19 November 2012 Action for ME Annual General Meeting Presentation
http://www.actionforme.org.uk/get-informed/news/archived-news/our-news/2012/research-at-our-agm-watch-now

Presentation with slides: http://vimeo.com/53777108

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Transcript Standing up for Fatigue 45 minutes
Begins at 2.00 mins

Julia: A run through of some of the research we have been doing at Newcastle and to finish off by telling you about the projects we are involved in moving forward. So looking ahead at the research that's about to start, and some of it that's already underway.

Slide 2 What is autonomic dysfunction?

For those of you that don't know me, what I am particularly interested in is the autonomic nervous system. And that's the sub conscious nervous system that does all those things in your body that go on outside your conscious control. So at the moment your heart is beating, your blood pressure's working, and your bladder is probably filling a bit after the lovely coffee, and you gut is working trying to digest those lovely chocolate biscuits that you've just eaten.
So those are the things that are under control of the autonomic nervous system. And in the human the cardiovascular autonomic nervous system, is a particularly important component of the autonomic nervous system, and this is just a schematic representation of the vascular system, with the brain at the top and your legs at the bottom, and your heart right at the centre of that autonomic nervous system.
And that's a challenge to us as humans, because physiologically it's a problem that your heart is at the centre and has to profuse your brain against gravity. So as humans we've evolved

over time from Neanderthal man where are heart and our head are in line with each other to actually an upright position to where we actually have to pump blood against gravity to keep our brain profused. And that's what your body does against all challenges – it keeps your brain profused.

And doing that is creates your blood pressure and your blood pressure is like a head of steam that keeps going round your body and one of the greatest physiological challenges that we as humans face, is when we stand up.

So as I stand up, 700ml of blood drops into my legs, and in order to try and compensate for that and keep my brain profused, my autonomic nervous system sends an impulse to my brain, and says "Whoa! I've detected a drop in blood pressure" and as a response to that it makes my heart go a little bit faster; and my peripheral blood vessels constrict to keep my brain profused. To keep that head of steam high in order to do that.

Now when I stand up, if that doesn't happen effectively, and it should be a micro-second response that happens, and if it doesn't happen as efficiently as it ought; then at the extreme end of things I'll 'black-out' – that's what I do in my day-job is investigate people with syncopy or 'black-outs' – at the middle range of things it might make you a little dizzy or light-headed; and at the more subtle end of things (if that micro-second head of steam response doesn't happen), then not enough blood might get to your muscles, your heart, your brain – and that's what I believe leads to the symptom of fatigue.

Slide 3 – The history

Rowe et al; Is neurally mediated hypotension an unrecognised cause of chronic fatigue? Lancet. 345(8950):623-4, 1995

So I like to think that's all my idea but it's not. It was first suggested in 1995 in a seminal paper in the Lancet – the biggest medical journal that we have in the UK – where it was suggested that low blood pressure (or a low head of steam) might be and unrecognised cause of Chronic Fatigue.

Slide 4 – AD in the pathogenesis of fatigue

- **In a range of diseases characterised by fatigue (MS and heart failure) – strong associations between fatigue and autonomic dysfunction.**
    - **Flackenecker et al. Neurology 2003,**

    - **Naschitz et al. Seminars in arthritis and rheumatism 2002,**
    - **Streeten et al. Am J Med Sci 2000,**
    - **Stewart Ped Res 2000,**
    - **Peckerman et al. Psychosomatic medicine 2003.**
- **Fatigue is a symptom in PAF & MSA which are characterised by abnormalities of blood pressure control**
    - **Mathias et al. Journal of Neurology 1999.**

And if you look at diseases where autonomic dysfunction is a problem, or where fatigue is particularly prevalent, like Multiple Sclerosis and heart failure then what we recognise is that autonomic dysfunction is very frequently found in diseases where fatigue is common and in diseases where there is autonomic dysfunction – like primary autonomic failure – then often fatigue is one of the worst symptoms that people experience.

Slide 5 – The history
200 publications looking a vascular function in CFS

And when you go to the medical literature, you find that there are a huge number of publications suggesting that in CFS/ME there are problems of the autonomic nervous system or the vascular system. So on the basis of that, that's sort of led to the work that we've been doing at Newcastle – looking at autonomic dysfunction.

Slide 6 – Symptoms of autonomic dysfunction

So the first thing that we want to confirm or suggest that autonomic dysfunction is a problem in people with CFS/ME – the first thing to do is to start exploring whether the symptoms might be a problem in patients and we can do that with questionnaires.

Slide 7 – Orthostatic Grading Scale [Graph showing results and comparisons of CFS, Controls, NAFLD, PBC, PSC, OLT, VVS, ITP and Sjorgen's]

This is a questionnaire called the Orthostatic Grading Scale which is a validated questionnaire from America; and on the bottom, on the X axis, there are a range of different fatigue-

associated chronic diseases and some control patients. And you can see the line going across at 4 – that's the normal level – above 4 is abnormal and all the controls are at 4 or below, but you can see what all of these fatigue-associated diseases (and particularly the CFS/ME column) that there's a huge spread of orthostatic rating scale scores with high scores being the worse orthostatic intolerance. And overall a huge range with large numbers having orthostatic intolerance.

Slide 8 – Orthostatic intolerance
CFS – 89%
NAFLD – 56% (Newton et al., CAR 2009)
PBC – 69% (Newton et al., Hepatology)
In all cases fatigue severity associates with increased orthostatic intolerance.

And when we summarise that, about 90% of people with CFS/ME have scores consistent with orthostatic intolerance, so have symptoms when they stand up. Fatty-Liver Disease, Primary Biliary Cirrhosis, are both liver diseases where fatigue is a significant problem; and again large numbers of those patient groups have orthostatic intolerance – and in every patient group that we have studied so far where fatigue is a problem; the more fatigued you are the more symptoms you have of orthostatic intolerance. So the more symptoms when you stand up.

Slide 9 – Newton et al., QJM 2007 - Chart

And that led us to hypothesise in a paper in 2007, that Dysautonomia (a problem with your autonomic nervous system) underpinned at least some of the symptoms experienced by patients with CFS/ME. [Referring to chart] So the CFS/ME patient group is the 'blue block', and a large proportion of those have Dysautonomia-Associated Fatigue (DAF); and the 'green block' could be any fatigue-associated chronic disease where the prevalence of fatigue varies according to the disease that you chose to study; but in those who have fatigue a proportion of those with have Dysautonomia.

Slide 10 – Objective testing of autonomic function

So that's symptoms. So we're shown that symptoms of autonomic dysfunction are common in patients where fatigue is a problem – what about how we test our autonomic nervous system?

Slide 11 – Actual autonomic abnormalities

- **Newton et al., Psychosom Med 2009**
- **Newton et al., CAR 2009**

Well, one of the easiest ways is to measure blood pressure – so to measure that head of steam. [Bar chart displaying results] And this is over 100 patients with CFS/ME and 100 matched sedentary controls, and the graph nearer to me [on the left] patients with Primary Biliary Cirrhosis which we consider to be a chronic disease which is a model chronic disease for fatigue; and you can see from the CFS/ME graph that the head of steam is significantly lower in patients with CFS/ME over 24 hours compared to matched controls.

Slide 12 [no title and shows no graph in this presentation version]

- **Newton et al., Liver Int 2006**
- **Newton et al., EJGH 2006**
- **Newton et al., Hepatology 2006**

And this is just one slide to illustrate years of my life and this is just to show you that when we measure autonomic function across a range of fatigue-associated diseases we consistently find that patients with fatigue have abnormalities with their autonomic nervous system when we measure it compared to non-fatigued controlled populations.

Slide 13 – Consequences of autonomic dysfunction

What does that mean? It's great. I can sit in the lab or a clinic and measure things all day long; but what does that mean in terms of consequences for the patients that I see?

Slide 14 – Syncope

[Syncope: a medical term for fainting; a transient loss of consciousness and postural tone , characterized by rapid onset, short duration, and spontaneous recovery, due to global

cerebral hypoperfusion (low blood flow to the brain) that most often results from hypotension (low blood pressure)… http://en.wikipedia.org/wiki/Syncope_%28medicine%29]

- **Newton et al., CAR 2009**

I don't want you to necessarily read this table; but the picture shows you what's called a 'tilt table' and to some people this is an instrument of torture but we use it as – in the clinic – a diagnostic tool to allow us to identify people who have a tendency to drop their blood pressure when they stand for long periods of time. The bed will go to 70 degrees and will measure people's heart-rate and blood pressure and we will look for their blood pressure dropping over time. We do that clinically to indentify people with Neurally-mediated Syncopy and we've actually performed that test in 64 patients with CFS/ME and matched sedentary controls – and what I want to just illustrate to you with this table is that people with CFS/ME tend to have more history of loss of consciousness (which is an indication to me clinically as a syncopy doctor that they should be being investigated for that) and that they are more likely to have Neurally-mediated Hypotension: so they have a tendency to drop their blood pressure when they stand up. And the final row on this graph is there to remind me that in addition to dropping their blood pressure we've now had three cohorts of CFS/ME patients and in each of those groups of patients they are more likely to have Positional Orthostatic Tachycardia Syndrome – about 30% on each occasion. And this is a dynamic abnormality that is well recognised in cardialogical and syncopy circles and is amenable to treatment with medication that would slow your heart-rate down. So for me it is a very important thing for people who are seeing patients with CFS/ME to look for, identify and treat.

Slide 15 – What might the mechanisms be?

- **Upstream**
- **Downstream**

So what might cause autonomic dysfunction in people with fatigue-associated diseases? Well it might be a problem in their brain centres or it might be a problem in that vascular system, where people are perhaps putting volume in places where it shouldn't be. So I just want to quickly run through with you some of the studies we've been doing looking at Upstream and Downstream mechanisms.

Slide 16 – Upstream

I don't need to tell you about memory problems in people with CFS/ME and this is [the graph] another questionnaire that quantifies cognitive failures and you can see that CFS/ME patients are significantly worse in terms of the cognitive failures that they have. And in a non-CFS/ME world it is well recognised that the lower your blood pressure is the worse you will perform on memory tests. And the more your blood pressure drops when you stand up the more likely your memory is to decline over time. So you would expect in CFS/ME is a disease where autonomic dysfunction is a problem that there would be a relationship between cognitive function and autonomic function and when we've looked at the symptoms of orthostasis and cognitive failures there is a relationship between these two – with people with more cognitive failures having worse symptoms when they stand up and also there's worse performance on neuropsychometric formal testing; with CFS/ME patients performing worse (and this is just one example of the tests we have been doing – [referring to next slide]).

Slide 17 – Upstream

- **Brain MRI whilst completing Valsalva**

We've been doing brain MRI scanning, and I've show this because this is my brain, where we've been getting people to do a Valsalva – so an autonomic nervous system stressor – while in the MRI scanner, looking at blood flow; and the bottom graph shows you that using simple measures (like your IQ) you perform worse on memory tests the less blood you have flowing to your brain during the Valsalva.

Question from audience: What is a Valsalva?

Valsalva is where you blow hard against…you blow really hard and it actually drops your blood pressure… it's a well recognised pattern of blood pressure changes

Slide 18 – Downstream

- **Muscle MR spectroscopy – 2 mins exercise**
- **Jones and Newton JIM, 2009**

And then in terms of downstream mechanisms, we've been doing muscle MRI scans where we've been asking people to exercise while in an MRI scanner; while we measure the amount of acid that accumulates in their leg muscles.

Slide 19 – Downstream

- **Results of above spectroscopy**

And when we've been doing that, we've been able to show repeatedly – in two series of CFS/ME patients and in fatigue-associated chronic diseases – that if you have fatigue or CFS/ME the acid you generate in your muscles is significantly higher and you have greater difficulty getting rid of that acid once you stop exercising. And between bouts of exercise your pH doesn't go back to normal. So the bottom graph just shows you the exposure that an individual muscle has to acid, which is the grey area compared to a normal healthy control, which is the white area. So there's lots of muscle acidity.

Slide 20 – Drug development?

- **Intra-cellular pH in cultured myoblasts from CFS and normal control subjects prior to and 120 minutes after treatment with dichloroacetate (DCA).**

And that just brings me to mechanisms by which we could perhaps manipulate or understand that, and this is the area that Action for ME have very kindly funded a PhD studentship to develop this more fully. Because we have begun to take muscle cells from people with CFS/ME and grow those muscle cells in the laboratory and we've developed a nano-sensor technology – where little nano-sensors can go across the muscle cells – and these sensors will fluoresce at different pH's. And we had a muscle gym in the laboratory whereby we can exercise those muscle cells over known amounts of exercise – we call it our muscle-gym – and we can watch the pH generated within these cells, and replicate what is happening in the MRI scanner, in the laboratory with actual muscle cells. And what that allows us to do is begin to manipulate this accumulation of acid.

And our preliminary experiments using something called dichloroacetate have shown that we can reverse that accumulation of acid in patients with CFS/ME by adding dichloroacetate to the cell culture where the muscle cells have been exercising. We've been able to show that it is reversible but dichloroacetate is a bit like using a sledgehammer to crack a nut, and what

we're now trying to do with the help of the Action for ME studentship is begin to tease out exactly where in the metabolic chain the abnormality lies. And what drugs we can use in the laboratory to manipulate very specifically these abnormalities which will then give us the drugs that are most appropriate to use in clinical trials.

Slide 21 – Cardiac MR

- **Hollingsworth et al., EJCI 2010 & JIM 2011**

One slide on Cardiac MR, we've been doing MRI scans on people to look at how energy is generated within the heart in patients with CFS/ME. And the long and the short of it is that in about a third of patients they don't generate energy within their heart walls as we would expect them to compared to controls.
19.46

Slide 22 – Conclusion

- **Symptoms suggestive of autonomic dysfunction are common in fatigue**
- **Autonomic Dysfunction is associated with fatigue severity**
- **Central and peripheral abnormalities are detectable in those with fatigue using state of the art techniques**
- **Cardiovascular response to standing may have potential as a diagnostic biomarker in fatigue**

So in terms of the work we've done so far, we've been able to show that symptoms are very common in people with fatigue and symptoms suggestive of autonomic dysfunction and cognitive problems are particularly common; the more symptoms of autonomic dysfunction that people have the worse is their fatigue which potentially gives us a target for treatments and we're beginning to detect abnormalities both centrally and peripherally using largely MR based techniques.

Slide 23 – Fatigue work is supported by:

- **ME Research UK**
- **Irish ME Trust**
- **Liver North**
- **Northern CFS/ME Clinical Network**

- **JRRG**
- **ME Association**
- **MRC Medical Research Council**

That's just a quick flag for the people who have funded the work so far.

Slide 24 – Looking forward:

- **MRC Medical Research Council**
    - **Understanding the pathogenesis of autonomic dysfunction in CFS and its relationship with cognitive impairment**
    - **Identifying the biological fingerprints of fatigue**
    - **Understanding Muscle Dysfunction in ME/CFS – developing a drug Pre-Testing System**
    - **A case controlled study exploring the qualitative experience of sleep, the roles of sleep architecture and patters of salivary cortisol in ME/CFS**

Looking forward, I am very pleased to say that in the recent round of applications for the CFS call from the MRC, in Newcastle we were very successful in securing £900,000 of the £1.5 million, 'pot'. So now we are in a very nice position to begin to understand what causes the autonomic dysfunction that seems to be so prevalent in CFS and how it relates to cognitive impairment. And what we are now able to do is do all of those investigations that I have highlighted, plus many more, in the same people – so we will be able to look in a whole-systems-way at what is the underpinning problems in people with CFS/ME.

We've also obtained a project where I am the co-investigator, and Dr Wan Ng is the principal investigator – he is an immunologist – to look at trying to identify an immunological biomarker for fatigue; and we've made an application to ME Research UK to try and allow us to straddle these two applications and make the very most out of both of them by maximising the samples we can take.

I am very grateful to you all [i.e. AFME members], for the support for our research because we were successful in obtaining two of your recent pump priming projects. The first is a PhD studentship to allow us to develop the muscle work more fully; and it is important for me to say that if any of you have any scientists in your family please encourage them to apply for

that because so far we haven't had any applications for the studentship, which is disappointing – so at the moment it is out to advert still, so we haven't actually started that project yet. But we have started the other project which is a study in collaboration with Cumbria where I am involved in providing the clinical input, where we are looking at sleep. That's a very exciting project and I'm meeting Jason tomorrow where we are going to finalise the first paper on that work, so that has started.

Slide 25 – Questions?

- **Don't forget to follow us on Facebook and like us! ME CFS Research Newcastle: https://www.facebook.com/pages/ME-CFS-Research-Newcastle/526359017390431?ref=ts&fref=ts**

Final slide. Please follow our Facebook page. I've just discovered Facebook and I'm an absolute convert, so we have a Facebook page which is 'ME CFS Research Newcastle' and we're using that as a mechanism to try and involve people in the research that we are doing, and helping people feel part of the research – particularly the MRC projects. So please, if you are interested, take a look and give us your input and feedback. Thank you.

23.35

Platitudes…

Questions:

[Note: the sound quality was pretty bad for this part of the presentation so transcription was especially difficult in places]

1. **What are the implications in your view of all this [research you are conducting] for things like Graded Exercise etc. because, you know, perhaps a minority of people benefit whilst it seems like the majority of people with this illness don't – so I just wondered what you thoughts were on that?**

We have a third application in to the MRC which was to phenotype – that is to get them to do muscle MRI and when we did muscle MRI we found there were two distinct groups of

patients. There are people who generate huge amounts of acid and there are people who don't. And actually we believe that the type of exercise that these two different groups do, needs to be different. There's a huge literature from the exercise physiology field that shows that actually some types of exercise may make one of those two types of muscle MRI abnormalities, worse. So, we believe that we ought to do a study whereby we get people's muscle MRI and find out which group they belong to and then we tailor the exercise for the Activity Management – I don't like the word 'exercise' because I know it raises antibodies in people – but that the Activity Management that they are then encouraged to participate in, is different according to what their muscle looks like.

For those people that do generate more acid in their muscles, what kind of Activity Management are you talking about?

Well we think it should be less intense resistance-based exercise, focusing on your anaerobic threshold, so that you need to know what your anaerobic threshold is – and that's different for everybody – and then you exercise below your threshold.

Which is very hard for people who have problems. You know daily living can send them right over… even just lifting a tea-cup…

Absolutely. Yeah-yeah. And I think what is very useful is to have objective measures of activity, anaerobic threshold – so that you can guide people as to what is effective for them and at what level. And it may be that it's a very tiny level in the beginning, and so I use tilt-training in people who have POTS – which is where we get people to do their own little tilt-tests at home – and at the beginning people will do three seconds of that and will keep a diary of the time and we'll go from 3 seconds to 4 seconds to 5 seconds and then I'll get an email from them saying: 'I got to 30 seconds!' and that's through being realistic about what your goals are.

Can people access these tools?

A lot of these tools are research tools. We do do tilt-testing for people, everyone who comes to my clinic gets a standing test and a EEG and more sort of autonomic-type testing; but the

MRIs at the minute are research tools so they are not immediately available to…but anybody can come to the clinic.

But you don't supply any kind of activity advice for others?

No. Not at the minute. Because we don't know what kind of activity is right for the right people – that's a research question.

28.51

2. Do you think you will be able to fix whatever is wrong in the muscles?

What I think is that we will produce a drug which would then allow people to participate in a rehabilitation programme – gradually. It won't suddenly make people active but will mean that the symptoms people are experiencing are reduced and their tolerance levels, their ability to participate in rehabilitation will be much more facilitated.

3. You mentioned POTS and I wondered what treatments you are thinking about?

So the treatments we have at the minute which haven't been around the NICE control trials as treatment for POTS so we utilise the physiological properties of drugs to slow your heart-rate down and increase your blood pressure. So we have a range of different treatments which are symptomatic – so it doesn't reverse any underlying cause. The way I describe it to people is that you've been spiralling down for a long time and the what the drug will do is not make you the way you were before all this happened, but it will help you turn a corner so that you can perhaps begin to participate more in getting better. So there are no evidence based treatments at the moment but there are physiological based treatments.

30.28

4. When might the drugs you are starting to experiment with become available?

Action for ME have funded a PhD Studentship, at the moment our great frustration is getting a body to work in the lab with [?] and it may be that I need to come back to the charity and

say actually we can't find somebody who would be able to do this who is a PhD student but what we may need to do is say, right well we may need to ask how much money for a research associate instead. But at the minute we are still trying to get an AFME PhD student which would be great if we did – so if anybody has anybody who wants to come to Newcastle then let us know. If we get somebody I don't think it would be very long because we know what the metabolic pathway's are, there are currently available drugs that we could use in the laboratory to test what would be the most appropriate thing to reverse the abnormality and then the next stage would be clinical trials.

The slowest part seems to be getting through NICE and all that stuff?

Yeah, if you do a clinical trial, at the minute you have evidence and you do a clinical trial and more often than not these drugs will be currently available drugs.

5. **And what about even the very simpler things you suggest people should have access to – you've got objective measures there to exercise regimes? So surely that should be widely available?**

Some of it is in the Sign Guidelines [?] so some of the research we've published is in the Scottish Guidelines – trouble is they don't have any doctors in Scotland to deliver it – so a lot of them come to Newcastle; I hope that when the NICE Guidelines are reviewed the new and emerging evidence that we have created since NICE was originally put together will be considered.

What does that mean in practice?

Well at least people will have an [??] or at least – at the minute a tilt-table is actively discouraged in the NICE Guideline – whereas I think everybody should have an assessment for POTS. Everybody who has had a blackout should have a Tilt-table test.

6. **I am a great fan of Tony Pinching's who I saw at Bart's and I'm very interested in your work on Orthostatic Intolerance and how it would fit perhaps with the work of Tony Pinching and [???] the people in Norway with their up-regulation of the immune system – it is so fascinating?**

You are absolutely right and that's the advantage of the MRC project. In the past we have been doing the research piecemeal. We had funding for some MRI scans of the brain, that's funding from the ME Association for MR scans of the muscle, we've had funding from ME Research UK for the cardiac scans – so they're not always the same people that are in each study. Whereas with the MRC project we are doing all of these scans with the same people and we're also doing HPA axis function, we're also doing [???] suppression test, we're also doing cortisol measuring, growth hormone, we're doing plasma-volume with meta-physics, we're doing red-cell mass; it's a massive undertaking for the participants which the ethics committee has lodged some concerns about – but at the moment we are inundated with potential participants and hopefully we will be able to answer some of those questions about how all these things link together. Because I think it is unlikely that one abnormality will account for this disease. It is a systematic approach and we've been modelling our autonomic findings – using a very clever mathematical-minded person whose a system's modeller – to look at whole systems changes in that vascular system and where the abnormalities might begin to lie. And to think about a diagnostic autonomic biomarker. We've published three papers now where we've suggested how objective autonomic measures might begin to be used as a diagnostic tool.

7. **When you are testing on the tilt-table for POTS are you able to tell whether it is say, the heart initially overworking to start off with your blood pressure dropping to account for that, or is it because your blood pressure drops naturally because of gravity, and your heart then overcompensates for that to get it right – but do you know which way round, which one…?**

No. There's very little understood about the physiology of POTS, we've been looking at the human dynamics [?] of the POTS patients we've got and we've just got a paper into the Journal of Internal Medicine where ME Research UK funded 200 patients who came into our clinic for a clinical cobalt study, and we looked at the autonomics of POTS and non-POTS and there are differences in the autonomic function which does make you think that physiologically POTS is a different disease than CFS is – you know I always think about CFS being a big umbrella and that underneath it POTS is one box, orthostatic hypotension is another box, and there will be x number of boxes…

But you can suffer from more than one thing?

You can have CFS/ME and POTS so we call that CFS/ME with a POTS phenotype and that's entirely because CFS/ME come under the disability discrimination act and POTS isn't so I often say to people swing your diagnosis whichever way is beneficial – there aren't many benefits to having CFS/ME so swing it to whichever…. But then people with POTS 50% of them are fatigued and 50% are not.

8. **Can you tell me underneath the general umbrella for autonomic dysfunction would you include control of blood sugar?**

That's a very interesting question because people will often come to us with autonomic problems and say I feel much better it must be hypoglycaemia because I feel better when I've had something sugary. Now, physiologically the way I explain that to them is it could be that you have got hypoglycaemia but equally, insulin raises your blood pressure – so there's a very close relationship between hormones – lots of different hormones – and blood pressure regulation. It is also possible that it's your body's response to hypotension and low blood pressure is to give you this craving for sugar in order to try very hard by whatever mechanism to keep that head of steam up. So in some people, that's a physiological mechanism that actually their sugars are fine but their body's are trying by whatever mechanism to preserve your brain.

I only ask because having recovered from all the other symptoms of CFS it is the one thing that I can't get on top of…

Right. A desire to have sugar?

Well, a feeling of light headedness which comes after I have eaten something…

That could be your blood pressure…

I know.

It's much more likely to be your blood pressure particularly if it is postural – so if when you stand up you feel dizzy or light-headed or you have a big meal – then… if you imagine that diagram of the vascular system where your gut is, if blood goes to your gut to digest a large meal it is not in your systemic system to keep your brain profused. Often people will feel light headed after a meal, or exercise or a hot shower, that's because blood is going to places it shouldn't necessarily be. And it's not where it needs to be such as going to your head.

9. **I was just wondering how the things you investigate relate to people with high and not low blood pressure?**

High blood pressure is a complicating factor in CFS/ME and they are probably the hardest group that we have to manage. Because a lot of the symptomatic treatments we use tend to push your blood pressure up so we have to be careful with people with high blood pressure. High blood pressure is just a dysautonomia like low blood pressure is but it can happen for a range of different reasons. One of the things I will often say at talks is that in the UK we have a problem because you either have high blood pressure or good blood pressure and we forget that low blood pressure can be a problem for people and make them very symptomatic. If we were in Germany, then for people with low blood pressure there are hypotension doctors in clinics where people get put on medication because they have got low blood pressure.

10. **What do you actually do in clinic with/for someone with CFS/ME with regard to treatments for autonomic dysfunction? What are your guidelines?**

We will reassess people's medication. Often people will be on anti-hypertensive's, anti-angina's and they've been on them for years and they don't really need them anymore but nobody's thought about that. We make people drink two and a half litres of fluid a day, and only up to five cups of caffeine – and there's as much caffeine in tea as in coffee. We encourage people if they have low blood pressure to increase their salt intake and then we will often encourage people to do tilt-training. In terms of simple things – now tilt-training… if we were in Holland and you had low blood pressure they would keep you in hospital and do that tilt-table every day until you survive for forty minutes of it. So we use that property that they think resets your pressure receptors – so we use that to get people to do their own little

tilt-test at home by standing fifteen centimetres away from a wall and leaning back for as long as they can, twice a day, and stopping when they get symptoms. And what we find is that people over six weeks get longer and longer [in terms of endurance]. And then once we've done all the conservative things we then think about symptomatic treatment to increase people's blood pressure: so fludrocortisone is a mineralocorticiod …that retains salt in the kidneys and….they all push the head of steam up [i.e. it increases blood pressure]…

11. **How does someone with POTS present themselves to a GP [in order to get them to understand, test and treat]?**

It depends a bit on whether you've ever blacked out or if you have postural dizziness then I would ask to be referred to a Syncopathy service. It is interesting that when we did our tilt-table test of people with CFS/ME they would be very symptomatic and I'd say to them, 'Well, what are you feeling?' and they'd say that this was their usual symptom, and I'd say well this is pre-syncopathy. This is the feeling like you might black-out. You know, the sparkles in your eyes, the tunnels coming… you know? And they [the GPs?] just hadn't recognised or appreciated that that was their [the patient's?] typical symptoms. And it's interpretation of the symptoms that you're experiencing [difficulties with in terms of your GP not recognising them] and I would perhaps go and take some stuff, you know, take them these slides… Syncopy should be investigated.

12. **Something about the exercise tolerance level studies being completed in the USA – should similar protocols be used in the UK to objectively measure a person's disability when it comes to assessments being required for benefits?**

I do think one of the problems is that there is no objective measures – there is no diagnostic objective test. Occasionally we have done activity monitors in people and used that data in reports that we've made… I think that I have learned recently is to try not to make reports – blanket reports – because that can get me into all sorts of trouble because I raise more questions with them than provide answers. So now what we try and get them to do is to give us a specific set of questions that they want me to respond to so that I only focus on what they are interested in. But in terms of objective measures then, yeah, activity monitors, we've got an MRC muscle performance laboratory, we can do anaerobic thresholds in people…

Generally these things aren't acceptable to the DWP…

No. I doubt it.

They do [the exercise tolerance test in the USA] a lot now and it would be great if we could get it over here…

Yeah. Right it would….

The End.