ME Association Transcript

Royal Society Conference:

Understanding the neurobiology of fatigue

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'Standing up for fatigue'

Abstract

Fatigue is a common symptom that arises in association with a range of chronic diseases and when it occurs with a recognised constellation of symptoms is Chronic Fatigue Syndrome or Myalgic Encephalomyelitis. Fatigue impacts significantly upon quality of life and recent research has confirmed is frequently associated with autonomic nervous system dysfunction.

The talk will focus upon research exploring the role of autonomic dysfunction in the manifestation of the symptom of fatigue. This will include both subjective and objective assessment of autonomic dysfunction and describe novel MR methodologies to explore the association of muscle, cardiac and liver dysfunction in those with chronic fatigue syndrome and fatigue associated conditions.

The importance of autonomic dysfunction as a recognised phenomenon in fatigue highlights the opportunities that there may be for targeted therapeutic intervention for autonomic phenotypes in those with CFS/ME and fatigue in chronic disease.

ME Association Transcript

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Note: the following transcript has been completed by Russell Fleming on behalf of the ME Association and any errors or omissions are my own.

Conference details:

https://royalsociety.org/science-events-and-lectures/2017/09/neurobiology-fatigue/

Audio download:

http://downloads.royalsociety.org/events/2017/09/neurobiology-fatigue/newton.mp3

Presentation slides can be found on the corresponding ME Association website blog

Professor Julia Newton

"Thank you very much. I'd like to add my thanks, to that of others, for the very kind invitation. I'm quite disconcerted about standing up as the first speaker, at a conference that's called understanding neurobiology. I'm a geriatrician by background and what I am going to do is focus on cardiovascular autonomic function. But I am going to take the opportunity to begin with, just to set the scene a little bit – as the first speaker – just to give you an indication of the significance and the severity of fatigue as a symptom.

For those of you who aren't familiar, chronic fatigue syndrome/M.E. is actually considered to be a neurological disorder by the world health organisation. It's given the ICD code 10, G93.3, but it remains a medically unexplained condition. It's recognised as being physiologically distinct from depression, and there are emerging, identifiable, immunological, neurological, endocrine, and particularly, autonomic, abnormalities.

For those of you who are not clinically familiar with CFS/ME or haven't actually met a patient with this condition, it's a diagnosis where a constellation of symptoms come together. They are heterogeneous in their nature, usually, but the individual usually has severe, debilitating fatigue for at least four months – together with other symptoms.

At the moment, and we may come to debate this throughout this meeting, there's no evidence of other medical or psychiatric problems, although patients do experience secondary psychiatric or mental health issues as a consequence of the significance and the severity of the symptoms that they are experiencing.

But as we sit here today, there are no biological-based diagnostic tools for CFS/ME, and we have no clinical pointers when seeing the patient, and generally, the routine blood tests that we do in clinical practice, are negative.

As we've heard, fatigue is a much more significant and broader symptom that is experienced by a large proportion of the population. For those of you who meet somebody who describes or experiences fatigue – or perhaps have had it yourself – you'll realise it is very different from the symptom of tiredness. And often it is very different from the sensation of sleepiness. And usually, as a symptom, it is not relieved by sleep or rest.

Increasingly, we are beginning to recognise fatigue as a symptom across a whole range of different chronic illnesses. The clinical practice that I have in Newcastle, focuses entirely upon managing fatigue in chronic illness, rather than in CFS/ME.

So, to give you an idea of some of the chronic illnesses that fatigue is recognised in, these are just an indication of some of those conditions. So, musculoskeletal neurological conditions – we're going to hear about stroke a little bit later on, it's the commonest reason why people fail to rehabilitate after a stroke. It's described by patients with Parkinson's disease as the worst part of their illness. It is the commonest reason why people who are having chemotherapy for cancer, have to stop that chemotherapy. So, it's well recognised in a range of different conditions.

In Newcastle, what we've done is take that as a very positive thing – the recognition that lots of different conditions are associated with fatigue as a symptom – and have pulled all those different clinical conditions – and the clinicians and researchers who are interested in the symptom of fatigue – together into a fatigue research centre. And what that allows us to do is to perhaps understand fatigue in one chronic illness and fast-track our understanding perhaps in another chronic illness. And

these are the conditions where we have recognised and quantified fatigue and phenotypical associates of fatigue in our clinical practice in large cohorts in Newcastle.

04.23

And the reason we've done that is a study we did a number of years ago, where we actually looked at fatigue across a range of different chronic diseases, and what we were able to show was that in fatigue-associated chronic diseases – and in chronic fatigue syndrome/M.E. patients – the perception of the symptom of fatigue is comparable. So, fatigue for somebody with Parkinson's disease, or stroke, is similar in its experience, as that in CFS/ME. It might be different in terms of its severity, but certainly the essence of the symptom and how an individual experience's it, is very similar. Again, suggesting that if we can learn things about fatigue in one condition we may be able to understand, for example in CFS/ME, the manifestation and underlying biology of that symptom.

So, to give you a few slides on epidemiology – I am aware that there are people in the audience who are better at epidemiology than I am. But just to illustrate the importance of CFS/ME and how common it is – certainly in the UK it affects about 0.2-0.4% of the UK population and the average primary care practice will have about 40 patients. So, it's relatively common.

But as we've heard already, fatigue as the more ubiquitous symptom is really very common – it's the commonest reason why people will go to see their GP. It takes an enormous amount of work for colleagues in primary care and occupies an awful lot of their time.

And it's expensive. It's costly to the individual that experiences that symptom but certainly when the individual is fatigued it has consequences for healthcare systems but also for productivity and for populations on a more broad scale.

We're probably I suspect going to debate this later, or through the next two days, but it's really important at this stage that I put my cards out on the table. Although CFS/ME, and fatigue as a symptom remains medically unexplained, this I believe is because we have not so far been able to elucidate the underlying pathophysiology of this symptom.

There are significant consequences for the individual that has fatigue as a symptom or is diagnosed with CFS/ME. And the consequences are very wide-ranging for that individual. Patients often have huge difficulties being believed by the healthcare profession, and getting the support they need to live their life to the maximum that they possibly can.

And what we are going to hear throughout the next two days is lots of emerging theories, lots of emerging evidence, to explain the physiological abnormalities that occur in these patients. And I would argue that the psychiatric and mental health symptoms that these patients experience, are secondary to the significance and severity of the symptom of fatigue.

07.50

So, moving on to my remit for this morning which is to talk about autonomic function. If we begin to think about a hypothesis around the underlying pathophysiology for fatigue as a symptom – and CFS/ME in particular – what we believe is that we have a susceptible individual perhaps who has a genetic predisposition, who at a particular time in their life may have psycho-social issues – a particular stressor at a particular time – and then has a triggering event – perhaps an infection – which sets off a cascade of physiological consequences within that individual.

There is evidence that there is a disordered immunological response – perhaps to that triggering event – that there may be an endocrine disturbance. There is considerable evidence of abnormalities of the autonomic nervous system – with syndromes such as POTs and postural hypotension which I'll talk about in a little more detail – and suggestions in the literature that there may be a mitochondrial abnormality. And all these things come together in an individual who simply doesn't recover from that triggering event.

09.20

So, what is autonomic dysfunction? I am going to focus very much today on cardiovascular autonomic function. And that's largely because measuring autonomic function is focused in clinical practice on measuring cardiovascular parameters. It's one of the limitations that we have in the autonomic field is that predominantly what we are able to measure, and what we have access to, focuses on cardiovascular function.

If you imagine that your cardiovascular system is a closed-loop system: with your head at the top and legs at the bottom, and your heart in the centre. There are pools of blood situated around us as a human, in various different organs. And our heart at the centre is pumping a known volume of blood around that cardiovascular system.

When I stand up, 700ml of blood drops into my legs. There is a very fast reaction from my autonomic nervous system that detects that drop in pressure in the baro-receptors in the arch of my aorta. When the baro-receptors detect that drop of 700ml into my legs, it sends off an impulse through the para-sympathetic component of my autonomic nervous system to my brainstem, which subsequently has a sympathetic response from the sympathetic component of my autonomic nervous system, and what that does is it makes my heart go a little bit faster and is vasoconstricts my peripheral blood vessels. All with the intention of keeping the blood going to my brain.

11.21

If you think back to that closed-loop system, the heart in its position is constantly challenged – pushing blood against gravity – to keep my brain perfused with blood. Physiologically, as humans, we are conditioned that we will always preserve our brain, and the blood flow to our brain.

With our autonomic nervous system, when I stood up, I didn't feel any consequences of that blood dropping into my legs. But if my autonomic nervous system doesn't react quickly enough, then there are consequences.

At the extreme end of things, I will black-out – because there isn't enough cerebral profusion keeping my brain perfused. The middle range of things, I might be a bit dizzy when I stand-up, postural symptoms. What we hypothesise is that if there is not enough blood getting momentarily to my muscles, my heart, my brain, that that manifests as the symptom of fatigue.

12.32

So, it's all about the head of stem, the blood pressure, that is pumping the blood round that cardiovascular system, and if that head of steam isn't doing what it needs to do and keeping my brain perfused then I will be symptomatic. And when I am symptomatic that is what we call dysautonomia. So, there is a microsecond imbalance between that parasympathetic and sympathetic response on assuming the upright position, and physiologically – if that doesn't happen quickly enough – that manifests as symptoms.

If my hypothesis is right, and this is a problem of fluid shifting around that system, and perhaps not necessarily getting to where it needs to be which is my brain, then you would anticipate that symptoms of autonomic dysfunction would be more prevalent in fatigue-associated conditions.

This slide is an illustration of a tool called the orthostatic grading scale, which is a clinically applicable tool, it takes a matter of seconds to complete – we use it routinely in all of our fatigue-associated chronic disease clinics. And this is just an example of a range of different fatigue-associated chronic diseases.

We've got chronic fatigue syndrome, a control population, non-alcoholic fatty-liver disease, primary-biliary cirrhosis – which is an autoimmune liver disease – and primary sclerosing cholangitis – which is another autoimmune liver disease – both of which are known to be associated with fatigue, vasovagal syncope – which is a form of dysautonomia where people have the extreme end of blackouts – ITP is an autoimmune haematological disease – and Sjogren's is an autoimmune musculoskeletal condition.

They're examples of fatigue-associated diseases where we've applied the orthostatic grading scale. A score of 4 or above, is orthostatic intolerance, and a score of 9 or above, is consistent with orthostatic hypotension.

The message from this slide is that there is a huge spread of values within these fatigue-associated chronic diseases, but consistently the average value, is above 4. There's huge proportions of each group have scores consistent with orthostatic intolerance, and in every condition that we have looked at so far, fatigue severity associates with severity of autonomic symptoms. So, nearly 90% of the CFS cohort have orthostatic intolerance and you'll see the other values there.

And that led us – a number of years ago – to suggest that in fatigue-associated chronic diseases, and in CFS/ME, there were a proportion of patients with these conditions – associated with the symptom of fatigue – where problems with dysautonomia were significant findings, which potentially gives us a target to begin to understand and explore the underlying pathophysiology.

16.08

So, if we are correct and symptoms were more common of autonomic dysfunction, what about objective abnormalities of autonomic dysfunction?

Well, this is two conditions – CFS/ME and the autoimmune liver disease primary biliary cirrhosis – and this is the culmination of autonomic dysfunction (that head of steam, blood pressure), where we've measured 24-hour blood pressure – every 15 minutes for 24 hours – in over 100 PBC patients and 100 CFS patients, with a comparable number of age- sex- and activity-matched controls. And what this illustrates is that blood pressure – the head of steam – is consistently lower in CFS and PBC compared to their matched controls. So, head of steam, objective abnormalities of autonomic function, are present.

And this is just one slide to illustrate nearly a decade of my life. For those of you who are familiar with autonomic testing, there are many, many, different ways that you can measure autonomic function. You can measure it dynamically, you can measure it statically, you can measure it in response to stimuli. This is something called heart-rate variability, and this one slide simply illustrates that we have consistently been able to show abnormalities of autonomic function using a range of different assessment methodologies, in fatigued vs. non-fatigued patients with a range of different chronic diseases.

So, what does that mean for an individual who may have fatigue?

Well, for those of you who are not familiar with autonomic testing, this instrument of torture – shown on the photograph – is known as the tilt-table and it is a test that we use clinically to look at physiological or haemodynamic responses to standing.

What we're able to do is to bring an individual on a mechanical bed, to standing at 70 degrees – which is the angle we know encourages blood to pool in your legs most effectively – and we stand them for 40 minutes, while we measure their heart rate and blood pressure, beat-to-beat. And what that allows us to do is look at the physiological stress of standing – or orthostasis – and what happens to that as more and more blood pools in your legs.

We've been able to use that test and apply it in fatigue-associated diseases – and what I am showing here in the table is a cohort of 64 CFS/ME patients and age- sex- and activity-matched controls – and what I want you just to see from this table is that patients with CFS/ME are significantly more likely to have a history of loss of consciousness – so that extreme end of drop in blood pressure – and they are more likely to have a condition which is recognised as a form of dysautonomia – postural tachycardia syndrome.

We, and other groups, have shown that up to a third of those who are given a diagnosis of CFS/ME, actually when they are tested in an autonomic lab, will have postural tachycardia syndrome. And that is a form of dysautonomia where we recognise an increase in your heart-rate by 30 beats-per-minute on standing associated with symptoms, and for which there are treatments that are defined by consensus criteria.

20.11

So, I am just going to move on to some of the physiological studies that we have done in Newcastle, trying to understand the mechanisms that might be underpinning the presence of autonomic dysfunction in those conditions where fatigue is a significant problem.

We've tried to understand whether or not this may be a central abnormality of autonomic brain centres, and we've done studies looking at downstream effects using a range of MR modalities to look at muscle, cardiac, and liver function, and I'll go through some of the results from those studies.

I'm just going to show one slide of upstream effects. Largely because we struggle to come up with brain abnormalities in patients with fatigue-associated conditions. We have developed a test in which we perform an autonomic stressor in the MR scanner. So, we get people to perform a Valsalva manoeuvre. A Valsalva we know stresses your autonomic nervous system and drops your systemic blood pressure, and what we've been trying to establish is whether that is associated with cerebral blood flow. The technique we've developed we've been able to look at cognitive performance, and have been able to show that swings in blood pressure during the Valsalva are associated with changes in cerebral blood flow, and that those do associate with performance using a full IQT score – and we've submitted that for publication which is coming out in Neuroimage Clinical in a few weeks' time.

22.18

But what I want to do is focus more on the downstream effects, where we have been looking at muscle and cardiac function. As part of a study that was funded by the MRC a number of years ago, we developed a technique where we encouraged patients with fatigue-associated conditions – primary biliary cirrhosis being the prime example and we also studied CFS/ME patients – and we asked them to exercise in the MR scanner where we were able to measure acid accumulation in their muscles.

We performed a protocol where they exercised for 2 minutes initially, and then subsequently rested and had 3 bouts of repeat exercise. What we were able to show during those studies was that CFS patients – and the same is true in a number of fatigue-associated conditions – that the acid accumulated in their muscles was significant and in CFS/ME in repeat exercise, the time that it took for individuals to recover from one bout of exercise was significantly longer – to the point where the muscle in CFS/ME patients was exposed to in the order of 20 times as much acid during exercise.

23.47

This was published a number of years ago in the Journal of Internal Medicine and what we were also able to show in this study was that the severity of these abnormalities associated with the severity of autonomic function using that heart-rate variability parameter. So, it looks like there is some relationship between acid, and how we remove acid, from exercising muscle and autonomic function which may be related to the calibre of blood vessels as we exercise, or may be related to the transporters that remove acid from exercising muscle, which we know are regulated by the autonomic nervous system.

24.33

We took muscle biopsies from those patients that took part in that previous study, and we've been growing those muscle cells in the lab ever since. And one of the charities very kindly purchased for us a device that allows us to study these exercising muscles in real-time.

One of the problems that we have in fatigue is that exercise is often very difficult for an individual patient to participate in. But with my exercise lab it means that nobody can refuse to go to the gym because these cells have to participate. And that allows us to take away the volitional element that can sometimes be a problem in studies.

With that exercise – and you may not quite be able to see – but Audrey who does these experiments – this made her year – because what we can see is exercising muscle cells – you can just about see them twitching, but in in vitro studies what we are now able to do is look at glucose and insulin uptake in exercising muscle and begin to tease out the abnormalities in the biochemical pathways in those exercising muscle cells and see whether or not these can be modified in vitro. With the intention that that may give us molecules, pharmacological therapeutics, that we can explore in clinical trials. And this paper in Plos One shows work done by the group where we were able to show that activation of AMP-kinase is impaired in CFS/ME muscle-cells as they exercise, compared to controls.

26.32

I showed this slide last week at the CFS/ME research collaborative in Bristol, this is Cara – one of my PhD students – and she's using a system called the Seahorse, and I have to show a picture of a seahorse because I don't really understand what a seahorse does – it's a machine – and what that does is allow you to look at metabolic function. And what Cara is doing is using muscle cells and PBMCs looking at glucose uptake and she's finding very real and significant abnormalities in metabolic function n PBMCs and she's now going on to look at muscle cells and this has been submitted for publication to Plos One.

27.17

Moving on very quickly to cardiac MR. Again, with MRC funding in a cohort a number of years ago, we were able to look at energetic function in the heart, using MR techniques. With 25 patients with CFS/ME we measured the PCR-ATP ratio. A ratio of less than 1.6 would be consistent with a sub-clinical

cardiac myopathy – and none of the controls hit that criteria – but a third of patients with CFS/ME had values less than 1.6, suggesting they may have a cardiac abnormality.

We developed a technique using cardiac tagging, where you put magnetic beads over the left ventricle, and watch how these beads move in the MR, that allows you to look if there is torsion in the left ventricle as it pumps. We were able to show – again this was published in ??? – in CFS/ME and we've been able to show the same is true in other fatigue-associated conditions, that some patients with CFS/ME have a problem with how their heart pumps.

28.54

And there is quite a literature out there about abnormalities of cardiac function in CFS/ME. This is a paper from a Japanese group who have repeatedly published, suggesting that there may be something called a 'small heart syndrome' in those with CFS/ME.

When we were able to take the abnormalities from the cardiac bioenergetic MR scans and look at functional consequences – this is something called left ventricular work index which shows how hard your heart is working – the poorer your PCR-ATP profile, the poorer your left ventricle was able to compensate when you stand up (so, that's stress when standing up) – and the CFS/ME patients again had more physiological abnormalities on standing, compared to matched controls.

29.52

We've repeated that in a second cohort of patients – which was funded by the MRC in a specific call to target CFS/ME – where we were able to perform all of our assessments in a cohort of almost 50 patients. We replicated the original findings but were also able to show that the patients with CFS/ME in a UK population had smaller end diastolic volumes and end systolic volumes compared to controls. Something that was completely unrelated to the length of their disease – suggesting that is was unlikely to be related to deconditioning.

30.40

In that same cohort we were able to measure the volume in the circulation. There were reductions in total plasma volume and red cell volume, and strong correlations between volume in circulation and cardiac volumes, and symptoms. So, there was a relationship between how much volume there was in a person's circulation and how fatigued they were – with lower volumes in a person's cardiovascular circulation – being associated with more significant fatigue. That study was published a year or so ago, in Open Heart, and to give you an idea of the significance of findings in this field, this is an open-access publication and it was downloaded, 20,000 times within a month of it going online. So, patients, researchers, clinicians, are very much craving new information.

31.50

In terms of stepping forward, and trying to develop biomarkers to help us identify patients who, phenotypically, may be in that group where they have cardiac abnormalities, brain natriuretic peptide (BNP) is now a diagnostic tool in clinical practice to identify those who may be at risk of cardiac endpoints. And in the MRC cohort we've measured BNP and shown that in those with CFS they have significantly higher levels compared to controls. Again, in those who have the highest levels of BNP they are more likely to have abnormalities of end diastolic and end systolic volumes – suggesting that this may represent a screening opportunity for us to identify within fatigue-associated groups those who may require further assessment.

32.54

So, I've taken you on a quick canter through some of the studies we've been doing, looking at autonomic function in CFS/ME and in fatigue-associated conditions. I hope I've convinced you that fatigue is a significant symptom and CFS/ME – a condition similar in characteristics to the fatigue experienced by those with a range of chronic diseases. We are going to hear over the next two days about very specific physiological abnormalities, predominantly focusing on the brain, but I hope I've convinced you that there may also be abnormalities in other organ systems, particularly the cardio-vascular autonomic system.

We know that autonomic dysfunction is fairly common, and it does associate with fatigue severity – suggesting it may be a target for therapies – and the studies that we, and others, have been doing suggest that there is brain, cardiac, and muscle abnormalities, in CFS/ME which, again, might represent future therapeutic targets.

34.17

I'd like to just finish off by thanking a few people. The charities in this field are enormously generous to us in Newcastle. We've been lucky enough to receive funding from some of the largest charities – Action for M.E., ME Research UK, and The ME Association. The MRC has been very generous to us in the past, and have had a specific call which we have benefitted from. The researchers that I work with come from a range of different areas within Newcastle and beyond – and I am very grateful to them. And, perhaps most importantly, I would acknowledge the support of the patient community who are fantastic, and will participate in anything to push this field forward. You can biopsy them, you can take as much blood as you like from them – because they are desperate for answers. So, thank you to them as well.

Thank you.

35.18