME/CFS. Teaching tools for management were developed, and this was available on their website.

At Stanford, 300 patients were enrolled in the Long Covid clinic. There was a wide age range. Patients had many symptoms, particularly fatigue, post-exertional malaise and brain fog. Many struggled to care for themselves and avoided many daily activities.

The mean age was 47, and nearly half had a high BMI. 50% of the patients had comorbidities. The illness was more common in females, and after 6 months, there was still a wide range of symptoms. It was noted that 2% of the population in the UK is getting Long Covid.

The immune system was described as “haywire”. Minute blood clots were found and there was evidence of viral persistence. Covid was associated with dysautonomia in 50% of the patients.

Recommendations were to pace very carefully from the very beginning of the illness. There is a need to educate GPs and support groups have proved useful.

DYSAUTONOMIA WORKSHOP

Report by Dr Sarah Dalziel:

Dysautonomia Workshop Dr Lauren Stiles Stonybrook University

Dysautonomia is an umbrella term for dysfunction of the autonomic nervous system. Damage can be structural (damaged or missing nerves) or functional (nerves are intact but are not working properly)

There are many causes of dysautonomia including diseases such as Parkinsons, Sjogrens, diabetes and other small fibre neuropathies. Other causes are syndromes such as neurocardiogenic syncope, POTs, ME/CFS, fibromyalgia, chronic migraine, gastroparesis/ IBS, interstitial nephritis

Dysautonomia affects a large number of people
60% of Parkinsons
25% Diabetics

50% Sjogrens

Large number of post covid patients

Autonomic nervous system regulates the function of many organs

It also influences blood volume, CSF volume, immune function, connective tissue synthesis and repair, pain perception, glucose metabolism, iron metabolism and gland function

Symptoms predominantly related to an overactivation of the sympathetic system

Orthostatic symptoms- fainting, lightheadedness, fatigue, exercise intolerance, dyspnoea, chest pains

Brain fog

GI dysmotility

Dry eyes and mouth

Abnormal sweating

Upper trunk/ facial flushing

Acrocyanotic legs- purple dusky discolouration when legs hanging down with delayed cap refill

Coathanger pain

TESTING

Standard and gold standard test is TILT TABLE, partic with ECG and beat to beat BP monitoring

Alternative is 10 minute STAND test- not as detailed, can have interference of results from venous valves and muscle pump

Can miss subtle autonomic defects

Risk fainting

COMPASS score (composite autonomic symptom score) is a symptom score chart. Can also use this to review symptoms/ checklist

Looks at 6 different domains: orthostatic, vasomotor, secretomotor, pupillomotor, GT, Bladder

VOSS; Vanderbilt Orthostatic symptom score

DYSAUTONOMIA IN ME/CFS

First described by Dr Peter Rowe and Dr Hugh Calkins in 1995

7 adolescents with chronic PEM, tilt table induced significant hypotension in all 7

4 had prompt improvement in fatigue when treated with atenolol or disopyramide

Peter Rowe also discovered high rate OI in Ehlers Danlos

In ME/CFS- dysautonomia types described are:

Vasovagal syncope/ neurocardiogenic (fainting)

Initial orthostatic hypotension

Delayed orthostatic hypotension (occurs after 3 minutes)

POTs

Neurally mediated hypotension- also occurs after 3 min

Orthostatic intolerance is term used when don't meet criteria for POTs or orthostatic hypotension

Chronic lightheadedness and other symptoms due to upright posture, due to blood flow problem.

See only mild instability in pulse/ BP on tilt table testing

POTs/ MECFS overlap

48-77% of patients with POTs have ME/CFS

19-70% ME/CFS patients have POTs

67% Long covid patients have mod-severe dysautonomia, predominantly POTS
The most common underlying disease causing POTS is Sjogrens

Heart rate variability in MECFS - Spanish study 45 patients, 25 Controls
Reduced heart rate variability predicts fatigue severity.
HRV is a measure of autonomic nervous system functioning

Underlying cause of dysautonomia- unknown
See later lecture for recent study findings on possible autoimmune and autoinflammatory causes

TREATMENT

www.dysautonomiainternational.org/salt

POTS is the model that is used for treating all types of dysautonomia

UK study 135 ME patients

Assessed activities of daily living score, fatigue scale and orthostatic grading scale
Found that orthostatic symptoms/ autonomic dysfunction is the key symptom to impact on functional ability.

Treatment focussing on treatments for dysautonomia makes an impact on functional score, despite still feeling fatigued.

Non pharmacological treatment

Salt 10g/ day (3816mg sodium)

Fluids 2-3L / day. Avoid sugary drinks – see other lecture notes re: glucose metabolism links

Medical compression stockings

Abdominal binders/ Spanx

Recumbent exercises

Good sleep habits

Healthy diet

Cooling vests

Avoid heat, prolonged standing , hot showers, alcohol

Education to help manage symptoms. Build coping skills to help with things that can not be treated

Exercise:

Harvard study of 77 POTS patients (did not have ME/cFS)

Supervised exercise programme improved QOL and at 6/12 77% no longer met POTs criteria, although they still felt fatigued.

Exercise is very helpful for POTS however needs to be balanced with pacing approach for ME/ CFS

Practical POTS exercise approach:

Start slow and low

Hydrate and medicate before exercise

Avoid orthostatic stress during exercise until tolerance builds up

Can feel worse before better

Exercise in bed, gentle stretching, yoga, floor/ core, aquatherapy, recumbent bike, rowing

Consistency is more important than intensity and duration

Learning how to pace takes time

Structured programme helps eg: OT, physio

HOW OCCUPATIONAL THERAPY CAN INCREASE FUNCTION AND QUALITY OF LIFE FOR ME/CFS PATIENTS

**Amy Mooney, MS, OTR/L; Melida Maxwell, PT, MA; Sallie Rediske, MPT, WCS
Independent Consultant, USA; ME/CFS PT/OT Facebook Group, USA; PT/OT
Resources for Treating ME/CFS, USA**

Content: This workshop will examine occupational therapy and the unique role OTs can offer in symptom management and treatments for people with ME/CFS. Occupational therapy utilizes multi-system treatment approaches to improve quality of life for individuals with ME/CFS specific to home, work, school, and community environments. The workshop will examine how OTs support PwME in symptom management, develop treatment strategies and provide resources for ongoing care plans. The presentation will describe pacing strategies and perform task analysis for severity specific levels.

DAY 2.

Key note address DAVID SYSTROM

- Harvard pulmonologist and co-leader of the OMF-funded Harvard Collaborative ME/CFS Center presented the keynote address for the conference.
- The invasive exercise testing Systrom employs in ME/CFS was first used to assess exercise intolerance in heart and lung disease. About 7 years ago, though, Systrom began to use it to dig more deeply into people who did not have heart or lung problems but exhibited a mysterious exercise intolerance.
- The one overriding dysfunction Systrom sees in ME/CFS – and he has now tested many people with ME/CFS – is something called “preload failure” which refers to an inability to provide enough blood to the heart for it to fill properly. Preload failure reduces cardiac output – and the amount of blood provided to the muscles during exercise.
- Two types of preload failure are found: low-flow and hi-flow. Low-flow appears to be caused by problems with the veins – which carry most of the blood in

the body – from constricting enough to force large amounts of blood back to the heart during exercise.

- In hi-flow patients, enough blood is getting back to the heart, but the muscles aren't taking up enough oxygen when it reaches them to fully power them. This appears to be caused by either a shunt that transfers arterial blood to the veins *before* it reaches the muscles and/or by damage to the mitochondria.
- After Systrom found mitochondrial dysfunctions in the muscle biopsies of patients who exhibit problems with systemic oxygen extraction, Astellas – a Japanese firm – funded an \$8 million clinical trial of a mitochondrial enhancer in ME/CFS. That trial is winding up.
- Similar percentages of small fiber neuropathy (40-50%) have been found in ME/CFS, FM, POTS, and long COVID (!) – suggesting the same process is killing the small nerve fibers in all these diseases. (That percentage rises when deeper nerves are assessed).
- Small fiber neuropathy could explain many of the issues in these diseases, but a study did not find a correlation between the extent of SFN and exercise problems in ME/CFS. Still, deeper nerves need to be assessed as does the functioning of the small nerves that remain. Systrom believes that poor functioning of the remaining small nerves could explain much.
- Systrom is assessing whether an immune response called “TRAIL” that kills damaged cells could be killing off the small nerve fibers in ME/CFS and other diseases.
- Systrom's exercise studies indicate that, physiologically, very similar responses to exercise are seen in long COVID. That's great news given the funding going into long COVID.
- Systrom's cytokine analysis indicates that a “who's who of pro-inflammatory cytokines” gets activated in the post-exercise period in ME/CFS. This inflammatory response could be producing much damage, including to the mitochondria – and helps explain the drop in energy production from one exercise test to the next.

- The Q&A session elicited some of Systrom's most interesting observations. He is agnostic on oxygen therapy but could envision how it could work in ME/CFS. The Warburg effect – which describes a weird situation in which cells in high-oxygen environments employ anaerobic energy production – could fit as well. Systrom is also trying to work himself out of a job, so to speak, by finding a molecular stand-in for his invasive oxygen tests that could easily identify preload failure in people with ME/CFS. After doing thousands of invasive exercise tests – which only last 5 minutes – Systrom could only count a handful of people who had had serious side effects. Finally, when his patients respond to orthostatic intolerance drugs like Mestinon, Systrom is able to use a carefully crafted graded exercise approach that starts with recumbent exercise, to help them gain functionality.
- Thanks to an 800K grant from the Open Medicine Foundation – Systrom is about to begin a large study that HR will report on shortly.
- Systrom ended on a hopeful note, stating that he does not view anyone with ME/CFS as permanently ill...he sees everyone as potentially treatable.

Provocative Manoeuvres – methods to induce symptomatic features of ME/CFS

After the introductory keynote address by David Systrom, the following session covered provocative methods to induce the symptomatic features of ME/CFS. 6 different presenters talked about their work in this field:

J.Mark Van Ness (University of Pacific, USA). His team does a 2-day CPET during graded exercise to observe post-exertional changes at anaerobic threshold and maximal exertion. A 2nd test was done 24 hours later. Day 1 was on a good day, and Day 2 was done in a PEM state. Most people took 7-10 days to recover. One litre of normal saline, IV, helped promote recovery. Results were abnormal on day 2 with a PEM decline. There was decline in fatigue, metabolism, cardiac output, pulmonary function and vascularity.

Peter Rowe (Johns Hopkins University, USA). Uses the Tilt Table. He did measurements pre-test, supine, stage 1 upright and Stage 2 optimal. The latter may provoke syncope.

Heart rate and blood pressure showed evidence of orthostatic intolerance. There were changes in cerebral blood flow velocity, total cerebral inflow or end tidal carbon dioxide. This may all provoke worse symptoms. Two litres of warm saline helped. Those with severe illness may not tolerate the test, and those under 10 years old may not co-operate.

Patients were compared to controls. Symptoms were provoked in patients. There was a high incidence of reduced brain blood flow and cognitive decline. Symptoms were still present at 7 days post-test.

Lucinda Bateman (Bateman Horne Centre, USA). Explained the NASA Lean test, which is suitable for clinicians to use. Patient rests for 20 minutes and then stands leaning back against wall for 10 minutes. 10 minutes is needed for rest and recuperation. Heart rate, BP and pulse are monitored plus other physical signs and symptoms. There is risk of syncope.

The goal is to guide and document treatment. Occasionally the healthy controls show masked vasovagal syncope.

Dane B Cook (University of Wisconsin, USA). Uses MRI during cognitive stimulation. He measures fatigue, cognitive performance, reaction time, cardiopulmonary responses to exercise, PEM experienced etc. He uses tests of PASAT. Tests are administered rapidly to gauge mental fatigue. Exercise is utilised also to see symptom increase.

It is evident that ME/CFS patients have up to severe mental fatigue with up to ten times increase in symptoms over following week. Cognitive errors increase significantly after exercise.

Alan Moreau (University of Montreal, Canada) Had done a longitudinal study of PEM. He used Maestro-ME testing (A Multi-Omics Study of ME/CFS). **Many blood and urine samples were tested plus brain oximetry. Neurocognitive testing was also undertaken. He talked of this being a new molecular diagnostic test for ME/CFS, showing much down-regulation post stress test.**

Luis Nacal (University of BC, Canada). He used a hand grip strength protocol. This could be a potential clinical marker for ME/CFS and is a clinical marker of fatigue. This test showed firm signs of decline in ME/CFS, and correlated with severity of symptoms. It was much lower than in healthy controls and those with cancer fatigue. He concluded that hand grip can be used as a marker of disease severity in ME/CFS.

IMMUNOLOGY .

Inhibition of Autophagy Induces Chronic Fatigue in Mice: A Potential Mouse Model to Study ME/CFS

Avik Roy, PhD Simmaron Research Inc, WI, USA

Conclusion: Our research previously demonstrated that inhibition of autophagy is clinically relevant to muscle fatigue in ME/CFS patients. Our current finding revalidates that a drug-induced inhibition of autophagy truly establishes fatigue in mouse model.

Investigating T-cell Populations for Immune Cell Exhaustion in ME/CFS Using Flow Cytometry

Jessica Maya, PhD Candidate Cornell University, NY, USA

Conclusion: Our data suggests that T cell exhaustion is present in some PWME, compared to healthy controls. Continued work includes analyzing additional CD4+ T cell subsets for a wider array of inhibitory factors and performing correlation analyses on our data and ME/CFS clinical data.

Immune Comparison of Male and Female ME/CFS Patients

Kristina K Aenelle, PhD Miami VA Healthcare System; FL, USA

Conclusion: Our study found evidence of chronic EV infection of the brain neurons without excessive inflammatory cells or glial activation by IPOX. MDA5 gene activation is more prominent than Rig-1, and TLR3, 7 gene upregulation are consistent with response to EV-specific dsRNA and ssRNA, respectively. A number of neurons are undergoing apoptosis, with presence of intracellular β -IFN production and few cells with A β . This paper provides an immuno-pathological explanation for patient's debilitating neurological symptoms.

METABOLISM

Feasibility of investigating oxygen consumption (VO₂), heart rate variability, blood pressure and lactic acid levels of people with myalgic encephalomyelitis during normal daily activities.

Nicola Clague-Baker, PhD University of Liverpool; Liverpool, England

Conclusion: Physiological measurement during everyday activity is feasible for PwME with mild to severe disability. The outcome measures identified abnormal physiological changes in all PwME. Further research is needed to develop diagnostic and possible treatment protocols.

Pre-Illness metabolomics data among college students following mononucleosis and ME/CFS reveals differences in multiple metabolites and metabolic pathways

Leonard Jason, PhD DePaul University; IL, USA

Conclusion: Our study analyzed baseline, pre-illness data from college students, some of whom went on to develop S-ME/CFS following Infectious Mononucleosis and some of whom recovered. The pathways that differed between cases and controls are essential for proliferating cells, particularly during a pro-inflammatory immune response. These changes are consistent with the elevations in pro-inflammatory cytokines that we (Jason et al., 2021) have reported for patients fated to develop S-ME/CFS 6 months after IM. Alterations in these pathways are also potentially consistent with previous reports of changes in energy production, nucleotide metabolism, TCA metabolism, and reactive oxygen species pathways in adults with ME/CSF (Yamamoto et al., 2004, Armstrong et al., 2014; Germain, Ruppert, Levine, & Hanson., 2017; Nagy-Szakal et al., 2018; Naviaux et al., 2016).

Urine metabolomics exposes anomalous recovery after maximal exertion in ME/CFS female patients 41

Katherine Glass, PhD Cornell University; NY, USA

Conclusions: Despite a small sample size, significant differences in urine metabolites emerged between ME/CFS patients and controls after CPET. The urine metabolome was altered in controls but not in patients 24 hours following exercise, indicating disrupted metabolic recovery in patients. Ongoing work includes investigating correlations between metabolites and ME/CFS clinical data and multivariate analyses.

METABOLISM/CO-MORBID CONDITIONS

Dysfunctional cerebrospinal fluid metabolites and lipids infer white matter dysfunction in ME/CFS and mitochondrial dysfunction in Gulf War Illness (GWI)

James Baraniuk, MD Georgetown University; DC, USA

Conclusion: Elevation of cerebrospinal fluid lipids implicated myelin and white matter dysfunction in ME/CFS, while elevated phosphatidylglycerols in GWI may implicate mitochondrial dysfunction.

Gender matters: perceived burdensomeness increased in males with chronic invisible illness

Cathy Pedersen, PhD Wittenberg University; OH, USA

Conclusion: Providers caring for chronically ill patients with suicide risk need to consider the impact of perceived burdensomeness in medical and psychological treatment. Furthermore, the impact of gender on one's feelings of perceived burdensomeness provides a new lens for both the treatment and understanding of suicide risk.

Do people with joint hypermobility represent a subgroup of myalgic encephalomyelitis/ chronic fatigue syndrome?

Kathleen Mudie, MSc Solve ME/CFS Initiative; CA, USA

Conclusion: By describing baseline characteristics of a large ME/CFS cohort, we hope to supplement what is known about this population's clinical and lived experiences, as well as their efforts towards successful diagnosis and treatment, and to identify any etiologic signals that could support prevention and treatment. This baseline analysis also serves as a first step in characterizing the stability and variability of these patient measures over time

DAY 3.

INFECTIOUS DISEASES

Dysbiosis in the gut microbiome accompanies skewed immunological and clinical parameters in patients with ME/CFS.

Daiki Takewaki, MD, PhD National Institute of Neuroscience; Kodaira, Japan

Conclusion: We revealed the characteristics of gut microbiomes in patients with ME/CFS and identified the specific microbial components significantly associated with various immunological and clinical parameters.

Phage borrelia qPCR in ME/CFS patients

Kenny L. Meirleir, MD Whittemore Peterson Institute/ University of Nevada/ Himmunitas Foundation; Reno, USA & Belgium

Conclusion: Recently developed methods to detect Borrelia were applied on a cohort of ME/CFS patients with no history of tick bites nor Borrelia infection. Not Lyme disease, but other Borrelia species seem to be the triggers or persistent infections in the majority of ME/CFS cases.

CLINICAL CASE PRESENTATIONS

A severe illness for the long-haul: patient experience, novel treatments, and current state.

Melissa Siller, BA Susan Levine, MD - Private Practice; USA

Content: A 62-year-old female patient with a history of cancer during childhood, who lived a very active and athletic lifestyle, presented with a cough, sore throat, and fatigue continuously for three months, as well as acute chest pain, beginning in early March 2020. The patient self-medicated with Amoxicillin, but then began experiencing trouble breathing, chest and head pain, worsening fatigue, lightheadedness, chills, dry eyes, and light sensitivity. She did not, however, have a fever or gastrointestinal symptoms. After one month, the patient experienced a 75% improvement in symptoms and began trying to return back to an active lifestyle by running. However, she felt deconditioned, had difficulty with proprioception, and got very fatigued after running short distances. The following month, patient reported intense worsening of symptoms and onset of new multi-systemic symptoms, including brain fog, body aches, chills, tingling and burning in the head, face, and shoulders, tachycardia, dysautonomia, sunken eyes, whole-body stiffness, bloating, acid reflux, tinnitus, rashes, sleep disruption, skin sensory sensitivity, skin discoloration, and tooth pain. After a few months of seeking answers, the patient found a doctor who attempted multiple novel medications including mast cell stabilizers and antiretroviral medication, while the patient took an OTC protease inhibitor. She noticed a moderate improvement in rashes, light sensitivity, and dry eyes after a month, but no improvement in other symptoms. Patient developed a tooth infection and received three rounds of antibiotics and a root canal. A year later, the patient has mild improvement in symptoms but is still disabled. She particularly notes that she gets very fatigued 36 hours after physical or cognitive exertion, can only manage basic activities in small time periods, and symptoms worsen throughout the day.

Can discordant identical twins become concordant for ME/CFS?

Lucinda Bateman, MD, MS Bateman Home Center; USA

Content: An identical twin became ill with ME/CFS at 17 and never recovered. The "healthy twin" married and had children. At 40, the ME/CFS twin crashed severely during the pandemic, trapped in another state, visiting healthy twin at her active home. At age 41, later in the pandemic, the healthy twin experienced a frightening change in health. Interventions needed for both mental and medical health issues, both twins, will be discussed. Format: Case presentation and discussion

Insights for the provision of long COVID psychotherapeutic care: a case report

Leigh Jerome, PhD University of Hawaii; HI, USA

Content: Laura G., a 38-year-old architect/ high intensity athlete, enjoyed a productive NY lifestyle with strong family/social ties & without medical/mental health pre-conditions. In March, 2020, Laura developed respiratory symptoms & fatigue. She received a pneumonia diagnosis at the ER but no COVID tests were available at that time. Laura slowly recovered. When her acute symptoms abated she went out for a few runs & subsequently became bedridden with a myriad of neurological and vascular symptoms. She presented to her PCP with a litany of persistent symptoms, sick for 2 years now & unable to work.

PROVOCATION STUDIES 1.

Recovery from 2-day cardiopulmonary exercise testing in persons with ME/CFS

Geoffrey E. Moore, MD Ithaca College/ Cornell University; NY, USA

Conclusion: These data indicate that the 2-d CPET exacerbates symptoms of ME/CFS for a prolonged period of time compared to Controls, with a mean recovery time of 12 days. Whereas, according to the serial SSS scores, risk of failure to recover following 2-d CPET was very low for ME/CFS (1 of 85 ME/CFS).

Physical activity levels in ME/CFS before and after a 2-Day cardiopulmonary exercise test protocol

Candace N. Receno, PhD Ithaca College; NY, USA

Conclusion: Preliminary data suggests those with ME/CFS spend a large portion of the day in sedentary activities and less time in moderate to vigorous activities compared to their healthy counterparts. Data analysis is ongoing with a larger sample size of ME/CFS and HC to further elucidate effects of exertion on PA level in ME/CFS. Stay tuned!

IMMUNOLOGY OF LONG COVID

Keynote address on Immunology of Long Covid

Akiko Iwasaki (Yale, USA)

- This account produced by Cort Johnson covers Iwasaki's immunology presentation, which started off the keynote session. Iwasaki is an accomplished immunologist who, with David Putrino, jumped on long COVID early.
- A mouse study found that a mild COVID infection in mice that does *not* reach the brain produces significant central nervous system damage including microglial activation, neuroinflammation, and damage to the myelin coverings of the nerve axons, particularly in the hippocampus region of the limbic system. Some evidence of myelin problems and neuroinflammation has been found in ME/CFS.
- She relayed the results of an unpublished study that assessed long-term long-COVID patients who had been sick for an average of 400 days.

- A large study of long-COVID patients who'd been sick *for well over a year* found numerous immune aberrations including high levels of monocytes, exhausted T-cells, and the presence of double-positive T-cells.
- High levels of anti-coronavirus antibodies indicated that even after all this time, the patients' immune systems were still responding to the virus – either because it or parts of it were still present, or because an autoimmune or inflammatory response to it remained.
- The coronavirus wasn't the only virus the immune system was responding to – high antibody levels and markers of activation suggested that herpesviruses, in particular, EBV and varicella-zoster, have become reactivated and were possibly having major effects.
- The factor that REALLY differentiated the long-COVID patients from the healthy controls, though, was low cortisol. Iwasaki called the low cortisol levels “highly predictive” and noted that they alone were enough to determine who had long COVID and who was healthy.
- Low cortisol levels were also predictive of severity: the lower the cortisol levels – the worse off the long-COVID patient was. Normal ACTH levels left the reason for the low cortisol levels a mystery. Autoantibodies that are whacking the hypothalamus/pituitary are a top hypothesis and she is looking for them now.
- The cortisol and EBV findings fit very well with ME/CFS. They also fit well with what we know of overtraining syndrome in which a plethora of endocrine abnormalities including reduced cortisol and hypometabolism have been found. Low cortisol has also been found in fibromyalgia.
- This is the second major long-COVID study to find evidence of low cortisol and EBV reactivation.
- Iwasaki is interested in doing a similar ME/CFS study but doesn't have funding for it.

The Keynote Address by Akiko Awasaki was followed by 3 presentations:

Ali Boolani

Clarkson University USA spoke about identifying the prevalence of ME/CFS diagnosis post-Covid and pre-existing conditions that might increase the likelihood of a positive ME/CFS diagnosis. He ran logistic regression analysis. The predictors were not strong. Caucasian males were the most likely candidates, and immunosuppression was an important variable.

Lisa Selin

University of Mass, USA

Found that CD4/CD8 T cell exhaustion was present in Long Covid, and aberrant cytokines such as those seen in ME/CFS were seen in Long Covid. There was also evidence of CD8-Tcell exhaustion as seen in infectious mononucleosis.

When comparing ME/CFS and Long Covid with healthy controls she found symptoms were very similar.

The drug Inspiritol (an anti-oxidant) was trialled. This is taken by inhaler, goes direct to the brain and has been shown to be useful in ME/CFS. 4 post-Covid patients improved with this treatment. There were no serious side effects.

Deborah Duricka

(Neuroversion Inc, USA)

Presented her work using stellate ganglion block to improve symptoms of Long Covid.

She described Long Covid as having many symptoms, which were reduced by use of stellate ganglion block. Local anaesthesia was used around the vertebral artery and involved cranial nerves. Clinical improvement was seen 95% of the time. The treatment prevents vaso-contraction in the carotid and vertebral arteries, thus promoting better blood flow.

PUBLIC HEALTH 1

How to ensure the voice of the severely affected ME/CFS patient is heard in research

Helen Baxter 25% ME Group; Scotland, UK

Conclusion: When people with very severe ME/CFS are made aware research is being undertaken and the necessary support is provided, without time constraints, they can make invaluable contributions.

Identifying healthcare system barriers impacting the care of Canadians with myalgic encephalomyelitis

Rosie Twomey, PhD University of Calgary; Alberta, Canada

Conclusion: ME/CFS is a condition in which self-reported symptoms are important to the history taking, diagnosis and treatment. Indeed involvement with all social institutions requires written or verbal communications. Accuracy of wording is important across many interactions with various institutions and erroneous language can cause adverse outcomes or errors. The participant stories identified an impeded ability to fully explain themselves, or select terminology, phrases or descriptors that conveyed their symptoms or experiences accurately, or appropriately. These issues impacted their interactions with various institutions and at times resulted in erroneous information and perceptions which, on occasions, created errors and other difficulties. For those interacting, such as healthcare practitioners or researchers, awareness of such issues would be essential to ensuring steps are put in place to check information or adapt methods to obtain information.

ME/CFS: Limitations of Vocabulary and Language

**Geoffrey Hallmann, BBus(Hons), LLB(Hons), DipLegPrac, DipFinPlan, LLM(Ent.Gov),
MClinEpid, MPH Southern Cross University; NSW, Australia**

Conclusion: ME/CFS is a condition in which self-reported symptoms are important to the history taking, diagnosis and treatment. Indeed involvement with all social institutions requires written or verbal communications. Accuracy of wording is important across many interactions with various institutions and erroneous language can cause adverse outcomes or errors. The participant stories identified an impeded ability to fully explain themselves, or select terminology, phrases or descriptors that conveyed their symptoms or experiences accurately, or appropriately. These issues impacted their interactions with various institutions and at times resulted in erroneous information and perceptions which, on occasions, created errors and other difficulties. For those interacting, such as healthcare practitioners or researchers, awareness of such issues would be essential to ensuring steps are put in place to check information or adapt methods to obtain information.

PROVOCATION STUDIES 2

Plasma proteomics reveals a distinct response to maximal exercise and recovery pattern between females and males ME/CFS subjects

Arnaud Germain, PhD Cornell University; NY, USA

Conclusion: Distinct sex-differences in plasma proteomics were observed at baseline, through maximal exercise, and after a 24-hour recovery period. These results concur with recent plasma metabolomics data from our lab showing sex- and exercise-dependent variations for pwME when compared to controls. The sex-disparity is especially important to take into consideration when assembling any future ME/CFS cohort.

Comprehensive gene expression profiling of the immune system in ME/CFS

Andrew Grimson, PhD Cornell University; NY, USA

Conclusion: This study identifies specific immune cells that are dysregulated in ME/CFS, and those that are not. The identities of the differentially expressed genes and gene sets within the dysregulated cells suggest novel paradigms for understanding ME/CFS.

DAY 4 – 30.7.22

Postural Orthostatic Tachycardia Syndrome Research Update & Review of Autonomic Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Lauren Stiles, JD Dysautonomia International; NY, USA

Content: This session will review the diagnostic criteria and pathophysiology of POTS, and will provide an update on current POTS research. The session will also review the role of autonomic nervous system dysfunction in ME/CFS.

Lauren Stiles from StonyBrook University presented an update on POTS. She discussed the diagnostic criteria for POTS, which was agreed upon at in 2019 at an NIH expert consensus meeting. POTS has now been given an ICD-10 code G90.A. She outlined the various funding streams for POTS research, noting that POTS received even less funding than ME/CFS.

An update on recent POTS research was discussed. In particular she presented research findings from Dr David Kem (University of Oklahoma), showing a probable autoimmune basis for POTS. Research has identified that >90% of POTS patients have adrenergic and angiotensin receptor antibodies using functional cell receptor based assays. These antibodies appear to have a sympathetic activating role. It was noted that using readily available CellTRENDS assays are not an accurate as many healthy controls also had a high +ve rate of these antibodies.

Other research from University of Toledo has suggested an immune dysregulation basis for POTS. A study of 34 POTS patients showed that 85% have a platelet storage pool deficiency, which is believed to be immune regulated.

There is also glucose dysregulation in POTS with findings showing an increase in C Peptide levels in a small study of POTS patients who were given a glucose load.. This also causes an increased propensity to insulin resistance.

Furthermore there is an increase in GIP which is a potent vasodilator. GIP is released after eating carbohydrates and it has been shown that after glucose consumption there is increased vascular pooling. This correlates with anecdotal reports that eating carbohydrates can trigger POTs symptoms, with the advice to try a low carbohydrate diet and/ or smaller, more frequent snacks.

Therapeutically there have been 5 trials testing vagus nerve stimulation in POTs. This is administered through the ear concha using a TENS machine with an ear clip, or a NEMOS device originally designed for seizure control. Generally this is done for 2-6 minutes per day, with better results using the right ear. Studies show decrease in orthostatic symptoms, decrease in orthostatic tachycardia and when used long term a reduction in more damaging inflammatory effects. Mestinon also has a vagus nerve stimulating effect.

A useful link for patients with healthy high salt diet tips : www.dysautonomiainternational.org/salt

(Dr Sarah Dalziel)

IMMUNOLOGY/ INFECTIOUS DISEASES 2

Immune-related profiles of long COVID patients in the Japanese population.

Wakiro Sato, MD, PhD National Institute of Neuroscience, National Center of Neurology and Psych; Tokyo, Japan

Conclusion: Substantial frequency of Long COVID patients in Japan showed immune profile abnormalities and autoantibodies to GPCRs, suggesting similar immune pathology to ME/CFS.
Funding: Supported by the Health and Labor Sciences Research Grants for Comprehensive Research on Persons with Disabilities from the Japan Agency for Medical Research and development, AMED of Japan and Intramural Research Grant (1-5) for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry.

Elevated ATG13 in serum of patients with ME/CFS stimulates oxidative stress response in microglial cells via activation of receptor for advanced glycation end products (RAGE)

Gunnar Gottschalk, PhD Simmaron Research Inc.; WI, USA

Conclusion: 1. Impairment of autophagy in ME/ CFS patients 2. Elevated ATG13 in patients' serum samples. 3. ATG13 is metabolically inactive and induces ROS and nitrite in microglial cells via activation of the RAGE receptor. 4. ATG13 could be a diagnostic marker in ME/CFS.

EBV and HHV-6A dUTPases contribute to ME/CFS by exacerbating TFH cell differentiation and extrafollicular antibody responses.

Brandon Cox, PhD Candidate The Ohio State University; OH, USA

Conclusion: Altogether, our data indicate abnormal GC activity in ME/CFS patients and highlights a mechanism by which EBV- and HHV6-dUTPases may alter GC and extrafollicular antibody responses

TREATMENT

An international survey of experiences and attitudes towards pacing using a heart rate monitor for people with ME/CFS

Nicola Clague-Baker, PhD University of Liverpool; Liverpool, England

Conclusion: Pacing with a HRM is beneficial for PwME leading to more understanding of their ME and PEM and increased activity in some people. HCPs need to learn about and support PwME to use pacing with a HRM.

Stellate ganglion block (SGB) improves symptoms of ME/CFS: a case series

Luke Liu, MD Neuroversion, Inc.; AK, USA

Conclusion: Multiple bilateral SGB treatments improved symptoms in all ME/CFS patients treated. Intensive (daily) treatment was more durable than weekly or biweekly treatment. Further investigation into sympathetic nervous system pathophysiology and treatment is warranted.

BREATHE: A mixed-methods evaluation of a virtual self-management program for people living with long COVID

Rosie TwomeyCathy , Kline, MA; Gloria Gray, ECE University of British Columbia; British Columbia, Canada

Conclusion: Learning directly from people with lived experience inspires compassionate care, a desire to learn more about poorly understood chronic conditions and public health advocacy. The BREATHE program is a safe, acceptable, and valued program for people living with Long COVID and could be considered for Canada-wide implementation.

Oxaloacetate Improves Physical and Mental Fatigue in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long-COVID

Alan Cash, MS; David Kaufman, MD CA, USA

Conclusion: This small, non-randomized open-label dose escalating "Proof-of-Concept" clinical trial yielded impressive highly significant improvements in fatigue in both ME/CFS patients and Long-COVID patients. Up to 33.3% of the patients with ME/CFS and up to 45.5% of Long COVID fatigue

patients improved to normal fatigue levels with oral anhydrous enol-oxaloacetate treatment at 6 weeks. This compares well with historical placebo that achieved 5.9% clinical improvement in ME/CFS patients. Both physical and mental fatigue were significantly improved in both ME/CFS and Long COVID fatigue patients. 1,000 mg to 3,000 mg anhydrous enol-oxaloacetate daily was both safe and tolerable in this population for the duration of the trial. This proof-of-concept study supports the further development of anhydrous enol-oxaloacetate for the treatment of ME/CFS patients and Long COVID fatigue patients with longer randomized placebo-controlled studies. Potential clinical applications with anhydrous enol-oxaloacetate, currently a commercial nutritional supplement and medical food, may help reduce fatigue in ME/CFS and Long-COVID patients.

PUBLIC HEALTH 2 – CHAIRED BY DR CHARLES LAPP

Engaging patients and caregivers In teaching health professional students about ME/CFS.

Cathy Kline (University of BC, Canada).

She and her team had organised patient-led workshops, teaching students about ME/CFS, FM and Lyme disease. The students, patients and caregivers worked together to develop a participatory workshop design. The 46 students were from 13 health disciplines: (occupational therapy, physiotherapy, nursing, medicine etc.) A range of patients and caregivers participated in 2-hour zoom workshops.

Stories were shared and understanding of various topics was covered.

At follow-up all attendees felt they had learnt a lot, were eager for more and realised there had been many deficiencies in their learning to date. They were asked for suggestions for improvements. All the students said they would recommend the workshop to others. Most students showed that most students had very little prior knowledge of the topics covered, and this format could bridge a gap. Most wanted more time and opportunity for breakout rooms for further discussion. With the panelists.

Learning directly from people with real experiences inspires compassionate care, a desire to learn more about poorly understood chronic conditions and public health advocacy.

Chronic absenteeism and ME/CFS in schools: a nurse-led approach

Erin Maughan (George Mason university school of nursing,USA).

School nurses, who are at the forefront of public health can identify and mitigate students' health concerns. Issues with ME/CFS students included school phobia and anxiety. Chronic absenteeism identified those who might be at risk as an indicator of ME/CFS as an example.

Nurses were encouraged to talk to students who were absent a lot, and then asked about symptoms. A nursing plan to help the school could be developed, and the information/results could then be shared with the principal and other relevant school personnel. Good relationships were established with parents and families, and gaps in knowledge could be addressed with them.

A pilot study was done over 3 years at 6 sites. An expert was needed as a guide. The programme involved school nurse training, data collection and the publishing of a manual. School nurses were found to be key members of the team. Many had not heard of ME/CFS. They expressed need for more information and videos were used.

This programme will be expanded to give greater understanding of these illnesses and is looked on as a model that could work for other illnesses. A school-based active programme could be used as a model for school nurses to establish surveillance to address need in identifying and tracking conditions such as ME/CFS, Long Covid and other post-viral illnesses.

Covid-19: Understanding recruitment strategies in a community-based assessment of fatigue, cognitive and functional impairments among those after SARS-CoV-2 infection.

Nancy Klimas (Nova SE University, FL, USA)

It is often difficult to recruit participants to studies such as these. But 750 patients were recruited. The post-viral phase was looked on as 3-6 months post infection. They were contacted via hospitals, and potential participants aged 18-65 years old were emailed. Quite a large percentage eventually recovered. A financial incentive was offered. Mass email did not work (only 2% response), but there was a 30% response from clinician referred patients. Access to technology and screen use were barriers to participation. Many patients did not realise they had Long-Covid. Approximately 11% reported themselves as unrecovered, and 43% reported themselves as recovered, when they were not.

It was therefore evident that to have successful community-based research there needs to be adequate patient enrolment and retention.

This study can provide opportunities and increase awareness of Long Covid.

FINAL SESSION- COVID 19 (written by S.J.Dalziel)

John Chia, from EV Med Research presented his research of patients with a diagnosis of ME/CFS and chronic enterovirus infection who then acquired covid19 infection, following patients over a 6 month periods. He studied 54 ME/CFS patients.

37/54 patients had mild symptoms

17/54 patients were bed ridden with flu-like symptoms , fatigue and brain fog for 2-4 weeks

8 patients were hospitalised and were treated with IV remdesivir (covid19 antiviral treatment) and dexamethasone.

In the longer term 54% of patients felt worsening of ME/CFS symptoms during and after acute infection. Interestingly 5/7 of the hospitalised patients who were treated with remdesivir showed marked improvement in their ME/CFS symptoms This may warrant further clinical studies. . In NZ this treatment is only used for certain patients who meet Pharmac criteria and need hospitalisation. Dr Chia's work is specifically focused around enterovirus infection in ME/CFS, which may not apply to all patients with ME/CFS.

Leonard Jason from DePaul University then discussed developing a consistent research case definition for PASC, using experience from ME/CFS field. Variation in the criterion defining PASC in research studies accounts for a large amount of diagnostic unreliability. Using DePaul symptom questionnaires, he studied 299 cases who had not recovered from COVID19 infection. Participants were classified into mild, moderate or severely infected. He found that no one in the mildly impaired group met the case definition for ME/CFS. However 62.6% in the moderately impaired group met the IOM criteria. IN the severely impaired group 89% of participants met the IOM criteria for ME/CFS. He concluded that a 5 point diagnostic system would be useful for diagnosing PASC. A universal definition is vitally important for research and to be able to compare study findings.

Axis 1: Variant of COVID infection and the type of documentation of infection

Axis 2: Time elapsed since infection

Axis 3: Organ damage from covid infection

Axis 4: Functional impairment classified into 3 categories: mild, moderate, severe

Axis 5: identified symptoms

Dr Jason presented a short form DePaul Symptom questionnaire with 14 items that can assess patients in 5 minutes. This may be very helpful as a screening tool to determine whether patients meets the criteria for PASC or ME/CFS

The final conference speaker was Dr Luis Nacul

University of British Columbia

He studied a cohort of 18 hospitalised patients from a respiratory clinic with Covid 19 infection and followed them up at 3 and 6 months. Fatigue was a very common symptom. Those with severe fatigue comprised 16.1% of participants at 3 months and 6.9% at 6 months. The long term symptoms of fatigue was not associated with the severity of the acute initial infection but was more likely to correlated with increased age and number of comorbidities.

He also presented some data from metanalysis of long covid studies. These also showed a high incidence of fatigue and cognitive impairment. A metanalysis of 81 studes at 12 weeks post covid showed that 32% patients reported fatigue and 22% had cognitive symptoms.

A further metanalysis of 14 studies at 1 year post covid showed fatigue in 28% of people, 19% memory loss and 18% reporting poor concentration.

Both Dr Jason and Nacul's presentations suggested that studies on Long Covid need to define severity of symptoms. Whilst fatigue is very common post covid it is the moderately and severely fatigued with functional impairment who are most closely aligned or fit an ME/CFS diagnosis.

Drs Sarah Dalziel and Rosamund Vallings wish to thank ANZMES for funding their attendance at this very worthwhile and educational event.

