Management of neuropathic pain

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[00:00:00] **Dr. Benjamin Greenberg:** We really enjoyed the conversations yesterday, as a lot of us have talked, it was very different from what we've done in other symposiums but I really think all of our speakers did a wonderful job of setting the stage of all the different issues that we face clinically in terms of patients, families and clinicians trying to help out of the wide variety of symptoms and challenges and triumphs and successes that people can have.

[00:00:30] So today we're going to shift gears and start going topic by topic of a lot of the different things that affect us in day to day life and we're going to start with the discussion of management of neuropathic pain, which I have to say from our speakers yesterday and from the informal conversations I've had with many of you and with my own patients is a common issue amongst these disorders, so Dr. Ram Narayan who did his fellowship in Dallas at the University of Texas and then was a traitor and left us and now runs a program at the Barrow Neurological Institute when invited to speak today this conflicted with travels that he had but despite that he agreed to join us regardless of the conflict all the way from India, so he is traveling and seeing family and Ram, what time is it where you are right now? You're on mute because it's—

[00:01:31] **Dr. Ram Narayan:** 9:30 in the night.

[00:01:33] **Dr. Benjamin Greenberg:** 9:30 at night. Okay, so we should have done this at one this afternoon and really get you out of bed. So, it really gives me a great privilege to introduce Ram to talk us through the management of neuropathic pain and so Ram I'll turn things over to you.

[00:01:51] **Dr. Ram Narayan:** Thanks a lot. Dr. Greenberg. I thank the SRNA for giving me this opportunity and it was very nice of you to accommodate me when I'm traveling and help match time zones so I really appreciate this opportunity, so I'm going to be talking about neuropathic pain and rare neuro-immune disorders, so I do not have any disclosures relevant to this talk and this is the summary of what I'm going to talk about pain in the context of rare neuro-immune disorders. What is neuropathic pain indeed? How common is it? What are some causes and mechanisms of neuropathic pain? How is this diagnosed, and then the meat of the talk is going to be on management.

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[00:02:45] Now this particular audience that I'm addressing, I'm quite sure that you're very familiar with this concept of neuroimmune disorders but amongst all of these that are listed and plus many more that are not listed, transverse myelitis or any kind of milo empathy for that matter and neuromyelitis optica spectrum disorders. These are the main disorders that result in many times debilitating refractory neuropathic pain. Now when I was looking up this literature on--Okay, so how is this different from another immune-mediated condition that I see more often namely multiple sclerosis, it turns out that the severity of neuropathic pain and the pain-related disruption in daily life was greater according to this study that I've just shown up here and this was published right in the midst of the pandemic.

[00:04:01] It was much greater in patients with neuromyelitis optica spectrum disorders than in patients with multiple sclerosis and now shifting gears on understanding what causes neuropathic pain, so this is something that I learned from Dr. Greenberg when he teaches his patients, so this pain pathway usually is a three-wire system. You have a wire, you have an axon from the receptor in the skin to this final core, you have a second axon a second nerve that connects this to a center called the thalamus in the brain which is a relay station and then there is a third wire which connects that to the highest center in the brain called the cortex.

[00:04:58] Now in this three-wire system, there are conditions that can affect the first wire which is very common in conditions called peripheral neuropathy and what we are going to focus for this talk is disorders that disrupt wires two and three namely the wire that goes from the spinal cord to the thalamus and the third wire that goes from the thalamus to the cortex, so that's where conditions like multiple sclerosis neuroma, neuromyelitis optica, stroke, ADEM, all of these conditions affect those two wires and it is very important for us to realize that neuropathic pain is different in many ways from the pain that's caused by inflammation and by that, I mean, so conventionally, what we think of as inflammation is, if you get a cut on your skin, you see how that turns red and warm and swollen up.

[00:06:00] Now that is inflammation on the skin. You can get inflammation in any internal organ as well so the pain from inflammation is very different from the pain that is caused by damage to the nerve itself and therefore it has treatment implications as well. It's treated very differently. A study showed that 10% of patients with chronic pain have neuropathic pain characteristics. Now it's important to realize that 50 million adults in the US have chronic pain so 10% of that is five million so that's a large number and from our day-to-day practice, we can tell you that this is one of the very challenging conditions to treat or challenging symptoms to treat plus this is something which is very important for one's quality of life.

[00:07:01] And so and many times patients have tried many options before coming to us and so this is indeed a challenging situation. Many times, I would say several times we've--it's also gratifying when we're able to help patients deal with this so again, a little more in-depth about how this transmission system works so here are the peripheral nerves that come from the peripheral receptors to the spinal cord and then you have in the spinal cord are numerous mechanisms that help integrate these impulses, these messages that come from the peripheral nerves and they send it to the higher centers of the brain.

[00:07:48] In one such center called the pons is where these signals are modulated and then they are sent up to certain other centers called the amygdala and the limbic cortex which are responsible for the emotional aspect of pain, so we're going to talk about some medications which we used to treat neuropathic pain and interestingly these are also medications we used to treat conditions like depression so it's quite intuitive to presume that pain and emotional pathways are very intricately related, and then, of course, the highest center is the somatosensory cortex, as I've mentioned here.

[00:08:37] Now, what are some characteristics of neuropathic pain? When a patient comes to my clinic and says, "Well, I have ANIMO and I also have pain, how do I just conclude that the pain is very likely from ANIMO

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and not from another condition, like let's say a peripheral neuropathy or from an inflammatory condition," so we look at patterns of pain. If you look at this on the left, you see that there are numerous patterns of pain that occur in peripheral neuropathy. This one such common condition that we see in patients with multiple sclerosis is a condition called trigeminal neuralgia. It's one of the main symptoms in multiple sclerosis, not so common with most other rad neuroimmune disorders.

[00:09:41] Now, talking about the central neuropathic pain, which I've shown here again, so someone can get a central neuropathic pain as a result of spinal cord injury and this is typically what the pattern of the injury, the pattern of pain, the distribution of the neuropathic pain might be. I'm not sure if you can follow my mouse on the slide but I'm just showing you the top panel on the right and I'm showing you the middleman where there is a spinal cord injury and pain below that level and then in the second panel on the right is a pattern of post stroke pain so if somebody sustains a stroke particularly of the thalamus, then a few weeks later they end up with refractory pain on the opposite side of the body and then of course.

[00:10:47] Many times what we see in clinic is a mixed pattern of central pain, whether there is a combined distribution of those that are observed in a spinal cord injury plus those that are observed in a stroke so more or less a combined pattern. When a patient comes to my clinic obviously, we get a good history to understand the characteristics of the neuropathic pain so to understand the characteristics of the pain and decide if this fits a pattern, also very importantly, we try to understand how much disruption has it cost in their quality of life and of course we try to find out what options they've tried. This is something which takes quite a bit of time.

[00:11:37] We quiz with them on names of various medications that they've been prescribed and the dosages, etc.., and sometimes patients find it frustrating to answer that question as well but that's very important for us to document that and make a decision on what to do subsequently. Now, after this, when we conclude that--well, this is a patient that might possibly have neuropathic pain, we examine the patient to confirm this and then we may or may not so at this point this is good enough for us to proceed with treatment but sometimes we may need to do additional confirmatory tests like those that are listed on the right.

[00:12:15] A very common test that I find useful is a quantitative sweat test that is sometimes helpful to corroborate with neuropathic pain. The reason is there are fibers that carry pain that also result in the sweating function so there is quite a bit of a connection between these and if I have a question as to whether there is a peripheral nerve problem like the wire one. Is there a problem with that particular nerve as in diabetes, etc.., for example, I might get a nerve conduction study now, typically in patients with the rare neuroimmune disorders that we are familiarized with namely NMO or transverse myelitis, a nerve conduction study is expected to be within normal limits.

[00:13:19] So the trust in management is to emphasize to ourselves and to our patients that a multidisciplinary approach is the more consistent way to go forward so medications alone or psychotherapy alone or acupuncture alone may not be the end of all. It's very often and what I find interesting is whether or not I tell patients about this, they end up in a multidisciplinary setup and I think that's very appropriate. A note about medications and I know this is the trust of what we offer in our clinic on a day-to-day basis. These are, so the first line therapies are medications like amitriptyline, nortriptyline, etc.., and a note on this would be patients look up these medications when we prescribe this for pain and find that they are antidepressants and get upset and they tell us, "Oh, I'm not depressed, I just have refractory pain."

[00:14:34] So that's what I was alluding to in the earlier part of my talk. These medications have the highest level of evidence probably out of the other categories, probably the most evidence I would say to treat pain with neuropathic characteristics, so these are one of these medications like amitriptyline and nortriptyline

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are some of the well-studied medications to treat this and of course anti-epileptic medications. Again, it is important to tell patients that we're treating neuropathic pain and not a seizure problem.

[00:15:08] These include medications like Toradol and tramadol. Second-line treatments include medications like topical lidocaine capsizing. Now if this is a patient that's been dealing with this for a while and has tried multiple options, I start offering these second-line treatments pretty earlier on. Tramadol is included sometimes as a second-line therapy. It is usually not preferred for first-line therapy because of sedative side effects and then you have third-line therapies which again, I get a little aggressive and I used them earlier on with the first-line second-line therapies. These include treatments like botulinum toxin, medications like mexiletine and prolactin which don't have a great amount of evidence but yes, there are numerous individual case reports that are published.

[00:16:10] Cannabinoids, I'm going to deal with this separately in a slide, low dose naltrexone, this is an option that is relatively popular, and I found out that these are popular in-patient support groups and opioids. Give me one second. All right now talking about opioids from neuropathic pain, so I have listed this study as a very important study here that was published in JAMA which is one of the leading journals and it is a systematic review which means that it provides the highest level of evidence for use of a particular medication short term studies, so these particular papers looked at two kinds of studies, short term studies that were completed within six months and intermediate term studies that were completed over a period of a few years.

[00:17:47] These short-term studies concluded that the role of opioids is equivocal for the treatment of neuropathic pain whereas intermediate-term studies concluded that opioids indeed have higher efficacy compared to placebo, which is not really surprising, but they clearly did mention with the caveat that there were unclear results on quality-of-life measures and the paper does. The authors do make a note on giving a caution regarding narcotic overuse and dependence issues and what we find practically is, so first of all, we're not a big fan of prescribing opioids for neuropathic pain because this is also at least as first-line or second line.

[00:18:48] One of the reasons also that this patient population may also run into problems with cognition, bladder control, bowel movements etc., so we use this very cautiously for neuropathic pain. Now talking about cannabinoids so when we think of cannabinoids, tetra hydro cannabinoid is the psychoactive component and cannabidiol is the ancelliaptic and it starts to have anti-inflammatory neuroprotective properties. Again, a Cochrane analysis of about 16 studies with more than 1000 individuals about 1750 people concluded that the benefits of cannabis-based medicine in chronic neuropathic pain may be outweighed by their potential harm and so I do not hesitate to recommend CBD for patients with neuropathic pain especially when they suffer from other problems like depression or spasticity or neurasthenic bladder all of which are very common in rare neuronal disorders.

[00:20:23] This is the paper that was published in 2019, interestingly again I guess this was right before the pandemic and then it is important so the authors do again mention a word of caution in interpreting these studies so non-neuropathic pain types can exist in patients with these disorders like NMOS, transverse myelitis, etc. so it is important for us to pay attention to the safety and duration of cannabinoids when prescribed so it's looking up at current ongoing clinical trials. These are some and the ones that I've boxed are the ones where Sativex, which is a THC product is used to treat neuropathic pain and the final conclusions from these studies have yet to come.

[00:21:35] Now, there are many devices that have a very important role in the management of neuropathic pain, be it neurostimulation, trans magnetic stimulation, motor cortex stimulation, even deep brain stimulation, or spinal cord stimulators, these being very common and vagal neural stimulators. Now, these are offered

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at select institutions by select pain management experts in collaboration with a surgeon. Last but not least, again whether we mentioned this to patients or not and I think it's very important for us to educate patients on this, there are numerous other options and different forms of alternative therapies that can be adopted as a complementary measure to conventional means of treating neuropathic pain, one of which includes scrambler therapy, and this was a paper that was published by Maureen Millie.

[00:22:42] Most of you who might be familiar with her, I had an opportunity to work at Hopkins at the same time she was there as well and she published a study in neurology in the neurology journal, again a very converted journal that clam breath therapy improves Spain in neurobiologists? Africa last but not least. This is also something that I emphasize to patients. Is it definitely worthwhile to pursue options of psychotherapy, particularly cognitive behavioral therapy as emotions, thoughts and behaviors are well connected.

[00:23:31] In the last few months, I have been getting a few reports from patients where their blood sample is sent to a lab, and we get a report on the response of individuals to different kinds of pain medications, and I think obviously this particular testing which we call pharmacogenetics testing is not universally available yet and I don't think it's covered by insurance. However, I think that is the direction where this particular field of medicine is moving towards to scatter pain medications based on somebody's response, an individual's response to that medication based on their genetic makeup so I'll conclude my talk here and take questions. Sorry if I exceeded my time.

[00:24:46] **Audience Member:** Hi, so it's not specific to the neuropathic pain portion, but just in your proportion of the cannabis topic, you mentioned the neurogenic bladder and how it might benefit from cannabis use. Have you seen that in any patients? Just trying to find other techniques that might assist with neurasthenic bladder symptoms.

[00:25:08] **Dr. Ram Narayan:** Can you repeat that question, sorry?

[00:25:11] **Audience Member:** All right. Yeah, it's specific for the neurasthenic bladder portion with the cannabis use, have you noticed if it helps alleviate symptoms or what kind of things or benefits have you seen or read about, I guess?

[00:25:23] **Dr. Ram Narayan:** Definitely, I've seen patients with the neuropathic pain, I've seen a benefit on that plus a benefit on Spasticity and MOG in general so all of this I've seen a positive effect on it. Now, this may not work for all patients, not all patients have access to it, not all states give equal access to this, and definitely, there is a problem with affordability but when it is given to the right patient, I think it does work.

[00:26:12] **Audience Member:** Thanks. One of my doctors prescribed buprenorphine for me after years of other things and it's really worked terrifically, and I've never heard anyone mention it in the talks so I'm wondering why that is.

[00:26:26] **Dr. Ram Narayan:** This is very interesting. I am still learning this to be honest because there are numerous times when patients come and tell me, "You know what? This worked" or "That worked," and I definitely learned that but when it comes to translating it to another patient, we definitely would want to look at research studies and I don't think there are any large--Not that I would still recommend it to a patient and say, "Well, there was a patient that told me about this particular option."

[00:27:03] I don't think there is any high-quality research behind this, but maybe it's worth for you to try this because you've exhausted everything else so I do tell that every now and then but however I would prefer the first see if any research has been done on that particular medication and then translated into practice.

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Thanks for letting me know about that. I'll definitely look this up as far as I looked this up for this particular topic. I did not see robust evidence for Nurofen in neuropathic pain and Nurofen is also an opioid.

[00:27:40] **Audience Member:** Yes. Hello, my name is Andrea Mitchell from the MOG project and I have a question, you were talking about a study with pain and NMO and I believe that's for aquaporin-4. My question is are there any plans to have some pain studies with MOG antibody disease?

[00:27:59] **Dr. Ram Narayan:** That's a great question. Aquaporin-4 and Dr. Greenberg is right there so he's the expert on this but has unique ways of causing neuropathic pain which MOG may do it, but not to that extent so we don't see that being a major problem with MOG and that's point number one, point number two is there is quite a bit of interest in doing high-quality studies in MOG antibody disorders per se so that our efforts through the neuro next team to develop a political trial in this area but as well as Spain itself is concerned, I think that's still a little far out, I don't know.

[00:28:52] **Audience Member:** Hello, my name is Emily Martin and I have a MOG diagnosis and I also have rheumatology. They don't really know what it is. My question is, both sets of my physicians, rheumatologist and neurologist are aware of the different pain I have, but it just hasn't been sort of like just deal with it, not rudely. I guess what I'm questioning is, is it time to look into a request a referral to a pain management doctor? I don't want so many chefs in my kitchen, but my pain is getting a lot worse and to the point where I was self-medicating with over the counter and it really upset my whole system, so I guess at what point and to which physician do I request a pain management referral?

[00:29:53] **Dr. Ram Narayan:** I'm sorry you're going through this; this is quite a bit of a frustrating situation for a patient. This getting hunted between different doctors or even trying to understand whom to reach out to. I guess anyone should be able to give you a referral to a pain medication doctor, it could be a rheumatologist, it could be primary care, it could be a neurologist and I think given that if an individual has--and this is not uncommon where somebody has a rheumatological problem, and a neurological problem, I really do think that these are patients that will have a combined peripheral and central neuropathic pain problem and I really do think that a pain management integrated multidisciplinary pain management team is very important.

[00:30:47] **Dr. Benjamin Greenberg:** Great. Ram, thank you very much. We really appreciate it and enjoy the rest of your trip and safe travels home when the time comes.

[00:30:55] **Dr. Ram Narayan:** Thanks a lot.

[00:30:55] **Dr. Benjamin Greenberg:** Thanks, Ram.

[00:30:56] **Dr. Ram Narayan:** Thanks a lot, Dr. Greenberg.

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