Wetenschap voor Patiënten
(Science to patients)

Webinar 43: Introduction /experience with ME

Prof. Julia Newton. Broadcast June 3rd 2014

My name is Julia Newton. I'm dean of clinical medicine at Newcastle university. I'm also professor of ageing and Medicine. I work at Newcastle University to do my research and I do my clinical work at the Newcastle hospitals NHS foundation trust in the UK.

How did you get involved in ME?

I originally did a PhD in laboratory based science here at Newcastle University, looking at physiological changes in the gastrointestinal tract. When I became a consultant working as an independent researcher, I then realised that to sustain a research career I needed to have something that would bring together my clinical practice and my research practice. So as a result I then started to investigate blood pressure regulation in my clinical practice which was falls and blackouts and began to apply that knowledge to the study of fatigue initially in patients with chronic disease.

What kind of research did you do regarding ME?

Over the last decade or so, we've been developing a range of different techniques to look at fatigue in patients with ME and in patients with fatigue associated chronic diseases. So we've been developing tools that allow us to measure autonomic nervous system function in the laboratory which were now taken into clinical practice. We've also performed a range of MRI investigations looking at brain, heart and muscle function in patients with ME and fatigue associated diseases.

What are the most important discoveries you made?

At the moment perhaps some of the most important things that we've been finding in our studies, relate to changes in how we manage ME in the clinic. So we've shown that patients are more likely to have problems with their autonomic nervous system and we've developed ways that we can integrate looking for these changes into the clinic. So we've recognised things like positional tachycardia syndrome and neurally mediated hypotension and we now look for those in our clinical practice.

The other things that we've found more recently are abnormalities on MRI scans, so we've shown that there are problems with cerebral blood flow on brain MRI, there are changes in cardiac bioenergetic function on cardiac MRI and we have also very recently shown that there are changes in muscle bioenergetic function when we exercise patients in the MRI scanner. More recently we've also taken muscle biopsy cells from patients with ME and

grown those in the laboratory and we're beginning to develop techniques that will allow us to detect changes in acid in the muscle cells and begin to modify those changes with medications.

In which direction is your research leading you now?

So at the moment, we're very excited about the studies that we're currently doing. We've a large MRC study going on at the moment, so funded by the British government, that is allowing us to biobank samples from patients with ME and also to look at the autonomic nervous system and where the problems related to its function might arise.
So we wonder whether there may be problems in the brain centres that control the autonomic nervous system or whether or not there may be a problem of the vascular system that is controlled by the autonomic nervous system. And our current studies are aimed at teasing out where these abnormalities might lie so that we can begin to develop targeted treatments.

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Webinar 44: Neurocognitive problems in ME

Prof. Julia Newton. Broadcast June 3rd 2014

What are the most common neurocognitive problems in ME?

So the most common neurocognitive problems that we see in the clinic with patients with ME, relate to problems of memory and concentration. About 90% of patients will describe brain fog and problems with memory and concentration. Our studies have shown that when we've taken patients with memory problems, that they have actual abnormalities when we perform neuropsychometric testing. So they have a reduced IQ and particular problems following instructions, so an area called executive function.

What are the causes of these problems? What's the role of the autonomic nervous system here?

In terms of our understanding of these neurocognitive functions, at the moment there's still an awful lot to learn. What we believe here is that the problems with blood pressure regulation that arise because of autonomic dysfunction, may play a part in these neurocognitive problems. We know in patients with autonomic dysfunction who don't have ME that the lower their blood pressure is, the more likely they are to have problems with their memory and concentration and the more their blood pressure drops when they stand up, the more likely their memory is to decline over time.

So our studies that have shown that autonomic dysfunction is very common in ME patients would suggest that autonomic dysfunction may also play a part in the neurocognitive problems that are so commonly seen in this patient group. So the autonomic nervous system probably plays a role in cognitive function by virtue of the fact that it's responsible for control of blood pressure regulation.

So brain perfusion is determined by the autonomic nervous system and if it isn't working properly then your blood pressure, or the head of steam that gets the blood to your brain may not be working properly. And as a consequence you won't get enough blood to your brain, which we believe will make you have a black out at the most extreme end of things, may make you feel a bit dizzy when you stand up in the middle range of things, but in the more subtle end may mean that you have symptoms of light headedness and dizziness or problems with memory and concentration because of lack of perfusion of blood to the brain on a regular basis.

What is the effect of ME on the memory? How is this caused?

Patients with ME tell us that they regularly have problems with their memory. But why that happens isn't really well understood at the moment. What we think is that problems related to blood flow to those areas of the brain that are responsible for memory may lead to the problems that patients with ME describe. So it may be that these problems related to the autonomic nervous system which lead to drops in your blood pressure particularly if patients stand up very quickly might predispose those with ME to the memory problems that are so commonly described.

What is the effect of ME on cognition? How is this caused?

So the effect of ME on cognition is probably via a similar mechanism as the memory. We know that if we drop our blood pressure in patients who have problems with their autonomic nervous system that this is associated with poorer performance on memory tests and that the more the blood pressure drops when we stand up, that this leads to a risk of cognitive decline over time. We know that autonomic dysfunction is a significant problem in patients with ME and it's probably this, that predisposes patients with ME to the cognitive problems that are seen so frequently.

What is the effect of ME on the senses? How is this caused?

Hypersensitivity of the senses in the context of things like hypersensitivity to noises, smell and sounds are very commonly described by patients with ME. It's not really very well understood why that might happen, but again it's possibly that those areas of the brain that are responsible for controlling those particular senses, are overactive or oversensitive. We need to do more research to try and understand why this might be in patients with ME, so that as a result we can understand why it's happening and begin to look at developing specific treatments.

What is the cause of a new type of migraine in ME?

Migraine is very frequently described by patients with ME and it's very interesting whether or not this migraine is a new type of headache in patients with ME. At the moment we have a PhD student here in Newcastle, who is helping us understand migraine a bit better in patients with ME. We're looking at the overlap between migraine and the symptom of fatigue in the migraine neurology clinic and also looking at how common migrainous headaches are in the patients we see in the ME clinic.

Really to help us understand this overlap and whether or not we can develop better treatments. In terms of new types of headache, we're also working very closely with a dentist who is helping us understand a condition called temporomandibular joint dysfunction, which is something that often is misdiagnosed as migraine or headache and is amenable to very specific treatments focused on the joints in the jaw. Hopefully as new information becomes available, we'll be able to understand the relationship between ME and headaches and then lead to better treatments as a result.

What role do hormones play in ME?

At the moment we're doing some research looking at hormones in patients with ME. Our current MRC funded study is looking at an area of the brain called the hypothalamic pituitary axis and this area of the brain is responsible for producing hormones that circulate around the body. We're trying to do experiments that will help us understand how the HPA axis functions and whether or not there are changes in patients with ME. Hormones are a very interesting thing in patients with ME, because patients will often describe to us changes in their symptoms that occur around puberty and around the time of menopause in women. So it really does make you think that hormones may play a part in the symptoms experienced by patients with ME and certainly understanding this complex system more fully will begin to point us in the direction for future studies.

What role do neurotoxines play in ME?

Lots of patients who come to see me in the clinic will describe having been exposed to potentially noxious gasses or vaccines and wonder whether or not neurotoxins might play a role in the symptoms they are experiencing. It's really difficult to answer that question, because at the moment we don't have large scale epidemiological studies to help answer those questions. One recent study that we've performed that is of interest in this context, is one where we've looked at cerebral blood flow and how it associates with the acid that we've been finding in the muscles of patients with ME when we exercise them. And there seems to be a very strong relationship between the abnormalities of peripheral muscle function and the abnormalities that we've found in cerebral blood flow. Suggesting that there may be a relationship between the acid that's accumulated in the periphery that has an impact upon our cognitive function and our cerebral function. So that makes you think that perhaps things in the periphery might have an effect on our brain.

Are viruses and bacteria involved in these neurocognitive problems?

It's interesting to speculate whether or not viruses or other infections might play a role in cognitive problems in patients with ME. Certainly in patients with fatigue associated chronic diseases such as Hepatitis C virus infection, cognitive problems are a real and significant symptom. And we know that viruses in HCV infection replicate in the brain. So it's not unreasonable to speculate that perhaps some of the symptoms that are experienced by patients with ME could in perhaps a proportion of those effected, be related to a past viral infection or current viral infection.

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On Friday June 6th 2014 Prof. dr. Julia Newton answered questions in a chatwing-session. These are the Q&A of this session.

Q: In your first college, number 43, you mention there are problems with the acid in muscles. Does this mean there is too much acid or does the acid change of quality? I ask about the quality because the experience of having ME- muscle pain is so different from having normal muscle pain.
A: We have shown that there is an increase in acid in muscles both on magnetic resonance spectroscopy whilst people with ME have exercised in the scanner - but also we have reproduced these findings in muscle cells taken directly from patients with ME.

Q: About the name ME: have the inflammations in the brain been proven or not at all?
A: inflammation in the brain is interesting and there is some controversy whether it is present in ME or not. Some scans suggest it is there - but more studies are needed to be sure.

Q: Why do those problems with acid occur??
A: Good question - we think the problems with acid might occur because of disordered muscle metabolism within the cells perhaps mitochondrial disorder. The severity of acid accumulation associates with autonomic dysfunction which might suggest that there are also problems of how the transporters get rid of acid (these transporters are controlled by the autonomic nervous system) or because of problems with vascular run off from exercising muscle.

Q: Patients with ME often also complain about restless legs. What is 'restless legs'? What is the difference between and resemblance with ME-muscle pain? Why is the combination ME with restless legs to be seen so often?
A: Restless legs is a recognized neurological condition for which there are licensed medications. So this is an important problem to identify and treat in patients with ME - because it can cause sleep problems (which can themselves be associated with fatigue). The post exertional malaise and muscle pain that is typical of ME is different I think.

Q: Do you think neurotransmitters could be the (main) problem? Or rather, do you agree with me they are?
A: I agree abnormalities of neurotransmitters could be a problem - but I am not sure there is enough evidence yet to suggest they are THE answer. So I suppose I half agree. A lot of my work focusses upon muscle function, and we have now identified significant abnormalities in ME (and other fatigue associated diseases). So there are clearly lots of different things going on. Or perhaps more likely a number of different diseases.

Q: In webinar 44 you mention that ME patients often have problems with the executive functions. Is it coincidental or related that in case of autism there are also often problems

with the executive functions?
A: Not sure about the autism question. I have to admit that I don't know a lot about autism so would be guided by you.

Q: Why does PEM at times occur later or postponed? Is that explicable? Does is have to do with the sympathetic nervous system?
A: I suppose it depends upon what the activity is that underpins the symptom. There are often delays in muscle pain after exercise even in those without ME.

Q: You start from the assumption that problems with cognitive functions and memory relate to blood pressure. If it is possible to restore blood flow, will the cognitive problems be solved then? Or is ongoing damage being caused?
A: This is a trial I would love to do. It is certainly an important question and until we do the study it is difficult to answer. We certainly know that the muscle acid accumulation is reversible in the laboratory - so it might also be that the cognitive abnormalities (if these are generic) are also reversible. But you are correct one way to answer that it is to see whether cognition improves if blood pressure is increased.

Q: Can pregnancy make the whole ME worse? The pain in the muscles? The nervous system?
A: Not sure, there is not much evidence in the medical literature to help us understand what happens to people with ME who are pregnant. In my clinic some people tell me that they feel better whilst pregnant and some not.

Q: You talked about headache that is caused by joint dysfunction and that there was a special treatment for this type of headache. Can you tell us more about this special treatment and does it involve medication? For the record: I sometimes have this type of headache, it involves my joint muscles and I use oxazepam to relax them. It helps if I don't use it too much, but I want to know if there are alternative treatments.
A: The joint problem is called temporomandibular joint dysfunction. It is known to be commoner in association with autonomic dysfunction - something we know is commoner in ME. In a non-ME setting gabapentin, pregabalin and acupuncture have been shown to be of some benefit. There are no specific trials yet in ME.

Q: If problems with cognitive functions relate to problems with the blood flow, why aren’t they more constant? Isn’t the blood flow a constant factor?
A: Blood flow is not a constant factor - it is constantly changing, controlled by the autonomic nervous system. So if we have a big meal the blood flow to the gut increases to digests that meal. If we stand up the blood flow increases to our legs, away from our central circulation. The human body is designed to try and preserve brain blood flow (and volume) at all costs. So the brain circulation has a special additional control system called 'cerebral autoregulation'. We think that this extra control system might be a problem in ME.

There have been anecdotal reports that if people receive IV fluid they feel better - in our current study we have measured blood volume and are looking at the results at the minute.

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Webinar 45: ME and the bloodflow

Prof. Julia Newton. Broadcast June 17th 2014

What causes orthostatic intolerance?

Orthostatic intolerance is a very common complaint by patients with ME. It is a symptom of lightheadiness or dizziness when assuming the upright position. And about 90 % of patients with ME will describe this symptom. It is very easy to quantify using validated tools in the clinic. Things like the orthostatic grading scale will allow you to quantify this and as a result decide whether or not orthostatic intolerance is present. So a score on the OGS of 4 or above would be consistent with orthostatic intolerance.

How can orthostatic intolerance be managed?

Managing orthostatic intolerance is fairly routine in our clinic here in New Castle. The first thing we do is recommend to people that they need to increase their fluid intake to make sure that their vascular volume is high as it can possibly be. So we encourage people to drink at least two and a half litres of water a day, to reduce how much caffeine they drink to no more than 5 cups of caffeine a day. And in people where they have a normal blood pressure when they are sitting we recommend that they increase their salt intake. We call all of that together conservative advice. We then also recommend that people wear support stockings or tights of a type called Duomed grade 2 which prevents blood from pooling in their legs when they stand up. In addition to that there is some evidence in patients with orthostatic intolerance and in ME that a process called 'tilt training' can be of benefit. Tilt training works by helping the autonomic nervous system reset itself so that your body is able to detect the drops in blood pressure more ably when you stand up. Tilt training is very safe and involves individuals standing tilted against a wall twice a day for up to half an hour each time.

In addition to those conservative measures and tilt training in some people where we detect drops in their blood pressure we will try medication. This medication is generally aimed at increasing the blood pressure. So we use medicine such as fludrocortison which is a mineralocorticoid that helps your body retain salt and pushes your blood pressure up by that mechanism. And another medication that we use is a tablet called Midodrine and this is something called an alpha agonist and this vasoconstricts your peripheral blood vessels and pushes your blood pressure up by that mechanism.

What causes POTS?

POTS is a very interesting condition. POTS stands for Positional Tachycardia Syndrome. And our studies have shown that up to a third of patients with the diagnosis of ME actually when they have formal autonomic testing will have a diagnosis of positional tachycardia syndrome. We diagnose this on the basis of your heart rate when you stand up. If it increases when you stand to above 120 beats per minute or by 30 beats per minute than this would be consistent with the diagnosis of POTS. POTS is known to be a form of dysautonomia. So it is an inappropriate tachycardia in response to the stress of standing. Usually it arises after a viral illness or after a pregnancy. So a similar presentation to that of ME.

How can POTS be managed?

The management of POTS is very similar to that for ME. So at the moment in New Castle, when we diagnose POTS we give people conservative advice. So we encourage them to drink two and a half litres of water a day, reduce the amount of caffeine that they are drinking and help them avoid blood pooling in their legs using stockings or getting them to squeeze their muscles regularly to get the blood out of their legs or the big muscles. We also try tilt training with them so we encourage them to become tilted against the wall for up to twice a day for six weeks. And then if that does not work then we will usually consider medication in people. So we might try the same kind of medicines as we try for orthostatic intolerance such as fludrocortisone and Midodrine. We also try using rate reducing drugs such as beta blockers and calcium antagonists. All aimed at trying to slow the heart rate down to allow people to feel better and as a consequence do more.

What is oxidative stress? What causes it?

Oxidative stress is something that happens inside cells usually in response to actions like exercise for example. So in your cells there is a whole range of biochemical processes that go on to create energy, to allow the cells to function. And if there is a problem with this, then sometimes the cells will create molecules that can be damaging to the cell. And this is called oxidative stress. There is some evidence that in patients with ME they are more likely to have oxidative stress and suffer more significantly from the consequences of oxidative stress. In terms of what we understand causes oxidative stress is still not really fully understood. What may happen is that there are deficiencies in those enzymes or molecules that form part of the chemical pathways that produce energy in the cells. In terms of studies that we are doing here in New Castle with our muscle cell experiments we are beginning to look at how oxygen free radicals are generated and how acid is generated within the cells to begin to explore how much oxidative stress there is and what the mechanisms might be that lead to the higher levels that are seen in patients with ME.

Are there other effects of blood flow disturbances (like pain)?

So the autonomic nervous system controls your blood pressure. And your blood pressure is the head of steam that gets the blood around your body. When we stand up 700 ml of blood will drop into our legs and as a consequence your autonomic nervous system has a microsecond response. It tries very hard to keep your blood pressure perfusing your brain and it does that by making your heart go a little bit faster and your periferal blood vessels constrict. All aimed at maintaining this head of steam your blood pressure circulating the blood around your body. If not enough blood is getting around your body, then you might not get enough blood to those bits of your brain that keep you awake and you may black out, or you may be a bit dizzy or lightheaded if you are not getting enough blood to your

brain. If you are not getting enough blood to you muscles or your heart then that's what I believe manifests as the symptom of fatigue.
We know in patients with autonomic nervous system problems that one of the symptoms they frequently describe is pain in their muscles. Particularly the big muscles across their shoulders or across their pelvis, the girdle muscles. And what we recognize this as, is something called coat hanger pain. A sensation of a coat hanger across the shoulders and up into the back of the neck. And this pain can be very debilitating for patients with autonomic nervous system problems. And actually when you ask patients with ME they frequently experience a similar type of pain. So as a result we believe that some of the pain that patients with ME experience is because of problems with blood flow to the large muscles. Sometimes people also describe pain in the extremities, in their fingers and their hands. And some of that might relate to low blood pressure. So if the blood isn't getting to the peripheries as well as it ought then the muscles aren't getting an adequate supply of blood and as a consequence they're accumulating acid and waste products within the muscles which causes malaise and symptoms of pain as a consequence.

How can these effects be coped with?

Coping with some of the problems of pain can be very difficult for patients. And often when I see people in clinic their biggest problem is pain as well as fatigue. We'll often use tablets just as Gabapentin to help with the pain and recommend sometimes for people to take regular pain killers to try and ease the pain. At the moment we are doing experiments in the lab to look at how acid accumulates in the muscles to see whether or not we can modify this and help people manage the pain that might arise because of the accumulation of acid in the muscles. At the moment we are excited about the results because it looks like the acid accumulation is reversible. And we are now doing further experiments funded by 'Action for ME' to look at teasing out the exact pathways so that we can identify medications that we may be able to use in clinical trials.

How might autonomic dysfunctions lead to gastrointestinal problems?

In terms of how autonomic dysfunction may lead to gastrointestinal problems there is a range of different ways that this could happen. We know in people who have problems of their autonomic nervous system, such as those with vasovagal syncope, that one of the frequent things they describe as they drop their blood pressure is nausea and a sensation of abdominal pain. So if patients with ME are experiencing drops in their blood pressure it is not unreasonable that symptoms like nausea and abdominal pain might occur at the same time. The other thing we know is that patients often will divert blood to their guts in response to taking their meal. Particularly a high carbohydrate meal. And as a result this can make people feel very dizzy and lightheaded because the blood is pooling in their gut just like it might pool in their legs when they stand up. And as a consequence we often recommend to people that they should not take high carbohydrate meals and take smaller meals with less carbohydrates.

Other things that people with ME frequently tell us is that they have symptoms consistent with irritable bowel syndrome. Now that is very interesting to me as somebody who is interested in the autonomic nervous system because there is quite an extensive scientific literature confirming a relationship between IBS and abnormalities of the autonomic nervous system. So again I would suggest that abnormalities of the autonomic nervous system are the underpinning phenomena that explains most if not all of the symptoms that people with ME experience.

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On Friday June 20th 2014 Prof. dr. Julia Newton answered questions in a chatwing-session. These are the Q&A of this session.

Q: It has been proven in ME/CFS patients that the blood flow to the brains and muscles is low. What are the effects of low blood flow in the long term?
A: It's not known. But we would hypothesise that this leads to cognitive problems.

Q: Just in order to be sure: do you mean by autonomic disorder a disorder of the autonomic nervous system?
A: Good point. Not necessarily an autonomic neuropathy i.e. disorder of the nerves themselves, but perhaps a problem with blood flow and how it gets to our organs and the regulation of this by the autonomic nervous system.

Q: Do you have any idea what the effects are on the brain when you have Orthostatic Intolerance?
A: We know in patients with orthostatic syndromes that they are more likely to have structural brain abnormalities and that they perform worse on memory tests.

Q: Does adrenaline get tested during or after exercise test of half a day? And are you doing that?
A: We don't measure adrenaline because it is known to be a very unreliable measure and very much influenced by posture etc. If we could come up with a better, standardised measure perhaps in response to a specific stimulus that would be interesting

Q: I am diagnosed with POTS and my eyes hurt. Is this a common symptom in POTS and is this due to low blood flow in the brains ?
A: POTS is a really interesting condition that is not well understood, but it does seem to occur with increased frequency in ME. Eye problems related to blurred vision are common. POTS is more common in Sjogrens syndrome where dry eyes are a problem.

Q: I have OI probably for a couple of years but how can I find out if my brain is effected by this?
A: Interesting . One way would be to treat the OI and see whether it makes any difference to your brain – to memory and concentration. An MRI would help identify whether there are structural brain problems such as white matter lesions.

Q: Do you know of any known or theoretical physiological similarities in the way the brain responds to hypoglycaemia and dysautonomia? Standing upright for too long causes very similar symptoms in my brain to hypoglycaemia (I have T1 diabetes) even though my BS are not low e.g. 7-8 when standing.

A: People with OI often describe craving sugar. We believe that this is because insulin (released when we eat sugar) also increases your blood pressure. So it is one way that your body can try and increase BP if it is low.

Q: You suggest that abnormalities of the autonomic nervous system are probably the underpinning phenomena that explain many/all the symptoms of ME. What causes those abnormalities of the autonomic nervous system? Is this one particular reason, are there many reasons, a chain of reactions? And where does it start?
A: We don't currently know what causes the autonomic nervous system abnormalities. However, our recent study has set out to look at trying to pin point where the problem is. We have now finished recruiting and studying people in this study and are now moving onto the analysis. So hopefully we will have more answers soon.

Q: My heart is checked completely, but there were almost no tests done standing. Could it be possible that the standing results of a good heart condition are different.
A: It is vital to look at how the heart and particularly the heart rate and the blood pressure respond to standing.

Q: As you say abnormalities of the autonomic nervous system are the underpinning phenomena. How is this to relate to the fact that symptoms of ME deteriorate after physical and mental activities?
A: If we exercise or perform a cognitive test, more blood goes to aid performance in that organ and as a result there might be less to go to our brain/heart/muscles. Which is why I believe problems of autonomic dysfunction get worse after exercise: all the blood is going to the muscles to keep them working ... or not...

Q: I had an MRI 6 years ago. Maybe it's a good idea to have one again to see if there are any changes in my brain. For the OI I wear "super socks" at the moment.
A: Great. Support stockings with graded elasticity are the best.

Q: Is it wise to wear the support stockings type Duomed grade 2 all day? Also if you're most of the time bedridden? Or are there risks?
A: Duomed grade 2 are best worn when upright, as they are intended to reduce blood pooling in the legs on standing.

Q: Does it do harm to wear support stocking when lying in bed? What are the risks?
A: Unlikely to do harm. But if you are lying in bed it’s not sure if it will necessarily help with OI symptoms.

Q: I read about tilt training, Nowadays I bicycle half an hour a day. Is tilt training a good advice to try in POTS ?
A: Tilt training is a good idea . There is evidence that tilt training 'resets' some elements of the autonomic nervous system and helps with symptoms. We have also trialled it in ME and found people are able to do it, and it works to help with autonomic problems.

Q: Why do 90% of the ME patients describe symptoms of orthostatic intolerance and only around 30 % POTS? May this be due to stages in the disease?
A: Pots is one form of OI. There are others such as neurally mediated hypotension and orthostatic hypotension. So OI is the symptom (which is common),whilst POTS or OH or NMH is the objective diagnosis.

Q: Is there anything known about pressure in the ears by me-cvs patients?
A: Pressure in the ears and ear problems is not something I am familiar with.

Q: If orthostatic intolerance is not yet officially diagnosed by a doctor, can an ME patient suffering from the symptoms of orthostatic intolerance start with the conservative advice without problems?
A: Absolutely. Starting with the conservative advise will be a good starting point and sometimes we recommend that to patients without the formal diagnosis.

Q: The skin on my upper legs is almost constantly burning, like of a sun burn. What can cause this? Is the blood circulation involved?
A: Sounds like some form of painful neuropathy.

Q: Do you ever test for autonomic nervous system antibodies in your patients with OI?
A: Sometimes, but not routinely we do in patients in the clinic with autonomic failure.

Q: Can you test for autonomic dysfunction in patients who can't stop taking Florinef as they take it for adrenal insufficiency? Would this invalidate testing?
A: Not necessarily invalidate testing. You just need to take it into consideration when interpreting the results, although having adrenal insufficiency is an exclusion for a diagnosis of ME.

Q: About the 'tilt training' you mentioned: I think many of us (with ME and POTS/orthostatic intolerance) are not able to stand for 30 minutes. The symptoms will get much worse and people will have fainted within that time. How can this training help? Should you increase the 'standing time' slowly?
A: Tilt training is 'up to' 30 minutes. Some people manage only seconds. It is for as long as you can do it without getting symptoms up to 30 minutes. So you stand until you get symptoms at which point you stop. If you go to the Newcastle Hospitals website and search for tilt training the procedure is there.

Q: Dichloroacetate (DCA) has been shown to reverse the muscle accumulation of acid in patients with ME/CFS. Is there a less toxic supplement we can use that also stimulates the pyruvate dehydrogenase enzymes just like DCA?
A: Not yet . That’s the focus of our research at the minute.

Q: In the Netherlands ME/CFS is also considered to belong to a group of so called "not medically understood complaints". Like amongst others fibromyalgia. Would you agree in considering ME/CFS as a complaint which isn’t understood, and develop research for ME as if belonging to that group?
A: Yes. But I would suggest caution. Not medically understood is not the same as not medically existent.

Q: If the blood flow to the brain isn't working good, shouldn't the blood pressure rise when I stand up to compensate the blood pooling in my legs? Instead of the blood pressure dropping?
A: Under normal circumstances perhaps . But in humans there are separate systemic (peripheral) and cerebral (brain) circulations that are regulated independently. I.e. when

your systemic blood pressure drops there should be autoregulation to maintain brain blood flow. It is possible there is a problem with this in ME.

Q: In patients with say thyroid disease or adrenal insufficiency where treatment is deemed adequate but the patient has ongoing symptoms they often get diagnosed with comorbid ME/CFS. Would you exclude such patients from your clinic?
A: Generally I do not exclude them. My clinic is a fatigue clinic rather than an ME/CFS one. So we see all patients, whatever the cause of their fatigue.

Q: In the previous chat you mentioned that maybe there is a problem with the cerebral autoregulation. Can you explain why do you think there might be a problem for ME patients with this system?
A: In OI patients (specifically the ones with NMH) studies have shown there are problems with cerebral autoregulation and our MRI studies suggest that there might also be in ME patients. This is part of the current study and we are doing the analysis now.

Q: You said that people with 'POTS' could take beta blockers to slow down the heart rate. But I thought the rising of the heart rate is a compensation mechanism for the decrease in blood flow to the brain in an upright position. If you reduce the heart rate won't that even worsen the lack of blood flow to the brain?
A: We use very low doses of beta blocker which are there to reduce the heart rate but don’t reduce the blood pressure. In POTS however the heart rate increase is inappropriate, so not always secondary to reduced BP.

Q: If the blood flow is (rather) constantly changing and cognitive functions relate to blood flow, why do the problems with cognitive functions not constantly change? In my experience those problems occur after having been active (physically and mentally). Therefore it does not seem logic to me that they directly depend on blood flow.
A: Yes I agree. But there is also the possibility that over time the changing blood pressure will lead to permanent damage to the brain.

Q: Not a question but a comment. I really like the way that you give credit to your team and "big up" your junior researchers when talking about the research you are conducting. I think this is a great way to get younger researchers involved. What young scientist wouldn't want to be involved in a team with such a leader.
A: Thanks, I love my work and I work with some great people.

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Webinar 46: The metabolism and the muscles

Prof. Julia Newton. Broadcast July 1st 2014

Why does acid accumulate in the muscles?

So our experiments performed with MRI scans where we've asked people with ME to exercise while we were measuring the accumulation of acid in their muscles, suggest that patients with ME have about 20 times more acid in their muscles than we would expect them to have. The findings from our experiments with patients with ME are very similar to those from patients with fatigue associated chronic diseases. In terms of why this might happen, in our experiments we've been able to show that the degree to which the acid accumulates seems to associate with the presence and severity of autonomic dysfunction. So we think in some way, the autonomic nervous system is regulating or modulating this accumulation of acid.

We know that the autonomic nervous system controls some of the transporters that are on the cell surfaces of muscle cells. So it may be that these transporters are not working as efficiently to remove acid from the cells as they really ought. Or it may equally be that the blood flow run off from the muscles as they exercise, which we know is modulated by the autonomic nervous system, perhaps again is meaning that the acid is not washed away from the muscles as they exercise. It's difficult to know why the transmitters don't work properly. It may be that there's some process that damages these transmitters or it may be that there's some problem in the metabolic chain that leads up to the development of acid within the cells. Our experiments performed with the muscle cells in the lab, suggest that there may be deficiencies of certain proteins or kinases within the metabolic pathway which could potentially be modulated by medication.

How to handle acid accumulation in the muscles?

In terms of handling acid accumulation in the muscles, that raises some very interesting questions. I frequently get asked: 'Will exercise influence the amount of acid that I accumulate in my muscles?' When we've done our experiments, both in the MRI scanner and in the laboratory with the muscle cells, it becomes clear that there are at least two different types of muscle abnormality, something that we call phenotypes.

When we've looked at these different phenotypes, it's clear that perhaps one of those phenotypes would improve with exercise and perhaps the second one would not improve with exercise. So as a result we would propose further experiments are needed to look at how the different types of muscle abnormality respond to exercise therapies such as graded exercise therapy. Because our finding of two different phenotypes of muscle abnormality,

might explain why some people feel they get better with exercise while some people feel that they don't or describe themselves as feeling worse with exercise.

How are the muscle cells influenced by ME and what are the consequences?

We've done experiments where we've taken muscle biopsies from patients with ME and we've grown those muscle cells in the laboratory into what we call muscle tubules. When we've done that, our impression is that the muscle cells don't grow as well as in patients who don't have ME. And when we've done experiments in the laboratory using something called nanosensors which are tiny little technological materials that go across the cell wall of patients' muscle cells. These nanosensors will fluoresce at different pH's so we're able to exercise muscle cells in the laboratory while we look at how they accumulate acid real time.

So when we do those experiments, we can then begin to put things into the experimental kit so that we can look at influencing how the acid is accumulated. And the experiments that we've done already suggests that this acid accumulation that we've reproduced in the laboratory is reversible. Which means that there is the potential with further experiments, that we can begin to tease out particular drugs that could be used in clinical trials to reverse these muscle abnormalities.

How is the autonomic nervous system influenced by ME and what does this cause?

So in patients with ME we know that about nearly 90% of patients will describe symptoms of autonomic dysfunction. And when we perform tests, objective tests looking at how the autonomic nervous system works, we'll find lots of abnormalities in the autonomic nervous system when we objectively test. We're not sure yet why these abnormalities are so common in people with ME. Our current experiments are looking at individuals, about 80 patients with ME, seeing whether or not we can begin to understand where the abnormalities lie. We wonder whether it might be problems of the brain centres that control the autonomic nervous system, so they are areas in the brain stem, whether or not it might be an abnormality of the hypothalamic pituitary axis, so how hormones are produced and the impact that they might have on the vascular system. Or alternatively it could be that the autonomic nervous system is having difficulties regulating the cardiovascular system and that the symptoms of autonomic dysfunction arise as a consequence of that.

Wetenschap voor Patiënten
(Science to patients)

On Friday July 3rd 2014 Prof. dr. Julia Newton answered questions in a chatwing-session. These are the Q&A of this session.

Q: Is CFS hereditary? My mother has the disease, and she says that it is hereditary.
She told me that it is like a little ball within your body and it burst suddenly. Now I have a problem in that I want children. But my husband and I have reached the decision that if it is hereditary, we will not have children. I show no symptoms of the disease. Hopefully you can help me out.
A: What do you mean by CFS ? Do you mean ME ? There is no gene been shown to be associated with ME. So although there is some evidence that it runs in families, it isn't genetic

Q: My mom told me that it's possible I have it and give it on to my children.
A: There is no current evidence that it is passed from parent to child. If you have no symptoms then it is important not to live your life worrying about whether you will develop the disease.

Q: Does that mean it is absolutely safe, or that you can't tell?
A: There is no evidence and from studies it is unlikely that the precipitating factor is primarily a gene abnormality.

Q: Can you say something about paralysis in ME? Is it is related to autonomic dysfunction? Have you worked with anyone who experiences muscle paralysis with ME?
A: Muscle paralysis is not common in the patients that I see. If I had a patient with paralysis I would ask one of my neurology colleagues to see them.

Q: When you refer such cases to a neurologist, what explanations do you get back?
A: Clonus or myoclonic jerks sometimes - restless legs syndrome.

Q: Can I deduct from your answer that spasms in ME (and I hear quite some people complaining about them) aren't caused by acid accumulation?
A: I suspect not.

Q: How can you tell if a POTS patient also has CFS since the symptoms of POTS are a lot like CFS?
A: By measuring their heart rate lying down and when they stand up. If it increases by more than 30 beats per minute or to about 120 within 10 minutes of standing , that would be consistent with a diagnosis of POTS. So if you simply consider the symptoms and don't do the proper measurement you can miss it.

Q: But how do you know if it's only POTS or both CFS and POTS? Since not everyone with POTS also has CFS. Or do you think differently about that?
A: It is difficult. Some people would argue that by having CFS you can't have POTS and vice versa. But I generally think about it as CFS with a POTS phenotype.

Q: In webinar 46 you mention that a deficiency of certain proteins, which possibly give problems in the metabolic chain within the cells, might be modulated by medication. Do those medicines already exist and do you have results from experiments with them?
A: We have done some experiments in the lab (funded by Action for ME) where we are adding different proteins to exercising muscle cells to see whether these proteins might improve how they work. At the moment we are still deciding what might be the best treatment to then consider in clinical trials.

Q: About the two phenotypes: are all patients in this experiment diagnosed with ME? And do they all suffer from PENE, or just the group that gets worse after exercise?
A: There was no difference between the two phenotypes. They all have CFS and all had the same amount of pain after exercising. They were equally fatigued.

Q: Is there an interaction between adrenaline and lactic acid?
A: There is a suggestion that some of the transporters that remove acid from muscle cells are modulated by the autonomic nervous system.

Q: Do you know anything about the spasms very severe ME-patients have? I have them when I am very exhausted, every day, together with a difficulty to pronounce words. They make the exhaustion only worse. Or is this symptom not studied (yet) because lighter cases don't have it, like paralysis?
A: Spasms are unusual. Not something that is well understood.

Q: After being ill for more than 5 years, my weight has steadily grown with more than 10 kilos and I hate it! It is tempting to start a low caloric diet with few carbohydrates. But of course I know that for people who are not ill those diets already give problems with the muscles. Is it for ME-patients even worse to follow such a diet, given the problems with their muscles? If it is, is there another diet that you would suggest specifically for ME patients?
A: I would consider trying it if you feel you need to for overall health benefits and see how it goes. Clearly stop it if it doesn't suit you.

Q: What do you think of rituximab? Is it safe (enough)?
A: We are currently involved in a rituximab trial in a chronic disease called PBC. The consent form and patient information sheet is very long because there are a lot of reported complications recognized with the use of rituximab. I think it needs to be used in very carefully selected patients with appropriate monitoring. So I think well performed clinical trials are important if rituximab is to be used in ME.
I think our current trial will provide some evidence for the potential benefits. This trial for 76 patients (50% get the rituximab) has cost over £1million with the drug costing over £250.000 alone.

Q: How is the trial going till so far?
V: It is proving more difficult to recruit participants than we expected. But it is otherwise going ok.

Q: You'd think people would be lining up. Any reason why they aren't?
A: It involves quite a lot of visits to the hospital, rituximab has side effects, it involves an infusion of medicine and only 50% get the active drug.

Q: Lately I saw an advertisement for a training for patients with ME, depression, burn-out, anxiety etc. Patients will be taught techniques to influence the amygdala in order to get out of the situation of chronic stress that is due to being patients with a chronic disease, according to the therapists. Do you consider this as a useful kind of therapy for ME patients? Or is it wishful thinking?
A: I am not sure about the evidence for such a treatment. Is it published ? Have there been properly conducted clinical trials to underpin the evidence behind its use ?
Q: In the website of the therapist they claim the therapy to be based on scientific evidence. But I can't find the articles where it is all based on.
A: ????? Say no more.
Q: A few years back there was a lecture during the Invest in ME Conference about this amygdala training by the developer.
A: I would be interested to know what diseases it has been used in and what evidence there is for its benefit.

Q: What do you think about a lot of ME patients that test positive for Lyme disease? Do you test your patients for Lyme when they come in?
A: We don't test routinely.

Q: Muscle cells of ME patients are low in AMPK. Could acadesine correct this and would this be helpful for ME patients?
A: We are doing some more experiments, so we can include this to see.

Q: About oversensitivity of the senses with ME-patients: could the statement that the senses of ME/cfs patients become oversensitive be reversed in: can highly sensitive persons (overreacting on all sensitive impulses) have a predisposition to get ME, as they are more prone to stress and influences on the senses and the nervous system? If so, is any research in that direction being done?
A: I'm not sure whether there is any research in this area. But it is a good question: is it that people with oversensitivity for some reason have a predisposition to ME ?

Q: It is a hot item presently: Lyme. A lot of people are testing positive on Borrelia and co-infections. Is that an eye-catcher in your practice as well? Is it an exclusion criterium for your research?
A: Not currently. Who is testing and with what ? It is important that it is a robust and validated assay.
Q: Most are being tested in Augsburg. When Elisa-bloodtests show no Borrelia in the blood, one is not considered to suffer from Lyme. But that appears to be a very shallow test in case the bacteria have retreated to other parts of the body.
A: Is there evidence that Borrelia retreats to other parts of the body? I don't know the literature.
Q: De Meirleir and other docs are testing people with LTT Melisa in Augsburg. Besides that Lyme is also a clinical diagnosis. There are a lot of patients who are responding to antibiotics or other Lyme treatments, although not everyone gets better in it.
A: They need to make sure they publish it.

Wetenschap voor Patiënten
(Science to patients)

Webinar 47: ME and sleep

Prof. Julia Newton. Broadcast July 15th 2014

What kind of sleep disorders do you find in ME? How can they be dealt with?

More recently we became interested in sleep in Newcastle, because of a collaboration with colleagues at the University of Northumbria. My colleague Professor Jason Ellis is an expert in sleep medicine. So we've begun to do some studies looking at the quality of sleep and the experience of sleep that patients with ME will have. We have a PhD student Zoë, who's been doing some interviews with patients with ME.

She subsequently looked at some data from a clinic in Holland to look at sleep quality measured by something called polysomnography. She's analysed a large number of sleep diaries from patients coming to the clinic here in the UK. More recently she has begun to do some polysomnography in patients with ME. In terms of results that we have to date, we've recently published a study using the data from the Dutch cohort, where we've been able to show there are four different types of sleep abnormalities in patients with ME.

Essentially, what that's been able to show us, is that there are patients who suffer from a type of insomnia and some patients that suffer from hypersomnia. So not sleeping enough and some patients who sleep a lot. So these four different types of sleep abnormalities or phenotypes are potentially amenable to specific treatments.

In terms of managing the different sleep phenotypes that we've identified in patients with ME, there's still work to be done to try and understand these different types and what the best treatments might be. But sleep experts tell us that there may be treatments available that we can apply to patients with ME. At the moment we're putting together a grant application that would look specifically at treatments targeted at the insomnia in patients with ME.

Which bodily functions are involved in sleep disorders in ME?

What bodily functions are involved in sleep disorders in ME is an interesting question. What we often find is that there is a relationship between autonomic function and sleep. We know that blood pressure has a circadian rhythm or a biological rhythm throughout 24 hours, and it's at its lowest during sleep. So it may be that there is a strong relationship between sleep function and autonomic dysfunction. Perhaps the two influence each other.

How to deal with sleeplessness in ME?

In terms of managing sleepiness or sleeplessness in patients with ME, in the clinic we describe something called sleep hygiene, where we try and encourage people to think very closely about their sleep pattern.

Encourage them to have regular bed times and wake times and to avoid napping, particularly during the day. Anything beyond that we continue to investigate as a research tool, and at the moment are writing a grant where we hope to look at more specific sleep interventions in patients with ME.

What causes extreme sweating at night?

Patients with ME and fatigue associated chronic diseases will often describe to me in clinic extreme sweating through the night. That's very common. We think it's related to problems of the autonomic nervous system. Particularly as the autonomic nervous system is involved in sweating, and things like your blood pressure are at their lowest through the night. So that clearly is a circadian rhythm of blood pressure and your autonomic nerve system. In some way we think this is related to sleep and sleep quality. Sometimes when people describe problems with sweating that are very symptomatic and profound, we've used evidence from a recent trial of escitalopram in perimenopausal women with some benefit.

Wetenschap voor Patiënten
(Science to patients)

Webinar 48: Ageing and ME

Prof. Julia Newton. Broadcast July 29th 2014

Which ME-symptoms worsen when getting older?

In my clinic I see adults and older people with ME. At the current time we don't have a clinic where I see children. So it's difficult to know what the differences are between children and adults in terms of symptoms. My impression when looking at adults and older people is that there are very little differences between the presentation of ME in older people compared to younger people, and the impact and the severity of their symptoms tends to be very similar.

Do children, adults and elderly people with ME have different symptoms?

ME is an interesting illness because it can affect any age group. It always used to be thought that it was a disease of younger people, but it is becoming clear that it can affect all age groups, including older people. We have now looked at those people coming to our clinic and found that a significant proportion are presenting for the first time over the age of 50. Up to 20% of patients coming to the clinic. So a quite significant number.

It is not really fully understood whether or not the disease is the same disease in older people as it is in younger age groups. In our study where we matched older people to younger people who had had the disease for the same length of time. Which was very important: it got rid of the confounding issues of length of illness. We did not find that patients had any significant difference in the symptoms they were experiencing. So the symptoms were as bad and had as great an impact in the old versus the young. But the real, significant differences were when we tested the autonomic nervous system and found that there were more profound abnormalities in the older age group. Which are perhaps the things that put that individual at risk of developing this fatigue associated disease.

Is there a difference of loss of memory due to age or due to ME?

Understanding why memory changes in patients with ME is very important. It may be that there is a relationship between what happens in people with ME and their cognitive function, and what happens in the brain as we age. We've done studies here in Newcastle looking at dementia and age-related changes in the brain, and been able to show that autonomic dysfunction associates with cognitive problems as we age. And that the severity of the autonomic dysfunction predicts how your memory will change over time. So we're beginning to see very similar abnormalities in patients with ME, which might suggest that

people with ME have a kind of accelerated aging phenomena. And that that is associated with the presence of abnormalities of the autonomic nervous system.

Should there be different diagnostic criteria between the old and the young?

Good question, should there be different diagnostic criteria between the old and the young. I think that raises the question of whether or not the diagnostic criteria we have at the moment fit the purpose. And I would argue that they probably are not. They are based on symptoms experienced by patients rather than anything biological or physiological. As a result I suspect we put together into one diagnostic group lots of different diseases. That makes it very difficult as a clinician understanding what are the right types of treatment for patients. And as a researcher it makes it very difficult to be sure that the research we are doing is with groups that are the same, that is homogeneous.

What tends to happen is that everybody who fits the symptomatic diagnostic criteria, like the Fukuda, gets put lumped together into a clinical trial, and then we are surprised when the trial does not show benefits for patients. If we were to understand the different types of disease that are under this umbrella diagnosis of ME or CFS, then that would allow us to begin to understand the pathophysiology of these diseases and direct more specific treatments. So for example, at the moment we clearly understand that there are autonomic phenotypes. So there are patients with POTS, there are patients who dropped their blood pressure or have a Neurally Mediated Hypotension.

We know that there are different types of sleep phenotypes, probably four different types. And we are also beginning to understand that there are at least two different muscle phenotypes. So all these different things are all lumped together into the one diagnostic category of ME or CFS. But really if we are to understand these diseases more fully and get better treatments, rather than lump them together we need to actually pull them apart and begin to do experiments with specific phenotypes, rather than the whole diagnostic group of ME or CFS.

Are ME-patients expected to live shorter than healthy people?

There is still very little known about the natural history of ME. Sometimes we see reports on the television or in magazines about people who have died very young with ME. So we really do need better studies where we follow up patients with ME for long periods of time. So that we can see whether or not they have an excess mortality by virtue of the fact they have ME.

Interestingly in the work we have done in patients with the fatigue associated disease called primary biliary cirrhosis, which is an autoimmune liver disease, in those patients we have been able to show that those who are fatigued over a decade were significantly more likely to die compared to those who were non fatigued. So that suggests that fatigue is something that is associated with an excess mortality. And that fatigued patients certainly with PBC are likely to live shorter lives than those who are non-fatigued.

What is your definition of fatigue?

Fatigue is a strange symptom and it means different things to different people. When I am in clinic I will always ask people ‘what does fatigue mean to you?’. Some people will describe it

as a sensation of sleepiness or excess sleepiness, particularly during the day. For some people it is brainfog, for some people it is muscle malaise or aches and pains. Interestingly in the studies that we have done, looking at blood pressure regulation where we have done tilt table testing in people with ME and fatigue associated diseases, it did set out to drop people's blood pressure using a tilt table.

And when we do that we always routinely ask patients: "What symptoms are you experiencing?" at the time that their blood pressure was low. What is interesting to me is that often when we say to people: "what are you feeling at the moment?" they will say: "These are my symptoms, this is exactly what I feel." And we see that this is something that they are experiencing in association with a low blood pressure.

So people have a perception that this is their symptom, their fatigue, their disease, their ME, but in fact what we are seeing is that their symptom is associated with a low blood pressure. And that to patients who will come and see us who have dropped blood pressure it is: "my blood pressure". They do not recognize the fact that this might be something that could be diagnosed as ME or CFS.

Wetenschap voor Patiënten
(Science to patients)

On Thursday July 31st 2014 Prof. dr. Julia Newton answered questions in a chatwing-session. These are the Q&A of this session.

Q: Do you observe changes in the illness during and after the menopause? I'm a little afraid my (very severe) ME will get worse because I'm extremely vulnerable for disbalance. On the other hand, my mother had also CFS-like symptoms and she fully recovered after the menopause.
A: Good question. Certainly with autonomic dysfunction we often find symptoms improve with pregnancy, menstruation and menopause - suggesting hormones might play a part.

Q: The last chat you answered a question about Lyme testing: "Is there evidence that Borrelia retreats to other parts of the body? I don't know the literature." I would like to let you know that the Borrelia bacteria retreats from the bloodstream into the tissue with an average speed of 11 minutes. See for example:
http://spirochetesunwound.blogspot.nl/2009/01/watch-videos-of-lyme-disease-spirochete.html
A: Thanks

Q: 1) Should people with ME be tested for POTS and pbc?
2) Are there treatments for POTS and pbc?
3) Who do you know in the Netherlands, or other European countries, who does this kind of diagnosis?
A: 1) Yes and yes.
2) Pots can be treated. I may be worth looking at http://www.potsuk.org Pbc is managed and there is evidence that treatments such as UDCA slow down progression of the disease.
3) I'm sorry, I'm not sure I know of anyone at the moment.

Q: Have you ever had patients reporting a pressure in their brain and other parts after antivirals and antibiotics?
A: I haven't seen patients who have taken antivirals.

Q: Did you find any explanation why elder ME-patients tend to have more profound abnormalities with the autonomic nervous system then younger ones?
A: The alternative explanation might be that autonomic dysfunction is an increased problem as we age, and therefore older people are more suspectible to specific types of autonomic dysfunction that are more likely to result in fatigue.

Q: You say that the diagnostic criteria that are currently used, don't fit the purpose. Which (set of) criteria would you suggest?
A: I don't think we currently have a diagnostic criteria that is fit for purpose and I believe that more work is needed to develop objective diagnostic tests.

Q: Do also the International Consensus Criteria not fit the purpose? What should be changed in this set of criteria according to you?
A: I personally think that a symptom based diagnostic criteria will always be difficult and that we need to work towards objective diagnostic tools.

Q: Can oxygen therapy be helpful at times?
A: Some patients do report benefits from oxygen therapy. I am not sure what the physiological mechanisms are for any benefit seen.

Q: are you familiar with prions? If so, in what way do they cause damage, and where?
A: I am familiar with what they are, but not how they might relate to ME. They are not within my particular area of expertise.

Q: How come that nausea is such a common symptom with most autoimmune diseases?
A: It might be related to gastroparesis and autonomic dysfunction directly of the gut (which is the organ with the greatest autonomic innervation) or due to reductions in blood supply via the splanchnic. Often people with hypotension report nausea.

Q: About training: what is the wisest thing to do. Can one best train e.g. 3 times a week to one's peak, the heartbeat rising up to 175? Or would you advise starting with lower exertion, not to push it and building up slowly?
A: I'm not sure what sort of training you are suggesting. I wouldn't do anything that is a peak. I would build up slowly.

Q: Can ME, when the complaints are severe, result in a drooping mouth or rapid blinking of the eyes?
A: Generally not.

Q: Which wrong diagnoses you have met with in your clinical practice? Based on which symptoms? Was that logical?
A: Often primary sleep disorders; PoTS; neurally mediated hypotension; symptoms related to medication etc... etc..

Q: Do many of your ME-patients report intolerances? Which one is on top (food-items. light, sound etc)
A: Many report intolerances. I suspect (although I have no quantitative evidence to support this; it is anecdotal) food intolerances-light-sound.

Q: Can you relate them to ANS dysfunctions?
A: Food intolerances for sure. High carbohydrate meals are more likely to drop your blood pressure and make you feel light headed compared to protein and fat.

Q: Is light/sound an intolerance or is it related to migraine/headaches?
A: Could be.

Wetenschap voor Patiënten
(Science to patients)

Webinar 49: ME and the future

Prof. Julia Newton. Broadcast August 5th 2014

In which field do you expect biomarkers to pop up?

Biomarkers are what we all consider to be the holy grail. Having something that we can measure in the blood or use as a diagnostic tool to help us identify patients with ME or different phenotypes within this umbrella diagnosis of ME are some things we all strive for. At the moment we have a MRC funded project trying to identify a biomarker for fatigue. We're using patients with a condition called Sjögren's where fatigue is very common, to try and look for a fatigue fingerprint using immunological markers. We're then going to take that fingerprint and apply it in patients with ME to see whether or not we can identify specific abnormalities that have potential to be an immunological biomarker in patients with ME under the fatigue associated diseases.

But of course for somebody like me who's interested in the autonomic nervous system, biomarkers aren't isolated to the blood. We've recently published a very small study suggesting that actually some of the many parameters that we collect, when we're assessing the autonomic nervous system in patients with ME, might also have the potential to be a diagnostic biomarker. So I think we shouldn't isolate ourselves to looking for biomarkers just necessarily in the blood. There are lots of different things that individually or combined together might help us understand ME more fully.

Which hopeful studies are going on presently?

At the moment we've got a range of studies going on here in Newcastle. We've got two large MRC funded projects which count for over a million pounds of grand funding from the Medical Research Council. One of these is to look for a fatigue biomarker using immunological samples. We're also doing a study where we're looking at understanding autonomic dysfunction and its associated cognitive consequences. In that study we're recruiting over eighty patients with ME/CFS to come in and have a whole range of different investigations including MRI scans and HPA axis tests, autonomic function cognitive tests, etc. That involves seven visits to the hospital, so it's quite a major undertaking for participants. We've also got a PhD student Gina, who's funded by Action for ME, and she's looking at our laboratory muscle experiments.

Looking whether we can come up with a drug that would reverse some of the acid that we've seen accumulate in the muscles of patients with ME. We've also got a PhD student, Luke, who's looking at the overlap between migraine, ME and temporomandibular joint dysfunction, and he's working with me and a colleague, doctor Justin Durham, looking at

symptoms and the overlap between those symptoms. We've also got a very close collaboration with colleagues at Northumbria University, where we're doing some experiments looking at sleep.

The quality of sleep, length of sleep and a range different sleep parameters. Those studies have been funded by Action for ME and the ME Association. ME research UK which is one of the other charities in the UK have also been very generous to us, helping us develop additional priming projects looking at MRI technologies and looking at something called 'systems medicine' to try and understand the complexity of all the results that we get and how all these different systems interrelate with each other.

What's your view on cooperative efforts like OMI, Simmaron, Mt.Sinai, Griffith and CMRC

It's really important that we form strong collaborations between clinicians and researchers working in this field. The way that we're going to improve our understanding of this disease and rapidly lead to better treatments and greater understanding is if we have a collective approach. So working collaboratively I see as a huge asset to move in this field forward. The other thing I think is really important is that we don't look at ME in isolation.

That we actually learn things from other diseases where fatigue might be a problem. For example, at the moment in Newcastle we have a trial of Rituximab in patients with primary biliary cirrhosis, that has fatigue as an endpoint. So it's the first trial specifically targeting fatigue in primary biliary cirrhosis with Rituximab as the intervention. I firmly believe that the lessons that we learn from this trial will have direct relevance to our understanding of fatigue in other diseases such as ME. And will allow us to fast-track treatments such as Rituximab very quickly toward the fatigue associated diseases.

How can ME become part of the tuition of medical students?

What's really important if we're going to understand ME is to make sure that people, particularly healthcare professionals such as doctors, nurses, allied health professionals understand what ME is. Understand the complexities of diagnosing and managing this disease, and recognize how important it is for us to do future research. Influencing these professional groups at a very early stage is really important.

Recently we've had two things here in Newcastle, which have been very exciting, in that myself and my colleague professor Jason Ellis did something called mini medical school, where 500 sixth-formers came in to the medical school. The sixth-formers were wanting to go to medical school and so we're gaining some experience of what it is like to be a medical student. Jason and I lectured to them about fatigue and sleep problems, for a couple of hours one evening. The atmosphere and the vibe and enthusiasm from these medical students, sorry sixth-formers, was really infectious.

The other thing that I've done just a week ago, was actually to speak to the fourth-year medical students in the medical school. As happens with these things I went along feeling a bit, you know, reluctant to do this lecture to 350 medical students. But was actually blown away by their enthusiasm and the sensible and appropriate questions that they asked me at the end of my lecture. As a result I now had emails from a number of them wanting to come and work with my group over the summer, during their summer vacation. So that they can learn a bit more about what it is to have fatigue and ME specifically.

So I think engaging with younger age groups particularly those who are expressing an interest in becoming a clinician, whether that be a doctor or a nurse or an allied health professional is really important if we're to help them understand the importance of this disease. What I will often say to medical students when I speak to them is: "When I sat in your seat as a medical student 20+ years ago, and I was taught that peptic ulcer disease was arose because of stress. And now 20+ years later we understand that peptic ulcer disease doesn't arise because of stress. It arises because of a bacteria and that there is now a multi-million pound industry eradicating Helicobacter pylori in people who've had a peptic ulcer. And if our understanding of a disease can change so dramatically in just over twenty years, imagine if we all work together to understand ME how far we could go in a similar length of time".