

Fatigue and Rare Neuroimmune Disorders

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[00:00:04] **Dr. Bardia Nourbakhsh:** First of all, thank you for the invitation. I am an MS neurologist and clinical researcher. I have a few patients with rare neuroimmune disorders, so I was here to learn more from you. And I did definitely learn. It was such a great group of patients, family members, clinician researchers, and I haven't been to a conference with this great mix of experience and expertise. So, thank you so much.

[00:00:32] **Julia Lefelar:** Hi, I'm Julia Lefelar and I'm the Co-Founder and Executive Director of the MOG Project. We're a global organization, people who advocate for MOG antibody disease and I'm a MOGAD patient myself. We work very closely with the SRNA and other groups and you know, I'm happy to be here. So, I'm going to moderate this and I'd like to talk a little bit first about what I've learned from the community and based on my own experience with fatigue in my own disease. There's been a lot of talk about fatigue and I'm really happy to hear that.

[00:01:12] My disease actually didn't start in the emergency room like most patients. It started probably 14 years before I ended up in the emergency room with bilateral optic neuritis. I started off with waking up with a lot of weakness when I exerted myself in my legs and I felt very heavy and tired. And I couldn't get answers from my doctor. That went on for a little bit. You know, maybe I'd get in a hot tub or something, I'd feel really terrible afterwards. And later on, I got a really bad cold and I noticed that after that, I had a little darkening vision but nothing to speak of. It was almost like I didn't realize it was dark and I was very fatigued.

[00:01:56] That lasted for two years and it was debilitating. It wasn't even something that was like I wasn't sleepy, I wasn't tired, I was debilitated with fatigue and exhaustion. And I went on disability twice during that. It kind of came and went, got a little better, got worse. And after a couple years, it went away. And then I got Lyme Disease a few years later and it came back for six months. It was kind of awful and that was what I dealt with.

[00:02:26] So a lot of patients as I'm finding out, you know, I talk in the MOGAD community have this just in general for all various reasons. I found other patients who had that as their first symptom. And they had it for a long time before the really big emergency symptoms started. And there weren't as many but they were out there. So, the notion is from the community that maybe this fatigue is caused by various reasons. And

so with that, it was a very difficult time for all patients. So, I'm glad we're discussing it. It's one of the biggest silent, or invisible disabilities that there are out there. So with that said, I'd like to pass it on to Dr. Nourbakhsh for comments and presentation.

[00:03:11] **Dr. Bardia Nourbakhsh:** Sure, thank you so much. Again, first thing when you're dealing with a medical issue is having a good definition. So, fatigue is such a broad ranging symptom and really difficult to define. Really it has -- even in medical community, not just among patients. In medical community, it has a confusing terminology, and there are several reasons for that. One is, it's completely subjective. So, there is no objective, measurable, behavioral surrogate for this symptom so far.

[00:03:45] And it has significant overlap with many other humanalities. For example, depression, apathy, sleepiness, not uncommonly or conflated with fatigue in one term, basically. So just coming up with a definition is important. So in MS at least, we define it as a subjective perception. So, it's very important subject. So, we do not have an objective measurable surrogate. That's important. We have to listen to the patient, whatever they say.

[00:04:21] A subjective perception of lack of energy, which can be physical or mental, and it's perceived by the individual or people around the individual. And the individual with usual sets of activities. Not someone who's exerting themselves all the time. And if they feel tired, that's kind of appropriate tiredness, not pathological fatigue. So that's an important point. Many times, I use the analogy of basically the person feels that their battery is drained or they look at their gauge and the gauge looks, it's drained. And it may not be drained, but that's how they perceive it. So at least I think, or that's a hypothesis, that the machinery in the central nervous system that is supposed to monitor the overall homeostasis, like homeostasis means everything is working fine. That machine is broken. And it gives you the signal that, oh, things are broken. Things are broken. Things are broken. And they may not be broken necessarily, but that's what the patient perceives in their consciousness. Okay.

[00:05:34] There are many concepts related to fatigue. Probably for the sake of time I'm not going to go through all of those. But again, in the medical community, fatigue and fatigability are two important overlapping but distinct concepts. Again, fatigue was the subjective lack of energy. Fatigability is something that our PMNR colleagues or our physical therapy colleagues can measure actually that with some physical exertion, your ability to do further exertion decreases. Or the same with cognitive function. If you solve a puzzle for 15 minutes, your ability to solve further puzzles is going to decrease. That's called cognitive fatigability, and it can be measured. So overlap, but not quite the same thing that we are talking about subjective feeling of lack of energy and exhaustion.

[00:06:29] Again, it's another diagram of how different entities in the central nervous system lead to the subjective feeling of fatigue. And again, these are hypotheses. These are not something that are easily demonstrated on an MRI or on a bloodwork or on even a functional MRI. But these are interesting hypothesis and concepts that researchers have come up with to kind of explain where does this feeling of lack of energy is coming from in the brain? Again, one big issue related to this topic and rare neuroimmune disorder is the literature about fatigue and neuroimmune disorders is very, very, very thin, and we'll get to that at the end.

[00:07:23] So most of our knowledge, most of our understanding comes from the most common neuroimmune disorder, which is multiple sclerosis. So fatigue is the most common symptom in MS. And a lot of studies have shown that it results in disability, loss of employment, reduced quality of life. And even they have shown people with MS who have fatigue compared to those who do not have fatigue, they experience more rapid decline and more rapid disability. So, it's a really important topic in MS, which was, even up to 10 years ago, pretty much not paid attention to.

[00:08:05] Again, learning from fatigue in MS, I want to separate lack of energy from sleepiness. There are people who experience lack of energy, but they are not sleepy. They don't doze off during the day. They are not having a hard time waking up in the morning, but they just feel exhausted during the day, unusually and pathologically. But there are some patients, again, using the analogy of MS, who have this lack of energy, but they also have excessive daytime sleepiness, similar to people with narcolepsy or sleep apnea. So they have this tendency of dozing off and falling asleep and also feel lack of energy. And there might be some importance from trying to separate these two group of patients regarding treatment. I will try to touch upon that later on.

[00:09:01] What causes fatigue in MS or neuroimmune disorder? So simple answer, we really don't know. Long answer, there have been dozens of different factors that have been associated with MS fatigue. So, when you see there are 30 different factors, it means that we really don't know. But it's a very long list of things. Look at this list of potential causes or potential associated factors with MS fatigue. If you dive deeper, look closely, there are two main themes coming out of it. One is injury to the central nervous system. So, damage to different parts of brain and spinal cord seems to be an important factor that has come up in various studies. The other is the presence of inflammation. So, whether this is the inflammation in the nervous system or inflammation in general throughout the body, what we call systemic inflammation. So, these are two big themes when you look at, MS or neuroimmune, perhaps, related fatigue.

[00:10:16] There is another concept of secondary causes of fatigue. So, these are conditions that are not directly related to the main disease, MS or MOGAD or NMO, but they commonly go hand-in-hand with the disease. For example, depression. For example, sleep disorders. For example, using medications. So, these are not directly caused by MS or neuroimmune disorders, but you can imagine they accompany these diseases, which can result in fatigue and really make things complicated. So again, another diagram trying to come up with themes. One is injury to the nervous system, white matter and grey matter injury, and the second theme is inflammation. And again, downstream, they lead to a breakdown in this machinery that we have all in our body to monitor the homeostasis of how things are, how good things are. And when that machine is broken down, we feel exhausted. We feel fatigued. The body tells us don't move, don't do activities because it senses a breakdown, whether the breakdown is there or not. Alright.

[00:11:38] How to measure fatigue? So again, anything in medicine, in health, if you can't measure something, you cannot really address that. But we mentioned that fatigue is a subjective symptom. So what we use is patient-reported outcomes. So basically, our gold standard is using questionnaires. There is a lot of science and art into making a questionnaire. And recently, actually, my colleagues and my collaborators have shown that the questionnaires that we use for MS, they are questionable in terms of how good they are for measuring fatigue. But basically, that's what we have. They are our gold standard, and, we use questionnaires or patient-reported outcomes for measuring fatigue. Getting to the treatment of fatigue.

[00:12:24] So as I told you that fatigue is the most common symptom of MS, and it has a huge factor on health and well-being and ability and disability of patients with MS. It is vastly untreated. Actually, it's been studied that many, many patients actually report their MS providers or their neurologists do not address or do not provide treatment for this very common symptom. So very, very common, but very, very untreated. For example, in this study from the United Kingdom, only 30% of patients reported that they have ever been offered any treatment for fatigue, which is, you know, very interesting. And this is not in a study from 20 years ago. It's a study from just 2 years ago. And, again, you're talking about MS. I can imagine it's even worse in rare neuroimmune disorders because, again, me as a neurologist and neuroimmunologist, I always paid attention. I always tell people with MOGAD, with NMO, with myelitis, what's important for them is prevention of attacks, you know. They had an attack. We try to help them recover from the attack and prevent the attacks. We never thought about invisible symptoms in rare neuroimmune disorders the way that we now

think in MS. But, again, I today learned or this weekend learned that we really need to pay a lot of attention to invisible symptoms in rare neuroimmune disorders, which can be as disabling as attacks, if not more.

[00:14:03] So, again, getting back to the treatment, what do we have to offer to patients with MS when they have fatigue? I kind of listed the big themes that we use in clinic. So, medication. We offer medication to patients with MS. Cognitive behavioral therapy is, I would say, an emergent theme, emergent important treatment for various neuropsychological issues in MS or in general population. For example, you might know that cognitive behavioral therapy, which tries to change or alter how people think about their disease or their condition. Also teaches them behavioral changes to help with the condition, is a very effective treatment for depression in general population, not in MS or neuroimmune disorders. Actually, cognitive behavioral therapy is as effective as medication treatment for depression, which is fantastic. So, there is a type of cognitive behavioral therapy that has been tested for MS fatigue, and there is a very good amount of evidence that it works.

[00:15:14] Various types of exercise actually has been shown to be effective in improving MS fatigue, and energy conservation and cooling. And there are some miscellaneous interventions that we kind of use or research. First thing, pharmacotherapy, that's kind of my expertise. So, what about first immunotherapies that we use, you know, whether in MS or in rare neuroimmune disorders, medication that you use to prevent attacks? Do they have effects on fatigue? Very interesting. We really didn't know much about that. Even in MS, recently, MS clinical trials, MS disease modifying clinical trials started measuring fatigue during their clinical trials. So up until five, six years ago, fatigue was neglected. But more recently, it's being paid attention to.

[00:16:15] And as what they call secondary outcomes, several disease-modifying therapies, they measured fatigue during the clinical trial. And very interesting, it seemed that disease-modifying therapies in MS that are more effective in terms of preventing attacks, they are also more effective in preventing worsening fatigue. So that's quite interesting. And these are two-disease modifying therapies. So Ublituximab or Briumvi, which is a newer, more effective disease-modifying therapy, was compared to an older, less effective disease-modifying therapy. And they showed over time, people who were on less effective treatment, their fatigue worsened more compared to people who were on Briumvi in the setting of a randomized controlled trial, which gives us the best level of evidence about how medication works.

[00:17:10] The same, another disease-modifying therapy called Ponesimod that was tested more recently against an older medication, and the same thing was shown. Ponesimod that is more effective in preventing attacks and slowing down disability-worsening in MS, did a better job in preventing worsening fatigue over time. So immune therapies are important. Preventing attacks are important over time. So that's a big message for people with MS and neuroimmune disorders.

[00:17:45] What about what we call symptomatic treatment? You know, stimulants or medications that are used for people with narcolepsy and sleep apnea. They are very, very commonly used in the field of MS and despite not having really good studies. So, we did relatively a good study several years ago, and we showed that all these medications that we use, such as modafinil, amantadine, methylphenidate on average. So that's very important. On average. When you average the response of all patients in the trial, they did not do better than a placebo. Okay. So that's a very important message for the MS community. You may say, okay. Yeah. Everything seemed to be effective. Why do you care if people are on a medication which is effective but not better than the placebo? The problem was they caused more side effects than placebo, you know. More anxiety, more sleep problems. So, they don't work better than a placebo, but they cause more side effects. So that's one reason that we have to think twice about using medications.

[00:18:55] But what about non-medication treatments? I talked a little bit about cognitive behavioral therapy and also about various types of exercise. And in this study, which is a systematic review, basically, it reviewed all the studies related to exercise cognitive behavioral therapy, and they showed very nicely that there are multiple types of exercises. Balance exercise. We talked about Tai Chi, for example today in another setting. In cognitive behavioral therapy, they seem to be effective in improving MS fatigue. Sounds a little bit counterintuitive how exercise might be effective for someone who has fatigue, which might prevent them from doing exercises. But in fact, they do improve fatigue in the setting of MS, and that might be the case in rare neuroimmune disorders. But as I said, I'm very cautious about extrapolating the data from MS to another disease.

[00:19:48] For example, that is not quite the case, in another disease that is associated with fatigue. Probably, you have heard chronic fatigue syndrome or myalgic encephalomyelitis. People who have that condition, actually, they get worse with exercise. That's one of the core features of the disease. And actually, cognitive behavioral therapy has been tested in them and didn't work. So, we have to be cautious about extrapolating data from one disease to another disease. But perhaps, there are more similarities between MS and MOGAD and NMO versus chronic fatigue syndrome. So, my point was, nonpharmacological treatments seem to be working. Again, in these studies, they have not really been tested against placebo or [sham] really nicely, but at least they don't have the side effects of the medication. So, my point is I usually prefer nonpharmacological treatment to medications when it comes to MS fatigue.

[00:20:48] What about what do we know about fatigue and rare neuroimmune disorders? There are really few studies that are reported in the past few years. So, for example, there was a study that compared people with MS and people with NMO, and they showed that, numerically, fatigue severity is less in NMO people. People with NMO compared to MS. But the difference was not statistically significant. So, there were small studies. They didn't have what we call a lot of statistical power. But just looking at the numbers, it seemed that average fatigue was higher in MS. But again, when you did a statistical testing, they were not different. Compared to healthy control though, in another study, they showed fatigue is more in people with NMOSD as compared to healthy people. And it correlates with sleep problems, daytime sleepiness also that we touched upon, and depression.

[00:21:51] Another study in patients with Aquaporin-4 antibody, fatigue was associated with higher age, longer disease duration, the number of clinical attack, worsening of disability, pain, anxiety, and depression. Relatively similar to MS. So, if you have more depression, if you have more anxiety, more pain, if you have more physical disability, severity of fatigue is going to be more if you have Aquaporin-4 antibody disease. The same in MOG antibody disease. In MOGAD, another study reported that pain and anxiety correlates with fatigue severity.

[00:22:34] There have been a few other studies. In one study that we did in collaboration with [Julian], we really are grateful for the opportunity. We looked at fatigue in people with MOGAD and compared the severity of fatigue with healthy controls. Basically, people who lived with, patients with MOGAD. And we showed that severity of fatigue is higher in people who have MOGAD. And very interestingly, you know, MOGAD presents with different symptomatology. It can present with optic neuritis, myelitis, ADEM. And our hypothesis was people probably who have more brain problems from MOGAD should have more fatigue. But that was not the case. Actually, people who had optic neuritis had more fatigue, which is a very, very interesting finding, and we can talk about that. Very thought-provoking finding, in fact. And also, the higher age, older people with MOGAD had higher fatigue as compared to younger people. And also people who were recently out of an attack and still using acute treatments such as steroids. Which again, not very unusual to see that.

[00:23:50] What about fatigue treatment in rare neuroimmune disorders? I would say there is almost no study or evidence, so that's the reason I was trying to extrapolate data from MS. There are a couple of studies about carnitine, which is a supplement that has been tested in MS with questionable efficacy. It was tested in... you should ask me if it was in Aquaporin-4 or MOGAD, and I don't remember, and I didn't write it in my slide. But in one of the rare neuroimmune disorder, it was tested and showed that it was not better than placebo. And in the pivotal trial of satralizumab, they tested fatigue between people who received placebo and the medication, and there was no effect on fatigue. So interesting.

[00:24:44] But, again, there is extremely low-level of evidence in that regard. So what would be my, quote, unquote, expert recommendation? So as I said, I try to use MS literature to base my treatment on MS literature. At this point, first step would be a thorough evaluation of secondary causes. Those are low-hanging fruit. So, if someone is on some medication that causes fatigue, and many patients with rare neuroimmune disorders are. Gabapentin or gabapentin-like medication, baclofen, pain medication, they can all cause or worsen fatigue. So thinking about that, addressing the dose, adjusting the dose is a low-hanging fruit.

[00:25:29] Sleep disorders. Again, probably, a neglected area in people who have neuroimmune disorders. Testing for those sleep disorders, treating sleep disorders, particularly sleep apnea, which is relatively easily treated if it's present, can make a big difference. Also, depression, treating depression can also improve fatigue. So those are low-hanging fruit. After that, if you address those and the patient still has unbearable fatigue, I would first go to nonpharmacological treatment, cognitive behavioral therapy, and various forms of exercise.

[00:26:03] Last step, even after using non-pharmacological treatment, if the patient has fatigue, I would think about using pharmacologies such as Modafinil and a stimulant reluctantly. Again, there are some patients who do respond to them better than placebo, but finding them is not easy, and we are doing some research in MS to try to tease that apart. But more important than all of this is paying attention to invisible symptoms, not assuming people with neuroimmune disorders only deal with attacks and recovery from attacks and prevention of attacks. Addressing and paying attention, that's the number one issue. And then doing research, measuring in groups of patients. So, we need sample size. The larger the sample size, the better our understanding of the symptom. And then doing rigorous clinical trials that we are trying to do in MS, do that in rare neuroimmune disorders. So that's my recommendation. And sorry for [inaudible] time.

[00:27:09] **Julia Lefelar:** Oh, no. No, that was wonderful. And you know one of the things, you know, of course I have so many questions but I wanna have time for audience questions. But one of the things that, obviously, there's not a lot of research in these rare neuroimmune conditions but would you, if you were going to do this research, would you target or really try to separate out not only the disease itself but the area of damage in the central nervous system where that occurs? Could you just speak about that real quick?

[00:27:09] **Dr. Bardia Nourbakhsh:** Beautiful question. Based on the study that we did together, I think that that's important. Trying to not just based on the antibody or the kind of name of the disease, myelitis or MOGAD and NMO, they affect different parts of the central nervous system. If we could be more granular, the better, of course. I understand that it's a rare disease by definition, and sometimes we need to put people with different symptomatology in one bucket. If we have more people with similar afflictions, people who have optic neuritis from MOGAD, myelitis from MOGAD, ADEM from MOGAD, or cortical encephalitis from MOGAD, that would be very helpful. Again, starting with low-hanging fruit and, even if we put all patients with rare neuroimmune disorder in one bucket, I guess that would be the first step.

[00:28:37] **Julia Lefelar:** Yeah. I mean, that sounds like it would be a really fantastic thing to fund in a grant.

[00:28:40] **Dr. Bardia Nourbakhsh:** Absolutely.

[00:28:42] **Julia Lefelar:** But one last question before I throw it over to the audience. How should the patients out there who may not have access to a Dr. Nourbakhsh in their area, how should they talk to their doctor about this fatigue to get them to understand? We get so many people coming back to us and this is the case with me, that, oh, you're just depressed, you know. How do you get them to take you seriously and help you do something about it? And maybe even find someone you can travel to go see.

[00:29:12] **Dr. Bardia Nourbakhsh:** Great, great question. And again, it's not just a problem of patients who live, for example, in remote areas. To be honest, as we said, because we don't have great, great treatments as doctors, we try to gloss over those symptoms. You know? If we had great, great treatments, that would be my first question. But because we do not, so that's probably our fault, you know, as clinicians that we feel bad that we don't have great things to offer. But we have something. So that's first. Educating your clinicians and letting them know that there are things to do, you know, that are not necessary medications. That's number 1.

[00:29:55] Bringing it up. Just, again, just when you're talking to your doctor, mentioning it and talking about it, I think that's first step. If your doctor hears that from several patients, then they would come up with, oh, this is a pattern. This is something that, it's a big issue with patients. And then they go and do their research or they try to find people if they are good doctors to help their patients with. So again, I understand that visits are short, and addressing many, many things is really, really difficult in a short 30- or 40-minute neurology visit with your provider. But, again, mentioning it and talking about that, and the more that people talk about the issue, us doctors, we take them more seriously, and we try to address them. And funding agencies also take them seriously.

[00:30:54] As I said, it's - there is a movement in MS in the past 10 years to pay more attention to patient reported outcomes. So, I would say 10, 15 years ago, patient-reported outcomes were a joke, basically, for scientists. They didn't pay any attention to patient-reported outcomes. If there wasn't something that you could not find an MRI or an electrophysiological test or a blood test or a spinal fluid test, we did not even pay any attention. But now there is a huge movement among clinicians, among researchers, among NIH, funding agencies, National MS Society, to pay attention, to listen to patients, to take patient-reported outcomes seriously. So, issues such as fatigue, depression, and pain, which are by nature subjective and based on patient-reported outcomes. So just talking and bringing them up and trying to getting more researchers and clinicians take them seriously, I think.

[00:31:55] **Julia Lefelar:** Absolutely. Well, thank you so much. And we are blessed to have a doctor out there to have our backs like you. And I don't know if you wanna take questions.

[00:32:04] **Dr. Carlos Pardo:** So we have four minutes for questions. Questions should be brief. (laughter) Brief. Okay? Question from the audience. No questions from the audience. Sorry.

[00:32:29] **Audience Member 1:** Thank you. I just was surprised. I thought it was just me, but 31% of people who report fatigue are treated, and the rest of us just go, you know, about our way. And I'm one of the other 69% or so that... And it's really irritating because I've talked to my doctors about not just my pain, but the fatigue, the immense fatigue that I feel during the day. And, you know, I take a nap or two, but I just you know? So, I'll continue trying to talk to my doctor and to see if but I don't want any of the drugs that really perk you up, but that's pretty... that's not a real cure. And I just wish that there was something more out there for us other than... So that was just a comment that I wanted rather than a question.

[00:33:53] **Dr. Bardia Nourbakhsh:** Yeah. Thank you so much for your comment. And as you said, you are in the majority, actually, of people who reported this. Even as I said, this was among people with MS who, you know it's been for a while that we knew fatigue was a big issue in MS, but still, it goes on under-treated for sure and undervalued often.

[00:34:18] **Julia Lefelar:** Yeah. And I always say, there were things that I did to combat my fatigue, like naps, several naps during the day after, you know. Power naps, I called them, for 20 minutes. But even then, I can still tell you the only real cure for fatigue is great disability insurance. (laughter) (applause)

[00:34:39] **Dr. Carlos Pardo:** Right. Thank you so much and thank you for this excellent presentation, Bardia.

[00:34:44] **Dr. Bardia Nourbakhsh:** Thank you.