Managing fatigue in rare neuro-immune disorders
2017 Rare Neuro-Immune Disorders Symposium
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00:00 All right. So, my name is Mike Sweeney.

00:03 I am a new relatively new faculty at University of Louisville and I am going to be talking to you guys about fatigue.

00:11 So just off the bat whether you are affected by a rare immune mediated neurologic disease or not how many people in this room have experience fatigue or deal with fatigue. Everybody. Right. At some point everybody deals with fatigue. So my goal today is to try to help define fatigue as it relates to neurologic disease and then.

00:42 Kind of explain or explore how we've studied it or how we try to study fatigue and then with that try to make some basis for why we use some of the medications we do and what might be helpful for people who have to deal with a lot of fatigue.

00:59 So what is fatigue. If I ask everyone in this room to give me a definition of fatigue I would have 150 different answers and they would be quite variable. It's somewhere it lives somewhere between. A sense of tiredness to just a physical feeling that they just kind of can't go on. It's different than muscle weakness but it relates to it and it's different than depression although it can feel like it. Some different studies out there have quoted it as. A difficulty in initiation or of or sustaining voluntary activities.

01:39 That's kind of a very clinical way to say it or a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities.

01:51 So that leaves a lot of room for interpretation. Right. It's very common. So fatigue across. The whole population. You know healthy people that are surveyed 20 percent. Will have some fatigue as it's defined in those surveys. And between 10 and 15 million visits to premier care providers each year the primary complaint is fatigue. So it's very common.

02:25 This is me after boards. So. Fatigue is way way more common when than when the brain is sick or the spinal cord.

02:35 I'm going to use multiple sclerosis as example a lot in this talk mostly because it's it's been studied a lot in multiple sclerosis. As you can imagine we have a lot
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more MS patients than we do TM NMO or ADEM. So we try to extrapolate a lot of what we know for a more common disease and try to apply it to related rare diseases up to half of people with MS will say that fatigue is actually their most debilitating symptom which is very surprising to a lot of people when they hear that. It seems to be more prominent in inflammatory diseases of the CNS than it than other CNS diseases. So if you look at if you compare stroke cohorts and MS patients MS tends to for the amount of accounting for the amount of disability have more fatigue than stroke patients. So I think we we used the same PowerPoint strategy.

03:36 So I have a lot of circles and diagrams like this. So fatigue has a lot of things that play into it. We have the CNS disease. We're all here to talk about we have other systemic inflammatory diseases that sometimes come with those things so people with one autoimmune disease that affects the brain can have other autoimmune diseases. So people with lupus can have a disease that affects the brain and then also can affect spinal cord can affect muscles can affect kidneys. We have a lot of medications so without knowing any of you guys as patients I know for a fact that your medication lists are long term psychiatric disease so depression plays into fatigue as we learned with the previous talk hormone dysfunction. So a lot of the things that happen in the brain can affect the adrenal access and hypothalamus and can throw off our hormone levels and that also affects fatigue. We have individual patient factors. So we’re not all playing on the same playing field.

04:42 So lots of things to take into consideration.

04:46 So when we talk about fatigue we try to separate it into a peripheral fatigue and a central fatigue so peripheral fatigue is like a physical motor problem is due to problem dysfunction the muscle that neuro muscular junction. It’s not directly the weakness that we’re talking about but it’s the muscles not working as efficiently as it should be. And so it takes more effort to do the same things previously were doing before the disease onset. This is more objective you can measure this with electrophysiology studies you can test it in clinic with sustained muscle contractions things like that. This is a more objective thing central fatigue is kind of the thing that bothers most people because you know we can’t really define it that well. Is due to dysfunction of the brain and spinal cord.

05:02 All right. So how do we measure that. There's a lot of things that we take into account so when you come to see somebody. If I see a patient that I’ve been seeing for a while and we’re working to sit down and address fatigue we talk a lot about what time of days or fatigue the worst what makes it better what makes it worse. Is there any relationship to medications. These are all things you
kind of want as a patient want to pay attention to and know because they may play a role into how we treat it. Look at things that make it worse. So I noticed that in the summertime my fatigue is a lot worse. Is that because of the heat. Is that because your kids are out of school and you got to deal with them all day. Is that some other reason.

06:33 There's a lot of things to take into account. What makes it better. So are there certain medications that you've been on that do help with your fatigue or are there other things that you've been doing that may help and then other symptoms that come along with it. So we use a lot of history to guide our assessment. We use laboratory test and some other ancillary tests to help. Guide us and convince us that there's nothing else going on. And we'll talk about some of those things. So if there's muscle weakness when we see you will do we may do different tests that look for reasons for why you might have muscle weakness other than just fatigue. So I just list some of the possible tests that we look at. So different blood test different tests we can do in the clinic to try to help narrow things down.

07:27 Do you have droopy eyelids your muscles fatigue. Could you also have other diseases that play like myasthenia gravis could also be contributing. I have at least two patients who have had myelitis in the past and have myasthenia gravis. So things can happen together. It's not common but there are other things so we want to always make sure we're pretty thorough.

07:52 Is there a history of chest pain shortness of breath. Are we dealing with cardiac or pulmonary problems. Those are things we need to address it can definitely make you fatigued. Do you have increased heart rate? Pallor want to address anemia.

08:10 Are you is are we dealing with sleepiness problem not so much a fatigue problem or are you falling asleep all the time.

08:16 So we think about getting sleep studies and ruling out sleep pathology and that we use our exam and we talk about mood changes and then I think probably everyone that has gone to a large center has filled out a number of different kind of surveys when they go there.

08:37 I'm not sure that everybody knows exactly what they're filling out when they do these things. But there's a number of scales I just listed here because there's a wide variety of them. There's a number of scales like the Fatigue Severity Score which we use to try to objectify fatigue and try to follow it longitudinally.

08:57 Because if I ask you when you come to clinic are you fatigued? Yes. Well how fatigue? So fatigue. And then the next time I see you is you're fatigued any better. No. But then if I compare your scores and you had 45 one day and then
the next time I see you it's a 20. It made a lot of progress so it's something that
we use to try to help objectify things and also helps us in research. It's kind of
the best thing we have to follow people with more subjective complaints. So
this is a scale where it has these nine components. And then you scale on each
one a one to seven on how severe they are and then we add them all up and
give you give you a score at the end. There's no specific cutoff value or anything
that means you're doing great or not. All right.

09:52

So what we're all here to talk about fatigue as it relates to rare immune
mediated neurologic disease mostly we're talking about myelitis or diseases that
affect the spinal cord. So looking back when polio was still a thing when Dr.
Greenberg was in high school. You know fatigue after polio was a big thing. And
there's a well-defined post-polio syndrome that develops years after polio. And
so a lot of what we know about. Fatigue as it relates to myelitis.

10:31

We extrapolate from that syndrome we don't know as much about fatigue as it
relates to idiopathic transverse myelitis. We know that it's commonly reported
more than half of kids report feeling fatigued after TM I would say 100 percent
of my patients report fatigue in my adult clinic. Fatigue definitely is thought to
play a major role in cognitive function.

10:59

Dr. Harder has shown us that there's no prospective treatment trials out there
currently so we're kind of shooting in the dark and a little bit ways when we're
talking about treatment. We'll talk about what evidence is.

11:13

So can we extrapolate what we know about post-polio and what we're dealing
with now. So there's a lot of similarities to the current recently described
phenomenon of acute flaccid myelitis and we talked about that in a small group
but there are a lot of differences as well. So it's not they're not the same
disease. We're dealing with primarily motor neuron involvement when we're
talking about acute flaccid myelitis where in a more inflammatory process like
idiopathic transverse myelitis we're not just affecting motor neurons we're
affecting white matter tracks.

11:53

So the pathology is different. And there's also the post-polio syndrome. Pain is
much more prevalent issue than it is in transverse myelitis. I'm not saying it's
not prevalent in transverse myelitis. It's just extreme in post-polio patients and
so that may impact the fatigue reporting and then a neuromyelitis optica. So
we're going to talk about specific things in NMO. So fatigue is more common in
patients who have had NMO than in control patients fatigued scores were lower
than those that were reported in MS patients but not by a lot and I'll show you
some data. And then so probably the biggest little cohort that was published
was 22 patients with NMO. And in those 22 patients they reported a lot of
issues with memory had decreased information processing speed. There were
there was damaged attention and all of those domains that were affected correlated with the fatigue. So all those things are thought to play a role.

13:12 And then Dr. Levy we can talk about some work that you did. So there's a Hopkins study that were or one of your fellows I'm not sure was her it was you know.

13:24 There there's 15 patients with TM, 14 patients with NMO and 23 with MS. And they kind of compared to the ways that fatigue looked in these patients. This was an older cohort so patients in their 50s on average the mean duration had been eight years in and NMO 6, and TM 10 and MS. So the disease had been going on for a while. These aren't patients in the acute stage fatigue overall did not differ amongst those groups.

13:56 So all of those patients had fatigue. But when you look at who had severe fatigue so people who scored greater than 37 on that fatigue scale that I showed you the patients with MS and TM had a higher percentage reported of severe fatigue.

14:18 All right.

14:19 So there will be a test on the slide at the end. So what causes fatigue in inflammatory disorders. If anybody can really. Give an answer to that question they're going to you know probably earn their Ph.D. there's a lot of work that has looked at it.

14:38 There's there's not a single one biomarker I can measure in somebody and say oh your fatigue is going to be. you know this so we think it has to do with circulating pro-inflammatory chemicals we call those cytokines and those lead to propagation of inflammation within the brain and spinal cord.

15:04 But you know if these if these are monophasic diseases so take transverse myelitis you have an attack on your spinal cord the inflammation happens. Inflammation is done. Why are we still having fatigue. Ten years later. So there's a lot more than just circulating inflammatory cytokines or chemicals that are causing you to feel fatigued. If you look at that third bullet point what that means is one part of the brain stops one or one part of the spinal cord stops being effective and another part of the brain or spinal cord has to take over and it's going to have to do its job and is going to have to do the job of whatever it is trying to take over. So you can think of it as trying to work in overtime. There's no way to prove that but that's kind of a theory. Why you might feel more fatigue down the line. And we know there's a lot of other chemical changes that happen in people who have MS. who have NMO.
As it relates to different neurotransmitters and things. So lots of reasons why you may have fatigue. I can't tell you exactly why so management of fatigue. so that's why we're here right.

The patients when they come to see me and we talk about fatigue they may be a little bit disheartened at first because we don't talk about starting new medications if we don't start about.

Talk about a cure to their fatigue.

We talk about things that may be contributing that we can address before we start piling on new things. So we look at their depression their depression being adequately treated. I can say in my patient population this is the number one contributor to their report of fatigue when we deal with their depression their anxiety their fatigue scores improve. They still have fatigue but it's a lot better. Where they're happier about it. We look at things like B-12 levels. We look at anemia. We look at ongoing inflammation. Are we sure that we're dealing with idiopathic transverse myelitis and we don't have some ongoing and inflammatory things that we can deal with and help speed up recovery process. We look at concurrent illnesses and infections for a while there I thought I was a urologist because we were just treating like urinary tract infection after urinary tract infection.

So there's lots of little infections that can be going on that make everything else worse. We look at sleep disorders. Keep the sleep lab in business and then we talk about pain specificity muscle spasms things that are all making your body work harder than it needs to. And then smoking cessation. I'm in Kentucky I don't know if anyone else is here from Kentucky but. Probably it will be like the last state to have smokers when the last smoker is there. It will be in Kentucky. So I'm fighting an uphill battle. But that's you know smoking cessation is a big thing. And then across all problems this is the biggest point I want to make is reducing polypharmacy so we go down the list one by one cutting off medication saying do you need this medication.

If so why. Why do you need it. If not we take it off. OK. So we have to simplify the medication list. Every medicine interacts with other medicines and none of us are smart enough to know how you know someone on 10 medications or their all can interact. So we need to simplify that other non-pharmacological points that we can make so exercise. Just like with pain is helpful in fatigue now. So how many patients. How many people here have been to see Dr. Greenberg? K. has he given you guys the talk about limiting the number of steps it takes to get your closet and having your quota of energy for the day. OK. So he has this good analogy about how you have a budget of energy and with TM it lowers
your budget and now you have a new budget and you have to be kind of stingy about how you spend your energy.

19:27 So. That's true for a lot of patients who have had transverse myelitis who are still dealing with a lot of fatigue. But it's not true for all patients so sometimes when I tell people that the analogy I worry that they're going to stop exercising or stop doing aerobic activity and we're going to get into a place where we're getting out of shape and we're producing our kind of muscle reserve. So it should be part of your budget. Maybe you got to kind of spend a certain amount of your budget on aerobics activity but this should be part of it because it has been shown to be beneficial across the board in all studies that look at fatigue.

20:12 It's been shown to be beneficial on cancer patients and post-stroke And in MS. So we talk about energy conservation techniques and then cooling techniques. Not everybody is sensitive to temperature but in some patients. Cooling apparatus and things are helpful in that regard.

20:33 The point of this slide if you if you are suffering from something as debilitating as fatigue can be you're going to be desperate for an answer.

20:44 And there are a lot of things out there that are marketing to people who have fatigue and kind of a new trend is kind of these cognitive games or cognitive exercises. And there's a number of them out there. It can be kind of expensive or you can have like to subscribe to them. What I want you to be aware of is that these haven't really been tested rigorously in research type of way. So we don't know if they are beneficial in fatigue or in cognition. So I would just use your best judgment if you're choosing to try these things out. They're not going to hurt anything other than your pocketbook.

21:24 So.

21:28 So before so what we're talking about now we're going to talk about a couple of drugs that we use commonly in patients with fatigue. None of these are on label for treating fatigue in patients with transverse myelitis. So these are all medicines that were kind of repurposed thing from other things. And one might. One person may try one of the medicines and say oh this worked great changed my life. And another person may say worst thing ever it made me more tired. So there is no one size fits all. It has a lot of trial and error.

22:07 We go through a lot of training to try to learn which may be the best fit for what kind of person. But when it comes down to it there's a lot of trial and error. So the first drug to talk about is Amantadine which was actually developed as an anti influenza medicine. It's used widely in the physical medicine rehab.

22:30 Community.
They like it for post traumatic brain injury patients. This has been used widely. It's pretty well tolerated. Some side effects may include some dizziness or trouble sleeping. Some G.I. upset some people get this weird lacy looking rash called Livedo reticularis that's not harmful it just makes you look pale and kind of have this Lacy appearance too. So I list a couple of different trials the ones I can that I could find that were the most pertinent to diseases that we’re talking about here. So the first one is the trial where they compared L-carnitine and amantadine. L-carnitine was actually better tolerated and showed more benefit in that study. So you could make the argument that hey why don't we try L-carnitine instead. Another trial looked at Post-Polio Syndrome related fatigue. Amantadine was no better than placebo. And then in 115 MS patients who they studied there was a small but significant.

Benefit when compared to placebo. But you should note that the placebo effect was also very high. So and that's true across a lot of these so just by taking a placebo. People reported their fatigue to be better. So there's Yes so there’s a lot of that in all of these research trials. It's not unique to fatigue.

We see that across the board in neurology the Aminopyridines are grouped together.

So these are a family of medicines that block the potassium channel with the goal of helping to signals travel faster down nerves. So Dalfampridine or ampyra is a medicine that is approved for improving walking speed and multiple sclerosis.

It is difficult to get approved sometimes through insurance for other indications So that's the only way to for sure get it approved. But it's well-tolerated.

We don't use it in people who have had prior seizures because it lowers your seizure threshold.

It can also cause some headache, seizures, paresthesia. Kind of that tingling feeling in your hands and feet this.

So all these compounds are kind of a cousin or similar. They metabolize the similar compounds. So, 3,4 diaminopyridine was looked at in multiple sclerosis in a small cohort it was helpful. 4 aminopyridine in a larger trial.

Fifty-four patients with progressive MS didn't show a benefit. So different patient populations not as helpful. And then when they compared 4 aminopyridine vs fluoxetine or Prozac 60 MS patients there was improvement in both groups on their, on their scores.
The second to the last one so Modafinil and or Armodafinil these are stimulant types of medicines which work to work on the histamine and serotonin pathways mostly in the brain. Their exact mechanism is not clear but they're used to or approved in narcolepsy. So we extrapolate that and tried them in fatigue different doses have been used. They're pretty well tolerated. So in. An blind trial in MS after five weeks with the titration up to 400 milligrams there is no improvement in fatigue versus placebo. And then a different trial that looked at doses up to 200 milligrams showed an improvement in fatigue after two weeks treatment. So conflicting results which is the flavor across all of these trials because as you can imagine it's extremely hard to study this right. And then the last group of medicines or the amphetamines.

These have limited use. There's a lot of side effects associated with these are difficult because you have to get a new prescription every month. They can be helpful in some situations so do you know I do have a handful of patients who take these but. We kind of have to keep a close eye on that. So this is the last slide just shows you a kind of. Common sense flow of how we think about fatigue. Again so we deal with the easy things first we eliminate or reduce medications that take away confounding things that are going to be contributing to your fatigue. And then we start to peel away at the more difficult things so things like depression which treat that are we still dealing with fatigue. Yes. When we look at other things that we can do. So just like with pain it takes.

A lot of work on your part. It takes multiple visits back to the neurologists probably you know after the first couple of visits we're not usually talking about transverse myelitis anymore we're talking about fatigue we're talking about pain we're talking about all the other things so kind of become more of a life coach than I am a neurologist at that point which I'm OK with that.

But so I put a question side to because nobody told me.