IACFS/ME VIRTUAL CONFERENCE – 2020

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On 22nd August at 2.00 a.m. we were privileged to attend the IACFS first virtual on line conference, at 2.00 a.m. because we are in New Zealand, so our time was 28 hours ahead of the event. It was strange not to be there enjoying the company of all the familiar friends and colleagues. But it was brilliantly organised by the IACFS/ME board and team, and all went smoothly.

The conference was opened by the President Fred Friedberg who welcomed us all and outlined the format. He brought us up to date with the work of the board, including production of the regular journal and support of investigators.

The conference was divided up into 5 main segments, with a question and answer time after each and a lunch break midway.

COVID-19 SESSION

The first presentation was by **Harvey Moldofsky** (Toronto, Canada) who had published research following the SARS Covid-1 disease in 2002. He outlined the recognition of ongoing symptoms following this respiratory disease, which had affected people in 24 countries and led to 800 deaths. The first reported case in Canada was traced to transmission via a lift button, to a person travelling from Hong Kong. The illness spread rapidly. By June 2003 the disease incidence had declined, but a number of patients (mainly a nursing cohort) studied remained ill with many post-viral symptoms and needed rehabilitation. CNS pathophysiology was prominent. Symptoms fitted the criteria for a diagnosis of ME/CFS. Many remained ill long-term and were unable to return to nursing duties

When Covid-19 was diagnosed in Florida, Moldofsky was there and much public interest in his 2003 paper was promoted. Since then people have been contacting him from around the world, reporting patients with ongoing symptoms, resembling ME/CFS. The key issue seems to be that there is, as yet, no idea of prevalence, and epidemiological studies are needed.

Leonard Jason (Chicago,USA) followed on talking about risk factors for developing Covid-19 and its aftermath. He described the 1918 influenza epidemic. There were 25-50 million sufferers and 2 million did not recover. Other studies have examined the relationship between viral illness and development of ME/CFS. After SARS-COV1 40.3% of people had chronic fatigue at follow up, with 27% fitting a diagnosis of CFS/ME. In one study looking at infectious mononucleosis, 13% were found to have ongoing illness after 6 months and 4% remained fatigued at 24 months. It was found that baseline autonomic symptoms and days spent in bed were predictors of developing ME/CSF.

Dr Jason outlined his current study of 4501 healthy college students, following infectious mononucleosis. Of the 5% that were diagnosed with IM 8% have severe symptoms at 6 months. They have found baseline deficiencies in several immune markers, IL5, IL6 and IL13. Jason continues his longitudinal study. 5% of the study group has been infected with Covid-19. This is a unique

opportunity to compare findings between infected and uninfected people, as there is baseline data and stored serum.

Data collected by Body Politik COVID-19 Support group has 640 COVID patients. 91% of patients have not fully recovered after 40 days and 70% have developed new symptoms at various stages. It is possible that those with ME/CFS may get a more severe illness should they succumb to Covid-19.

Sadie Whittaker (Solve ME, Los Angeles, USA) followed on with further thoughts on understanding susceptibility or resilience to chronic effects of Covid-19, and the hope that this will deepen our understanding of ME/CFS. Their team are developing an on-line registry tracking symptoms and collecting data. This went live in May 2020. Collaboration seems to be the key, along with co-creation including people from UK and EMERGE, Australia. She presented their current enrolment dashboard. So far they have 1208 with ME/CFS and 154 controls. 39.8% of these people have severe impairment, with 81% females. They will collect longitudinal health information and biological samples from those with confirmed Covid-19, and aim to characterise molecular variation underlying resilience vs susceptibility to persistent symptoms.

The pandemic presents a unique opportunity to understanding susceptibility. There is coalition building with other organisations and data harmonization. Participants will provide confirmation of Covid-19 status through serology or viral PCR. A tracking app will be used to track longitudinal symptoms and activity. Dried blood spot cards, whole blood, saliva and faecal samples will be collected.

It is hoped to uncover genetic, epigenetic, transcriptomic , immune and other vulnerability factors. This may lead to better characterisation of ME/CFS and even to drug development.

Youandmeregistry.com/

Ronald Tompkins (Open Medicine Foundation, Harvard University, USA) addressed the issue of conversion of Covid-19 patients to people with ME/CFS. Covid-19 is likely to increase our understanding of the pathophysiologic features that can be associated with those who ultimately develop ME/CFS. 4 collaborative centres are involved in this study, thus providing many opportunities. At this stage the incidence of ongoing illness is unknown and could be anything from 25-75%. The actual severity of the illness may not be relevant but is likely to give more understanding in general. This could lead to greater understanding of the genomics, proteomics and metabolmics in those that develop ME/CFS as well as identify potential biomarkers and drug targets etc.

Three phases of the illness will be studied:

1. Hospitalised ICU patients with COVID-19 . Blood and Cerebrospinal fluid will be collected for multiple “omics” analysis. Comparisons can be made to a huge database of people with massive injury.
2. 6 months post-discharge – assessment/recovery status will be at 1-3 months for many patients. Some at 6 months may be worsening and evolving over time. Looking for biomarkers and treatments would be appropriate.
3. 6-24 months – longitudinal follow up of those who still have pathologic fatigue, with same “omics”analysis.

Current observational studies anticipate that 30-50% of patients will fail to recover. And at 18-24 months a diagnosis of ME/CFS would be appropriate.

RNA-sequencing analyses of the leukocyte transcriptome, CyTOF immune cell profiling, plasma, urine, and CSF proteomics and metabolomics, DNA methylation assays, microRNA expression profiles, whole genome sequencing, and viral loads/viral reactivation will be determined. This will provide an enormous amount of potentially useful information.

Luis Nacal (London School of Tropical Medicine and Hygiene, UK) looked at the impact of Covid-19 on the risk and prognosis of ME/CFS. This epidemic provides opportunities to look at the long-term effects of Covid-19 on those who already have ME/CFS. Also studied will be the incidence of post viral fatigue syndrome and related conditions following Covid-19 infection.

Studies will be done in 5 sites across British Columbia with post-covid-19 follow up at 2-4 weeks and then at 8 -10 weeks. A UK biobank will also be used. They will capture the effects of infection in people with previously diagnosed ME/CFS and other chronic illnesses. Longitudinal investigations on the impact of Covid-19 on the incidence and duration of PVFS will be followed.

Patients from Canada, the UK and Brazil will be followed to explore early biomarkers, by comparing those who recover with those who do not. The consequences of Covid-19 on those with already established disease will also be investigated.

Pilot study results of patients with ME/CFS following mild COVID-19 infection shows higher rates of PEM, brain fog and fatigue following infection, but no increase in autonomic symptoms.

Opportunities to understand disease causation, pathophysiology and early possible interventions are likely sequelae.

Then followed a Q and A session which brought up several important points:

Future analyses will be done looking at genetic predisposition

Racial issues will be looked at – there seems to be a greater prevalence among latinos and blacks. Hispanic population is well over-represented.

There was no ability to test for a cytokine storm post-SAR-1. NK cells were analysed and numbers tended to decline.

Most people with CFS (90%) do not have a diagnosis.

In order for studies to be useful it would be important to have a unified case definition.

Are vaccines for Covid-19 going to pose a risk for those with CFS – we do not know.

Studies will look to see if T-cell status is playing a role in Covid-19

There is much heterogeneity in Covid-19, and unknown yet if organ damage plays a role in development of post-covid-19 ME/CFS.

Clinics have been set up for post-covid studies. They will look at issues such as whether use of antivirals or steroids has made post-covid ME/CFS less likely.

SUMMARY

Previous studies have shown that severe viral illnesses such as SARs-COV1, Ebola, EBV have caused a high prevalence of significant fatigue after 6 months. The current pandemic of COVID-19 presents an opportunity to research into pathophysiology, and risk factors for developing CFS/ME. Early observational studies of COVD-19 suggest a high incidence of post viral fatigue. Many studies are underway collecting data to enable longitudinal study. It may be possible to identify risk factors for developing ME/CFS, pathophysiology, identification of biomarkers and drug targets as well as developing prevention strategies and future treatments.

IMMUNOLOGY/METABOLISM/HEART RATE VARIABILITY SESSION

This session opened with a presentation by **Wakiro Sato** (Tokyo, Japan). He described ME/CFS as a neuro-immunological disease, and there is evidence of immune abnormalities. He had looked at B-cell depletion therapy (rituximab). But as the Norwegian studies had not proved efficacy, he suggested heterogenous features of immune mediated pathology.

He showed a slide of the molecular mechanism and explained B Cell Receptor (BCR) sequencing. The BCR repertoire in patients' lymphocytes was skewed compared to healthy controls. Specific IGH gene usage was increased in ME/CFS. Plasmablast antibody secreting cells correlated with severity score. Gene expression analysis of plasmablasts was compared to healthy controls. Expression of MXI was higher in patients with acute onset. Using ROC, he showed that the AUC was as high as .906, indicating that this analysis could become a good biomarker for diagnosis of ME/CFS. Brain abnormalities also correlate with ME/CFS symptomatology.

The overall aim of these studies is to elucidate the immune-related pathogenesis of ME/CFS and to develop objective diagnostic biomarkers, thus leading to treatment strategies.

Ina Petterson (Bergen, Norway) had investigated if defective energy metabolism was contributing to mechanisms in ME/CFS. Various metabolic processes were analysed. ME/CFS patients were found to have a changed amino-acid profile. The function of pyruvate dehydrogenase (PDH) was previously found to be impaired. They then found that there is upregulation of PDH kinases which do inhibit PDH activity. This leads to increased lactate. Previous studies showed increased PDK may lead to an energy-starved condition.

Further studies exposed healthy muscle cells to ME/CFS serum and there was increased mitochondrial respiration leading to increased lactate production. This may indicate a serum factor inducing metabolic changes. This is to be further investigated.

Looking at metabolomic analysis in 83 patients and 35 controls, 159 of 660 metabolites were different, and suggested metabolic stress. There are possible candidate genes in families and there is possibly an immune response going on correlating with metabolic stressors.

Fred Friedberg (Stoney Brook, NY, USA) addressed the issue of why ME/CFS patients improve or worsen. About 50% do not improve. He discussed whether push/crash, being home bound or stressors/life events, or having "uplifts" played a role. Is there a biological indicator – such as heart rate variability? (HRV). Reduced HRV is associated with worse morbidity, so can this predict non-improvement? – particularly if associated with major life events or autonomic dysregulation. Improvement tends to occur associated with careful pacing, major positive life events plus improved autonomic regulation.

A 6-month observational study was undertaken of 125 ME/CFS patients, 90% female with an average duration of illness of 16.5 years. Study involved questionnaires, web diary, accelerometry and HRV measurement, with a 6-month interview. 36 had improved at 6 months, whilst 89 were unimproved.

There was no significant difference between improved and unimproved groups in push-crash scores, limited activity scores and healthy pacing scores. There was a significant difference in HRV between improved and unimproved groups. Improved patients had higher heart rate variability. There was also significantly increased uplift intensity scores in the improved group.

Second phase studies are continuing. There was association between actigraphy counts, healthy pacing, limiting activity and practical support seeking. Weekly scores for push/crash patterns and autonomic functioning were correlated. Weekly HRV and sleep HRV were lower in the non-improved group. This was also consistent with poorer health status. Using machine learning, 6 actigraph clusters were generated.

There is potential for these objective measures to predict crashes, relapses and non-improvement.

James Baraniuk (Washington, USA) addressed heart rate variability in exercise-induced postural tachycardia and POTS. Subjects were recruited from 3 groups: ME/CFS, Gulf war illness (GWI) and healthy controls. HRV was not significantly different between the 3 groups. Lying and standing measurements, MRI, submaximal bicycle exercise and EKG heart rate variability were measured. Three groups were identified: STOPP (normal) change in heart rate of 10-15bpm from lying to standing, POTS (heart rate >30bpm with postural change before and after exercise) and START (Stress activated reversible tachycardia) showing a change in heart rate normal before exercise, but a >30bpm postural change in heart rate after exercise. ME/CFS, GWI and HC had equivalent rates of POTS (17%), START (25%) and STOPP (58%). ROC analysis of HR after exercise distinguished the 3 groups ,

Parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) indices were plotted against each other. POTS subjects showed increase in sympathetic nervous system and decrease in Parasympathetic nervous system, however START subjects showed a decrease in PNS indices only, suggesting a dysfunctional baroreflex.

The START phenotype was not unique to ME/CFS or GWI. However, GWI START and STOPP have significant metabolomic and other differences, which may indicate mechanistic importance in GWI.

It is possible to separate START from STOPP groups in 80% of subjects. There is a significant difference in the parasympathetic index between the 3 groups, and after exercise the curves change.

It is possible that exertional tachycardia is a variant or component of PEM.

Then followed a Q and A session:

The use of commercial devices (such as fit-bits) as to whether they are good enough for measuring HRV was brought up – Their accuracy is probably improving. (F.F.)

Discussion re "uplifts" - these are positive experiences during the day. The highest degree of uplift was seen in the improved groups. (F.F.)

It was questioned as to why there are sympathetic and parasympathetic abnormalities - is this due to brain "injury"? – the mid-brain modulates autonomic traffic and in ME/CFS there is likely microglial dysfunction/increased activation causing autonomic dysfunction. (J.B.)

Use of tilt table was brought up. JB felt this was artificial and he prefers to use standing or lying (J.B.)

Are therapeutic immunoglobulin studies warranted – Yes (W.S.)

TREATMENT SESSION

Violetta Renesca (Nova Southeastern University, USA) presented her work on the effect of a self-management group programme on health status, fatigue severity and self-efficacy in patients with ME/CFS. She outlined the difficulties in the USA of 2.5 million ME/CFS patients with no known cure, many who are bed bound, are have difficulty getting to medical appointments, long distances to travel and limited access to knowledgeable physicians.

Her project was to evaluate the effectiveness of a self-management programme teaching energy conservation, relaxation techniques, healthy eating etc. Four weekly 2 hour sessions were involved. Primary outcome measures were assessed at baseline, at end of course and one-month follow-up. 33 patients were enrolled. Data was collected from self-report, questionnaires and functional capacity scales.

Average age of participants was 50 and most were somewhat overweight.

At one-month follow-up there was significant positive change in mental fatigue, energy and symptoms. This provides implications for practice change. Self-management educational intervention is clinically effective in reducing the impact of the illness on physical and psychological well-being. It would be useful to be able to reach homebound patients and have involvement of a personal life coach.

The benefits of oral rehydration on orthostatic intolerance in children with Postural Orthostatic Tachycardia Syndrome (POTS) was discussed by **Marvin Medow** (New York, USA). He outlined the symptoms, which were induced by rapid gravitational displacement of 500-700ml from central to splanchnic and lower extremity beds. He studied 10 patients with POTS who also had a diagnosis of ME/CFS. There were 15 healthy controls. He compared the effects of one litre of isotonic Saline IV infusion over thirty minutes with an oral rehydration solution (ORS) containing sodium and glucose also taken over 30 minutes, using a lower body negative pressure machine.

POTS subjects with orthostatic intolerance had about 1/3 of tolerance to orthostatic stress than controls.

ORS, but not saline (IV) was able to maintain cerebral blood flow velocity during orthostatic stress. Both ORS and IV saline mitigated the effects of orthostatic stress compared to controls and untreated POTS patients

The oral rehydration solution is convenient, safe and effective for short term relief of orthostatic intolerance. Sodium is more effectively absorbed if the solution contains glucose, as is available with commonly available ORS.

Rhonda (Jane) McKay (Vancouver, Canada) outlined the Vancouver experience of use of low dose naltrexone (LDN) in ME/CFS and FM. Her studies have had 3 objectives: a review of the literature, a look at results and proposing a randomised controlled trial (RCT). LDN has shown successes and promises in these illnesses. Case reports have shown minimal adverse effects. One paper showed 73.9% of patients were relieved of many symptoms. Side effects were mild and included insomnia, nausea and dizziness and GI upset.

Naltrexone modulates the immune system, decreasing inflammation via microglial cells. TNF production is supressed. There is an enhanced endorphin effect by stimulation of opioid receptors.

It is used "off label" in Canada. She retrospectively reviewed the charts of 97 cases, and LDN had been used in one third. The dose varied from 0.25 to 4.5mg. Particular beneficial effects were on energy, pain and sleep and cognition. Side effects noted included insomnia, rash and G.I. upset. The study showed good improvement in PHQ9 and McGill Pain Questionnaire.

A randomised, controlled trial is warranted as the drug is safe, has potential benefits and minimal side effects.

Then followed a Q and A session:

What formulation of the oral rehydration solution should be used? Water alone causes dehydration. 2 options were cited: Normalyte or the WHO formulation (Jainus bros) Need to watch cost (M.M.)

Can Palmitoylethanolamide (PEA) be considered for pain relief? It might be useful (R.M.)

Can higher doses of LDN be used? e.g. 20mg. The literature is vague and there are no trials done in these illnesses at higher dose. (R.M.)

If the patient has insomnia or nightmares, what is best approach? - reduce the dose (R.M.)

RESEARCH/CLINICAL NETWORKS

Caroline Kingdon (LSHTM, London, UK) Gave a compassionate overview of her work visiting the housebound patients severely affected by ME/CFS. She was supported by an NIH grant and had visited 80 severely affected patients up to 5 times each at home. These patients were often bedbound, in a darkened room in intense pain and needing artificial feeding.

The illness for these people is worse than terminal cancer and represents up to 25% of the total number of ME/CFS patients. She pointed out that we have a duty of care, and the home visits provide validation and skill for reliable diagnosis. There is no biomarker and no effective treatment. Organising the visit may

be hard, and much wisdom and skill is needed. Past negative experiences can lead to ill effects. It is important to be aware of such issues as resultant post-exertional malaise, adverse effects of things like odours/perfume, cognitive difficulties etc.

She looks on it as a privilege to be in the home. She listed her 6 Cs which she uses for guidance:

Compassion
Care
Competence
Communication
Courage
Commitment

The aim of the healthcare provider can certainly improve the quality of life of the individual severely affected by ME/CFS.

Matthew Schu (N.C,USA) outlined ME/CFS focussed data portal supporting data discovery across multiple biological disciplines. He presented a single platform designed to bring data together, thus promoting a sharing of data. This impacts on many systems, with every system requiring different tools. Very specific training is needed to involve thousands of data points, leading to mapping of ME/CFS.

The website has been developed so far hosting: metabolomics, miRNA sequencing, gene expression, DNA methylation and RNA sequencing. The researcher can explore the data and work through several tables to do searches of data sets. This can be likened to a website walk-through. Previous versions can be explored to look for changing patterns. This provides robust data which can be shared. The system is based on cloud-based infrastructure.

mapMECFS was launched in January 2020. The platform is secure. It will be developed to become available to the wider research community.

Eliana Lacerda (LSHTM, London, UK) reported on a longitudinal assessment of clinical severity indicators and determinants of quality of life in people with ME/CFS. This was a prospective cohort study using the UK ME/CFS biobank. The objective was to assess the clinical evolution of those with ME/CFS considering severity of symptoms and quality of life indicators.

601 participants were included (including 57 with severe illness). Comparisons were made with an MS and control groups. Clinical assessments, using blood CPK and hand grip, and questionnaires were used. Levels of 4 groups from healthy controls to severely ill patients were compared on a correlation matrix. There were high correlations between symptom domains. Follow up was done at 4 time points.

Particular use was made of the phenotyping questionnaire (PPQ). There were strong associations between SF36 PCS scores and post-exertional, neuro-cognitive, autonomic and neuroendocrine domains of the PPQ, and also FSS scores. Correlations were weaker for MCS scores, which were moderate for sleep and neuro-cognitive domains. All other correlations were weak or very weak.

PPQ value is of value to ascertain symptom severity and to relate to quality of life measurements. Hand grip strength is a clinical marker and serum CPK was significantly lower in the severe symptom group. The PEM score is strongly correlated with physical ability and fatigue severity, but use in prognosis is yet to be explored. The results confirm the protracted nature of ME/CFS with no significant changes over 6 to12

month follow-up. This is a jigsaw which is beginning to fit together. Patients are finding better understanding and acceptance of diagnosis. This heralds a better future.

Then followed a Q and A session:

Has there been any study looking at whether patients are bedbound because of POTS or OI? A study that is needed, but these patients are too ill to do a 10 minute standing blood pressure, may only tolerate one minute. (C.K.)

Does the low CK level affect activity? This was an unexpected finding – and needs follow up to validate. (E.L.)

IMMUNOLOGY/METABOLISM

Ryan Whelan (Incline Village. NV, USA) presented his work on ME/CFS and Autoimmune Associated small nerve fibre neuropathy (aaSFPN). This is a neurodegenerative disorder characterised by loss of peripheral autonomic nerve fibres. It was deemed important to identify ME/CFS patients who present with co-morbid aaSFPN . Symptoms of dysautonomia between ME/CFS and aaSFPN are almost clinically identical. Skin biopsy for diagnosis shows a degenerative reduction in small fibres in aaSFPN.

This was a pilot study. He looked at other diseases with similar symptoms to see if there was evidence for autoimmunity with elevated antibodies. He found many patients had elevations of β1, β2, cholinergic 3 and cholinergic 4 antibodies. 52% were positive for at least one antibody. 80% of the patients had POTS or orthostatic intolerance. 38% of those with ME/CFS had symptoms suggestive of small fibre neuropathy.

A pilot study indicated that Intravenous immunoglobulin can be effective as treatment for those with elevated cholinergic receptor 3 and 4 antibodies. There was significant improvement in one case study. He stressed the need to identify the subset which may respond to this treatment.

Daniel Missailidis (Melbourne,Australia) discussed his work on dysregulation of mitochondrial function and fuel preferences in ME/CFS lymphoblasts. Mitochondria produce cellular energy. There are 2 signalling pathways. He used seahorse respirometry to measure respiration in ME/CFS lymphoblasts. He described the electron transport chain.

ATP synthesis was found to be lower in ME/CFS cells, leading to inefficiency. Resting ATP supply was unchanged. Compensatory upregulation of respiratory capacity occurs – complexes 1-4 were functioning normally. Complexes 1-5 were upregulated in respiratory capacity – this occurs translationally. TORC1 activity was chronically activated in ME/CFS lymphoblasts, suggesting a persistent stress response. AMPK activity was slightly up. Processes that help support all this are increased mitochondrial transport and non-mitochondrial metabolism. The TCA cycle was elevated in transcriptome and proteome. Glycolysis was unchanged. Pentose phosphate pathway was upregulated. Fatty acid β oxidation enzymes were up regulated, as were amino acid degradation and proteolysis.

Since stress-sensing and compensatory mechanisms would already be chronically activated to satisfy resting energy requirements, this could render the cells inflexible in the face of additional energy demands.

Then followed a Q and A session:

How many patients were in the Melbourne study? 51 – variability clustered with severity. (D.M.)

Will you be distinguishing cause from effect in future – Yes (D.M.)

Were other antibodies looked at, or was this study more specific? Controls did have other auto-antibodies (R.W.)

Is an increased diet, or addition of supplements likely to be of use? This is anecdotal and too early to say. Future studies will be useful (D.M.)

Was a tilt table use for diagnosis of orthostatic intolerance/POTS? Most were diagnosed using the lean test. (R.W.)

The conference ended on a positive note and **Lily Chu** (IACFS/ME Co-Vice-President) thanked everyone for their attendance and work towards so many excellent presentations. She acknowledged her brilliant support team. Having an online conference such as this certainly heralds the possibility of similar future evets.

We would like to acknowledge the IACFS and ANZMES for enabling us to attend this prestigious event.