0:03
Hello and good morning to everyone.

0:06
Thank you so much for tuning into today's session on small fiber neuropathy with guest presenter doctor ....

0:13
My name is Lindsey Kolbert I am the Executive Director of the Foundation for peripheral neuropathy.

0:19
And I am beyond thrilled that we're doing today's program and hope that it will be of great value to everyone joining and watching again in the future.

0:27
Before we get started, just a few logistical matters to address.

0:31
First off, the webinar is being recorded for future access. We will upload the recording and related materials, including the PowerPoint slides that you will be seen today, in the next 24 hours or so onto our website at WWW dot foundation for ... dot org.

0:50
Towards the end of this session, we will be having a question and answers session. So if you do have any questions, feel free to submit them at the questions box. We will try to answer them at the end of our webinar.

1:03
And if for any reason you cannot hear me right now or have trouble using trouble with your audio throughout the session, I encourage you to dial in by phone.

1:13
That number is included in the e-mail with the other instructions on how you access this webinar.

1:21
And now I am pleased to introduce today's guest speaker adapter, Emre ....

1:26
He is an assistant professor in the Department of Neurology and the University of Michigan Michigan Medical School, Division of Neuromuscular Medicine.

1:35
He has expertise in the treatment of neuromuscular disorders with special clinical and research interests in the care of patients with acquired peripheral neuropathy.

1:45
Doctor Sarno went on to pursue a Bachelor of Science Degree in Brain, Behavioral, and Cognitive Sciences from the University of Michigan, Ann Arbor, which he completed in 2006.

1:56
He received his medical degree from Wayne State University School of Medicine in Detroit, Michigan in 2010, and completed a transitional year internship at Saint Joseph Mercy Hospital in Ann Arbor, Michigan.

2:10
He then completed his neurology residency training at the Wayne State University School of Medicine Detroit Medical Center followed by a fellowship in Clinical Neurophysiology Neuromuscular Medicine at the Mayo Clinic in Arizona.

2:24
He joined the Ohio State University Faculty in 20 15 as director of the Peripheral Neuropathy, Clinic and Autonomic Lab, and he joined the University of Michigan Faculty in 2019, as director of the Peripheral Neuropathy Clinic and co-director of the Autonomic Lab.

2:43
Currently he serves as site Principal Investigator on Multi-center Studies in the Realms of Metabolic and Autoimmune neuropathy.

2:51
And today we are so thrilled that he will be speaking today about small fiber neuropathy, so thank you, and I turn it over to you.

3:02
Thank you.

3:04
Thank you for that introduction, Lyndsey, and welcome to all our attendees. Hopefully everyone can hear and see me. I see that we have roughly 230 attendees and counting. So certainly the foundation picked a good topic, and I'm happy to help and contribute.

3:24
I'd like to thank Banker Foundation for their really impactful work in the field of peripheral neuropathy, both research, education and, you know, in supporting us as faculty.

3:36
So today I'll be talking on small fiber pawley neuropathy or small fiber neuropathy testing, clinical evaluation and research.

3:45
And this is a area that I think is now really well appreciated in the general medical community, community appreciated amongst patients as well.

3:55
And it's unique in that it is a type of neuropathy that is not detectable on EMG or nerve conduction testing. So we'll kind of talk a lot about many different aspects of small fiber neuropathy today, and hopefully leave you with pearls that you can take into your clinical evaluation, you know, as well as be aware of research advances in the field.

4:24
So our objectives for today are to address somatic and autonomic casting modalities and small fiber neuropathy evaluation S F and for short, appreciate the differential diagnostic considerations and recognize various applications of small fiber testing, especially in the research space.

4:45
And just to let the audience know, there will be 20 minutes at the end for Q and A This talk should take about 40 minutes all in all.

4:53
So, what are we going to talk about today?

4:56
So, why this is important, looking at different fiber anatomy, print testing modalities that look at somatic and autonomic fibers by somatic. We're simply referring to fibers that control.

5:08
Uh, sensation, So specifically with small fibers, it's in terms of temperature and pain sensation.

5:16
Autonomic fibers are a different fiber type.

5:20
That really pertains more to what I call automatic functions. So your blood pressure, your heart rate, your sexual functioning, those sorts of things, and there is some overlap with small fiber optic.

5:32
Talk about certain typical presentations of small fiber and then interesting applications, there's a fair amount of research going on and areas of interest.

5:43
So why is objective testing important?

5:46
And this is something that I as a peripheral nerve Specialist deal a lot with which is do you have small fiber neuropathy or not when your EMG is normal?

5:56
And while EMG is easy or large fiber not is easy to capture on EMG, small fiber can be trickier.

6:06
And so it often comes up you know, do I fibromyalgia, do I have small fiber neuropathy what do I have?

6:14
And small fiber neuropathy by definition is when patients have early small fiber involvement that is preferentially present or preferentially defines the disease course and so patients who have large Fiber Involvement might have balance problems, weakness.

6:35
Small fiber patients, usually do not have those symptoms, they don't typically have, balance, or weakness issues. Their vibration and position, sentence testing is normal.

6:47
It's really just predominantly a dysfunction of pain, as well as temperature. Perception so cold and heat perception. But why is it important?

7:00
Not only can it precedes small. large fiber involvement.

7:05

So it can be a warning sign of large fiber injury later down the road, but it's also reversible. OK, and I'll talk about that later today. Again, it can be reversible. Not all types are reversible, but it is much more reversible than large fiber.

7:19
Um, and it also, when we test for it and show that there is objective evidence of small fiber involvement, We can beyond a shadow of a doubt know that there is small fiber injury and separate that from patients that might have what we call central pain disorders. No problems with pain perception. So fibromyalgia, what's called central pain syndrome, or ... which are both equally debilitating but are different disorders.

7:51
That's core. Good history and exam should uncover small fiber neuropathy.

7:58
This is a little bit technical but I'd like the audience to be aware that there are different fiber types when we as neurologist's approach neuropathy starting from the largest to the smallest or the beta fibers, the delta fibers see somatic fibers.

8:18
As you'll notice, beta are large in ..., meaning they are covered in an insulation the myelin.

8:26
They conduct rather fast.

8:27
These fibers control vibration at position sense.

8:32
A delta fibers are small and myelinate, they also have the installation, and they perceive cold temperature. And they conduct about 20 meters per second.

8:43
At the very bottom, we have what are called C somatic fibers and these are small myelination meaning they do not have the installation based conduct.

8:51
Heat or temperature sensation, specifically thermal heat assumption and these conduct the slowest.

8:59
So when we are testing for small fiber neuropathy, we are typically looking.

9:09
Is small ... fibers the C somatic fibers on skin biopsy which I'll talk about later.

9:17
A beta is picked up usually on EMG testing and then the C somatic are really the fibers of interest.

9:26
When we're looking at a small fiber on skin biopsy, it is important to realize that even though small fibers are small fiber neuropathy involves small fibers.

9:37

They are not insignificant by any means, as you'll note, from this, right here.

9:44
Most of our fibers are small diameter, most, so two thirds of any human being fibers are two thirds of myelinate at fibers, small diameter, meaning for every three ... fibers, two out of those three are a delta fibers.

10:01
Also, the ... needed to myelinate at ratio is about 4 to 1.

10:05
So out of every five fibers or are going to be C somatic.

10:12
OK, so our nervous system is predominantly small fiber, peripheral nervous system.

10:21
I wanted to make a point because this is a point of confusion sometimes that you do also see autonomic fibers, but these are part of your autonomic nervous system.

10:31
And these, without getting into too much technical detail controls, what function, these are tested on what's called a ..., or Q Sweat machine, which is part of the dynamic testing. And that's kind of the only point I wanted to make from this slide.

10:46
So let's focus this first section on somatic sensory testing.

10:50
Again by somatic, I'm referring two fibers that control sensation as opposed to autonomic fibers.

10:57
So these are ways that we can look at small fiber integrity and function.

11:04
Start with Corneille Confocal Microscopy.

11:06
So this is a modality that is still, not by any means, a gold standard. It is mainly used in the research setting.

11:13
but I wanted to bring it up because it is an interesting modality in which, um, samples of the cornea are looked at under this specialized, uh, No confocal microscope, essentially, to evaluate for the density of these skin fiber or the small fiber endings.

11:38
And has been shown that these fibers are specifically in the sub bazel nerve plexus of the cornea OK, so, this is an in vivo measure meaning it's done.

11:54
In the tissue itself, it does not involve an extraction or a biopsy in which the sample is taken out.

12:01
Has fehr accuracy.

12:04
Most experts in the field, who specialize in sort of small fiber neuropathy testing and evaluation would certainly say it's not as good as as intra epidermal nerve fiber density or skin biopsy, but it has some potential benefit.

12:20
And it seems to track improvement in diabetic patients in certain settings. But this is mainly a research application.

12:28
Skin biopsy, which we'll dedicate the majority of our talk of our testing portion today on. It's really the gold standard, and it involves this three mm biopsy.

12:39
That's done at different sites where you actually get visualized image under the microscope of the density of of small fiber and nerve endings and so, for example, can be here on the right. You can see a greater density of, of, of arc.

12:56
Essentially, it is fiber bugs or endings, terminating in the press.

13:01
Here on the left. And a there's not as much so this would show reduce density.

13:05
So, for example, taking a diabetic patient you can imagine given the stocking, love distribution of nerve damage and diabetes, you'll have more dropout in a length dependent patient, still the us, compared to higher up in the thigh.

13:23
So as we said, the successes, somatic C fibers, recall the ones that see thermal sensation or heat.

13:32
And these are different from the autonomic small fibers, which terminate in your sweat glands.

13:39
Or blood vessels can do a different site. So you can do the still lag. You can do the Stall thigh or you can do the proximal thigh.

13:49
And these are just three commonly used standardized locations that have some normative data. The best normative data we have is for the distal leg.

14:00
But most of us, or most centers will do at least 2 or 3 sites, sort of look for a pattern, OK?

14:09
These fibers, once they're collected and processed, are stained with Hispanics, tunnel marker protein, look at the fiber density.

14:20
Here's an illustration of what is seen under the microscope in terms of a normal healthy mount of terminal fibers in the epidermis, on the left.

14:31

Then, on the right, you have a normal thigh and a normal calf and then a diabetic thigh and a diabetic. So a couple of observations.

14:39
Density does seem to dropout most most patients in the normal in the in the thighs compared to the calf, even in healthy, normal subjects.

14:47
And that is factored in when we're looking at normal densities.

14:52
No surprise, diabetics have a reduction in these fiber endings compared to normal healthy controls.

14:58
So this is an important to be aware of that Skin biopsy is currently the best and gold standard for diagnosing small fiber neuropathy object.

15:11
Moving on to other modalities. These are testing modalities that are probably going to show up mainly in research settings, they are not as used.

15:21
As widely in the clinical setting but are still worth discussing.

15:25
Quantitative, sensory testing, or Q S T, is used in clinical setting settings in certain institutions, like the Mayo Clinic, for example, but it's not nearly as widely used as skin biopsy.

15:38
And essentially what happens is, um, you are applying a certain stimulus, it could be heat, it could be cold, it could be vibration, and noting when the patient first picks up this sensation. So it's a threshold testing.

15:58
And it's been shown to be helpful when looking at small fiber neuropathy diabetic's at capturing early diabetic, small fiber injury.

16:07
Distinguishing painful from non painful, small fiber narok fee and distinguishing healthy patients from those with small fiber.

16:15
The challenge is there's lack of consensus on stimulus application location and sensations testing, sensations test it in terms of making it standard, universally.

16:27
But I will say that this is a very valuable adjunct and certain countries, for example, in Germany, where they have a very good standardized consortium for testing like this. It could be used more widely. But in the US, for example, most academic centers, I would say, for most centers, in general, don't use it. Some do.

16:48
It's still a valuable adjunct.

16:51
Just skin biopsy evaluation.

16:54
There are other tests that are certainly not nearly as widely used. I just wanted to bring these up in case you come across them.

17:01
They might have a little bit more of a commercial application, but they've still been studied and still have some value. So I would not discount these but they're just not as widely used.

17:10
So the neuron emitter, same idea but it uses sort of a current instead of a temperature or heat sensation.

17:19
And it selectively stimulates different fiber types and uses sort of similar principles to kind of, you know, for perception testing.

17:31
Neuro quick is similar in the sense that, again, you're using threshold testing, but it is specific to cold perception threshold.

17:41
So the patient notice is when they first perceive that cold airflow.

17:46
So as you can imagine, if it's cold, it's going to stimulate those a delta fibers.

17:53
There is also what's called a narrow path or plaster test, again, not as widely used, but still studied and has some value, this looks at the autonomic C fibers.

18:05
So if you recall, the autonomic C fibers are looking at your sweat and the fiber, the autonomic fibers that control your sweat and blood vessel controls.

18:16
So this looks at the fibers that control your sweat function.

18:20
And if you have normal sweat function should change color.

18:24
If it doesn't change color, it tells you there's damage to those small ... fibers that controls one. And this can be used as a surrogate of small fiber.

18:36
There's something called a pseudo scan.

18:37
So, the pseudo scan is also something that has looked at sort of point of care testing.

18:44

It's an electrochemical conductance test, essentially, um, know, where the subject places there are palms and soles on a, on a preset sort of insertion sites.

18:56
And essentially applies the slow voltage constant electrical current, and essentially measures conductance. And this is another measure using the sweat function.

19:08
But again, I would say that these tests are valuable, They have clinical and research application, but not as well validated or standardized as skin biopsy.

19:19
Skin biopsy is the gold standard of objective, small fiber testing.

19:25
As we said, and alluded to autonomic testing, often overlaps with small fiber testing and can be used as a corollary to evaluate for small fiber sensory loss.

19:35
And specifically, here, we're talking about the autonomic reflex screen, specifically, the Q star or quantitative pseudo, motor axonal reflex test.

19:45
So I just wanted to point out that ... reflex testing is used in many labs across the country, we do it.

19:53
Here at Michigan, Madison, and most institutions, I think, are most states, I should say, will have at least one lab, um, and this looks at different fiber tags. So, small fiber or sweat fibers, cardiac vigo fibers, ... fibers.

20:08
But we are specifically interested and Q Start testing.

20:12
Thermal regulatory, sweat testing, which is used in certain number of institutions across the country, not as many as another valuable modality, which looks at your sweat glands, sweat, fibers, and can thus also look at small fiber injury.

20:27
So the sweat test, or Q start essentially is based off of this concept of what's called a pseudo motor acts on reflex not getting too technical.

20:38
Testing sites will apply, settle coleen gel over a patch of skin in a multi compartment capsule.

20:45
Current is run through using this sort of naturally built in reflex that our bodies have.

20:53
That's what Glen picks up acetylcholine, an instance, sweat gland starts to sweat.

20:59
So you're actually measuring the swept volume produced from an essence, sweat gland.

21:03
And this can tell you out of those small C, autonomic fibers are doing. But by extension those small fibers that are also somatic typically get also involved.

21:15
You can use this to look at a pattern.

21:17
So for example, in this subject the foot is not sweating that much the distal like a little bit more ..., like a little bit more of the forum normal.

21:25
So this is what's called a length dependent pattern, which would also mimic love dependent pattern on your exam or a length dependent pattern on your skin bias.

21:36
Thermo Regulatory, sweat just as I said, is, is sort of used at a few centers, not as many and essentially applies this indicator powder over a subject and it says them inside this heated enclave and the percentage or total body surface area of spots that are not affected.

21:56
We'll show you sort of the pattern of small fiber involvement, so in this subject, for example, had an upper body is not sweating.

22:05
You can imagine if you're a diabetic with length dependence to what dysfunction that feed won't sweat as well.

22:10
So another useful test, but not as widely available.

22:18
This can show you, dependent patterns of small fiber like diabetes, read from, allowed Jeff Fabry, disease or length independent patterns, sjogren's the perennial plastic or leprosy, amongst others.

22:33
I just wanted to include a couple of slides on research that's been done, looking at autonomic impairment.

22:39
Painful neuropathy.

22:40
So this is a, again, skin biopsy is the gold standard, but autonomic testing has been well validated in evaluating for small fiber neuropathy.

22:49
So this is from Ohio State Group basically practiced and essentially looked at 92 subjects and found those with painful neuropathy, half of the abnormal, half with normal nerve conduction studies and showed that they had a fair amount of autonomic impairment, autonomic testing. So about 72% have sort of normality, 63% of cardiac bagel.

23:16

42% ortho static hypotension and there was a fair relation between Q start and skin biopsy testing with those who had abnormal nerve studies having more severe autonomic changes.

23:26
So, sort of pearl number two, if I had to say one was, autonomic impairment often goes hand in hand with small fiber neuron, So that is a valuable sort of finding that might assist patient evaluation and might be worth evaluating for other reasons that we'll discuss.

23:49
So it's from the Mayo Clinic group and looked at about 125 patients with distal small fiber neuropathy per nerve studies or history, and basically looked at the prevalence, um, Q star or Thermo regulatory swept testing abnormality, which was seen in about 93%.

24:08
You start showed a length dependent pattern in about 62%.

24:13
And, as you can see, the vast majority of these patients, Interestingly, 125 we're idiopathic.

24:24
So as I'm sure many of you might might know, or might have heard, it is a great frustration for patients to be told at the end of multiple visits and multiple evaluations, that we don't know what's causing your neuropathy.

24:40
But I don't want you to let that frustrate you, because you are not alone.

24:46
Despite sometimes the best testing and the best devaluations, a very big chunk of patients can still have idiopathic not, I wouldn't say, as high as 73%. probably closer to.

24:58
maybe a third to 40% still have a clear cause, and that's OK.

25:05
Speaking of, let's talk about the causes of small fiber neuropathy, that we know.

25:10
So this is a nice review from the early two thousands, that looked at small fiber neuropathy, looked at various causes. I highlighted some that are probably more important.

25:22
I shouldn't say more important, but more that come up more often, I think, in discussions, certainly, sjogren's is really important.

25:31
We'll talk about that, Malloy Dose. This is a hot topic these days with now three FDA approved.

25:40
Fabrice and hereditary sensory neuropathy. These are important because fabrice has a treatment available.

25:48
..., Sensory Autonomic neuropathy, these now are valuable, they are the subject of, no drug trials, and, and might be valuable.

25:57
But I think they, I bring them up here because they're often not as, it's a screen for as aggressively, but might be worth keeping in mind in the differential. But they are rare disorders.

26:11
So common things being common, and again, this is something that I can't stress enough, Common things are common.

26:20
Make sure you get a good word prep for common things before you pursue an extravagant workup for uncommon. Things.

26:26
So not rocket science, diabetes, diabetes, diabetes, and pre-diabetes are huge.

26:35
Alcohol and timing deficiency are really important to think about, and I think or Underdiagnosed, I tell all my patients, I'm not judging you, it's not a guilt trip, it's just a matter of possibilities So you don't have to be dependent or abusive to possibly have alcohol related neuropathy.

26:57
How much is too much?

26:58
I don't think anyone really knows, but I tell patients, if you're having a couple of glasses each night or most makes the week for 20, 30 years, it might be worth considering as a possibility.

27:10
B 12 deficiency, Gus monoclonal come up with heap, undetermined significance, and then chemotherapy.

27:19
So, I beat diabetic neuropathy and pre diabetic Neuropathy are really important, I'm not gonna go into too much about the diagnostic criteria other than to say, A one C alone is not enough.

27:31
You should probably have at least a fasting blood sugar at some point in time.

27:35
Or a two hour glucose tolerance test at some point in time.

27:38
Using these cutoffs listed here are labeled as either a diabetic or a pre-diabetic impaired fasting glucose for 100.

27:51
Renders you are pre-diabetic an impaired glucose tolerance test of over 140, which is the two hour glucose tolerance test.

27:59
Author Unders you're pre-diabetic.

28:01
Once you hit fasting over 126 or 2 hour over 200, that is a frank diabetic.

28:07
So this notion that my A one C is under 6.5. It excludes diabetes is a false notion.

28:13
It is not 100% sensitive.

28:15
So I always tell patients you should probably get a fasting or two hour test at some point.

28:23
What do we do for diabetic neuropathy?

28:25
Well, there's a lot of emerging data as I'll talk about later on the role of moderate intensity, aerobic exercise, or high interval in high intensity interval training.

28:36
The key numbers I tell my patients are 30 minutes a day or 60 minutes, three times a week.

28:41
Could be rowing, could be biking, could be swimming, could be walking.

28:46
From work that's been done here at Michigan Medicine by Doctors EBA Feldman and Brian Callahan amongst others in the field nationally.

28:55
Glycemic control is certainly important for type one diabetic diabetics, but not as impactful for type for type two diabetics.

29:03
So, for type two diabetics, really the emphasis is on controlling those metabolic syndrome risk factors, exercise, diet, weight control.

29:13
Amongst others, I often recommend Alpha ...

29:16
acid 600 milligrams once a day, even though the trials did not meet FDA approval, but there were some trends towards possible benefit.

29:26
one Pearl is that patients who are on metformin for Type two diabetes have been shown in some studies Metformin to be associated.

29:34
The B 12 Deficiency?

29:36
So, just be aware to get your B 12 packages, especially if you're on Metformin pain management, of course.

29:45
Can Diabetic over correction cause neuropathy? Absolutely.

29:49

So if you drop your A one C level more than 2% points over three months, you can cause treatment induced neuropathy or diabetes or what's called Tend.

30:00
And this can happen about 2 to 6 weeks after the Glycaemic over correction, and it can be length dependent or independent.

30:07
Just to step back for a moment length dependent simply means that your pattern of nerve injury isn't a stocking glove distribution. So it starts from the tips of your toes works its way up.

30:20
Fingertips works its way up.

30:22
Length independent is when it is patchy and does not respect that principle.

30:27
So you might have damage in your hands.

30:31
Your left hand and your right hand and your left foot your face.

30:34
Even that is what is meant by length, independent, does not follow that stocking distribution that answer.

30:44
What about chemotherapy induced neuropathy? This is a big problem, very painful, often leads to change in chemo regimens.

30:51
If the pain is too severe, it can occur immediately sub acutely or chronically after exposure.

30:58
Certain drugs have stronger associations. Certain drugs are more dose dependent.

31:03
The good news is most are sensory related.

31:06
They don't lead to motor deficits, meaning, typically, you don't develop weakness from the came up, but it does happen with some drugs, and depending on the severity, if they're off with you, the oncologist may choose to switch the chemo, but I always tell my patients, don't let the side effect tail wag the dog.

31:26
So, treating the cancer still takes precedence over the side effects, but if the side effects become so severe, then it may be worth considering an alternate drug.

31:41
B 12 deficiency is very important.

31:44

Most patients don't realize. it can give you peripheral nerve but also spinal cord damage, OK? So this is what's called majella neuropathy when you infect the spinal cord and the peripheral nerve if it affects just the peripheral nerve, it's called ... neuropathy.

31:58
How do you know if a patient has spinal cord while you test the reflexes that their needs and their risk?

32:04
Possibly, amongst other findings, they might have bladder dysfunction they might have spasticity 12 can also give you systemic signs of deficiency.

32:15
So confusion or memory loss, depression, vision loss, and might have dryness of your tongue or other deficits throughout.

32:26
So some patients, you might want to have brain or cervical spine imaging persued as well.

32:35
This is a really important point.

32:38
Again, I think another really important pearl or take home is that, yes, in the U S a 200 cutoff is used as deficiency, but I've seen patients with values at 250, 290 for a baleen who've had gastric bypass surgery to have clear signs of B 12 deficiency, be told, that their B 12 is normal.

33:03
So just have a bit of a flexible mindset when approaching this topic. In Europe, they use a cutoff of 400, which I prefer.

33:12
I'm not saying, I'm right and other doctors around, but I'd just like to be a little bit more flexible in diagnosing B 12 because I think it's under diagnosed and can lead to major damage as we said.

33:25
Certain populations are higher risk, Alcoholics, vegans, those who've had very ... surgery.

33:32
Notice we have mal absorption from pernicious anemia or inflammatory bowel disease.

33:37
Meant for many users and Anorexic or ...

33:40
treatment is a bit of a personal decision.

33:45
I personally put all my patients on 2000 micrograms daily of B 12 oral.

33:51
And then I also supplement with intra-muscular for at least a year. Yeah.

33:55

This is not a gold standard, this is not No the one and only treatment, that's just my personal practice choice based off of my training.

34:05
They have deficiency.

34:07
I'm worried about B 12, who I am, and oral for a year together, and then continue them on oral afterwards.

34:14
I am regimen that I use as daily for a week, weekly for a month and then monthly for a year about a thousand micrograms.

34:21
But everyone is different so just be aware that this is something, no patients, doctors are going to treat them.

34:30
Alcohol and timing is really important.

34:32
There is no good way to know how much is too much cage questionnaire, Which we are taught to use to look for, alcohol abuse, or dependence is really not a very sensitive measure.

34:43
So you might want to look for subtle cue. So if there's magnesium, or phosphorous deficiency, borderline 12, you know, chronic, daily use, you might want to consider treatment.

34:55
... test is helpful but not always accurate.

34:58
So I just often go ahead and counsel patients to try to cut down on their consumption and to take 100 milligrams daily of one and timing deficiency as what 12 can affect their organs.

35:10
It can give you more specific voice can now be present and patients in underdeveloped parts of the world and can lead to what's called wet very, very where they have congestive heart failure.

35:23
The US, I've only seen it severe enough to cause hospitalization when patients have had bariatric surgery, significant weight loss: significant, mal absorption, and then they go in with significant P one related complications, but most outpatients it's really quite mild Worth thinking about.

35:45
Common, but important causes that we'll talk about our show grandes, more doses eight, then just be aware that hereditary sensory autonomic neuropathy are also important in the small fiber fiber appealed amongst other conditions.

36:01
We're running a bit short on time, and I wanted to go through the slides, so bear with me.

36:04

It's going to be a little bit of a, a whirlwind here, but this was a study that was done, I believe, in the early two thousands, that looked at small fiber presentation.

36:16
And this was kind of helpful and most patients out of this cohort of 32 have the chronic progressive length dependent pattern.

36:25
While small minority had an acute generalized hypersensitivity, OK, the point that was made here is that skin biopsy testing was able to capture that some patients had greater reduction distillates compared to approximately.

36:42
Those were the ones that were length dependent.

36:45
The typical majority of patients, but a subset have, quote, reduction, their thigh and the distal like and these are what are called length, independent and length independent.

36:55
Like I said, it means it's affecting sites in Apache fashion, OK, and it tends to be more autoimmune related.

37:05
This was a separate study that identified 68 patients with pure small fiber neuropathy to 41% of patients did not have a clear awes at two year follow-up.

37:17
About a quarter of those, it was determined what cause was.

37:21
So you're still left with about 30 to 40% of patients on average not having it lior cause of their neuropathy.

37:28
Small fiber winds.

37:30
So, it's a small slide, but it's just showing that no, out of 125 patients, for example, 67 had small fiber neuropathy.

37:41
Of those you identified the majority had diabetes or diabetes or ...

37:47
monoclonal mathy.

37:49
Sylvia about funny. It not have a pause.

37:54
So that's a big chunk of those patients, and do your follow ups still?

37:57
2628 did not have a clear call, so that is what we call cryptogenic or idiopathic neuropathy.

38:05
... is really common.

38:07
I always ask about, and I always look forward, especially in patients that have dry eyes or dry mouth, are sick as symptoms, and should always be considered.

38:19
Any patient who has a length independent pattern should always be screened for chevrons and I always tell my patients, even if you don't have dry eyes and dry mouth.

38:31
This is another study looking at a non length dependent pattern of neuropathy. And it basically showed that the most common diagnosis was ....

38:40
How do you go about diagnosing sjogren while that lab testing is not the most sensitive?

38:45
We often will do what's called a minor lift salivary gland biopsy which N T or rheumatology can do.

38:53
Predatory amyloidosis is really important.

38:57
It involves production of a mutated protein.

39:00
Other TTR protein, this is different from AL or acquired light chain.

39:05
Amyloidosis, it is now commercially test.

39:09
It's available commercially through free genetic testing.

39:13
And what's really nice is there's two and now three, FDA approved therapies that are in modifying.

39:21
You should ask about if you have this genetically confirmed amyloid neuropathy because it will actually not only stabilize, but reverse the disease course.

39:35
Predatory Sensory autonomic.

39:36
Neuropathy is another topic of interest and this is just publication about no family members that might have it.

39:44

So I'm sorry for the smallness of the slide but there's five major subtypes, and you want to ask about foot ulcers are on deformities or hearing loss, or symptoms like lack of tearing or lack of sweating in infancy and that should really raise concern.

40:00
I think we don't do a very good job. At least I don't always screening for it.

40:05
But something to think about if you have an genital onset neuropathy.

40:11
Um, now we're at the 40 minute mark, so Lindsay or Tonya, if we want to do a hard stop now, certainly let me know, or I can maybe talk for another 5 to 10 minutes. But please cut me off if we're need to do a hard stop.

40:26
Yeah. Why don't you keep going? I think we can have five more minutes. This is great.

40:31
Perfect.

40:32
So I wanted to touch in the remaining part here on some, some interesting applications, then some aspects about pain management. I know you're all waiting to hear about it.

40:43
So I just wanted talk about metabolic syndrome, which is this constellation of features That's circumference, high triglycerides, low HDL, high blood pressure, obeys that fasting blood sugar, You have to have three out of those five to have metabolic syndrome.

40:59
So, another take home Perle, I want everyone to know, as you do not have to have Frank diabetes or even pre-diabetes, to have neuropathy.

41:07
You can have neuropathy just from metabolic syndrome, and again this is something that it has been proven really quite substantially through the work of doctor Brian Callaghan Hiba Feldman. others across the country have really shown this association quite strongly.

41:24
This was a study done here at Michigan Medicine a while ago, which really has been followed with many other studies showing that patients who had pre diabetic neuropathy, or had metabolic syndrome, which often go hand in hand, have their intrepid thermal nerve fiber densities improved or stabilized through exercise.

41:47
It's really cool.

41:50
And these are just showing that the nerve fiber densities at follow-up showed stabilization or improvement. So these small fibers are really quite robust and regenerative, and quite hard, in terms of being able to come back.

42:03

This is a study that was just published from our Center.

42:09
Brian was Lead Investigator which showed that I carry weight loss in people with severe obesity, stabilizes neuropathy and improve symptoms.

42:18
So again, so the 131 patients, they had dietary weight loss of kilos.

42:26
Will aspects of their metabolic syndrome improved except for blood pressure?

42:30
Nerve fiber densities at, to your follow-up stabilized, which is actually an improvement because natural history shows decline over time.

42:39
So for patients who are obese, severely obese, this is an, might be an effective intervention as to pursue weight loss dietary.

42:51
There's actually a study going on right now from our center, which just did recruitment, which is looking, which I'm involved in, the investigator looking, and Brian is sort of leading the study, looking at high intensity interval training, as well as very ettrick weight loss in four different arms, OK.

43:09
So, together, surgery alone, High intensity interval Training alone, or neither on small fiber neuropathy function.

43:20
I intensity interval training is basically form of exercise in which you have short periods of extremely demanding physical activity, alternating with less intense activity.

43:31
So just keep your eyes peeled for the role of weight loss through diet and surgery on the future of small fiber neuropathy.

43:39
Op spin was a study I was involved in, both at Ohio State and here at Michigan, Madison, which looked at ..., which is a weight loss drug.

43:47
Unfortunately, did not mean its primary endpoint. We sometimes still used to pyramid for pain control on the basis of a 2005 study. And the authors did find that it might improve quality of life, but I think the data's still not published. But the primary endpoint was not. Unfortunately.

44:08
... is an interesting area where you have red, hot, painful, extremities, provoked with heat, relieved with removal of heat.

44:19
And this is just a point I wanted to make that they actually are a subset of small fiber neuropathy that have both vascular apathy or vascular dysfunction and neuropathy or nerve dysfunction.

44:32
Again, this was done at the Mayo just showing what I just said.

44:35
Fibromyalgia is an area of great debate. I was just involved in a study. A small group setting a single center study looking at this.

44:43
Can we distinguish patients who have fibromyalgia alone, from those that have fibromyalgia and small fiber neuropathy on the basis of symptoms alone? And the answer is, no.

44:54
So, symptoms alone do not distinguish patients that have fibro and small fiber from those that have fibro alone.

45:05
If you do a certain nerve fiber, a certain nerve test.

45:11
The I believe it's the medial plantar did seem to be affected more than those that had superimposed small fiber neuropathy and those did seem to have more glucose dysregulation.

45:21
But, in general, symptoms alone did not distinguish.

45:25
So, in the last, just give me two more minutes, and I'll wrap up here about pain management.

45:31
It's a huge topic, and the point here is you want to go class by class gabba ...

45:40
and then sodium channel blockers, these have been codified in the American Academy of Neurology pain. A diabetic neuropathy pain guidelines that were recently published.

45:50
So the general idea is, Start low, go slow, give each drug at least eight weeks before you call it a failure.

45:57
set expectations.

45:57
We might not be able to take the pain away completely, but we try to reduce it ideally by about 50%.

46:04
Then find out what the side effect is. Can you actually reduce the drug to remove side effect, or do you have to toss it out completely? Make sure there's no drug drug interactions, because that's another big problem.

46:16
So I usually personally start with ...

46:19

so pregabalin or gabapentin you want it again, start low.

46:24
Go slow, can increase in weekly increments or every three days to your target dose, which can be 600 B times a day sum up to 900.

46:35
Rarely go up to 1203 times a day.

46:40
Pregabalin is a good option, but it tends to be a little bit more costly.

46:45
The second class, the tri cyclic anti-depressants you have nor tripling or Amitriptyline, I'm biased towards nor tripling.

46:52
Because the side effect profile was less than amitriptyline Make sure there's no drug drug interaction that can cause QT prolongation.

47:00
It's a really good option for those with insomnia and migraines.

47:05
Third class is ..., so these are things like ..., again, July occitan usually 30 a day per week than 60 daily thereafter. And you can go up to 60 twice a day.

47:19
And ... is favored in the extended release form.

47:24
Again, you want to give drugs at least eight weeks, 6 to 8 weeks at maximal dose before you call it a failure.

47:31
And, fourth, I want to really bring your attention to another Pearl, or Take. Home point is mixed. ...

47:35
is a really good underuse drunk.

47:38
Most patients that have come to me that I've seen, you know, 3, 4, or five different neurologist's. Sometimes.

47:44
I'll often be surprised that no one ever thought of mixed Philippine and it works very well.

47:49
It's a sodium channel blocker initially developed for arrhythmias or heart Rhythm problems. But we use it very works really well for pain.

47:58
It's one of the final EKG.

48:00

Then you start again low and go slow. So 150 at night, or a week, 150, twice a day, and then 153 times a day.

48:10
Other drugs that I'll mention, I can't go into too much detail for time, but to pyramid might be helpful, Might for pain. I've had good success with it. But you want to monitor for kidney stones.

48:21
Sorry.

48:22
Then oxcart base a pin as well as carbamazepine are two other ones, but you have to monitor for low sodium and ... gene.

48:32
You want to monitor for Stevens Johnson Syndrome, which is quite rare?

48:37
Yeah, Summary.

48:39
Make sure there's a good history, good exam.

48:41
Corroborate that with good objective testing. If possible, skin biopsy is not absolutely necessary but if you want to get a test, it should probably be skin biopsy.

48:51
Go through the common things first, and then look at the uncommon things.

48:55
If its length independent, definitely think of show Grins, then recognize that you can sometimes also have large fiber involvement, but it's still small fiber predominant.

49:07
OK, with that, I'd like to thank you for your attention and an open it up to questions, and I apologize Lindsay and Tanya for going over, no, no apology needed, This is fantastic. We did receive a million different questions, so apologies to all of those that were not going to be able to get at this current session, but we will try our best to follow up. So you listed a gamut of drugs and also other kind of lifestyle changes that people can undertake to kind of help improve their symptoms.

49:38
And one of the questions that came in that we hear all too much is when drugs and physical therapy, and diet, and other types of treatments, like, spinal cord stimulators, acupuncture, when all of that doesn't help relieve the pain, what should a patient do? What's the next step?

49:57
Other than give up, because at the end of the day, there's always hope that there can be something that can help relieve it mm. Yeah, that's a common problem in a really good question. Hopefully, I'll help other patients on the call, too.

50:09

So, I see a lot of patients who are told they have small fiber neuropathy or peripheral neuropathy who actually have pinched nerve roots in their low back. So lumbar radicchio off if it is a really common problem.

50:25
that people I don't know why, because somehow someone put the label neuropathy.

50:32
No one thinks to look at the low back.

50:34
And the low back is a huge source of foot pain that you have to think about because it doesn't always causes low back pain and sciatica.

50:43
It can just be foot pain or distal leg pain.

50:48
But what you want to think about is, is it asymmetric? Is there a history of low back discomfort? Is their history? So definitely think about an MRI of the low back.

50:58
And I would just say no to get a new set of opinions.

51:04
So if things are just not working, seeing a specialist, or peripheral nerve specialist, or a pain specialist always helps, because not everyone does spinal cord stimulation with the same quality, not everyone does physical therapy with the same quality. And not everyone manages with the drugs the second.

51:19
So, I've had a lot of patients where they'll try a drug for two weeks, or a month, and they say it doesn't help, and they weren't tried for two months, for example, so there's a lot of nuances there.

51:31
Yeah, and I think, as you had mentioned, also, towards the end of your presentation as well, I think 6 to 8 weeks is typically the standard bar of trying something new before you give up, hope that it hasn't helped, because it takes that long for your body to respond.

51:46
Absolutely.

51:48
So do you know off hand, and this might be an impossible question so apologies for putting you on the spot, but do you know what percentage of the population who has small fiber peripheral neuropathy has a mild case versus a severe case? I mean are we 50, 50?

52:05
Or what what what, what are your thoughts on that?

52:10
Yeah.

52:10

I think the main the way to sort of stratify severity for small fibers really be by pain, and so if I were to look at painless versus painful, um, I think that, again, this is just a guesstimate from my experience managing over the years. I would say that.

52:28
Um, probably when you're dealing with small fiber, there's going to be a higher percentage of pain compared to just all comers with large fiber as well.

52:38
So I would say it's probably skewed towards 75% being painful and then 25% might be painless. most have some pain.

52:47
Out of the 75% that have pain, I would say probably two thirds are at least moderate to severe and then a third half have might have mild pain.

52:56
But, yeah, I mean, it's it's a debilitating condition, because I think, like most patients are going to have at least moderately severe pain.

53:06
Yeah.

53:07
And has there been any new or recent advancements? Or even future hope for stem cell treatments in the field of neuropathy or small fiber neuropathy specifically?

53:18
Yeah, so I think the simple, the short answer is not currently, but I know that there's a lot of active research going on with gene therapy.

53:27
Hopefully, we've reached a point when we can sort of optimize the pharmacogenomics, John Genomics of it, so you can get a sense of who has a certain mutation or pain profile, and give them a targeted drug.

53:41
But stem cells, I don't know if it's gonna be accepted by all patients, because it's a little bit of overkill for some. I mean, I wouldn't say it's overkill for pain pain. It's certainly debilitating, but it might not be.

53:54
It might be a little bit too invasive for some patients.

53:56
So, I think, I think it's hopefully going to be a Farmer Cajon Genomic approach where you can tell what the profile is and go straight to that drug rather than trying 4 or 5 people.

54:08
And what are your thoughts about IVIG, specifically for idiopathic patients, obviously you might have a different answer for all the different types of causes of neuropathy's but we have a lot of idiopathic patients, obviously, their cause is unknown. They try a lot of different treatments. Is IVIG, something that you think could be an option?

54:31
Um, so, I think it kind of goes back to that issue of, of the appropriateness of the treatment for the complaint.

54:40
So, I have used ...

54:44
in select patients who have not only small fiber neuropathy, but debilitating autonomic neuropathy so, severe gastroparesis or slowing of their gut or severe ortho static hypotension. But, I have to say for just small fiber neuropathy alone, I don't use IVIG.

55:04
Because, IVIG carries risks of clotting, it's very costly. Patients pay a lot out of pocket.

55:12
And from a from a just efficiency economy standpoint, it's more about finding the right lock and key pain management fits. I try to really optimize the pain, the nerve Pain Medicines, rather than do IVIG.

55:25
Great.

55:26
And you had mentioned at the start of this, and I'm not going to quote you, so if I say something wrong, please correct me about, you know, reversing some forms of neuropathy or perhaps even curing neuropathy. Could you comment, I know that's a very big question. And depending on the length of time we have, we might have time for another one, but could you comment on that.

55:51
Yeah, so, so these small, the nice thing about small fiber nerves as they're very regenerative, so, that kinda, kinda, makes them ideal for research studies.

56:02
So exercise, for example, in small, sort of, non randomized control studies has been shown to improve nerve fiber density at the end as soon as sometimes as soon as 10 weeks.

56:18
Um, I think that we'll see what comes of the current study that Brian's running Bryan Callahan on surgery and high intensity interval training on does it actually reverse it, or is it just stabilizing it?

56:33
We've seen that dietary weight loss stabilizes the drop off.

56:37
Um, but I will also say that and hereditary amyloid those two new FDA approved therapies.

56:45
Some of the outcome measures, now, I don't believe they were skin biopsy based, but it did show not only stabilization but improvement in disease burden.

56:58
So, I think it's very plausible that you can reach a point when you can go.

57:04
I don't know if we can go back to baseline, but go pretty close to baseline, if properly treated, because these nerves have a really good ability to regenerate And last question, which is kind of the big picture research future question.

57:22
Do you have any thoughts on what might be in the pipeline in the future, whether it's treatments, more answers, more more research findings, Is there a specific niche where you're seeing a little bit more quicker results than others maybe?

57:41
So I think that, um, diabetic pre-diabetic And metabolic syndrome neuropathy, I think the paradigm is going to definitely change.

57:52
where if I were to guess, I think that the sort of what, whether it's high intensity interval training or certain exercise will be prescribed like a drug or stabilizing or reversing neuropathy.

58:05
So again, maybe in our minds, we sometimes dismiss exercise.

58:09
It's not, you know, a cool drug or whatever, but it's there, it seems to be, at least from the data we have, quite effective. So I think that that should become more standardized for diabetic pre-diabetic metabolic syndrome patients.

58:22
For amyloid, I think there's a lot already there.

58:26
I think for ..., which I touched on briefly again, whatever, you have a specific diagnosis that will really help sort of the research element.

58:35
But again, pain is front and center the biggest problem for patients with small fiber.

58:41
And I think that there's a lot of work being done on fino typing or genotyping pane profiles and knowing what drug works for them.

58:53
And right now, it's basically just trial and error.

58:57
We have no idea who's going to respond to gabapentin or deluxe a team. Or we just try. And and that can really be a problem for patients if you're waiting years, before you get good pain.

59:09
Right? I think spinal cord stimulation is also exciting. There was a trial that was done, that did show some Promise, but it hasn't really been standardized, or a universally adopted, for refractory pain.

59:20

But that's something that I didn't talk about, but I've used that through the pain clinics for pain management, but I think, yeah. I think pain will really evolve in a ... for small fibers.

59:32
Now, and that's and that's promising. And I think, you know, at the end of the day, that's kind of what the Foundation is here for as well. We're a resource where we have connections to, to you, and a lot of other of our scientific advisors, and researchers and medical experts experts in the field, where you guys have questions about a specific treatment option. We can at least tell you if it's a possibility.

59:56
But at the end of the day, we always encourage everyone to seek specific personalized medical consultation with within your own spectrum, just because nothing is working for everybody right now. There is no one cure or one answer. But I think that there are a lot of different options out there. And hopefully, one, or at least a mix of various ones, will at least improve the quality of life. And that's, that's the goal at the moment, but tomorrow is another day. So we're hopeful, as well.

1:00:27
Well, with that, thank you. We, unfortunately, ran out of time. This was an amazing topic and amazing presentation. As I said, I'm very sorry that we weren't able to get to all of the questions that were raised throughout and even before this session even started, but we will try our best to do as much follow up as we can.

1:00:47
Um, we will be, again, highlighting this webinar on our website, so, recording will be uploaded by tomorrow. So, if anyone wants to rewatch or get a transcript of this, or similarly gain access to the power side, PowerPoint slides, excuse me, all of that will be provided. And, again, we, again, we just, we appreciate everyone just joining these types of programs. They're really fantastic, and, it really allows us an opportunity to get our patients in front of experts like yourself. So, thank you for, for participating with us as well.

1:01:23
Thank you, Lindsey. And if you do want to afford many of the questions to, like, I Can be Happy to answer those and get back to you as well, so well. Thank you. We, we might take you up on that one! So be careful what you ask, but know that. That would be really appreciate it. Thank you so much. Awesome. Thank you all. Again, Thank you everyone for joining, and hope you have a good rest of your day. And if you need anything, just let us know.

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