

Selected presentations from the report of the third UK CFS/ME Research Collaborative conference, 28-29 September 2016

A full final report of the conference is being prepared – meanwhile, please find overviews of the following presentations, with kind thanks to volunteers Emily Beardall, Katrina Pears and Karen Hainsworth, who wrote them.



- Welcome – *Prof Stephen Holgate, UK CFS/ME Research Collaborative Chair*
- SAIL Database: routinely collected data for research – *Prof David Ford, Swansea University*
- Biological Fingerprints of Fatigue in Primary Sjögren's Syndrome – *Dr Nadia Howard-Tripp, NIHR Academic Clinical Fellow in Rheumatology, on behalf of Prof Fai Ng*
- Understanding the pathogenesis of autonomic dysfunction in CFS/ME and its relationship with cognitive impairment – *Prof Julia Newton, Director of Newcastle Academic Health Partners and Clinical Professor of Ageing and Medicine, Newcastle University*
- Persistent fatigue induced by interferon alpha: a new immunological model for CFS/ME – *Alice Russell, King's College London, on behalf of Prof Carmine Pariante*
- Mapping global research funding over the last 10 years: a UK CFS/ME Research Collaborative-sponsored report – *Sonya Chowdhury, Chief Executive, Action for M.E.*
- Enhancing research funding applications into CFS/ME: part one – *Dr Lindsay Keir, Senior Portfolio Developer, Wellcome*
- The Brain in Pain studies: central sensitisation in CFS/ME and fibromyalgia – *Dr Julius Bourke, Queen Mary's University, London*
- Voxel-based morphometry shows reductions in brainstem white matter in CFS/ME – *Dr Andreas Finkelmeyer, University of Newcastle*
- Immune-pain interaction following exercise in CFS/ME: associations between exercise-induced hyperalgesia, complement system and elastase activation – *Dr Andrea Polli, University of Brussels*
- Involving severe and very severely affected CFS/ME individuals in research: a clinician's view point – *Victoria Strassheim, Newcastle University*
- Fatigue in Primary Sjögren's Syndrome is associated with lower levels of pro-inflammatory cytokines – *Dr Nadia Howard-Tripp, NIHR Academic Clinical Fellow in Rheumatology*

Welcome

Prof Stephen Holgate, UK CFS/ME Research Collaborative Chair

“This is the third conference at a time of terrific excitement in the field [of CFS/ME],” said Prof Holgate in his welcome address. “It’s exciting because the world is beginning to wake up now to new ways of approaching this complex group of conditions.”

He was referring specifically to -omics, the mapping and analysis of large scale biological information. Fundamentally different from standard research, -omics produces huge volumes of data allowing researchers to unpick disease sub-types and come up with new ways of diagnosing and treating them.

Prof Holgate hailed two recent studies from the US that showed the true potential of this approach. In the paper *Metabolic features of chronic fatigue syndrome*, Naviaux et al looked at differences of over 600 plasma metabolites from 63 biochemical pathways in CFS/ME patients compared to controls: “What was quite remarkable, when they did their analysis, [was that] they got a very distinct collection of metabolites that emerged in these relatively severe CFS/ME patients.”

Prof Holgate noted that there were several differences between males and females too. In a nutshell, CFS/ME appeared to be a reduced metabolic (hypometabolic) state caused by a variety of environmental insults, and this state seemed to trace back to the cells powerhouse – the mitochondria.

Flagging up a different and smaller research project by Hanson et al, he was excited by the correlation in results. “I think this is a real breakthrough. What’s interesting about these two studies is that despite the fact they were using different methods and different analytical procedures they came up with a very similar answer.” An attempt is already being made to repeat this research.

Scientists in the UK are also keen to use metabolomics to investigate CFS/ME, said Prof Holgate, and highlighted the work of the ME/CFS Epidemiology and Genomics Alliance (MEGA).

Led by Prof George Davey-Smith, a clinical epidemiologist in the Medical Research Council (MRC) Integrative Epidemiology Unit, Bristol, MEGA contains expert scientists from across the UK. One of the collaborators is Dr Warwick Dunn, from the new Birmingham Phenome Centre, who has promised that CFS/ME will be a key focus in his lab.

At the time of the conference, Dr Dunn was at a metabolomics meeting at the National Institute of Health (NIH), the main research funding body in the US. He did however send a message of support, saying that Prof Francis Collins, head of the NIH, had highlighted the Hanson metabolic paper as a real achievement. “So CFS/ME is important to important people,” he concluded. Prof Holgate agreed, saying, “If somebody like Collins is saying this is a great example of metabolomics, then that should give us great confidence.” He added that efforts will be made to link to -omics activities in this disease area in the US and beyond.

Prof Holgate then laid out how MEGA would proceed. “Starting with genomics and DNA sequencing but then spreading all the way through the cellular processes, through

transcriptomics, proteomics, metabolomics and even microbiomics and serumomics, we'll be looking to pull this all together and come up with some pathways."

There was one important element he was keen to stress. "We can have all the -omics in the world but unless we get the patients and the phenotyping right then it's all a waste of time."

After thanking the conference organisers and delegates, Prof Holgate expressed the deep need for continued commitment to and enthusiasm for this project from scientists, patients and the CFS/ME community. This, he said, was essential to get the study funded. Presaging the new and exciting era to come, he concluded, "We are on the threshold of an extraordinary journey."

Routinely collected data for research
Prof David Ford, Swansea University

Prof Ford explained that he would be offering something different to previous speakers, in that he would be looking at how he and his team use data to examine health from a social perspective. Social circumstances are significant causes of ill health, and ill health has enormous social impact on patients and their families, he said. This is a societal problem that has an impact on us all.

In trying to understand this, Prof Ford will provide three linked case studies from his group's work to illustrate how routine data can support research into poor-understood conditions such as CFS/ME.

The first example described was Secure Anonymised Information Linkage Databank (SAIL). Set up in 2006, it captures data from the Welsh population, with around 20 billion recordings made to date. Originally it focused just on healthcare but is now a citizen-based repository that includes data from many sources including social care, housing, education, police and many others, all linked together to provide millions of anonymous individual 'stories' going back 20-30 years. Around 500 data sets are supplied every month, including general practice data from around 80% of GP surgeries in Wales.

The privacy of individuals whose data we keep is our first priority, said Prof Ford. The data never leaves SAIL and any researcher who uses it must access it via an online platform so the team can monitor how it is being used. No identities are contained in the data set, thanks to an automated process that keeps names and addresses separate from sensitive data.

Prof Ford then presented a case study of how the Swansea team operates a new Administrative Data Research Centre as part of a UK Network funded by the ESRC, which gives social and economic researchers access to a wide range of administrative data from central government departments such as social welfare, the Census, education, and many others.

He then moved onto to describe a programme of work that has been running for about five years, funded by the MS Society – the UK MS Register. By taking data from 25 clinical sites around the UK, and linking it to information provided by people living with MS directly, via a web portal, they have established a scalable register of people with MS, 15,000 to date, across the UK, regularly measuring their quality of life, functional ability and mood as well as many other aspects of their lives, condition and treatment. Those who share their data have given full consent to supply data regularly and routinely, building up a longitudinal resource – about 390,000 questionnaires have been completed so far.

"We also ask them to tell us a lot about their pre-illness history, life stories, social circumstances, employment, medications and treatments – some of which we get echoed in GP and hospital data, but some of it we don't, as there's lots of self-medication going on," commented Prof Ford. Data on fatigue, pain and cognition is also collected, and real-time collection of data on mood, and activity is about to start being collected using a patient portal smart phone app.

This sort of data is hugely valuable for anyone looking at a complex and disabling course of illness, and is supplemented by robust clinical data from a number of clinical sites across the UK.

Prof Ford ended his presentation by coming back to CFS/ME. “Until such time as there is a universal therapy for this very difficult condition, we should also spend time trying to understand how it’s presented and the affect it has on people’s lives,” he said. “I think the approaches described could really help illuminate CFS/ME, and I hope we will be able to help in the future.”

Biological Fingerprints of Fatigue in Primary Sjögren's Syndrome

Dr Nadia Howard-Tripp, NIHR Academic Clinical Fellow in Rheumatology, on behalf of Prof Fai Ng

Using a cohort of patients with Primary Sjögren's Syndrome, Prof Ng's team looked for unique patterns of biological changes that create "biological fingerprints." These can be found in the blood and may be relevant to CFS/ME.

Sjögren's, a chronic, inflammatory autoimmune disease, is systemic but its main symptoms include ocular dryness and profound fatigue. "Seventy percent of people with this illness report a disabling fatigue," explained Dr Howard Tripp, with up to two-thirds of patients fulfilling the criteria of CFS/ME.

With the emphasis on immunological pathways, the hunt was on for a biological profile, looking particularly at differential expression of certain genes between those with high fatigue (equal to or above 75 on a visual analogue scale) and those with low fatigue (equal to or below 25 on a visual analogue scale).

Using the UK Primary Sjögren's registry, which contains a biobank with serum samples and biological and clinical information, they looked at whole blood RNA in a relatively small sample. They found no differences between these two different fatigue states. But the comparison between the Sjögren's group and healthy controls was a different story, with 334 genes expressed differently.

They then took a look at type I Interferon gene signature as it is present in the majority of patients with Sjögren's and implicated in numerous immunological processes and disease. But fatigue levels and this particular gene signature were poorly correlated.

Moving on and hoping to find exactly which genes were relevant to fatigue, they used a statistical approach called Gene Set Enrichment Analysis which identifies clusters of genes that are functionally relevant to a particular disease.

"The aim was to find a fatigue related metabolic pathway," said Dr Howard-Tripp. Using software (Leading Edge) that picks out core genes that account for altered gene signalling, they found 19 pathways that were relevant. Interestingly, three of these had previously been implicated in CFS/ME: the Actin pathway, G-protein signalling and the Incretin pathway.

Using a machine learning approach, they were able to reliably sort between high and low fatigue groups. The results have been published in a recent paper.

Understanding the pathogenesis of autonomic dysfunction in CFS/ME and its relationship with cognitive impairment

Professor Julia Newton, Director of Newcastle Academic Health Partners and Clinical Professor of Ageing and Medicine, Newcastle University

Prof Newton gave an update of Newcastle's autonomic projects. First was a case control study designed to better understand the role that autonomic dysfunction has to play in the pathophysiology of CFS.

Initial investigations looked at whether autonomic dysfunction was a primary abnormality in brain autonomic centres or due to abnormalities in the HPA (hypothalamic pituitary adrenal) axis. They also considered whether it could be a problem downstream of the autonomic nervous system that is secondary to hypovolaemia. This in turn might result in compensatory autonomic abnormalities.

Secondly, they explored autonomic dysfunction and cognitive impairment in CFS/ME. The researchers wondered if underlying central processes cause damage to both autonomic and cognitive brain centres, or whether cognitive impairment is secondary to peripheral hypotension arising from autonomic dysfunction. They also looked into whether the potential reduced cerebral perfusion had caused cerebral damage.

A wide range of investigations was carried out in a cohort of over fifty patients with CFS/ME. Funding allowed three MRI scans per participant of brain, heart and liver, and a number of nucleotide investigations including plasma volume, red cell volume and MIBG.

"We also performed a full gamut of autonomic tests, a dexamethasone suppression test as a measure of HPA axis function and a full battery of neuropsychometric assessment all in the same participants," said Prof Newton. "The considerable advantages of that mean we have the ability to look at a whole systems approach to CFS/ME."

Though the ongoing analysis is taking a huge amount of time due to lack of continued funding, the team have developed a number of new methodologies around liver and brain MRI so will be publishing methodological papers.

Further outcomes of the project were wide ranging and abundant. The PhD muscle function work has gone on to receive funding from the MRC Confidence and Concept scheme for Audrey Brown, lead author on the PLOS paper on muscle glucose uptake (Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with CFS. Brown, AE et al. *PLoS One*, 2015). Prof Newton expressed her delight in recently being invited for full application from MRC to develop this work.

Currently three additional papers are being written. Though the HPA axis and autonomic dysfunction study show no correlation, the cardiac data MIBGs (a type of scan) have been very positive, as has research looking at plasma volume and red cell mass. Cardiac work suggests that patients with CFSME have small hearts and small cardiac volumes, something that both the Newcastle team and others have shown before using different methodologies.

“People with CFS/ME have low plasma volumes, and the lower your plasma volume is the more fatigued you are,” explained Prof Newton. “This is the basis of a current study where we are looking at expanding plasma volume with oral fluid and intravenous fluid.”

Funded by Action for M.E., this proof of concept study will underpin the MRC DPFS (Developmental Pathway Funding Scheme) application to be submitted in the new year. Some of the cardiac data already been published in *Open Heart* (Reduced cardiac volumes in CFS/ME associate with plasma volume but not length of disease a cohort study. Newton et al. *Open Heart*, 2016) has been downloaded more than 10,000 times.

“One of the big things we learnt from this project is that doing research with this population is really doable and that people really want to participate,” said Prof Newton. The key to success is the recruitment team’s exceptionally good relationships with the local patient support groups and the patients themselves. Despite it being really difficult for patients to undertake the assessments, every one of them completed all of the tests. And she confirmed the team had utilised every single bit of information the participants had given.

Academic papers and grants were the obvious tangible outputs of her research group, but gains from the MRC and charity funding went much further. “It’s brought us credibility in Newcastle,” she said. “We now have a recognised Newcastle University fatigue research centre, which cross-faculty. That gives us a small amount of funding to allow people to come to meetings and to facilitate Fellows and researchers to come and work with us.”

This in turn has produced a large number of national and international collaborations, including Faisal Kahn in Dundee, the mitochondria group at Oxford University and across the globe with researchers in Poland, Australia and the US.

“It’s great talking to people about the science we’ve done and helping facilitate their science. That can only be good for the field,” she concluded.

Answering a question from a delegate, Prof Newton explained why she thought the HPA function test showed no difference to controls. “We’ve now looked at HPA function in two different ways with the dexamethasone suppression test. We’ve looked at not only cortisol levels but a range of different cytokines to look at whether there are changes when we depress HPA function and we have not been able to find any changes that are significant in CFS/ME compared to controls.

“We’ve also taken a cohort of patients where we’ve taken salivary cortisol over 24 hours and looked at circadian rhythms and again not been able to find abnormalities in CFS/ME versus controls,” she said. The main reason for the difference could be that researchers screened out rigorously for depression.” It maybe that depression as a cofounder is the complicating factor.”

Persistent fatigue induced by interferon alpha: a new immunological model for CFS/ME

Alice Russell, King's College London, on behalf of Prof Carmine Pariante

Prof Pariante's team looked at the pro-inflammatory cytokine interferon alpha in relation to persistent fatigue. A natural part of the immune response, interferon alpha is also created synthetically for therapeutic use in Hepatitis C. Patients inject it for six to 12 months to boost their natural immune response and inhibit replication of the virus. It does however have a wide range of side effects.

According to a survey conducted by the Hep C Trust in 2010, 60% of patients report problems with fatigue 6-12 months after the treatment has stopped and around 40% are still fatigued after a year post-treatment.

"It's not just fatigue, it's a range of symptoms that are very similar to what you see in CFSME," explained Miss Russell. "And that's why we think interferon-alpha induced persistent fatigue is an interesting proxy model."

The first part of the project was a prospective cohort study, following patients from four sites across London who were receiving Interferon Alpha for Hep C. Fifty eight patients completed the treatment and were seen a minimum of 6 times including before during and after treatment.

The second part was a case control cross sectional study with CFS/ME patients. Fifty two CFS/ME patients from two sites in London and 58 healthy controls attended for one of visit where a raft of measures were taken. These were the same as those taken from the Hep C patients over time.

Initially looking at Hep C patients, they compared those whose fatigue had persisted post-treatment, to those whose fatigue had resolved, to try to understand whether there were any differences between the two groups even before treatment, which might explain the different outcomes later on.

Predominantly male, which Miss Russell acknowledged as being very different from standard CFS/ME cohorts, they had similar socio demographic data, Hepatitis C genotype and level of virus and similar damage to their liver, assessed by a fibroscan.

Results so far have proven interesting. Illness severity (viral load) measured before treatment made no difference to post-treatment fatigue levels. When the treatment worked more quickly (the virus was cleared after four weeks) there was more likely to be a resolution of fatigue. However, whether the treatment worked, and the virus was still cleared six-months post-treatment, did not make a difference. This was contrary to the expectations of the liver consultants, who thought that any fatigue would be due to a persistent Hepatitis C infection.

"That's important because what's starting to come out is that this early analysis is that this early response to the trigger might be the important thing in this group," explained Miss Russell.

The research team then looked at cytokine levels in the blood in a subset of patients. While levels of IL-10, IL-17A and IL-6 were increased in response to Interferon-alpha in all patients, they were significantly higher in those patients whose fatigue persisted post-treatment, suggesting a greater inflammatory response to the trigger in these patients. The increases in these cytokines in the first four weeks of exposure seemed most important.

Interestingly, this was despite those particular cytokines returning to baseline levels once treatment was completed. IL7 was markedly different however, in that it was higher six months after treatment in persistent fatigued patients compared to the resolved fatigue group. More results will be available soon. Miss Russell reiterated Prof Newton's experience, saying that the level of enthusiasm of patients wishing to participate was overwhelming.

NEW RESEARCH

Mapping global research funding over the last 10 years: a UK CFS/ME Research Collaborative-sponsored report *Sonya Chowdhury, Chief Executive, Action for M.E.*

Key point summary:

- The ÜberResearch Dimensions database of over 200 of the world's most influential research funders was queried.
- Over the ten years covered by the report there were 99 grants awarded globally, with a total of around £49m.
- CFS/ME receives only 0.02% of the overall total of research funding
- Considering the burden of CFS/ME and the number of people affected, research receives disproportionately low funding compared with that for other neurological illnesses.
- The CMRC will offer support to researchers to develop better quality funding applications and study design.

Sonya began the New Research plenary session of the conference by presenting the findings of a report into CFS/ME research funding over the last ten years. The report gives hard evidence of the chronic lack of research funding for CFS/ME from the major funding agencies. While this is already widely acknowledged, the CMRC will use this as evidence to present to the MRC, NIHR, Wellcome and other research funding.

The method for the report involved working with a company called ÜberResearch, using their Dimensions database of over 200 of the world's most influential research funders. There are gaps in the data in terms of the database, which does not include research funded by charities, but it nevertheless gives a snapshot of the major research funding over the last 10 years. Over the ten years covered by the report, although there are some omissions, there were 99 grants awarded, with a total of around £49m. A breakdown by country is shown in figure 1.

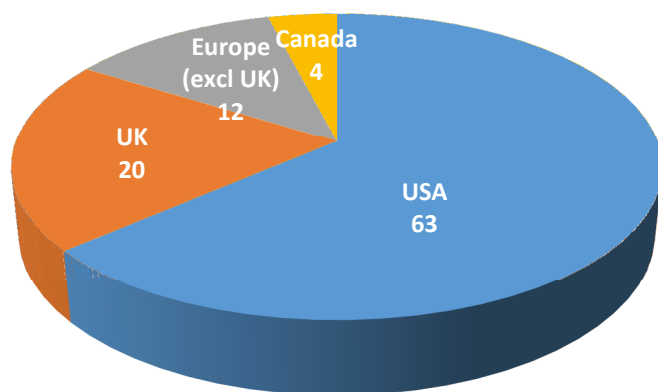


Figure 1: CFS/ME research grants per country over the last 10 years

Figure 2 shows the number of active and starting projects each year, excluding the UK, for the ten years up to 31st December, 2015. The number of new projects varies from year to year but on average there are six new projects funded per year excluding the UK, and this is low compared with funding for comparable illnesses. Most of the funding awards have come from the NIH in the US, and since the US Institute of Medicine's 2015 report there has been a review of funding.

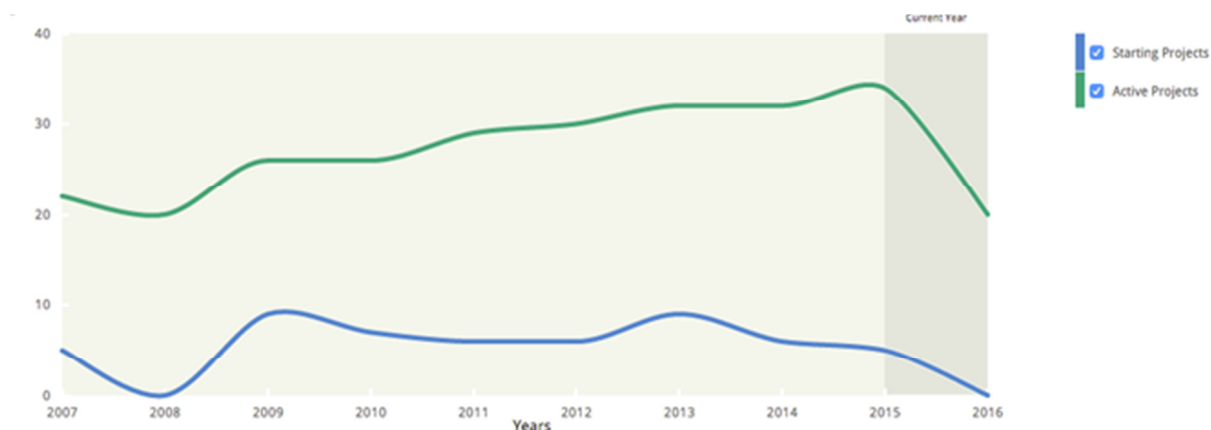


Figure 2: Global CFS/ME starting and active grants (excluding the UK) since 2007

Figure 3 shows that for UK CFS/ME research funding since 2007 there were on average only two grants awarded per year. There is a spike due to the MRC highlight notice in 2012. A breakdown of grants awarded per institution and by PI recipient can be found in the full report. Of the 20 grants in the UK, two fifths went to the same two researchers.

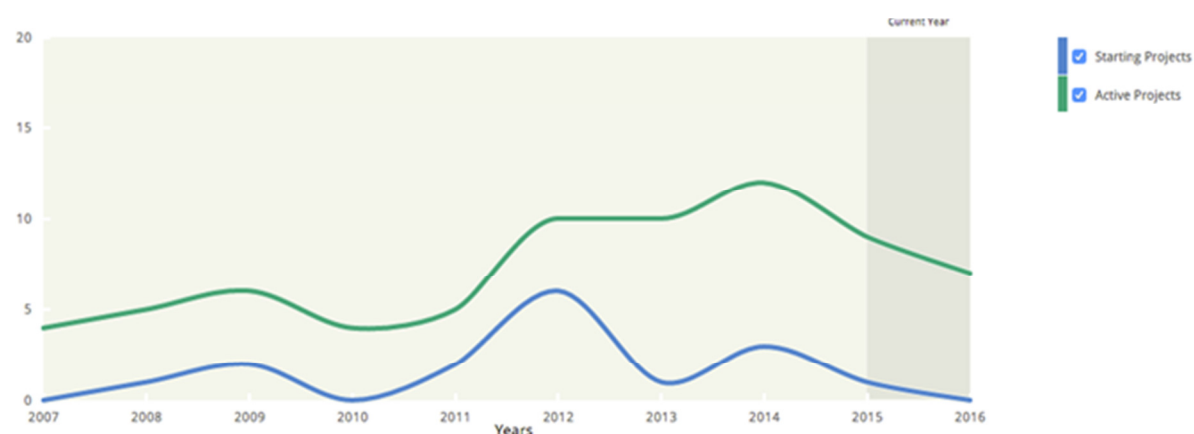


Figure 3: Grants for CFS/ME research from funding agencies in the UK since 2007

There has been no funding from other UK and European funders, such as the European Biotechnology and Biological Sciences Research Council, or the European Research Council for whatever reason.

Of the 20 grants funded in the UK in the 10-year period, the breakdown by funder was:

- 12 from the MRC (due to the highlight notice)
- 6 from the National Institute of Health Research (NIHR)
- 1 from the Chief Scientist Office in Scotland

- 1 from Wellcome.

Funding was then compared with that given for other neurological conditions, as shown in figure 4. In the ten years to 31 December 2015 there were 34 international active grants in the Dimensions database for CFS/ME, with a total value of around £17m. To put this into context, the MRC funded around 2,000 active grants and Wellcome around 200 active grants at that point in time.

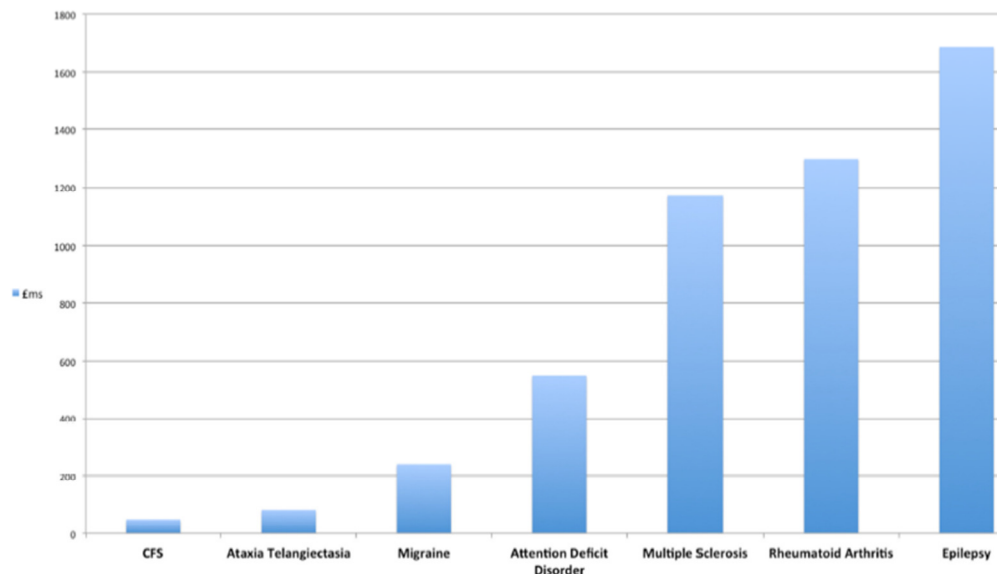


Figure 4: CFS/ME funding compared with other neurological disorders (worldwide funding)

As can be seen in the full report, there is disproportionate funding. For example, ataxia telangiectasia affects 1,200 people in the UK, but gets twice as much funding as CFS/ME which affects around 250,000. Multiple sclerosis affects around 100,000 but receives about twenty times the funding. Each of these illnesses deserves funding and we are not saying that CFS/ME should not be prioritised over other illnesses. These comparisons are purely made to demonstrate the need for fairness in funding research to improve the lives of people with CFS/ME, as it was found that this illness receives only 0.02% of the overall total of research funding.

The scale and the impact of CFS/ME is significant in terms of the cost of disease burden but research funding has been low and patchy. More skills and expertise are needed in research applications and design of studies.

The CMRC has been in consultation with the MRC and other UK funding agencies to increase investment. The MRC are going to formally review the report and their highlight notice, which is a major first step. The CMRC will be writing to each of the funding organisations to encourage them to work with us to increase research funding for CFS/ME.

A critical analysis of the categories of research funding will be carried out in order to identify under-researched areas of CFS/ME research for future investment.

The CMRC will be working with researchers to improve the success rate of applications for funding. The CMRC will offer advice to researchers in the early stages of their career to enable them to submit high quality applications to the mainstream research funders.

There has been an incredible lack of research and focus which needs addressing, so the CMRC encourages researchers to work with them and give their feedback, as the spotlight on funding will be ongoing.

Sonya ended her talk by showing a photo collage of patients affected by CFS/ME from the Millions Missing campaign, to remind delegates that the overall aim of research is to improve the lives of people affected by this illness.

A copy of the report can be read and/or downloaded at
www.actionforme.org.uk/uploads/pdfs/mecfs-research-funding-report-2016.pdf

Enhancing research funding applications into CFS/ME: part one

Dr Lindsay Keir, Senior Portfolio Developer, Wellcome

Dr Keir explained that she was going to present on the funding opportunities presented by Wellcome, formally the Wellcome Trust.

Wellcome is a charity but does not source funds from the public or donations, but instead funds research through a trust. Its remit is to improve health for everyone by helping great ideas thrive.

“To do this, we have four main aims,” explained Dr Keir. “These are to understand health and disease, to improve health, to engage with the public – including patient groups – and to influence policy.”

Many teams are involved in this work, including for example the Innovations Team, which works globally with researchers and organisations to transform ideas, discoveries and inventions into treatments and products; the Culture and Society Division funds researchers looking at the humanities and social sciences.

Dr Keir explained that her area of work was broadly improving healthcare via various funding streams, including molecular sciences and all the way through to population-based studies. Her team was established this year to particularly focus on clinical research, led by Sarah Marshall, a clinical immunologist by trade.

Wellcome supports research across the career structure, with different schemes available, including:

- an undergraduate scheme for basic and clinical researchers that includes a “biomedical vacation” scholarship to enable them to get laboratory experience
- postgraduate schemes that help fund PhDs across the UK
- Sir Henry Wellcome postdoctoral fellowships, which allow researchers to travel between labs and take ownership of their career direction
- clinical career development fellowships, which can run for up to eight years over two flexible stages
- Sir Henry Dale fellowships, which support the best researchers to progress towards independence
- re-entry fellowships, for those who have had to take time out of research for any reason.

Dr Keir then explained more about each of Wellcome’s specific funding streams for established researchers.

Seed Awards in Science help predominantly early independent researchers develop novel ideas that will go on to form part of larger grant applications to the Wellcome Trust or elsewhere. Awards can be up to £100,000 over two years and applications are considered three times a year. You must already have a salary in place for the duration of the award, so it’s really targeted at someone already in post for example a newly appointed lecturer or someone is more established but who wants to move into a new area. Applicants must have very clear follow on plans.

Larger awards aimed at funding established scientists include Investigator Awards in Science, which offer flexible funding support to researchers at all career stages working on important questions of relevance to our scientific remit, and can be anywhere from £300,000 up to £3million over seven years, although most people apply for 5 years of funding. You need to show that you have a strong track record relative to your career stage, and an over-arching research vision for the whole project. Applications are considered three times a year, and joint applications from researchers working closely together are being received more frequently.

Senior Research Fellowships are designed to support the best independent researchers asking important questions in their field. Offering up to £1.5million over five years, they can be renewed after that period. Around seven to 12 years' research experience at postdoctoral level is required, and an international track record, with sponsorship from your head of department.

Dr Keir stressed that the Wellcome team is very happy to give advice and guidance on individual applications, and that anyone interested should get in touch.

She then finished by talking about some of the newer awards that are available to researchers, including the Collaborative Award. The aim of this is to promote development of new ideas that speeds up the pace of discovery. "We fund teams of three to seven researchers, consisting of independent research groups, to work together on the most important scientific problems that can only be solved through collaborative efforts," she explained. These are large awards of £4million over five years, and eligibility includes having a "multi-disciplinary dream team."

How are these applications assessed? Dr Keir was keen to de-mystify this process.

She reiterated that some of the awards require preliminary application. This goes through an eligibility check, and a proportion will then be invited for full application. Expert review groups, made up of specialists in the field, will assess applications, around 40% of which will be successful and progress to the next stage.

These will be sent for sub-specialist peer-review, and then onto an interview panel, made up of people working across all six funding streams. "Your application will be seen by all these different audience, so you must pitch it correctly," advised Dr Keir. Overall, around 15-20% of all applications received are ultimately successful.

The final award outlined by Dr Keir was the Biomedical Resource and Technology Development Grant, aimed at researchers who want to establish or maintain resources or technology for the benefit of the wider scientific community, eg. a biobank. This award of up to £1.5m over five years is only considered once a year.

For more information, please visit www.wellcome.ac.uk where each award page has a contact lead.

The Brain in Pain studies: central sensitisation in CFS/ME and fibromyalgia
Dr Julius Bourke, Queen Mary's University, London

As part of this presentation, Dr Bourke shared raw data and has asked that it not be presented here, as publication in a peer-reviewed journal is being sought.

By way of general overview, the Brain in Pain studies are comparative studies of central opioidergic and dopaminergic neurotransmission in cases of fibromyalgia and CFS/ME that demonstrate central sensitisation and healthy controls that do not.

The principle of central sensitisation is derived from pain medicine and essentially infers a state of central nervous system hypersensitivity. This in turn results in unfiltered information being transferred up to the brain and all stimuli being treated the same – as a threat, as pain and with the need for preferential processing. Pain is a case in point but the effect is multimodal. Normal pain processing is shown in figure 1, and the effects of central sensitisation are shown in figure 2.

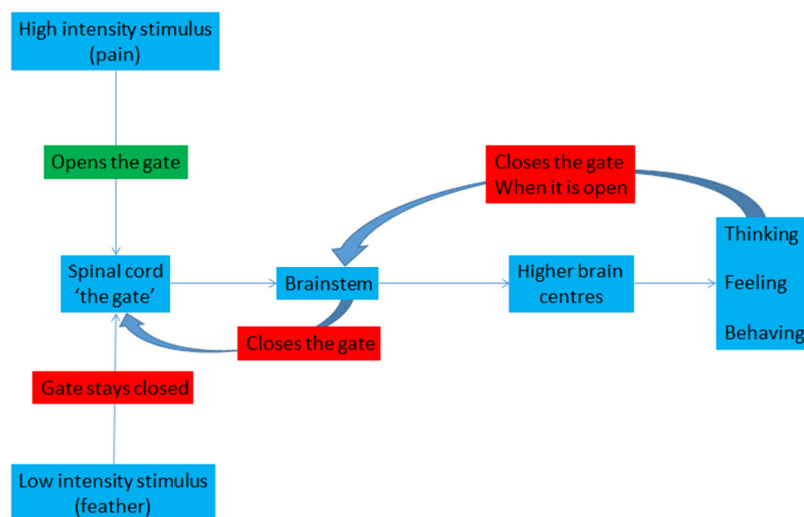


Figure 5: Normal pain processing

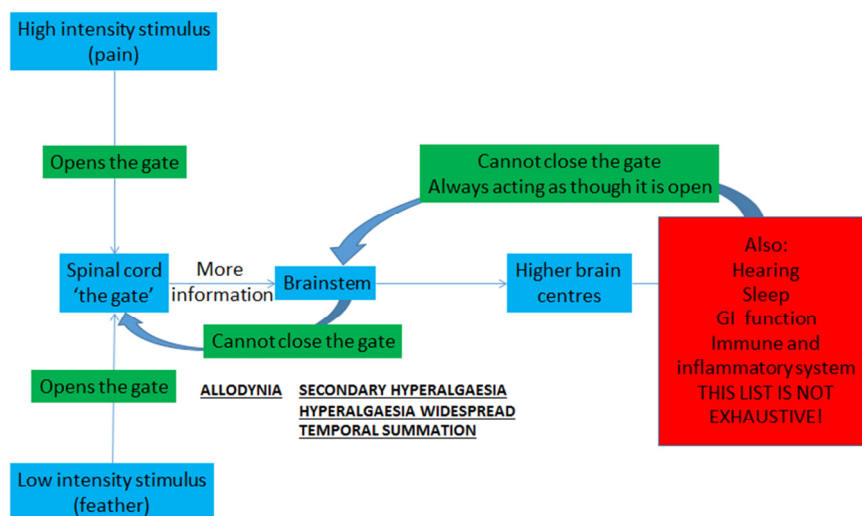


Figure 6: Pain processing in central sensitisation

Central sensitisation is found in numerous chronic pain disorders and is thought to play a role in CFS/ME, fibromyalgia, and other related disorders such as irritable bowel syndrome (IBS),

Pain thresholds have been demonstrated as being lower in these conditions and temporal summation or “wind up” has been reported. However, central sensitisation and temporal summation are not equivalent and low pain thresholds alone are not sufficient to demonstrate this altered state. CFS/ME and fibromyalgia are heterogeneous conditions but both involve chronic pain. Central sensitisation may help introduce greater homogeneity in research samples.

Although central sensitisation is thought to be a neurophysiological explanation of chronic pain, it may also explain the following:

- Heritability
- Susceptibility to developing CFS/ME and fibromyalgia
- cognitive and emotional dysregulation
- comorbidity of similar disorders (e.g. IBS)
- sleep dysregulation
- neuroendocrine dysfunction
- autonomic dysregulation
- sensitivity to noise, temperature, environment – social and occupational
- immune system dysfunction.

A better understanding of the central chemical processing underlying this hypersensitive state may lead to an enhanced understanding of conditions such as CFS/ME and may provide a target for future pharmacotherapy.

Voxel-based morphometry shows reductions in brainstem white matter in CFS/ME
Dr Andreas Finkelmeyer, University of Newcastle

Key point summary:

- A significant increase in brain grey matter (GM) volume and significantly lower WM volume, but similar cerebrospinal fluid volume was found in patients with CFS/ME compared with healthy controls.
- The specific brain regions affected are responsible for interoception (the relationship between bodily sensations and emotional experience), salience (focusing attention) and valence processing (feeling pleasant or unpleasant, and feeling activated and energized).
- These findings need to be replicated with larger sample sizes.

The presentation began with a quote from Natelson (2013):

“These studies led to our current working hypothesis - that a subgroup of patients with CFS/ME has an underlying neurological disease which leads to the symptoms of fatigue and cognitive dysfunction.”

Dr Finkelmeyer then displayed a list of brain morphology studies of patients with CFS/ME compared with healthy controls to demonstrate that there have been very few studies so far with findings that have been replicated and that there are contradictory results:

- Okada (2004): reduced GM in the prefrontal cortex, related to performance status; no white matter difference
- De Lange (2005): Global GM volume reduction, related to physical activity
- De Lange (2008): Increase in GM volume following CBT (prefrontal cortex, global)
- Barnden (2011, 2015): no global or regional volume differences between groups; various interactions
- Puri (2012): reduced GM & WM in occipital regions
- Zeineh (2015): global WM reduction; localized cortical thickness (GM) reductions
- Van der Schaaf (2016): no global or regional GM differences, but association with chronic pain in prefrontal cortex

The aim of this study was to investigate differences in grey matter (GM) and white matter (WM) volume between CFS/ME patients and healthy controls using modern voxel-based morphometry (VBM) methods.

In VBM, MRI scans are analysed by software to more clearly define the areas of white matter and grey matter and to morph them to a common template. Subsequent smoothing of the images makes the scans from individuals easier to compare mathematically, and hence aids the statistical analysis of GM and WM volumes.

In this study, 42 patients (32 female), with a mean age of 45.2 years who fulfilled the Fukuda criteria, with co-morbid psychiatric conditions excluded, were compared with 28 healthy controls (19 female), with a mean age 48.4 years.

All of the MRI scans were produced by the same 3T Philips Achieva MRI scanner at Newcastle Magnetic Resonance Centre, using a standard T1-weighted anatomical scan sequence. Pre-processing used the Computational Anatomy Toolbox in SPM12. Voxel-wise statistical comparisons controlled for total intracranial volume, age, and sex.

Whole-brain differences

When whole-brain volumes were compared (see figure 1), there was a significant difference in the total intracranial and WM volumes, with patients having lower volumes than healthy controls. This could just have shown that the study had recruited patients with smaller head size (total intracranial volume) than controls, but when the results were corrected for this variable by dividing the segment volumes by head size, a significant increase in GM and significantly lower WM were seen, but similar cerebrospinal fluid (CSF) volume (see figure 2).

Figure 7: Comparison of whole-brain volumes in CFS/ME patients and healthy controls

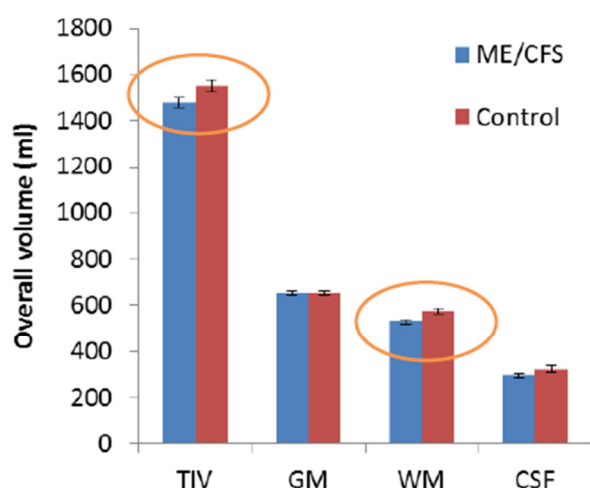
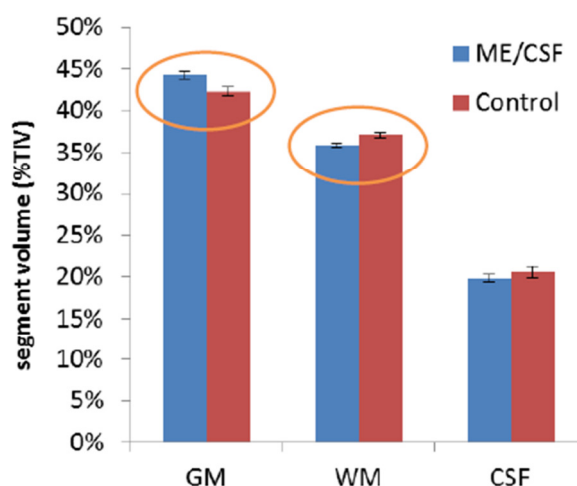


Figure 2: Comparison of segment volumes (%TIV) in CFS/ME patients and healthy controls



Regional brain differences

Regionally there were increases in GM in CFS/ME patients, with clusters in the right posterior insula, the right amygdala, left amygdala, and the right medial temporal lobe.

These findings have not been reported by previous studies and so have not been replicated, so they should be interpreted cautiously, but the potential clinical significance is that the insula is concerned with interoception, (the relationship between bodily sensations and emotional experience), and the amygdala with salience (focusing attention) and valence processing (feeling pleasant or unpleasant, and feeling activated and energised).

There were decreases in WM in the patients, primarily in the corticospinal tracts of the midbrain, the brainstem (specifically in the pons), and the median temporal lobe. These brain structures are involved with pain perception, which may be the clinical significance of these differences.

A previous study in CFS/ME patients by Barnden et al in 2011 found midbrain WM volume decreased with CFS/ME duration, and pulse pressure related to signal intensity in the brainstem. The reduced volume in anterior temporal WM (uncinate fasciculus), perhaps confirms speculations regarding reductions of crossing fibres (Zeineh et al, 2015) presented by Prof Montoya at the 2015 CMRC conference.

Conclusion

Dr Finkelmeyer concluded by pointing out that these interesting findings need to be replicated with larger sample sizes, and although VBM has been around for quite some time, it is still being developed in terms of the software used, and the methodology needs to be consistent.

A limitation of this research method is that segmentation based on image contrast may produce results that are not actually down to brain matter volume. It is not known whether differences seen between CFS/ME patients and healthy controls are a result of the illness itself and whether and how they relate to the clinical symptoms.

Immune-pain interaction following exercise in CFS/ME: associations between exercise-induced hyperalgesia, complement system and elastase activation

Dr Andrea Polli, University of Brussels

Key point summary:

- The complement system and elastase have been found to be associated with fatigue and/or pain.
- Participants of this study carried out an exercise test which was repeated a week later.
- Blood samples and pain pressure threshold (PPT) before and after each exercise test and showed that PPT and complement system changes were only associated in patients with CFS/ME and not healthy controls.
- In healthy controls PPT increased, whereas this decreased in CFS/ME patients.
- There were no changes in elastase levels, or differences between patients and controls.

Pain is the second most important symptom to people with CFS/ME and it can often be more distressing than fatigue. There is possibly a shared underlying pathology between fatigue and pain, as 70% of patients also have fibromyalgia, which is characterised by widespread, disabling pain.

Although interleukins were thought to be a good measure of immune system activation, systematic reviews have shown that they do not explain CFS/ME symptoms and exercise-induced changes, whereas the complement system and elastase have been found to be associated with fatigue and/or pain. Studies have shown that C4a, but not C3a or C5a, increased six hours after sub-maximal exercise.

Method

This study recruited 22 patients with CDC-defined CFS/ME and 22 healthy controls. In experiment 1, the participants performed a standardised test known as sub-maximal exercise or aerobic power index using an exercise bike, cycling with a 60-70 pedalling rate per minute, and the resistance of the machine was increased by 25 Watts minute by minute until the participant reaches 75% of their target heart rate.

Before and after the exercise test, pain pressure threshold (PPT) was measured. PPTs are thought to be an effective way of measuring central sensitisation and central nervous system hyperexcitability. Blood samples were also taken before and after, to measure complement system and elastase activation.

In experiment 2 a week later, the method and measurements in experiment 1 were repeated, but in order not to worsen the participants' CFS/ME symptoms more than necessary for the experiment, the exercise was self-paced and physiologically limited. This means they were able to estimate themselves how long they could cycle for, and their heart rate and anaerobic threshold were monitored so that the exercise could be stopped in order to prevent symptoms worsening.

PPT responses were similar for both experiments but were significantly different between healthy controls and CFS/ME patients (see Fig 1).

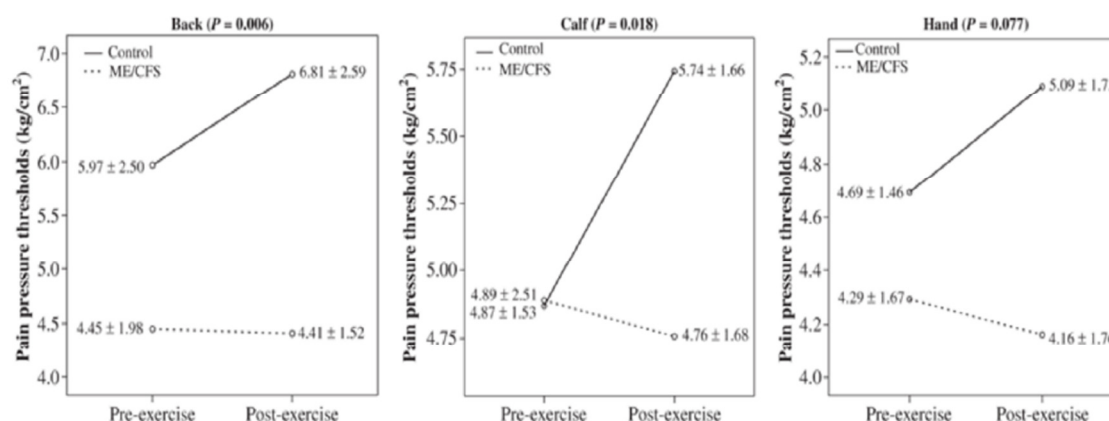


Fig 8: Pre- and post-exercise PPT in CFS/ME patients and healthy controls in experiment 1

For the healthy controls, PPT increased after exercise, meaning that more pressure was needed in order to reach their threshold, whereas for CFS/ME patients, the threshold decreased. The changes made to the exercise test in experiment 2 were unsuccessful in preventing worsening of CFS/ME symptoms.

Immune system changes did not differ between patients and controls but the complement system activation significantly decreased after exercise in both experiments for both groups. There were no changes to elastase levels after both types of exercise.

When correlation analysis was performed, PPT and complement system changes were only associated in patients with CFS/ME and not healthy controls (see Fig 2). Regression analysis found that changes in the complement system can partly explain (24%) the change in PPT results.

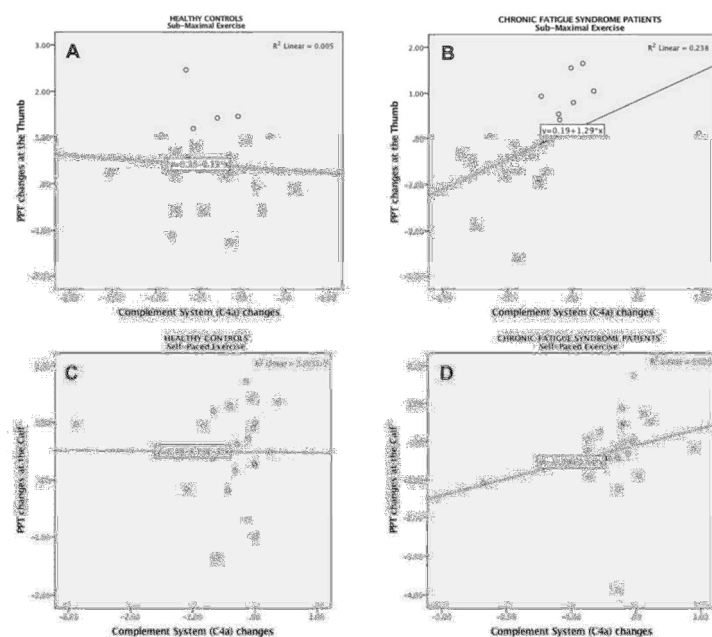


Fig 9: Correlations between exercise-induced changes in PPTs and changes in the complement system (C4a)

Limitations of the study were that it was only a small sample and very indirect measures were used and the results were not straightforward. Interesting findings include a moderate or strong associations despite using these indirect measures. Changes in the complement system seem to explain part of the change in PPTs after the sub-maximal exercise test in patients with CFS/ME.

A self-paced, physiologically limited exercise test had similar effects in CFS/ME patients to a more demanding sub-maximal exercise test at 75% of the target heart rate suggesting that the type of exercise is perhaps not important but that any form of exercise can cause immune system changes in people with CFS/ME.

Investigating the treatment of Paediatric CFS/ME
Prof Esther Crawley, University of Bristol

Key point summary:

- CFS/ME in children is important to study, as it is a disabling illness severely affecting school attendance and teenage development, as well as being costly to the country in terms of health resource usage.
- There are problems with investigating treatments because there is no clear and consistent way of defining and measuring recovery.
- The treatment outcomes wanted by children and their parents differ from those of clinicians, so a patient-reported outcome measure has been defined with input from children and their parents.
- The MAGENTA and FITNET trials are explained, with a progress report.

Prof Crawley talked about a variety of methods her clinic has used in working with children and their parents to try to improve treatment outcomes.

In children, CFS/ME is very common. It affects 1% of secondary school children, causing them to miss 20% of school, and 0.1% of 13 year olds are housebound. The illness is also very disabling, as within specialist services, mean school attendance is only 40%. 30% of the children also develop anxiety or depression in addition to their CFS/ME.

The illness has a high financial and emotional impact on families, and high healthcare costs. In the years prior to CFS/ME diagnosis, children seeing their GP more often, receive more prescriptions, and have more investigations, as shown in the poster by Simon Collin.

The problem

To design trials in children there needs to be better Patient Reported Outcome Measures (PROMs) and Minimally Clinically Important Difference must be defined. All children and parents ask questions about recovery such as “Is my child going to get better, and when?” and we cannot answer this question because there is no definition of recovery and what factors affect it, said Prof Crawley.

Systematic review: recovery definitions

A review has been carried out looking at every trial, prospective study, and epidemiological study which had a measure of recovery in paediatric CFS/ME. Some trials use a single measure such as school attendance or fatigue, whereas some use multiple measures. The more robust studies use a composite measure to define recovery.

What children and commissioners need to know

Children who have access to specialist treatment have over 60% chance of complete recovery at six months, using a composite score for recovery, whereas those without have a less than 20% chance. This means we have an obligation to provide specialist treatment, says Prof Crawley. Children are much more likely to recover than adults, though it is not known why this is.

How did the children/parents define recovery?

This was difficult to ascertain because children were reluctant to talk about recovery because it made them depressed about what they could no longer do, while those that had recovered did not want to be reminded of how ill they had been. Each child has their own definition of recovery, such as being able to play sports again or going back to school. There are different ways of defining recovery but it would be ideal to have either a combined score or a defined single question on recovery.

Developing a new PROM

When developing an outcome measure, we need to understand how patients conceptualise the illness, then define the domains and the questions, as shown in figure 1.

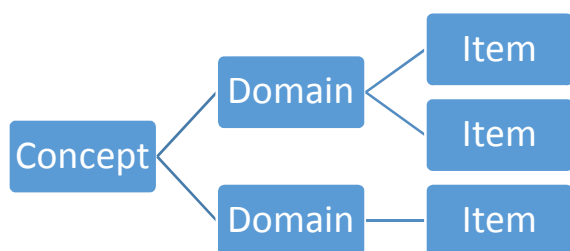


Figure 10: Process for developing a new PROM

Methodology

A variety of approaches were used but mainly semi-structured interviews which were child-friendly and interactive. The ideas were then discussed with a Young Person's Advisory Group (YPAG).

It was found that children with CFS/ME and clinicians have a completely different conceptual model of CFS/ME. The children's model is linear: they see it as getting CFS/ME and feel terrible, which then causes a whole raft of symptoms, causing them to reduce physical activity and social participation, which in turn has an effect on their wellbeing. Other factors played a part, such as how people engage with them at school. Clinicians have a different model and think it is more complex, with each factor affecting others.

When children were interviewed about factors which were important to them, they come up with a huge number of domains they wanted measuring, and this is difficult to put into a questionnaire as it would be too lengthy. Interestingly none of them mentioned biological

measures. A method called card-ranking was used to establish which the most important factors to children were.

Recruitment of participants was through the paediatric CFS/ME services, so they fulfilled the NICE criteria for mild-moderately affected. Twenty one children (16 females and 6 males) with a mean age of 14.4 years participated. Quantitative analysis was carried out on the card-ranking exercise by the children and their parents of what they wanted to see being measured as treatment outcomes.

Results

An example was shown of the card-ranking exercise by a 15 year old girl with CFS/ME and her mother to compare their different priorities. The top priorities of the girl were the measurement of symptoms, but also the fluctuating nature and instability of the illness. The mothers of the children were more concerned with mood and self-esteem. Overall, there were similarities in how the children and parents prioritised measuring symptoms, tiredness, and payback (or crashing), but there were also differences.

There were gender differences in priorities for measuring outcomes, with “symptoms” being more important to girls and “activities and hobbies” being more important to boys. There were also age differences, with “mood” being ranked higher by older children (14-15 years old) and “family impact” being more important to younger children (12-13 years old).

A great deal was learnt about the effects of illness through the interviews. When using the card-ranking to prompt more questions asked about symptoms, one participant explained, “They’re always there and on a bad day they get worse”. When asked about an outcome measure for activities and hobbies, another participant said, “I think being able to do a certain activity, if I’m doing it for longer, or having more energy to be able to do it”. This shows how complicated the problems of measurement are. Are we going to measure how many activities a child can do, how long they can do it, or how frequently they can do it?

On why symptoms are important to measure, one participant explained, “so I can try and get rid of the symptoms so that I can get to school more and see my friends”. The participant’s mother said “I think the confidence is affected by her symptoms, so she’s not sure she can anymore”.

The final conception model with the domains and the questions asked for each was then shown. The four domains identified are: Hobbies and leisure, Friends and family, Fatigue, and Symptoms. This new PROM is now finished and is entering the final testing phase. It has been designed to be completed online.

In research, results are usually presented in terms of whether there is a significant difference in outcomes but the MCID concept instead looks at whether what we are measuring is as an important difference to patients. There are three methods for this: the consensus method, the anchor method, or interviews, and this study used all three of these.

The consensus method involves a group of clinicians making a decision on behalf of the patients on what change is actually important. The anchor method looks at improvement by

comparing the outcome scores before and after treatment to observe a change, and the SF-36 scoring was the most popular with patients.

The MAGENTA trial

The aim of the trial is to investigate the effectiveness and cost-effectiveness of Graded Exercise Therapy (GET) as there are no RCTs of GET in children currently, even though NICE recommends it. In Prof Crawley's experience, children choose GET when it is available. It is difficult to recommend it, without being certain that it is effective.

The feasibility phase has just been completed. The trial used integrated qualitative methods, which means that throughout the trial the children, parents and clinicians were consulted about the interventions and trial process.

The aim of both interventions in the trial is to convert the boom-and-bust pattern to a stable baseline of activity, which involves cutting back on activity, which is not popular, as the children want to keep doing their physical hobbies, such as sports and ballet. All children are offered advice and symptom control, for example sleep and medication, and are then part of treatment arms:

- **Activity management:** All activity – mostly cognitive activities (school, school work, reading, socialising, and screen time).
- **Graded Exercise Therapy:** detailed assessment of current physical activity and focusses on evening out physical activity and then very slowly increasing.

It is now one year into the trial, and recruitment has been excellent, and the children like both treatment arms and have been sticking to the treatments well. Retention and follow up have also been good. Children also report that they have liked being part of the trial as they want to help improve treatments for other children with CFS/ME in the future. A data safety monitoring committee report recommended MAGENTA moved to full study

The FITNET-NHS trial

This is a new HTA funded trial and recruitment begins in November 2016. Many children do not have access to a specialist service; families are travelling four or five hours each way and staying in a hotel to attend the service in Bristol, which is expensive and also very tiring for the children with CFS/ME, and because of this Prof Crawley wanted to develop an intervention which can be delivered locally to the children.

FITNET is an abbreviation of Fatigue in Teenagers on the interNET, and this was originally published in the Lancet (Nijhof, 2012). It showed that 63% of the children in the FITNET arm had recovered at 6 months compared with 8% in the "standard medical care" arm. This might be a way of providing an intervention for adolescents with CFS/ME in the UK.

Children are referred to the study via their GP, then assessed by a paediatrician for their eligibility, and if they wish participate in the trial are randomly assigned to one of the two treatment arms: Activity management and behavioural therapy via Skype; or FITNET-NHS internet CBT modules. The trial will be the largest in CFS/ME in adults or children, at 660 participants.

Involving severe and very severely affected CFS/ME individuals in research: a clinician's view point

Victoria Strassheim, Newcastle University

Key point summary:

- Involving severely affected patients in research is difficult because they are too unwell to take part.
- Results may only really reflect the better-functioning patients with severe CFS/ME as they were more able to complete the questionnaires and home visits.
- Semi-structured interviews were preferred over lengthy questionnaires
- Reaching these patients to include them in studies is hampered by the standard ethics rules that patients must volunteer themselves rather than being directly approached.
- These problems need to be overcome in order to study severe CFS/ME and ensure that research is including the full spectrum of CFS/ME severity

Victoria Strassheim is a chartered physiotherapist who has a background in neuro rehab, and has been working on a project to define the prevalence of severe CFS/ME in the northern region of the UK, including understanding the clinical characteristics of severe CFS/ME and the relationship with cognitive and autonomic dysfunction. The project used Prof Diane Cox's descriptors for severe CFS/ME in the 2002 CMO report, so patients who are housebound, wheelchair-bound and bed-bound. Victoria shares her experience of involving people severely affected as research participants for this project in this talk.

Population breakdown

The size of the population in the geographical area of the study in 2011 census is just over 2.5million. If the estimated prevalence of CFS/ME as 0.4% is correct, there are roughly 10,000 people affected by the illness in the region. As 25% of people with CFS/ME are thought to be severely affected, this gives a figure of around 2,500 with severe CFS/ME.

Recruitment process

In research, potential participants cannot be approached; they have to apply to be participants themselves. The research group advertised for participants through specialist services, GP practices, local and national charities, and social media. A questionnaire pack was sent out to those interested, including an "expression of interest", a patient information leaflet, and three questionnaires. These questionnaires were demographics, the De Paul questionnaire, and a Barthel questionnaire to measure performance in activities of daily living.

Initially, 58 questionnaire packs were sent out and 38 were received back. It was taking a long time to recruit enough participants, so local support group ME North East was approached to see if they had any advice on where recruitment was going wrong. It was

suggested that there was too much involved for people with severe CFS/ME in sending back and forth information. The research team asked the ethics committee if they would approve of a substantial amendment to the process by sending questionnaire packs to ME North East for them to then send on to patients in their membership. 425 packs were sent out by ME North East but only 25 were returned, taking the number of participants to 63.

This obstacle of patients not being well enough to participate needs to be overcome somehow in order to make sure CFS/ME research includes severely affected patients. This may need to mean waiving some of the consent issues so that patients can be contacted directly.

Barthel Functional Outcome Questionnaire

A score of 12 is the pivotal score at which point a person moves from independence to dependence on someone else for their personal care and mobility. Of the 48 Barthel questionnaires returned, 30% scored 12 or less. Scoring less than 17 but more than 12 suggests help is needed to perform activities of daily living, and this applied to 67% of the responders.

De Paul Symptom Questionnaire

This is a comprehensive questionnaire which can ascertain which criteria fits the patient, out of the CDC, Canadian and Fukuda criteria. It involves scoring 54 symptoms on a scale. A reason for not returning the questionnaire may be that it is too long for someone who is severely affected, so the questionnaires returned will only reflect the less severely affected of the patients with severe CFS/ME.

From the 56 De Paul questionnaires returned:

- 60% fulfilled both the Fukuda and Canadian diagnostic criteria
- 18% fulfilled either the Fukuda and Canadian diagnostic criteria, but not both
- 22% did not fulfil either of the diagnostic criteria

This suggests that 40% of the patient group require further investigation to produce a definitive diagnosis. There were a total of 65 different conditions in the participants' past medical history, and there were 16 different current comorbidities, so it is possible that these people have other conditions that have gone undiagnosed.

Phase 2: home visits

The next stage of the study involved visiting five patients in their home four times. 3 patients (60%) managed all four visits and the other 2 patients (40%) only completed three visits, with one not managing to complete the full session and the other having to decline on the day of the visit. The patients wanted to participate as much as they could and they tried really hard to but their illness limited their ability to participate.

The first of the visits was for the consent procedure and the autonomic testing. Visit 2 was neurocognitive testing. Visit 3 was semi-structured interviews, and the final visit was a physical physio assessment to find out what the patients were physically able to do.

The patients found it very upsetting to realise through the assessments how bad their symptoms are affecting them, and would have been left having to cope with the emotions themselves after the visit, so a clinical decision was made not to do some of the assessments for some participants.

The semi-structured interviews were popular as it gave the patients the opportunity to tell the world their story and what their life is like, when they are usually not heard. The participants that lived with their parents were more able to complete the assessments, possibly because they were receiving much more support.

Conclusion

Confirmation of the diagnosis of the third of the participants who did not fulfil the diagnostic criteria to verify their CFS/ME diagnosis is needed. More investment into accessing patients with severe CFS/ME is needed, with allocation of advocates to aid involvement.

Fatigue in Primary Sjögrens Syndrome is associated with lower levels of pro-inflammatory cytokines

Dr Nadia Howard-Tripp, NIHR Academic Clinical Fellow in Rheumatology

Primary Sjögrens Syndrome is a chronic autoimmune inflammatory condition with 70% of patients suffering from fatigue alongside other systemic manifestations.

“The pathophysiology of fatigue is unclear, no biomarkers have yet been identified and it is challenging to study,” explained Dr Howard-Tripp. “We think there may be an immunological or inflammatory basis to this.”

This is partly because the phenomenon of post infectious fatigue and the fact that it’s incredibly common in a number of autoimmune diseases. And there is “a huge body of research has suggested that there is some immune dysregulation of some sort in patients who have CFS/ME.”

Using Sjögrens as a model of fatigue they recruited 159 patients from the UK Primary Sjögrens Syndrome registry along with 28 healthy controls. Fatigue questionnaires were completed, clinical and demographic data collected and levels of 24 cytokines were measured. The research team then looked at the differences between Sjögren patients and controls, then the association between cytokine levels and fatigue levels and, using logistic regression analysis, they teased out which variables were associated with fatigue.

“We classified the Sjögrens patients into minimal, mild, moderate and severe fatigue based on the PROFAD physical fatigue score which is validated for use in Sjögrens,” said Dr Howard-Tripp. Patients had similar demographics, disease duration and importantly similar medication use.

Of the 24 cytokines, 4 differed between patients and controls: IP10 (interferon gamma producing protein), interferon gamma and lymphotoxin alpha and TNFa.

Explaining the results, Dr Howard-Tripp said: “Its potentially a bit counter intuitive, in that as fatigue level increase the level of these pro inflammatory cytokines is actually decreasing. It was a slight decrease, she said, but statistically significant.

The team performed a logistic regression analysis using the array of data they had collected including levels of all 24 cytokines, white cell counts, measures of clinical disease activity as well as patient reported anxiety, depression and pain.

“We then looked to see if the computer could predict the level of fatigue,” she explained. “Using all of that information, in 67% of cases it could predict the level correctly.”

Continuing to refine their findings, they stripped down the data to reveal a reduced model in which IP10, interferon gamma, pain and depression were able to predict fatigue with the same accuracy.

“It is worth mentioning that anxiety and depression alone and just the cytokines alone were not as good. It was the combination of both that worked best,” she said.

Looking again at their results where a decrease in cytokines is associated with increased fatigue, Dr Howard-Tripp said, “What we wondered was that in the context of a constant

immune challenge such as in Sjögrens, where there is always a chronic low level of inflammation, could that cause an increase of the regulatory or the negative feedback mechanisms.” This in turn could cause inappropriate negative feedback and a reduction in the pro inflammatory response.

“And that could be either a by-product or a cause, that blocks the recovery that some patients have and leads to the persistent fatigue,” she said. The team have now joined forces with biochemists and scientists with a special interest in cytokines to work out why this might be happening.

Though this is a speculative model, explained Dr Howard-Tripp, there is supporting evidence for their theories. She cited the work of Hornig et al (2015) which looked at short and long duration (less than 3 years and more than 3 years) in CFS/ME and controls. With a far larger cohort, these researchers found that a number of pro inflammatory cytokines were lower in the CFS/ME patients who had were ill for longer. “Perhaps there is a temporal process going on that means initially there are higher levels of inflammation but over time the inflammation is decreasing,” she said.

Referring to a slightly older Dutch study which looked at adolescents compared to controls, researchers found IL6 and TNFa were lower in those who had CFS/ME while IL10, which is typically anti-inflammatory, was higher.

Dr Howard-Tripp highlighted the limitations of their own study, saying that cytokines fluctuate widely at a given point in time, the cohort included females only and the model is speculative rather than proven. Further work is required, she said, to examine role of anti-inflammatory and regulatory pathways to see if they do have a role in fatigue.