The ME Association

SUMMARY REPORT

4TH ANNUAL CMRC RESEARCH CONFERENCE

By Dr Charles Shepherd | 18 September 2017

'One of the biggest mistakes made by modern medicine is to have arrived at the conclusion that diseases such as ME/CFS, FM, GWI, and 'CLD', are a figment of patient's imagination.' Professor Jose Montoya, CMRC 2017.

Introduction

This is a summary report of what I felt were the highlights and main points to emerge from this year's CMRC conference that took place in Bristol on 13 and 14 September.

Overall, it was a busy, stimulating, and very enjoyable event. It has also been the most impressive open international biomedical research conference to take place this year and the only one where the public are provided with almost instant access to videos covering most of the presentations and to this summary. A much more detailed report is being prepared by the conference writing group and will be published in due course.

I would like to add my congratulations to the CMRC and the event organisers. Well Done CMRC!

We were fully booked with both UK and overseas researchers – a good proportion being students or established researchers who are new to ME/CFS research. This year the ME Association (with the help of a private donor) sponsored 5 students to attend the conference.

There was no particular emphasis to the conference – with presentations, posters and workshops covering a wide range of research topics. However, a theme running through many of the key presentations was the need for meaningful collaboration among researchers, and involvement from the patient community when research is being planned and protocols developed. It was also stressed that while fatigue is an important part of ME/CFS, this is a multisystem disease with a range of other core symptoms.

What I found particularly helpful was to have the world's two leading experts on autonomic nervous system dysfunction in ME/CFS – Professors Julia Newton and Peter Rowe – together to talk about orthostatic intolerance, neurally mediated hypotension and PoTS in ME/CFS. And, having several presentations on how different types of neuroimaging are helping us to understand the neuropathology of ME/CFS, were very welcome.

As there were so many presentations and posters I will not include every single one in this report. The summaries below are brief – if you want to follow up what was said, most of the presentations now have a free access video attached. There are a few exceptions – mainly due to new pre-publication research information being presented.

Dr Charles Shepherd, Hon. Medical Adviser, The ME Association

DAY ONE

1. Professor Stephen Holgate - University of Southampton

Prof. Holgate is the current chair of the CMRC and opened the conference with a review of some of the most recent developments in ME/CFS research.

He announced that Professors Julia Newton and Hugh Perry are leaving the Board of the CMRC – although both will be maintaining their interest and involvement in ME/CFS research as well as continuing as members of the CMRC.

A welcome new addition to the CMRC Board is Professor Patrick Chinnery, who leads the MRC mitochondrial biology unit at the University of Cambridge.

We also now have three representatives from the pharmaceutical industry taking a close interest in ME/CFS research and attending some of our Board meetings.

There will be a meeting with Dr Vicky Whittemore from the US National Institutes of Health in a few weeks' time to discuss USA–UK research collaboration.

The Royal Society is holding a meeting next week to discuss the neurobiology of fatigue – Professor Holgate will be at this meeting and is taking some ME Association 'Exploration of the key clinical issues' books with him!

Professor Holgate also announced that the MEGA research study had failed to obtain funding from the MRC.

Prof. Stephen Holgate - video presentation

2. Dr Avindra Nath - National Institutes of Health

Dr Nath is an expert in neurological infections and neuroimmune disorders and is relatively new to ME/CFS research.

He gave an excellent and detailed presentation on the exciting new study of post-infection ME/CFS that he is heading at the NIH. This involves what will be the most thorough evaluation to date of a cohort of people with ME//CFS (along with healthy controls) who have a definite and clear-cut onset to their illness following an infective episode. There has also been extensive consultation with the ME/CFS patient community in the planning of this study.

The ME/CFS patients and controls (40 of each) are being admitted for 5 to 10 days to the NIH research centre hospital where, in addition to recording very detailed clinical histories and having an extensive battery of blood tests, they will have a muscle biopsy, functional and structural neuroimaging scans, autonomic nervous system testing, cerebrospinal fluid analysis, an exercise stress test, and various other investigations.

This study has only just started – so it will be some time before any results will be available.

Dr Avindra Nath - video presentation

3. Dr Matt Wall - Imanova Centre for Imaging Sciences

Dr Wall explained that Imanova is a translational research company that specialises in applying positron emission tomography (PET) and magnetic resonance imaging (MRI) scanning techniques to early drug development and improving our understanding of disease causation.

Established in 2011, Imanova involved an alliance between the MRC, Imperial College London, King's College London and University College London, to act as a centre of excellence for imaging sciences in the UK and as a conduit between academia and industry. Imanova is now part of a USA company called Invicro.

By working with academics and commercial pharmaceutical companies, Dr Wall explained how new types of neuroimaging (including combinations of MRI and PET scanners) could be used in both research aimed at causation of disease such as ME/CFS and in clinical trials of new drug treatments.

PET scans, for example, can demonstrate that a drug crosses the blood brain barrier and enters the central nervous system.

If you want a good overview of the latest developments in neuroimaging have a look at the video for this presentation.

Dr Matt Wall – video presentation

4. Professor Maria Fitzgerald – University College London

Professor Fitzgerald is a leading expert in the anatomy and physiology of pain.

Going right back to basics, she explained some of the key differences that occur when the body's response to an acute pain – that follows an obvious injury – is compared to the development of chronic unresolving pain – that may follow an injury or occur in a situation where there is no obvious injury or event that could be initiating the pain.

She went on to explain how various neural pathways are involved in the recognition of pain at the site where pain occurs, how pain is then transmitted to the brain, along with the possible modification of messages about pain as they pass into and up through the spinal cord. Finally, how key centres in the brain (including the brain stem) process this information and tell us that something is painful.

Having a better understanding of the underlying anatomy and physiology of the neural transmission of pain at different levels can obviously help in the development of therapeutic interventions for pain.

Professor Fitzgerald also described some of the difficulties in trying to measure pain objectively, including the use of the McGill Pain Questionnaire.

5. Professor Don Staines – Griffith University, Australia

Professor Staines summarised some of the work that his research group have been carrying out into the role of immune system dysfunction in ME/CFS, especially the role of natural killer cell dysfunction, and the way in which changes in calcium ion transportation at a cellular level could be playing a key role in ME/CFS.

Research: Impaired calcium mobilization in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients is associated with transient receptor potential melastatin 3 ion channels

6. Professor Alan Silman - Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford

Professor Silman explained that in addition to the classic symptoms and signs in arthritis, debilitating fatigue can also be a very important feature in inflammatory arthropathies such as rheumatoid arthritis and lupus/SLE.

He went on to look at possible mechanisms of fatigue production in arthritis – especially the role of what are called pro-inflammatory cytokines such as tumour necrosis factor, and interleukins 1 and 6 – and what happens to fatigue when drugs used to dampen down inflammation in arthritis are used.

Although the use of powerful anti-inflammatory drugs (like rituximab) in inflammatory arthropathies will often cause a significant reduction in pain, and sometimes fatigue, the fatigue can often persist despite the reduced level of inflammation.

As there appear to be some important overlaps between fatigue and pain in ME/CFS and inflammatory arthritis, and the way they are treated, the CMRC is working closely with Arthritis Research UK and we are grateful for their support of this conference.

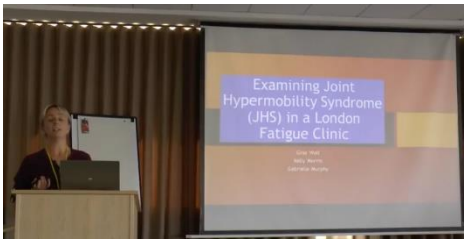
Research review: fatigue in musculoskeletal conditions

Prof. Alan Silman – video presentation

7. Mrs Gina Wall – Royal Free Hospital, Liverpool

Mrs Wall is a chartered physiotherapist who works at the Royal Free Fatigue Service and has an interest in hypermobility syndromes – which appear to be more common in ME/CFS.

She explained how hypermobility syndromes are caused by what appears to be an inherited defect in the production of collagen – an important chemical substance that provides biological scaffolding for a variety of tissues and ligaments, especially those involved in maintaining the strength and stability of joints.



She then spoke about her research that has been looking at the prevalence of joint hypermobility in ME/CFS (possibly affecting around 25%), the diagnosis of hypermobility – the use of the Beighton scoring system, and the symptoms that hypermobility (where it occurs) can cause in people with ME/CFS.

Mrs Gina Wall – video presentation

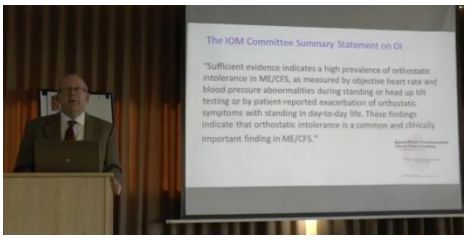
8. Professor Peter Rowe – John Hopkins Children's Centre for CFS, Baltimore, Maryland, USA

Professor Rowe is a paediatrician with a longstanding research interest in orthostatic intolerance, neurally mediated hypotension and PoTS in ME/CFS.

He reviewed the history of how orthostatic intolerance (i.e. a clinical condition where various symptoms are produced or exaggerated in an upright position) came to be recognised as a core symptom in ME/CFS and some of the key research papers that have been published from his group in America and from Julia Newton here in the UK.

He then went on to describe some of the key research that has been looking at the possible cause of OI symptoms – especially the changes in cerebral (brain) blood flow when a change in posture occurs.

It was good to hear him emphasise the fact that orthostatic intolerance should be regarded as a core symptom in ME/CFS as it is in the Institute of Medicine report recommendations on diagnostic criteria.



He was (quite rightly) very critical of the NICE guideline on ME/CFS for failing to acknowledge this fact and omitting any information on how to manage OI, orthostatic hypotension and PoTS.

This presentation also covered some of the drug treatments – including Florinef and Ivabradine – that have used to treat more severe symptoms. Peter led a Workshop on managing OI in ME/CFS on the second day of the conference.

From Peter Rowe's presentation at the 2016 IACFS/ME conference:

'Among newer treatments for NMH and POTS are desmopressin (DDAVP) and ivabradine (Corlanor™). DDAVP causes the kidneys to retain water and therefore increase blood volume, which can rapidly reduce tachycardia and symptoms in POTS (Coffin sore throat, Heart Rhythm 2012). Ivabradine selectively inhibits the cardiac pacemaker and decreases heart rate. It is FDA-approved to treat heart failure, but works well to reduce heart rate in POTS without having to use a beta-blocker.'

More information: Prof. Peter Rowe – Orthostatic intolerance and treatment

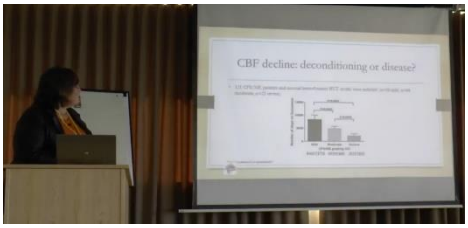
Prof. Peter Rowe – video presentation

9. Professor Frans Visser and Dr Linda van Campen – Cardiac Care Foundation, Netherlands

Professor Visser and Dr van Campen, are cardiologists who have developed a research interest in ME/CFS, especially the role of orthostatic intolerance.

They described some of their current research in this area, especially the use of tilt table testing and neuroimaging to examine the role of cerebral hypoperfusion (= decreased blood flow to key parts of the brain), and the use of pyridostigmine – a drug that is primarily used in myasthenia gravis – as a treatment option.

Dr van Campen explained how they had focused on determining whether reduced cerebral blood flow might be a result of deconditioning and how their research – which also used CPET testing and actometers – had concluded it was not.



Research: Efficacy of a half dose of oral pyridostigmine in the treatment of chronic fatigue syndrome: three case reports.

Prof. Visser – video presentation

Dr van Campen – video presentation

10. Professor James McCullagh – University of Oxford

Professor McCullagh is an expert in the use of mass spectrometry to measure metabolomic profiles in disease and is relatively new to ME/CFS research.

He has been working with Dr Karl Morten at Oxford and presented some preliminary results from the work he has been doing on blood samples sent from a new research group in Poland, who were also at the conference.

These preliminary results indicate that there could be some important abnormalities occurring in relation to chemical changes that take place during energy production at a cellular level. These are interesting and would link in with other research on pyruvate dehydrogenase that has recently been published.

Professor McCullagh and Dr Morten are currently working on a ME Association grant that will examine chemical clues left behind after changes in cells in 300 blood samples from the UK ME/CFS Biobank.

This metabolomic research study is based on the research from Dr Naviaux published last year which suggested that ME/CFS could be caused by the body going into a state of semi-hibernation.

Prof. James McCullagh – video presentation

11. Dr Joanna Elson – University of Newcastle

Dr Elson is an expert in mitochondrial muscle disease. She has been looking at the genetic material of mitochondria – mitochondrial DNA/mtDNA – and whether there are any obvious mutations in people with ME/CFS.

Her research has examined the complete mtDNA sequence of 93 ME/CFS patients from the UK and South Africa – where she failed to find evidence of clinically proven mtDNA mutations. This research demonstrates that clinically proven mtDNA mutations are not a common element in the aetiology of disease in ME/CFS patients.

Research: Clinically proven mtDNA mutations are not common in those with chronic fatigue syndrome

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Poster presentations:

Before the final talk on day one, we were given a series of 2-minute poster presentations. This was followed by a poster viewing session.

Most conferences now have what are called poster presentations - where researchers (often junior or PhD students) who are not doing a presentation produce a large poster outlining the key points about some research they have been doing.

The posters are then viewed at some point during the conference - but they are there all the time for other viewing. We decided (which I think is a good idea) to also include some 2 minute 'rapid presentations' of poster presentations during the main conference from 4 people who were presenting posters. We sometimes have a competition for 'best poster' but did not do so this time.

More details on the research posters – including one covering a study aimed at improving recognition of ME/CFS in Poland – will appear in the main conference report.

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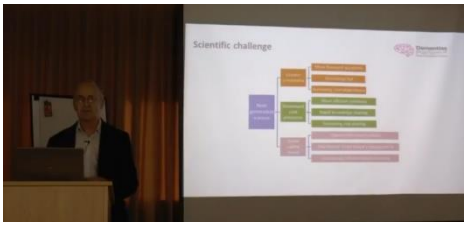
12. Professor John Gallacher – University of Oxford

Professor Gallacher closed the first day of the conference with a very interesting presentation on the government's 'dementia platforms'.



This is an impressive multi-million-pound private-sector partnership that aims to identify and answer some of the key questions in dementia research – hopefully leading to early diagnosis and more effective forms of treatment.

There are lessons to be learnt here in relation to taking forward ME/CFS research. We now know how this has been achieved in the case of dementia and discussion followed on about how a similar well-funded initiative really ought to apply to ME/CFS.

Prof. John Gallacher – video presentation

END OF DAY ONE

PLEASE HELP SUPPORT THE ME ASSOCIATION

If you have found this information helpful, then please donate – whatever you can afford – to help us continue with our research work to make the UK a better place for people with M.E.

Just click the button opposite to donate to our Ramsay Research Fund. We invest only in biomedical research studies and infrastructure projects, like the UK ME/CFS Biobank, and make no charge for administration.

Donate to us through mydonate BT The free online donation service

Or why not join the ME Association as a member and become a part of our growing community? For a monthly (or annual) payment you will not only be helping to keep us doing what we do best, but will receive our exclusive ME Essential magazine.

DAY TWO

13. Professor Julia Newton –University of Newcastle – and Dr Karl Morten – University of Oxford

Professor Newton and Dr Morten opened the second day of the conference with a presentation on what funders, researchers and other interested parties need to be doing to increase the amount of high quality research being carried out into the cause and treatment of ME/CFS – in particular the need to stimulate more collaboration between different research groups both here and overseas.

This was illustrated by the way in which the ME/CFS research groups in Newcastle and Oxford have been collaborating on muscle research – like the ME Association funded study which is assessing the validity of the Acumen test for mitochondrial function. Overseas collaboration with a research group in Poland, where ME/CFS is barely recognised, was also described.

> The research relating to Acumen has encountered several challenges trying to validate this test – which they have so far failed to do – and in finding a way of accurately measuring ATP levels. The results of this research will be submitted for publication in due course.

Dr Morten, an expert in mitochondrial function, has been funded by the ME Association to carry out research into mitochondria and ME/CFS.

He described some of the research taking place in Oxford and the way in which new investigative techniques are becoming available.

One example here being 'Seahorse", which can provide important new information on the role of mitochondria (intracellular structures that play a role in many disease processes – not just muscle).

These presentations were followed by a general discussion, which was initiated at the conference dinner the night before, on factors that both weaken and strengthen research collaboration.

Prof. Newton and Dr Morten – video presentation

14. a. Professor Carmine Pariante – King's College Hospital, London

Professor Pariante has been carrying out a very interesting MRC funded research study which is examining the effect on markers of immune system activity when patients with hepatitis C infection are given a treatment called interferon alpha.

When this treatment is given, a significant proportion of hepatitis C patients develop side-effects, including fatigue, which might be considered to mimic symptoms relating to ME/CFS.

These are thought to be caused by the production of what are called pro-inflammatory cytokines such as interleukins 6 and 10 (which were measured in this study). Many of those with fatigue continued to experience this symptom for several months after treatment had stopped.

CS note: This study is probably the nearest human model we have that creates an ME/CFS-like illness that can be used to examine the effect on immune system regulation during the very early stage of illness, *without the use of an infection*.

The results, which are being prepared for publication, contain some very interesting observations that could make an important contribution to our understanding of the sequence of events that do follow a triggering viral infection in ME/CFS. If, that is, we are looking at a process that involves an abnormally exaggerated and persisting immune system response, possibly because of a genetic predisposition.

Prof. Pariante – video presentation 1

b. Professor Carmine Pariante – King's College Hospital, London

Professor Pariante continued with a second presentation on research that is examining the role of inflammation in depression and the fact that some people with depression have raised levels of pro-inflammatory cytokines (interleukin 6) – which may therefore be a key factor in maintaining some cases of depression.

He also discussed the role of hypothalamic-pituitary-axis dysfunction in depression and ME/CFS – because people with depression may have raised levels of cortisol whereas those with ME/CFS tend to have lowered levels of cortisol.

The curious fact that some people with depression have raised cortisol and immune system activation at the same time (when cortisol causes immune system depression) could be explained by the development of glucocorticoid resistance.

Professor Pariante referred to some interesting results from clinical trials where anti-inflammatory drugs had been effective in some forms of depressive illness.

Infliximab, a powerful anti-inflammatory drug and tumor necrosis factor antagonist – (this has a similar mode of action to the monoclonal antibody drug rituximab that targets immune system B cells) – has also been used as an experimental form of treatment in people with resistant depression who have high levels of inflammatory markers.

More information: Infliximab, rituximab, and other drugs in this group.

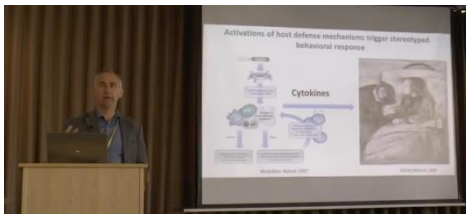
Research: A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers.

Prof. Pariante – video presentation 2

15. Professor Esther Crawley – University of Bristol

Professor Crawley gave an update on her MRC funded research which has been looking at the prevalence and possible risk factors (especially sleep and activity levels prior to becoming ill) that may be involved in the development of childhood and adolescent ME/CFS. This research is making use of the ALSPAC cohort. Several papers have now been published on this research.

16. Dr Neil Harrison – Brighton and Sussex Medical School



Dr Harrison spoke about the role of neuroimaging in ME/CFS and two new research studies that he is involved with – both of which are about to start recruiting in the Brighton and Sussex area.

The first is on the neurobiology of post-exertional fatigue and is being funded by the MRC. The study is using MRI scans to investigate the core symptom of post-exertional malaise in 20 people with ME/CFS and 20 healthy controls. This will involve blood testing for immune system changes and MRI imaging (to see what happens in the brain) before and 24 hours after an exercise challenge.

The second study, which is involves rheumatologist Professor Kevin Davies, is being funded by Arthritis Research UK. This will be focusing on pain and whether there is an exaggerated

response following an inflammatory (i.e. typhoid vaccine) and autonomic nervous system challenge.

Dr Harrison also covered:

- the role of what is called 'sick behavior' (the natural physiological response to acute infection that involves fatigue, cognitive impairment, withdrawal, anorexia, and increased pain sensitivity),
- the role of the vagus nerve (during immune system activation),
- what happens when cytokines enter the central nervous system (during an acute episode of virus or vaccine induced immune system activation),
- microglial activation following immune system challenges, and,
- the possible role of specific centres in the brain – like the insula cortex and substantia nigra – in symptom development in ME/CFS.

This was an excellent presentation on a very complex area of neuroscience – so the video is well worth watching if you are interested in this topic.

More information: ME Association report from 2015 CMRC conference on the MRC funded study into PEM

Dr Neil Harrison – video presentation

17. Dr Jade Thai – University of Bristol

Dr Thai described the results of her survey of all the neuroimaging studies – structural and functional MRI scans, PET scans, etc - that have been carried out between 1991 and 2016 in ME/CFS and published in the medical journals.

Although we now have a considerable number of studies in this area, many of them have used small numbers of patients and produced inconsistent results. What is needed are much larger studies, longitudinal studies (i.e. following changes over the course of time) and multi- site studies that make use of multimodal neuroimaging.

18. Phil Murray and Rachel E Patient Advisory Group – MEGA bioresource project

Mr Murray gave an excellent presentation on how patients can play a constructive and (where necessary) critical role in helping to develop research protocols. Rachel gave an equally good presentation from home via video recording.

Workshops

Part of the final afternoon was then devoted to a choice of three Workshops covering:

- The management of orthostatic intolerance – Prof. Peter Rowe, John Hopkins Children's Centre for CFS
- How can we work better together to drive scientific breakthrough in ME/CFS? – Dr Mark Edwards, ST&I Partnerships, and,
- Daily fluctuations in fatigue: using technology to identify patterns, predictors and potential solutions – John McBeth and Katie Druce, University of Manchester

19. Dr Mark Edwards – ST&I Partnerships – Pharmaceutical Industry

Dr Edwards led the afternoon workshop that I attended on how the patient community, researchers, clinicians, and the pharmaceutical industry, can all work together to drive scientific breakthroughs into both causation and management of ME/CFS.

Among the topics discussed were how to get the pharmaceutical industry interested in drugs where there is already some existing evidence of efficacy (e.g. valganciclovir and melatonin) and cases where drugs used in other conditions could be useful in ME/CFS (e.g. rituximab).

20. Professor Jose Montoya – Stanford ME/CFS Initiative, Stanford, California, USA

Professor Montoya had flown over the same day at his own expense to give the Ann Faulkner Memorial Lecture – which closed the meeting.

This was another excellent presentation covering the extremely thorough research work that his team are conducting in relation to cytokine regulation, viral reactivation involving HHV6, and the role of antiviral drugs – valganciclovir in particular – in the management of carefully selected patients with ME/CFS.

More information: Stanford ME/CFS research initiative

Key Research (1): Cytokine signature associated with disease severity in chronic fatigue syndrome patients

Key Research (2): Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome

Prof. Montoya – video presentation (50 mins.)

End of 2017 CMRC research conference

Professor Stephen Holgate closed the conference by thanking everyone who had helped to put this meeting together, noted the way in which several new collaborations had occurred as a result, and indicated that new initiatives, including a research conference for the patient community, would now be followed up.

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