

19th & 20th September 2018

The ME Association Summary report

The 5th annual CMRC conference, Bristol

UK CFS/ME RESEARCH COLLABORATIVE



wellcome trust



“ME/CFS: The last medical enigma of the 21st century.”
Professor Alain Moreau, CMRC 2018.

Charlotte Stephens

8TH OCTOBER 2018

Forward

The aim of the CFS/ME Research Collaborative (CMRC) is to promote the discovery of the biological mechanisms that underpin CFS/ME, which will drive the development of targeted treatments. The ME Association is an active board member of the CMRC.

- Background: [The CFS/ME Research Collaborative](#)

The 5th annual CMRC conference was held in Bristol on the 19th and 20th of September. There was a very high turnout, which included researchers from the UK and overseas, health professionals, academics, students, people with ME/CFS and carers.

It was two days full of interesting talks, exciting new findings and a general sense of passion for biomedical research. There was also lots of stimulating discussion and networking taking place among the professionals, as well as a chance for people with ME/CFS and carers to give feedback during workshops and to ask questions of the researchers.

The resounding feel from this conference was a much greater sense of focus and direction. There seemed to be a tacit agreement among researchers that there exist multiple subgroups within the ME/CFS cohort, each with different pathologies, and a need for them to be identified and separated – in order to create more targeted diagnosis and treatments.

There was a wonderful metaphor used, referring to the subgroups as “different types of elephants” – ME/CFS being the elephant in the room – and that what works for one group will not necessarily work for another.

Another point that all speakers seemed to agree on is the lack of funding available for ME/CFS research. This situation has not enabled the large studies that are required to create reproducible results and make progress in the field. However, Professor Moreau commented, things are looking more positive, with the National Institutes of Health (NIH) in America seen to be setting the standard.

The Medical Research Council (MRC) – who contributed financially to the conference – still have the [highlight notice](#) in place for ME/CFS research. It tries to raise the profile of this condition in an attempt to attract more researchers to field.

Both the MRC and National Institute of Health Research (NIHR), are working with the CMRC on separate initiatives to also try and improve the biomedical research funding situation.

Videos of most of the presentations from the conference will [be available on YouTube](#) later in the week. However, the talks are quite lengthy and often filled with scientific jargon.

Some of the speakers declined to be filmed due to the presentation of unpublished data. There are also similar constraints in the presentations given by Professor Alain Moreau, Tiffany Lodge, Dr Neil Harrison, Dr Elisa Oltra, Dr Jackie Cliff and Cara Tomas, where significant new research findings have not yet been published.



This is because the scientific journals do not like to see this type of publicity before a paper has been accepted and published in the journal.

Therefore, this report offers an approved summary of each talk, in the order in which they occurred.

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1. Welcome and Introduction

Professor Stephen Holgate (University of Southampton) CMRC Chair.

Professor Holgate is such a fundamental part of the conference and always gives brilliant introductions to each speaker, as well as insights and comments when linking each section of the conference together.

He started by expressing the need for a single international voice and emphasising that collaboration is key. He also commented on the valuable contributions of the Patient Advisory Group.

Being the 5th annual conference, there was a reflection on what they have achieved so far, followed by a look at where efforts need to be concentrated going forward and what needs to be done politically and scientifically, with a focus on evidence for causative factors.



He talked about a new initiative with the [James LIND alliance](#), in which patients and clinicians get together and help determine research priorities for a given illness that are then published. Working with this group is now a priority for the CMRC.

- [For more about the James Lind alliance see CMRC minutes from July 2018](#)

Professor Holgate commented that biological research is moving forwards at a tremendous rate and that real progress is being made. Also, that it's good news that other organisations are taking an interest in 'chronic fatigue' as a potentially common symptom (such as Arthritis UK and [The Kennedy Trust](#)), which is important in moving the agenda forward nationally.

He reported that the National Institutes of Health (NIH) is making tremendous progress in America and that they have now funded 4 ME/CFS research centres. The CMRC is currently trying to link with them in the UK to form an international alliance and to collaborate and share data.

His speech ended by saying that it had been a slow start for the CMRC, and it has taken a long time to get to where they are today.

But the pace of progress is certainly picking up and they are now in a position to apply pressure on UK funding bodies for high quality research to "uncover the mysteries of this devastating disease".

2. The views of a Doctor with ME on educating Doctors and medical students about ME

Dr Nina Muirhead (Buckinghamshire Healthcare NHS trust)

Dr Muirhead is a speciality doctor in dermatology and Oncology, as well as a teacher of Junior doctors. She fell suddenly ill with glandular fever at age 36, which, like many others, subsequently developed into ME/CFS.



Dr Muirhead mentioned that her grandmother and aunt were both also thought to have suffered with the illness. And, based on her own experience, she came to realise that many GP's either had little understanding of ME/CFS, or that they simply didn't believe in it.

She said that the NICE guideline "didn't even come close" to what she was experiencing. Astounded that ME/CFS wasn't something that was taught about in medical school, she has set out on a mission to educate doctors:

"We need to revolutionise the thinking from a biopsychosocial model to a biomedical model."

Improve education for medical students

Dr Muirhead has sent out a questionnaire to try and find out if medical schools currently have ME/CFS on the syllabus for medical students. She has asked them what it is they are teaching, if students are being tested, and if the content is being delivered by psychologists.

Her aim is to introduce ME/CFS into the medical school curriculum and she is currently conducting a pilot trial in Cardiff, consisting of E-learning and lectures. If this is successful, she will take her program proposal to the medical education board for implementation into all medical schools.

She closed by saying:

"...there is a lack of infrastructure to support doctors caring for ME/CFS patients and this needs to change."

This was a very engaging talk and Dr Muirhead's passion shone through it all. I would definitely recommend watching the video.

I think it is wonderful that she is using her medical background and illness experience to help bring positive change to the care that people with ME/CFS receive through better education of medical students.

She is also working with Forward ME to help ensure her initiative gains wide support with charity members. It has certainly impressed the ME Association!

3. Identification of post-exertional dysregulated circulating microRNAs in ME/CFS pathogenesis

Professor Alain Moreau (University of Montreal)

Professor Moreau is a relative newcomer to the field of ME/CFS, who, like many other researchers, became interested in it due to friends and family members with the disease.

“The last medical enigma of the 21st century.”

Professor Moreau presented a dynamic model of ME/CFS, stressing that genetic and environmental interactions are important.

He said that there is probably some genetic predisposition to the disease which is then triggered by environmental factors such as infections and chemicals.

He used this apt depiction of an elephant to explain how, in ME/CFS research, there seems to be lots of people specialising in specific areas and no one is really looking at the “whole picture”, suggesting this is why collaboration is so important.

His Hypotheses is that ME/CFS is caused by a disturbance in the expression of microRNA's, which modulate the immune function, energy metabolism and physiological stress response.

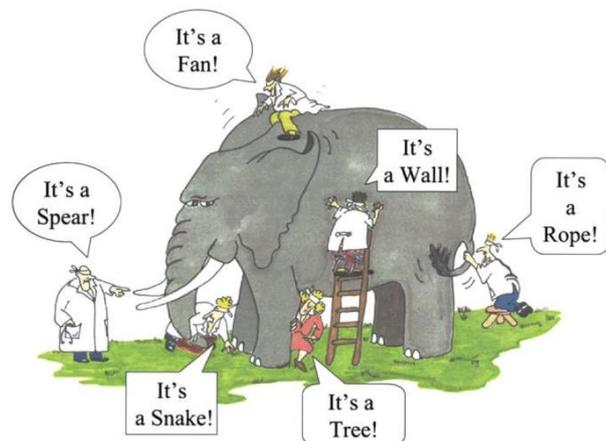
The purpose of his study was to identify circulating miRNAs linked to the disease, in order to better understand the cause.

- Note: miRNAs are small molecules that can affect the expression of certain genes and therefore the production of certain proteins. miRNA's can be used as biomarkers for diagnosis and therapeutic drugs can modulate their effects.

A test for PEM without involving exercise...

Professor Moreau's team developed a 'stress test' to reproduce post-exertional malaise (PEM) in patients, without the need for exercise. This involved wearing a cuff (similar to a blood pressure cuff) that massaged the arm.

They took blood samples from the participants (including mostly bed-bound ME patients, and healthy controls) before and after the “stress test” and then analysed the levels of circulating miRNAs in the blood.



This stimulation was so gentle that it failed to produce a response (a change in miRNA levels) in healthy controls, but it did in those with ME/CFS.

They found that in ME/CFS there was a distinctive molecular footprint (an expression of different levels of miRNAs) at baseline and after stimulation (with the stress test), compared to controls.

They also found that the differences in the stress-activated levels of miRNAs (representing PEM) were more specific than the ones at baseline; some levels increased after stimulation and some decreased, compared to controls.

The results were very preliminary and still undergoing analysis and so are not conclusive, but they seem promising and appear to agree with the findings from other studies in this area.

Among the main miRNAs found to be different in ME/CFS was a miRNA that regulates IL-10 (a cytokine often found to feature in the disease), miRNAs involved in the receptor (SLC6A2) responsible for norepinephrine reuptake.

Phenotypes

Perhaps more interesting than the individual miRNA differences themselves was what Professor Moreau said was the most important finding from this study; that there are subgroups of patients.

Using molecular profiling of the miRNA levels in the ME/CFS samples, he was able to separate them into 4 distinct subgroups, shown by differences in the levels of circulating miRNAs that also correlated with symptoms and differences in response to fatigue questionnaires taken from the patients.

This means that we cannot 'lump' all ME/CFS patients together in studies as it is going to 'blur' the results; we must first separate them out into their distinct subgroups and then study the causes and potential treatments for each group as what works for one group may not work for another.

The team are currently carrying out a replication study in the same cohort two years later, to see if the test is robust and if they get the same results.

Then they will validate these selected miRNAs in a larger cohort and try to replicate the findings. If validated, these could be used to develop specific diagnostic tests, as well as potential drug targets.

4. European collaboration in ME/CFS: The EUROMENE network

Dr Eliana Lacerda (London School of Hygiene and Tropical Medicine; CureME)

The EUROMENE network's aim is to establish a multidisciplinary approach to research and to form collaborations across research groups throughout Europe.

Their objectives are to collect population-based data and establish a synchronised European database in order to access potential biomarkers.

- More info: The ME Association [summary report](#) on EUROMENE



Dr Lacerda came to report on the progress of the EUROMENE network in the last year. They have set up 6 working groups, focusing on different key areas; Epidemiology, Socio-economics, Biomarkers, Clinical research and diagnostic criteria, Conferences and seminars and patient involvement.

There are currently 2 annual meetings per working group, as well as 2 annual management and core group meetings. There are currently 36 countries participating in the network and they are trying to recruit more.

- Worth a look: EUROMENE recently published [an interesting review of all evidence](#) pertaining to chronic viral infection and ME/CFS

The current challenges they're are facing include lack of funding, lack of involvement by some countries, ethical requirements and the effects of BREXIT.

Moving forward, they're immediate projects include trying to map existing resources, seeking agreement for a standardised protocol for ME and raising awareness and education.

5. What will it take for the pharmaceutical industry to engage in CFS/ME drug discovery?

Dr Mark Jonas (UCB Pharma)

Dr Jonas came to the field after his daughter fell ill with ME/CFS.

After delivering a heart-felt story of her illness experience, he showed a video about personalised medicine, that included his daughter.

Dr Jonas then went on to highlight the key barriers that are in the way of drug development and delivery.

These include, regulatory bodies, who weigh up the benefits of the drug against the risk of side effects, and NICE, who assess the cost-effectiveness of a drug.



Looking at what current drugs we could be using to help alleviate ME/CFS symptoms and improve quality of life, instead of trying to develop new ones, could also be a valuable approach. The need for patient feedback from advisory groups is also important.

Emphasis for the need to move towards precision medicine (or personalised medicine) was conveyed.

This involves looking at particular biomarkers that will allow more precise targeting of drugs, in order to determine who will respond best based on their genes, rather than through the process of trial and error.

He stressed the need to identify the subgroups within ME/CFS with a clear phenotype in order to identify specific drug targets.

6. The Economic impact of CFS/ME

Dr Rachel Hunter (University College London)

Dr Hunter explained that her job as a health economist is to look at health care costs, social care costs, admissions cost and loss of productivity (cost to the individual and society) of a disease.

She puts these costs together and presents them to the Government and says, 'This disease is costing you X amount, which could be 'wiped away' if a treatment was available.'

She found that only 6 studies (and only 2 in the UK) have been carried out looking into the economic cost of ME/CFS and that these studies were very small and of poor quality.



Biggest cost is loss of productivity

Previous studies had found very low health care costs, probably due to the fact that there is no effective treatment available or that people with ME/CFS are simply too ill to seek care or attend medical appointments.

- It was not clear if Dr Hunter had included [the most recent economic cost estimate report](#) published in 2017 by 2020Health in her study. It found an annual total cost of £3.3bn.

The biggest cost of ME/CFS was found to be from loss of productivity (people not able to work). These studies combined suggested an overall cost to the government of £110 million per year.

Dr Hunter is currently collecting data from the UK ME\CFS Biobank in order to calculate her own estimate of costs.

Her data analysis is still in progress but, so far, she has found that health care spending costs are hard to judge as there is a lack of access to healthcare and no effective treatment.

Unsurprisingly, she found that people with ME/CFS are less likely to be in employment and are more likely to be in receipt of benefits (estimated at around 66% of the patients from the Biobank).

The cost of benefits was calculated at £170 million per year. The difference in average annual income between a healthy person and someone with ME/CFS was around £10,844.

This means that in lost productivity alone, ME/CFS is costing the government nearly £1 billion per year. And demonstrates just how important it is to develop effective treatments from an economic and political perspective.

7. CFS/ME, IBS and Fibromyalgia: Chance association or common pathway?

Rachel French (County Durham & Darlington NHS Foundation Trust)

Ms French, who is a surgeon specialising in gastroenterology, has been looking into the possible link between ME/CFS, IBS and Fibromyalgia.

All three conditions are diagnosed; based on reported history and symptoms, with no 'formal' diagnostic tests. There is strong anecdotal evidence for a link as they are often diagnosed together.

She carried out a database search and the reported prevalence of each shows that they are all co-morbidities of each other and there are many studies on the association between ME/CFS and Fibromyalgia.



It was also demonstrated that people with ME/CFS and Fibromyalgia are more likely to have bowel disorders.

Ms French suggested there may be a common pathophysiological pathway for all three of the conditions, either linked by infection, genetics, microbiome or autonomic dysfunction.

She is currently carrying out a questionnaire-based data collection to try and determine if these conditions pre-dispose each other.

8. Twins and the study of chronic pain genetics

Professor Frances Williams (Kings College London)

Twins UK is a charity that collects data in the form of questionnaires and biological samples (blood, saliva, urine) from twins throughout their lifetime.

This enables the study of genetics and environmental factors involved in the development and progression of various diseases.

Professor Francis and her team has recently conducted a study on pain genetics in which twins underwent a pain test using increasing heat, in order to identify variants influencing pain perception.



The results revealed that the more 'insensitive' people to pain had a higher number of rare genetic variants. Also, the risk of experiencing chronic pain increases with increased age and BMI.

They have also shown that chronic pain syndromes (including IBS, Fibromyalgia and chronic pelvic pain) are heritable diseases and their results suggest that having a chronic pain genetic disposition is 68% heritable and neuropathic pain is 37% heritable.

Furthermore, Chronic widespread pain and neuropathic pain were shown to have shared genetic factors.

9. The UK ME/CFS Biobank: Accelerating global research in ME/CFS

Dr Luis Nacul (London School of Hygiene and Tropical Medicine; CureME)

The UK ME/CFS Biobank stores and manages a wide range of biological samples, as well as clinical data, taken from patients and controls with for use in research.

The benefit of the Biobank for researchers is that the samples are standardised, and quality assured and it's time and cost effective.

The data can be used to formulate and test hypothesis, to look at disease pathways, for biomarker discover and for investigating disease subgroups.

The Biobank includes patients with ME/CFS of all disease severities, ranging from ages 18 to 60, who have a medical diagnosis and who also meet the CCC, CDC-94 and IOM criteria.



They also have samples and data from healthy and Multiple Sclerosis (MS) controls. All patients will have a 5-year follow-up on their data in order to see any changes in disease progression.

The Biobank currently has over 30,000 aliquots of blood samples stored. They also have clinical data, such as blood pressure, BMI, routine lab tests and hand grip strength, as well as questionnaire data such as quality of life and pain and fatigue scales. All of the data is confidential and ethically approved.

- More info: [The UK ME/CFS Biobank](#)

The samples have already been used by researchers in the US, Canada and countries in Europe, as well as in the UK.

Dr Nacul also showed that the samples are not only used in biomedical research; the data has been used for health education and socio-economics.



For example, he showed an analysis of the data that found that ME/CFS is more disabling (a worse quality of life) than MS – in particular ME/CFS was found to be more physically disabling.

The UK ME/CFS biobank is a valuable open resource for both academic and commercial use.

Dr Nacul feels that this is the way forward in research; to have a network of ME/CFS bio-resources and to share data globally.

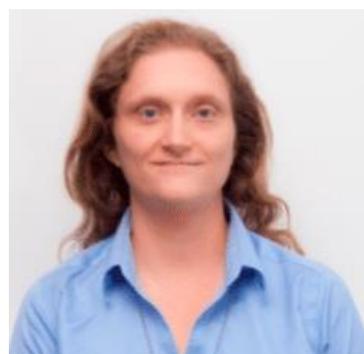
The ME Association Ramsay Research Fund covers all the basic running costs of the ME/CFS Biobank and the steering group is chaired by MEA medical advisor, Dr Charles Shepherd.

10. Investigating the possibility of a role of mtDNA variation in ME/CFS

Jo Elson (Newcastle University)

Ms Elson started investigating the role of mitochondrial DNA (mtDNA) mutations in ME/CFS after finding that 50% of people with mitochondrial dysfunction reported severe fatigue. However, mitochondrial dysfunction is not found to be higher in the ME/CFS population.

After completing 270 mtDNA sequences from ME/CFS patients, her group found no confirmed mutations at a level sufficient to cause a biochemical defect. Therefore, ME/CFS does not fall into the spectrum of classical inherited mitochondrial disease.



Next, she looked into the possible role of mtDNA variants (or polymorphisms) in the susceptibility to ME/CFS. She found that the majority of people with ME/CFS have no deleterious mitochondrial DNA variants.

There was a significant difference between controls and ME/CFS patients; that more of them have no deleterious variants. This observation has also been replicated, so is not a chance find.

She concluded that classical mitochondrial dysfunction, relating to ATP production, is most likely not the problem in people with ME/CFS.

However, she proposed that there may be a problem with the cells utilising the ATP that is produced. Also, she pointed out that she was only focusing on mitochondrial defects in relation to the production of ATP.

Mitochondria are involved in many other processes, such as immunity and cell signalling, which may be where the fault lies that is causing the disease pathology.

11. Alteration of cellular metabolism observed in muscle cells, indicating possible factors present in plasma of patients with ME/CFS capable of modifying cell function

Tiffany Lodge (University of Oxford)

Ms Lodge presented some hot-off-the-press initial results coming from one of the studies being carried out by Dr Karl Morten's research team at Oxford University.

This relatively small pilot study, funded by the ME Associations Research Ramsey Fund, was investigating the effect of factors present in the plasma of ME/CFS patients on metabolic function.

They used a fluorescence intracellular oxygen sensing probe to detect changes in oxygen levels of muscle cells in response to plasma treatments.

They took muscle cells from healthy controls and applied plasma from healthy controls to one sample and plasma from ME/CFS patients to another.

Unfortunately, we cannot share the results until they are published.

More information:

- [Update on metabolomics research with Dr Karl Morten at Oxford](#)
- [The use of Raman spectroscopy in the search for biomarkers at Oxford](#)

12. Effects of whole-body cryotherapy among CFS patients- preliminary results

Pawel Zalewski (Nicolaus Copernicus University, Poland)

Mr. Zalewski started off by saying how poorly recognised and understood ME/CFS is in Poland and that it is gravely underdiagnosed.

In Poland, cryotherapy has been recognised as a safe and effective therapy option for a range of different conditions.

He commented, to polite amusement from the audience, that:

“In Poland, cryochambers are commonly used but ME/CFS doesn’t exist. In the UK, ME/CFS exists but people are afraid to use cryochambers!”

Cryostimulation is the most extreme stimulation you can apply to organs. However, cryotherapy is different to cold water immersion therapy as there is no water involved, it produces no pain and is less of a sudden shock to the body.

It produces acute and delayed strong modulatory effects on the cardiovascular system, as well as on the sympathetic and parasympathetic nervous systems and the immune system.

This presents as a safe alternative to exercise for those that are exercise intolerant as it produces the same effects on the body.

Recruitment of patients for the study was very thorough, with a lot of exclusion criteria and assessments. However, half of the recruited patients dropped out as they did not like the therapy (couldn’t tolerate the cold)!

The therapy involves patients sitting in a cryochamber at -120°C for 3 minutes (built up in increments of 30 seconds), followed by some gentle stretching for 30 minutes after.

The preliminary results showed that cryotherapy improved autonomic symptoms and the patients reported significant improvements. However, it is too early to determine how long-lasting these results will be.

13. MRC-funded update: Imaging exercise-induced Post-Exertional Malaise in ME/CFS

Dr Neil Harrison (University of Sussex)

Dr Harrison’s hypothesis is that people with ME/CFS show a heightened and more persistent inflammatory response to stressors (e.g. exercise) that disrupts healthy brain function.

His research team are conducting several studies (using the same set of data) looking at a cardinal symptom of ME/CFS, post-exertional malaise (PEM), through the use of cardiopulmonary exercise testing (CPET).

The study is still on-going, and they hope to recruit 20 patients and 20 controls all together, but the preliminary findings from the 10 patients and 5 controls that have taken part in the study so far were presented.



The study

Data collected from the participants include blood samples, questionnaires and a series of different brain images taken before and after the exercise challenge, which is repeated after 24 hours.

Prior to each exercise test, participants are also given an interoceptive heartbeat tracking task, to see how good they are at reading their bodies physiological symptoms (known as interoceptive accuracy). Blood pressure and electrocardiograms (ECG) were also taken at rest pre-exercise.

The exercise test involves cycling on a stationary bicycle for 8-12 minutes (or until they ask to stop), whilst recording physiological markers of exercise performance, including heart rate (HR), total exercise time, power output, oxygen consumption (VO₂), expired carbon dioxide (VCO₂), ventilation (VE) and respiratory exchange ratio (RER).

Perceptual markers of performance, including rate of perceived exertion (RPE) and rate of fatigue (ROF) were also taken at baseline, during and 5 minutes after exercise.

Aims and results

1. The first aim is to investigate how physiological and perceptual markers of exercise performance change during a standard incremental CPET in ME/CFS patients.

The measures taken during the exercise test at ventilator threshold (VT) and peak performance were compared between the patient and control groups.

At VT (the point where lactate first begins to accumulate in the blood), oxygen consumption (VO₂) and rating of fatigue (ROF) were higher in the ME/CFS group compared to the controls, despite no differences in perceived exertion (RPE).

However, at peak exercise, oxygen consumption (VO₂), power output, HR and total exercise time were all higher in the controls, whereas RPE and ROF were both higher in the ME/CFS group.

These preliminary findings suggest that individuals with ME/CFS have a lower tolerance to exercise and higher fatigue rating during all stages of the test, showing a physiological and perceptual difference compared to controls.

2. The second aim is to investigate whether awareness of changes in internal physiological state (called interoceptive awareness) is altered in ME/CFS and how this relates to exercise performance and exercise-induced PEM.

The preliminary results show that on day 1 of the exercise testing, interoceptive awareness positively correlated with VO₂, VCO₂ and RER and negatively correlated with rate of perceived exertion (RPE) at ventilator threshold (VT) (meaning those that had a better awareness had better respiratory readings and had a lower rating of perceived exertion). However, on day 2 of testing, these correlations had markedly reduced in all but RER (respiratory exchange rate).

On day 1 at peak exercise, interoceptive awareness positively correlated with RER and VCO₂, but on day 2 these effects also became small. However, large positive correlations were present between

interoceptive awareness and power output and total exercise time (meaning those with better awareness were able to perform better and for longer on the exercise test).

These preliminary results link awareness of interoceptive signals with respiratory processes during incremental exercise prior to the development of PEM and with exercise performance during PEM. This suggests that abnormalities in visceral signalling may contribute to PEM in ME/CFS.

3. The third aim is to compare the stability of physiological and perceptual exercise parameters during repeated CPET testing (24 hours apart) between individuals with ME/CFS and healthy controls.

The preliminary results show that at peak exercise, patients showed decreases in oxygen intake (VO₂) and total exercise time between day 1 and day 2; an effect that was not observed in controls. Power was also reduced between the days, but this was also observed, to a lesser extent, in controls. Additionally, patients reached a higher RER and HR on the second day compared to controls.

The ME/CFS group reported higher rate of fatigue (ROF) on both days compared with controls, but the scores were higher on day two compared to day 1, at rest and during exercise.

These results show a decline in both physiological and perceptual exercise parameters in people with ME/CFS that was not observed in controls. This suggests a potential physiological basis for perceptual experience of fatigue and PEM.

Dr Harrison's team will also be using advanced brain imaging in order to understand more about the neuronal networks that underlie the neurobiological basis of PEM in ME/CFS. They will compare advanced brain imaging data in concert with changes in blood markers and behavioural data before and after exercise.

Recruitment and data collection for all parts of this dynamic study is still ongoing and so a larger data set will be presented next year, from which more conclusive results can be drawn.

They hope to complete the study by early 2019 and the initial data analysis by mid-2019.

Day 2

14. Anne Faulkner Memorial Lecture: Big health data and open science: a powerful combination to generate new understanding of disease

Professor Cathie Sudlow (Chief scientist at UK Biobank)

Professor Sudlow gave an informative talk on ‘Big data’ and the value of perspective studies in research and how the UK Biobank is doing this.

Big data is a large volume of data, a large variety of data or data that is increasing at a high velocity or that is of significant value.

Only 10% of all Big Data is ‘structured’ data, meaning it is easily accessible and easy to analyse. The other 90% is unstructured (or unprocessed) data that is not easy to make sense of or use, for example ECG’s and medical images such as brain scans.



Professor Sudlow explained the need for more of this big data for ease of use in research. She also stressed how important it is to have very large sample sizes, especially in genetic studies, to be able to identify differences. Larger numbers of participants allow for clearer patterns and more accurate findings.

The UK Biobank is trying to collect large scale ‘big data’ to create a prospective population-based cohort. This means gathering data from large numbers of healthy people and following them up regularly throughout their life to see changes.

It would enable them to see diseases developing within that population and determine what factors might have led to the disease. This could also allow the study of the effects of potential risk factors on a range of diseases, for example smoking or hormonal birth control.

The UK Biobank currently have over 500,000 people recruited, between the ages of 40 and 69. They have taken clinical data, biological samples (blood, urine and saliva), questionnaires, genotyping, biochemical panels and multimodal imaging (MRIs, brain scans) and have been following up the participants long-term.

Medical records taken from hospitals and GP surgeries can be used for ‘follow-up’ data, with permission. All of the data stored by the biobank is open access for approved research groups and has currently been used by many researchers worldwide studying a wide range of different diseases.

Professor Sudlow also highlighted the challenges with large prospective studies, such as follow-up being hard (getting people back for testing) and also security issues with accessing primary care data.

15. Differential microRNA profiles in PBMC's and plasma EVs of severely affected ME/CFS

Dr Elisa Oltra (Universidad Católica de Valencia, Spain)

MicroRNAs (miRNAs) regulate genes and can modulate the expression of certain proteins. They are a good candidate for biomarkers of disease.

Dr Oltra's team studied differences in miRNA expression in two types of cells in 15 people with severe ME/CFS and 14 healthy controls to try and identify potential biomarkers of disease.

These two cell types were peripheral blood mononuclear cells (PBMC) (white blood cells) and plasma extracellular vesicles (EVs).

Biochemical panels taken from blood samples of the ME/CFS patients revealed significant differences in clinical parameters, which might aid in clinical diagnosis.



Extracellular vesicles (EV) are small 'packages' that are released into the blood from the cells of different organs, as well as from bacteria in the gut. They are involved in long-distance cell communication throughout the body.

Dr Oltra found ME/CFS patients had an increased number of extracellular vesicles (EVs) when compared to those obtained from healthy individuals.

This feature has been formerly associated with diseases presenting a relevant inflammatory component and agrees with the results published this year by Dr Alegre's group from Hospital Vall d'Hebron, Barcelona, Spain.

miRNA profile analyses revealed over- and under-expression of several specific miRNAs in both cell types from the ME/CFS patients. The top overexpressed miRNAs in EVs found in this study are abundantly expressed in tissues commonly affected in ME/CFS patients, such as muscle, brain and thyroid gland.

In general, the differences found were more pronounced in the EV's than in the PBMC's, suggesting that EV's might be a more sensitive fraction for measuring changes in miRNA expression.

Interestingly, Dr Oltra added that many of the miRNA's found to be altered in her study match those found to be altered in previous studies, as well as those reported by Professor Alain Moreau from his study, presented on day one of the conference (see above).

Larger studies need to be carried out in order to validate these miRNA's in order to identify a reliable biomarker. Evaluation of the cellular pathways linked to deregulated miRNAs might lead to an improved understanding of ME's pathophysiology.

16. MRC-funded update: Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome

Professor Carmine Pariante (Kings College London)

Professor Pariante, who gave a presentation at last year's conference on his study on a proxy model of 'chronic fatigue' following infection, came to give an update on his work.



A chronic fatigue illness model

His study involved injecting patients with interferon alpha (IFN- α), a pro-inflammatory cytokine used to treat hepatitis C.

Patients treated with IFN- α often report experiencing marked and lasting chronic fatigue which might act as a model of induced ME/CFS, resulting from immune dysregulation and inflammation.

This model allows examination of what happens before, during and after an immune trigger – something that cannot be done in ME/CFS patients as you cannot pre-empt them developing the illness.

This means it may allow a determination of what pre-disposed the development of persistent fatigue; what separated the patients who developed it after treatment from those who didn't. This could in turn help in the understanding of inflammatory triggers – which might also occur in the development of ME/CFS.

30% of the patients reported persistent fatigue over 6 months after treatment with IFN- α ended. Professor Pariante's team measured changes of key inflammatory cytokines: IL-6 and IL-10.

Cytokine activity

They found that IL-6 (a pro-inflammatory cytokine) increased more in the patients that developed persistent fatigue early on in treatment (around 4 weeks) compared to those who didn't develop this symptom. However, at the end of treatment, these levels had dropped back down to the same between both groups.

IL-10 (an anti-inflammatory cytokine) also increased early on (4 weeks into treatment) and was much higher in those who developed persistent fatigue; but fell to pre-treatment levels 6 months after treatment ended.

When comparing the group who developed persistent fatigue 6 months after treatment ended and the group whose fatigue resolved, no differences were found in the level of reported fatigue before treatment started. There was also no difference in cytokine levels between the groups 6 months after treatment had ended.

This shows that the difference happened early on in the treatment; an over-reaction of the immune system, that lead to chronic fatigue.

It might mean that we may not be able to see noticeable differences in cytokines in people with ME/CFS now as the differences happened early on in the development of the disease. It could be that people who develop ME/CFS after an illness are more sensitive to immune activation.

Not the same as depression

Professor Pariante also said that there were no differences in cytokine levels between the control group and ME/CFS group that they studied.

The study found that those who developed depression during treatment did not have the raised cytokine levels seen in those who developed persistent fatigue, showing a clear separation between depression and ME/CFS.

They also found that the longer patients were treated, the more likely they were to develop persistent fatigue, meaning that perhaps the longer the immune system is over-acting after an illness, the more likely they are to develop chronic fatigue.

This presents as an interesting potential model for ME/CFS and shows something might have happened in the immune systems in the initial onset of the disease that is no longer traceable.

17. Working together versus the pain, isolation and fatigue of arthritis

Stephen Simpson (Arthritis Research UK)

Arthritis Research UK have recently merged with Arthritis care to form a new charity called 'versus arthritis'.

The new charity has insight-driven research funding, focusing on pain, cures and improving health services for people with arthritis.

Mr. Simpson said that there is a lack of public understanding of pain and that pain research is massively underfunded and not a priority in the UK.



The charity is trying to increase national efforts in pain research in the UK. They are currently conducting a study on fatigue, the autonomic nervous system (ANS) and immune regulation.

The results of this study may have relevance to ME/CFS research.

18. Workshops

Part of the afternoon involved a choice of one of three workshops:

- a. Activity as treatment- myths and methods (Dr Sue Pemberton, Yorkshire Fatigue Clinic)
- b. Biomedical research priorities (Professor Chris Ponting, University of Edinburgh)
- c. Nutrition and CFS/ME- the search and research for evidence (Sue Luscombe, Hampden Health Limited and Dr Michelle Dobrota-Gibbs, Freelance Dietician)

19. Cellular immune function in ME/CFS

Jackie Cliff (London School of Hygiene and Tropical Medicine)

Ms Cliff's research team are attempting to create a diagnostic lab test using blood samples.

Their hypothesis is that ME/CFS is associated with immune dysfunction; specifically, alterations in T cell and/or NK cell phenotype and function.

This may lead to or result from alterations in cytokine production and altered expression of immune cells.



They conducted cytokine analysis and transcriptomics in 251 well-characterised ME/CFS patients (197 mild/moderate and 54 severe), 46 MS patients and 106 healthy controls. The results of which cannot be reported as they are unpublished.

They have just finished collecting the last samples from this and are about to start analyses, which is very exciting and could yield some interesting findings.

20. Is inflammation the link between the body and the brain?

Professor Carmine Pariante (Kings College London)

Professor Pariante returned in the afternoon to give another fascinating talk, this time about inflammation's link to chronic illness.

He spoke of how the immune system communicates to the brain about infection to promote what is termed 'sickness behaviour' (fatigue, lack of concentration, muscle weakness etc.) as a way to conserve energy so that it can be directed towards fighting off the infection and healing the body.

The brain also communicates to the immune system the presence of 'stress' in the environment (which can be physical or emotional), that then activates the immune system in the same way as if it's fighting an infection.



Low levels of cortisol in ME/CFS

In his studies carried out in patients with depression, he has found IL-6 (an inflammatory cytokine) to be raised, along with Cortisol levels. Cortisol has anti-inflammatory effects and acts to keep inflammation caused by IL-6 under control.

In ME/CFS patients, however, cortisol is often found to be low. This could mean that the IL-6 is then not being kept under control. We also need to find out if low cortisol levels are a cause (if they predispose people to developing ME/CFS) or are a consequence of the disease.

Pregnancy and immune system development

Professor Pariante also touched on the subject of genetic predisposition and its role in leading to a tendency for immune over-activation. Interestingly, he spoke of how the uterine environment (in the womb during pregnancy) could affect the child's immune response.

Some studies have found that high levels of stress or depression during pregnancy results in high levels of inflammation, which changes the immune system of the child, increasing their inflammation.

This can result in the child being more reactive to stress and having an increased risk of inflammatory disorders and depression later on in life.

This biological signature of high immune activation is passed on through generations, which could be due to heritable genetic changes or epigenetic changes in-utero (during pregnancy).

21. Cellular bioenergetics in ME/CFS

Cara Tomas (Newcastle University)

Ms Tomas enthusiastically presented some exciting results from the Newcastle study.

They are looking at the cellular bioenergetics of PBMC's (white blood cells) from patients with ME/CFS and the effects of disease severity, freezing and glucose concentration.

The group studied mitochondrial respiration and glycolysis, focusing on three key measures; basal respiration, maximal respiration and reserve capacity (the ability of cells to increase energy demand when put under stress).



- See more: [Cellular bioenergetic deficiencies in ME/CFS – Cara Tomas](#)

The results showed differences in all three parameters of mitochondrial respiration compared to the controls, showing reduced mitochondrial function in people with ME/CFS.

They hypothesised, based on data from Dr Myhill's previous studies, that the severely affected cohort would have a greater reduction in mitochondrial function than the moderate.

However, they found no differences in mitochondrial function between the two groups, suggesting that severity does not affect mitochondrial function.

To examine differences in research methodologies, they compared the same measures in fresh and frozen PBMC samples. They found that, although the differences could be seen in the frozen samples, a much larger, clearer difference was observed using the fresh samples.

Next, they incubated the cells in different glucose concentrations to see if it would affect the mitochondrial function.

The results showed an impairment in both low and high glucose concentrations; the lower glucose solution did not improve function, suggesting that the mitochondria are already working at their maximum capacity and are unable to utilise any more glucose.

The group hypothesised that the ME/CFS patients would have increased glycolytic function to compensate for the lack of ATP production via the oxidative phosphorylation pathway.

However, they found no difference between the control and ME/CFS groups, suggesting that the cells are not compensating for their lack of ATP production via increased glycolysis.

These results suggest that ME/CFS may be a hypometabolic condition, however, it is not clear if this is the cause or consequence of having ME/CFS.

Ms Tomas pointed out that these results do not mean there's necessarily a problem with the mitochondria themselves but could actually be a result of a dysfunction somewhere further upstream in the metabolic pathway, such as problems with pyruvate conversion.

"We may just be seeing the results of the problem at the end of the chain." she said.

Moving forward, she said that they now need to check if these findings are due to deconditioning and they also need to check if they are specific to ME/CFS, or if they are also found in MS or other diseases.

Longitudinal studies also need to be carried out to see if these results change over time due to changing activity levels or changes in symptoms. They also need to see if this is only found in PBMC cells or if it also occurs in other cells in the body.

22. Conference reflections

Professor Chris Ponting (CMRC deputy chair)

Professor Chris Ponting closed the conference by thanking everyone who helped organise and attended what had been a very enjoyable, friendly and constructive conference.

- David Tuller [who gave a talk at the conference](#), reviewed the event on Virology Blog. This featured his thoughts on several of the main presentations and also the workshop held by Professor Ponting.

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