Invest in ME Research

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13th Invest in ME Research International ME Conference

Invest in ME Research - 13th International ME Conference

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Report by Rosamund Vallings &Sarah Dalziel

On 1st June, 2018, I was privileged to attend the 13th Invest in ME Research conference in London. This was preceded by a day for young and new researchers to present and discuss their work, and then a 2-day colloquium for researchers from around the world to gather and discuss their current work in the field.
These unique meetings should result in sharing of ideas and collaboration.

The conference held in Westminster in the shadow of a scaffold-wrapped Big Ben was opened by Dr Ian Gibson.
He formerly acknowledged the sterling work of Invest in ME Research, who have always devoted so much time and energy to organising these meetings over the past 12 years, in a purely voluntary capacity. Ian felt that there was surely an “eureka moment” coming as the research progresses so positively in this illness.
Many countries were represented at these meetings.

The first presentation was by **Dr Beth Unger**, The Chief of the Chronic Viral Illnesses branch of the CDC, Atlanta, USA. CFS/ME has now been added to an ongoing surveillance system (BRFSS) in 15 US states. Data is collected looking at such things as prevalence rates and health burden. Advocacy by Dr Lily Chu and ME Action had given a “call to action”. Latest figures from an enormous self-reported study (54000 surveyed) show a lifetime prevalence rate of 1.6%, a current rate of 1.2%. 81.6% were female and 71.4% still had a possible CFS diagnosis. However it must be remembered that these were self-reported figures and may thus be biased, and many of these people may not fit the CFS diagnostic criteria. Of those with a possible diagnosis of CFS, 78% had limitations in at least one area, and 83% had comorbidity with at least 2 other chronic conditions. 90% of those surveyed had health insurance and 91% had a healthcare provider. However, only 16% had regular health care and check-ups.

The future plan includes:
Surveillance in schools, as ME/CFS leads to a lot of absenteeism.
Developing a case definition for 9-39 year-olds.
A vaccine-safety datalink project.
More healthcare provider education.
In relation to this last plan, there is already good information on the CDC webpages for both patients and physicians. There has been a round-table physicians’ meeting headed by Dr L

Bateman, with plans to put more physician information on Medscape. (Medscape spotlight CME planned for November 2018) There will be more of these roundtable discussions. Also there is to be education for healthcare providers serving the paediatric population. There also needs to be a look at differences in clinical practices working with clinical experts. Physical examination needs to be standardised (e.g. using the NASA "lean test"), and research protocols need to be developed. (e.g. 2 day CPET, NK cell examination etc).

Vicky Whittemore, a programme director at the NIH, USA, gave an overview of the work going on at NIH in relation to ME/CFS. It was gratifying to see that funding for this illness has doubled over 6 years and there are now 27 offices funding research. 4 research centres are being funded, all using different approaches. There is collaboration with Canada. The money for research is not just for those in the USA, as anyone can apply. A working group – the NINDS advisory council is being put in place. There are plans for a NIH ME/CFS conference to be held in Bethesda on 4-5 April 2019.
A Common Data Elements project was started 10 years ago, providing a universal standard and a way forward. This is not a database, but a way of using data. This provides information for researchers for clinical data collection and sharing. There is a range of domains from demographics to symptom websites. This helps to standardise data for research using a standard format with common definitions. This can be found on www.commondataelements.ninds.nih.gov

Dr Avindra Nath, Intramural clinical director, NIH, USA looked at challenges in study design and identification of patients with post-infectious ME/CFS. The ICD classifies this as a neurological illness. The money set aside can be used internationally. At the NIH, the enormous Building 10 is a clinical research centre, and is the only dedicated research hospital in the world. Patients can be admitted (usually for about 10 days) and are tested for a battery of information. This is a truly "bench to bedside" approach. They are of course also checked for other illnesses. It is vital that many of the tests performed are done within an hour of collection.
Currently a 4 year study is underway seeing 40 patients and 40 controls. Phase 1 focusses on diagnosis, and phase 2 on the effects of exercise. Dr Brian Walitt (rheumatologist) at present coordinates everything. They are now doing muscle biopsies. To be included in the research, the patient's disease must have been triggered by an infection.
There is also a panel looking at possible links between HPV vaccine and auto-immune disease and POTS. There has been no linking as yet.

2 PhD students from **Quadram Institute Bioscience**, Norwich, UK then presented and discussed their work looking at the gut microbiota in ME/CFS:
Katharine Seton is looking at whether an altered microbiome can lead to auto-immunity. She explained how a viral intestinal infection can lead to an altered microbiome – i.e. an unhealthy gut with less variety of microbes, a leaky barrier and an autoimmune response. She has 10 pairs of severe ME/CFS patients and is using "household" controls (i.e. same diet, living conditions etc). Blood and stool samples are being examined.
Fiona Newberry studies faecal samples for virus isolation – i.e. viral DNA extraction and sequencing. She is looking also for alterations in the microbiome if viruses are present.

Viruses are of course enormously variable, and only a fraction of those in the faeces have so far been identified. Many remain unidentified. Diet does affect the microbiome, and food diaries are also kept.

Kristian Sommerfelt, (Bergen, Norway), then showed some fascinating videos of his work with ME/CFS patients and has found that in up to 80% involuntary movements (myoclonal jerks) are characteristically common. These are often fast and small and never impair function. But he feels are a frequent neurological component of the illness. Most of the patients he illustrated had not been found to have any specific neurological abnormalities on MRI.

Peter Johnsen, (Tromsø, Norway), discussed the use of faecal microbiota transplantation in ME/CFS. Earlier studies on IBS patients had proved useful with improvement of symptoms and less fatigue. 90% patients with IBS have fatigue, and 90% patients with ME/CFS have experienced IBS. He explained how there were "do-it yourself" movements afoot, but caution was needed. Donors need to be healthy. He explained the microbiota – gut – brain axis. In IBS and ME/CFS there is altered diversity and composition of the microbiota, an altered immune profile and altered central processing (as shown on fMRI). He questioned whether this was cause or effect.
In the first trial on IBS patients, he used placebo for controls. There was follow-up at 3 and 12 months. There was a positive 65% symptom response at 3 months, and a declining response at 12 months. The fatigue response at 3 months was good, but there was none at 12 months. In 56(% quality of life had improved at 3 months and in 51% at 12 months. 80 patients are now enrolled in the ME/CFS trial and will be followed up at 3 and 12 months.
Diet and probiotics being taking by these patients will have influence, and a questionnaire will be completed to assess these issues. Blood and urine will also be checked. There will be collaboration with other researchers looking at biomarkers and metagenomics. Faeces, blood and urine will be biobanked for metabolomics.

Karl Johan Tronstad, (Bergen, Norway), presented his work on Cellular Energetics in ME/CFS. He used a translational research strategy. His hypothesis was that ME/CFS is triggered by an abnormal immune response that leads to defective energy metabolism. The aim is to identify the risk genes. There is cellular adaptation to a metabolic defect. Glucose metabolism passes through the complicated TCA cycle to ATP. If one pathway is blocked, there are usually back-up pathways.
If healthy muscle cells are exposed to serum from ME/CFS patients, there is increased oxygen consumption and increased lactate production. They are looking for cellular energy/metabolite sensors. Adaptation will occur following events such as starvation, hypoxia, overtraining, metabolic stress, ageing, cancer etc. For homeostasis to occur, fuel passes through the cell to provide energy. There may be need to increase fuel to aid recovery.
In ME/CFS, there may be a need to look for an alternative fuel source, or perhaps the fuel may not be able to be used correctly – there may be less efficiency and a waste problem. It is possible to mimic the metabolite defects in the lab. One can use pharmaceuticals or genetic modulation.
He concluded that there is a cellular struggle for energy.

Donald Staines, (Gold Coast, Australia) discussed the emerging Transient Receptor Potential (TRP) pathology, building on calcium ion channels. Calcium ions are critical in biochemistry, mitochondria etc. Much of their work has previously focussed on Natural Killer cells (NK cells) where there has been shown to be immune dysfunction. NK cells destroy cancer cells, viruses etc. The need to measure NK cell function is therefore critical. The immune system does reflect the changes in other body systems. Blood for these investigations cannot be frozen and needs to be used immediately.
He then discussed that what happens in NK cells happens in all cells in the body. In ME/CFS patients there are far fewer functioning TRPM3 (Transient Receptor Potential melastatin) receptors, and some are found to be defective. These receptors control the movement of calcium in and out of the cells.
Their hypothesis asked: "Is there a relationship between TRPM3 dysfunction and disease?" Differences have been identified, with significant differences between ME/CFS patients and controls. TRPM3 on cell surfaces and cellular calcium needs to be measured. Normally intracellular calcium sends a message for its need for more or less. Abnormal TRPM3 is like leaving a battery on – and it depletes. He asks the question "Is this illness therefore reversible?"
The mechanism seems to be:
Damaged SNP (single nucleotide polymorphism) → Decreased TRPM3 receptor → changed function → decrease in calcium in cell → impaired lysis. There is a need to block the calcium loss. Trials with pregnanelone sulphate have not changed the calcium balance.
TRPM3 is widely distributed in the white matter, the eye, pancreas, GI tract, CVS, trigeminal and ciliary ganglia and there is co-location with mACh receptors (eg lipid rafts). TRPM3 changes are likely to affect cAMP/ATP and ACh regulation.
This team's latest very important finding is that there are novel TRPM3 receptors in the gut. Also, that there are changes in the muscarine receptors with reduced expression of mAChRM3 – i.e. an effect on the acetylcholine receptors.

Theoharis Theoharides (Boston, USA) gave the **Anne Örtegren Memorial Lecture**. The lecture was preceded by a moving tribute to Anne, who came from Sweden, and who had died recently after a 16 year battle with ME/CFS. She had contributed much as an advocate to the world of ME/CFS.
The lecture focussed on "Brain mast cell involvement in ME/CFS". He described atopy as a big umbrella, with allergies being worse in association with ME/CFS. Mast cells hone into tissues from the bone marrow. There are a number of associated diseases including "Mast Cell Activation Syndrome". Blood tests for this condition are very unstable, and urinary investigations must be done "cold". On the skin, there is a response to pressure, with raised red marks. This is not an allergy.
Mast cells may affect every organ in the body. They have been shown to be involved in a number of diseases, (including interstitial cystitis, fibromyalgia) which are associated with cognitive impairment and many widespread symptoms. There are multiple things that can trigger mast cells including environmental factors, drugs, microbes, cytokines, peptides and toxins. Mast cells increase blood brain barrier permeability affecting the microglia. This releases proinflammatory factors causing neurological symptoms such as brain fog.

All those with this illness will have neurological symptoms. Mast cells communicate with other immune cells. The symptomatology is not related to allergy. There are many mast cells in the hypothalamus. Release of CRH causes increased skin permeability, and increased blood brain barrier permeability (allowing entry of toxins directly into the brain). Mast cells may explode and release cytokines and inflammatory molecules. This can all contribute to ME/CFS symptoms directly or via the microglia. The mitochondria may release mast cells, and this can cause brain inflammation. Toxins and moulds (liberating toxins) can lead to a chronic inflammatory response syndrome, leading to mast cell activation. Mast cells activate the microglia, via release of tryptase, neurotensin and histamine, leading to pro-inflammatory mediators, which then leads to ME/CFS. Measurement of urinary tryptase is not usually part of the diagnostic procedure.
Luteolin (a flavonoid) is known for use in autism, and methoxyluteolin is a potent inhibitor of mast cells, and could be a useful treatment approach. Those with the illness should avoid colourings, perfumes etc. and also histamine-rich foods such as ripe avocados and ripe tomatoes.
Other useful treatment approaches can include: doxepin, ibuprofen, propranolol, ranitidine and cyproheptadine (an antihistamine)

Mady Hornig (New York, USA) outlined her 3-strike hypothesis, involving genes, environment and time, with effects on development of a disease such as ME/CFS. She described distinct immune signatures present early in this illness. She compared classical with atypical illness. There is usually Blood-Brain-Barrier disruption, allergic symptoms, change in neurological function, severe cognitive dysfunction, and many gastro-intestinal symptoms.
She has looked at the faecal microbiome and its possible role in ME/CFS, with further research into metabolomics, and predicted metabolic pathways. It may well be that these changes could lead to subgrouping those with ME/CFS phenotypically.

Maureen Hansen (Ithaca, NY, USA) has studied the illness widely. She has looked at within group and between group heterogeneity. She follows each patient carefully depending on whether they get worse or better. There are ongoing studies looking at use of faecal transplants and ampligen. She is also looking at provocation studies, looking at challenges to see the effects of worsening or improvements in those with ME/CFS compared to healthy controls.
She outlines the ongoing studies using the CPET 10 minute exertion studies based on the protocol from Betsy Keller at Workwell Foundation:
Study with Dr D. Shungu looking at increased brain lactate using neuro-imaging to evaluate the role of oxidative stress and microglial inflammation in the brain.
The role of extra-cellular vesicles in ME/CFS (these regulate the immune responses)
Dr Andrew Grimson's laboratory will be isolating white blood cells to identify and sequence genes that are being expressed. She feels there could be "one bad actor" among the white blood cells.
She is looking for correlations between these tests. She emphasised the need for biomarkers for the development of treatments, and the hope to develop new drugs.

Markku Partinen (Helsinki, Finland) looked at ME/CFS from a sleep medicine perspective. He outlined the regulation of sleep by the orexin system. The orexin system is based in the hypothalamus, and is regulated by the circadian clock. The sleep system is not working properly in ME/CFS.
Orexin cells sense glucose levels. Low glucose leads to activation of orexin. If glucose is up, one feels sleepy, and orexin goes down. Orexin cells are also "salt-sensing". If sodium is up, orexin rises leading to wakefulness and elevation of BP. This mechanism can be helpful in ME/CFS. When lying down in bed, being horizontal leads to low salt level, which in turn lowers orexin levels, which increases fatigue and reduces wakefulness. Whereas slight elevation improves salt level, higher orexin levels and improved fatigue and orthostatic hypotension.
6-9 hours of sleep is needed, and this is a time for "waste" removal via glymphatic system. Lack of sleep increases fatigue. Sleep disorders may be co-morbid with ME/CFS and must be treated before a diagnosis of ME/CFS can be made. To sleep well we need immune homeostasis, a need to increase vagal tone (by nutrition) and relaxation.
Many patients have previously been sporty, and have "athletic" emotion. They will need parasympathetic activity to promote good sleep. He compared this with dogs, who need 14-16 hours of sleep because they are constantly on high alert when asleep. He measured autonomic function during sleep in ME/CFS patients and found parasympathetic activity to be down. There is something wrong with autonomic control. His hypothesis was that there are abnormalities with deep sleep with decreased parasympathetic activity, with subsequent waste product accumulation, leading to pain and fatigue.
There is a typical past history in childhood in those who develop ME/CFS – they are often sporty, get a lot of infections, and are emotional, sensitive and excitable. He describes them as "autophiliacs".
The aim of treatment should be to get a good sleep to restore homeostasis, and to avoid benzodiazepines. CBT, nutrition and small doses of H-antagonists should be used (e.g. doxepin). Vagal stimulation at bedtime may be useful – e.g. gargling, singing. Some ME/CFS patients get better with a reversed rhythm. Sleeping too much is worse than not sleeping enough.

James Baraniuk (Washington, DC, USA) outlined his research. He used questionnaires towards diagnosis, a baseline MRI, then a 30 minute CPET. The next day the exercise was repeated followed by MRI and lumbar puncture. The questionnaire for depression revealed that 30% ME/CFS patients were not depressed. Tenderness was assessed at 55% (i.e. less pressure was needed to elicit symptoms). Exercise studies are ongoing, and were found not to worsen orthostatic intolerance, using dizziness scores. The MRI data is still too new to utilise, but he stated that something different is happening.
In the cerebro-spinal fluid, microRNA levels were higher in those who did not do exercise. Levels went down after exercise.

Ron Davis (Stanford, USA) outlined his main areas of current research:
Using Seahorse metabolic assay kits. Looking at the differences in stimulated T cells between patients and healthy controls.

Nano-needle – this provides millions of measurements. Cells are made to "work" using salt. This can be used for diagnosis with $7X10^8$ reliability. He has done "plasma-swap" experiments, and the plasma from ME patients mixed with healthy cells shows up positive.
Microfluidic platform – red blood cells tend to be "hardened" and do not flow freely, leading to problems in the microcirculation. The design is not yet completed, but there is a difference. There is too much variation, for this to be a diagnostic tool.
Blood flow - main measurements still being developed. This will be to measure cell deformability.
Biomarker- free sorting of rare blood cells. Magnetic levitation can sort cells out.
Biomarker- free sorting cancer cells and clusters from blood. Looking at white blood cell density. And at what goes on when a patient gets a bacterial infection and "feels" better.
Mobile health platform, using cell phone.
They are looking at a biomarker diagnostic test (BAKEOFF) – using 5 different instruments to get consistency. There is a need then to look at other diseases.
Big data approach (2 million $) looking at the severely affected patients. This focusses on 20 patients and 15 families with one affected member.
General conclusions so far in his work show that many patients are more severely incapacitated than in many other diseases. Looking at multiplex viral testing, they found that controls had more viruses and patients had minimal viruses. Therefore using antivirals is unlikely to be helpful. The gene expression for trypanosomes and parasitic infection is very similar to ME/CFS. The illness caused by trypanosome is "sleeping sickness". When looking for heavy metals – analysis showed no increase in heavy metals in relation to ME/CFS. Those who had some increase in mercury levels were usually high fish consumers. In general there were many changes in the immune system parameters.
He went on to describe the fact that patients may be caught in a metabolic trap. Something like an infection can lead to disruptive changes in the metabolome, which then becomes "stuck". It may be that simple measures at normalising the metabolome could prove successful.

Ian Gibson ((UK) then closed the conference after a very long but informative day, emphasising the enormous progress and excitement generated in this field, and thanked the many prestigious presenters and attendees from all over the world.
Richard and Pia Simpson were thanked for the enormous amount of effort put in to organizing this event.

I must thank Invest in ME Research and ANZMES for their support in helping with attendance at this conference.

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