

Transcript of RELIEF podcast with Anne Louise Oaklander:

RELIEF: Hello everyone, thanks for tuning in to RELIEF's podcast series. I'm Neil Andrews, editor of RELIEF. I'm thrilled today to have the opportunity to speak with Anne Louise Oaklander. Dr. Oaklander is Associate Professor of Neurology at Harvard Medical School and Associate in Neurology and Assistant in Pathology at Massachusetts General Hospital in Boston. Dr. Oaklander is also director of the Massachusetts General Hospital Nerve Unit, which is a lab that studies peripheral nerve problems. She is an internationally recognized expert for her discoveries in many, many areas of pain research, including small-fiber polyneuropathy, which is the focus of today's podcast. Dr. Oaklander, welcome to the podcast. Thanks so much for being here.

Anne Louise Oaklander: Thank you very much, Neil, for having me, and I say that with sincerity because, as you know, I think that RELIEF and other similar organizations that are trying to get research messages out to other colleagues and to the public are playing a critical role in this area. We need more people to learn about small-fiber polyneuropathy. So thank you for giving me the opportunity to help with that.

RELIEF: What is small-fiber polyneuropathy?

Anne Louise Oaklander: Well, that's the key question. Most people are saying that—what is it? They've never heard of it. The other name that it's known by is small-fiber neuropathy; the two are used interchangeably, and it's a specific kind of peripheral neuropathy or polyneuropathy. Polyneuropathy or peripheral neuropathy just means neurologic diseases that are affecting the peripheral nerves that run through our body, as opposed to our brain or spinal cord. These peripheral nerves are cables, like those that run under the street, and they carry a mixture of different kinds of neurons, which have different functions. Different diseases affect those different axons. So small-fiber neuropathy means the diseases that specifically or mostly target the small-fiber neurons or nerve cells.

RELIEF: What are the symptoms of this condition?

Anne Louise Oaklander: Small fibers are very thin unmyelinated nerve fibers or thinly myelinated A deltas. The unmyelinated ones are known as C fibers. And this is evolutionarily among the oldest type of neuron before our bodies and our nervous systems got to be as sophisticated as they are now. Because they evolved a long time ago, these primitive nerve cells actually have a bunch of different functions, not just one. And I think that's the root of the difficulty with this kind of disease—that these nerve cells having several functions. When you get small-fiber neuropathies, different patients have different symptoms or mixtures of different symptoms. And therefore, it's not so clear what the diagnosis is.

We're very interested in the question of what the symptoms are of small-fiber neuropathy. If you asked a doctor, they would say that the most common symptoms are tingling or reduced sensation or pain that's most often felt in the longest axons, the ones

that start in the feet. But what we're finding is that when you ask patients who have this what their symptoms are, they give a very different picture. We actually have a manuscript that's under review right now that surveyed almost 200 patients with small-fiber polyneuropathy, to ask them what their most common and most severe symptoms were. To our complete surprise, what patients rated as the most severe symptom was actually fatigue or tiredness, with number two being reduced endurance or strength for activities, and number three being difficulty with thinking, concentrating, or remembering. They did report, about 90%, having tingling or pins and needles, [a symptom] that neurologists [are aware of]. But the point is that we haven't really looked at the symptoms before in a comprehensive patient-centered way, and now that we're doing so, I think our definition of what the symptoms are is likely to change a bit.

I'm looking at our list, and it's got literally 25 or 30 different symptoms on it, but let me mention the ones that are reported by 50% or more of the patients; we'll say those are the most common. And again, just to be clear, we surveyed patients who had proven small-fiber neuropathy on the basis of skin biopsies, autonomic function testing, or nerve biopsies, and those are the tests that we're going to discuss next.

These were people who had the condition, and they reported a variety of symptoms, among which I already mentioned the very most common ones, but others were feeling dizzy or faint when standing up— about 75%. That's called orthostatic hypotension. [There were] headaches in about 70%, and gastrointestinal problems were very common, also in 60 or 70%, including feelings of being quickly full or bloated after meals, weight loss, diarrhea, constipation, or alternating, which is known sometimes as irritable bowel. Others report changes in sweating patterns, and about half report difficulty emptying their bladder. So again, a larger range of symptoms than we had previously recognized.

RELIEF: How is small-fiber neuropathy diagnosed?

Anne Louise Oaklander: That sounds like a simple question, but it's actually more complicated than you think, because the problem right now is that there is not yet what is called a case definition and diagnostic criteria for small-fiber polyneuropathy. So there are no standards that are used around the world to make sure that different hospitals and different doctors are diagnosing patients the same way all around the world or even from one side of the street to the other. This is the big problem, and because of this, my group is actually grant funded to work with neuropathy experts from all around the world to try and develop that very first case definition and diagnostic criteria.

I will mention our website, which is neuropathycommons.org. I know you're familiar with the site, Neil, but others may not be. In addition to providing information to patients about small-fiber neuropathy, this [site] also lists the leading neuropathy experts around the whole world, and there're about two dozen who are working with us to develop the case definition and diagnostic criteria. We're not yet finished, so I can't give you the final answer, but what I can say is that looking at the information that these experts have entered, the test that every single one of them recommends is a test that involves a very small skin biopsy that's performed under local anesthesia from the lower leg. [The biopsy

is] sent to a specialized lab, such as ours at Mass General, to immunolabel the nerve endings, the small fiber nerve endings in the skin, and count them and compare them to what is expected to be there. So the experts recommended that as the most important test for diagnosing small-fiber neuropathy.

RELIEF: Now that we've talked about what small-fiber neuropathy is, what the symptoms are, and how it's diagnosed, can you talk a little bit about causes? What are the causes of small-fiber neuropathy?

Anne Louise Oaklander: I think that's the 64 million dollar question. Other people might be saying, why bother having this test, skin biopsy, or they used to even do nerve biopsies to diagnosis this. I mean, what's the point? The point is that if you do have small-fiber neuropathy, what we recommend next is looking into what the underlying cause is in *you*. Small-fiber neuropathy just means that your small-fiber neurons are damaged, malfunctioning, and firing when they shouldn't, and ultimately degenerating. But it doesn't tell you what the cause is. There are any number of causes that can produce this.

It's like asking, what is the cause of cough? Well, the way you treat a cough depends entirely on what the cause is in *you*. Somebody who has a cough that's caused by asthma is going to be treated entirely differently than someone who has a cough that's caused by pneumonia, tuberculosis, or a lung tumor. So you hit the heart of it, Neil. The heart of it is that if you do get diagnosed with neuropathy, your doctor should next look very carefully into what the specific cause of this is in *you*. And there are about 15 or so causes that have been published by various authors around the world as potential causes of small-fiber neuropathy.

What our group has done is developed a list of recommended blood tests, because that's the way most of these causes are identified. And that list of blood tests is also available for free to the public on our Neuropathy Commons website. We also have looked into about 200 patients of our own to try and get our own data about what the cause is, but before I mention that, I want to make clear that the most important cause of small-fiber neuropathy in the US and in other developed countries is actually diabetes. Diabetes damages nerves; it damages blood vessels. The high glucose levels that these patients have for many hours of the day are tremendously damaging to the nerves. So that's the most common cause, here at least. In other parts of the world, leprosy is a common cause, or HIV may be a common cause. So again, the causes vary very much depending on who the person is and where they live and what they do. Alcohol abuse, for instance, is a cause.

I think the heart of that question, though, is, what is the cause in people who don't have a known underlying cause? And what I mean by that is that if a person develops neuropathy symptoms, but let's say they're a cancer patient getting chemotherapy, well, then the cause is obvious in that person. It's going to be the chemotherapy, which is very well known to be toxic. Or again, if a person is a diabetic, and they get neuropathy symptoms, it's going to be clear that this is a diabetic cause of their neuropathy. So the

much more difficult question is, what is the cause of neuropathy, small-fiber neuropathy, in patients who don't have a clear-cut cause? That's known as, initially idiopathic small-fiber neuropathy, meaning at the beginning, neither the patient nor the doctor are clear on what the cause might be. For patients such as that, a panel of blood tests is recommended, and again, this is a panel that is available for patient use on our website.

[There is] data from 200 of the patients that I evaluated here at MGH, and again, these are patients who have the small-fiber neuropathy diagnosis confirmed by objective testing, so these are definite cases. To our surprise, we found actually that diabetes or prediabetes, which is also known as impaired glucose tolerance, were actually not common causes of neuropathy. Fewer patients turned out to have this than they're found in the general public in the US; a quarter to a third of the population may have unrecognized impaired blood sugar or diabetes, and it was not a higher percentage among the neuropathy patients. So we did not find undiagnosed diabetes to be a major factor. I think that's because I work in Boston where there's excellent medical care, and so the majority of people who do have diabetes are already aware of it. I think the situation is very different in other parts of the world and even in other parts of the country. There's a paper published from Utah, for instance, where they found that undiagnosed diabetes or undiagnosed prediabetes is a common cause of initially idiopathic small-fiber neuropathy.

I just want to mention what the most common causes were in our group, because they're not exactly what you would think. The most common blood test abnormalities in our group were actually high erythrocyte sedimentation rate, also known as ESR, the presence of antinuclear antibody, also known as ANA, low complement levels, and markers for Sjögren's syndrome and celiac [disease]; [these] were all far more common in our idiopathic neuropathy patients than in the [general] population. Taken together, I think what this suggests is that autoimmune and inflammatory conditions, such as Sjögren's [syndrome] or celiac [disease] or rheumatoid arthritis, are probably more common causes of small-fiber neuropathy than we currently are aware of.

RELIEF: If a patient receives a diagnosis of small-fiber neuropathy, can it be treated?

Anne Louise Oaklander: My answer is a wholehearted, yes, yes, yes! And again, that's why it's so important for each person diagnosed with neuropathy to find out what the cause is in *them*—because effective treatment depends entirely on treating the cause in individual patients. For instance, if the cause does turn out to be diabetes, then the best treatment for that person may not be painkillers, not that I have anything against them, but ultimately in the long run, the most effective treatment is going to be to get rid of their diabetes. And that's very much a realistic possibility for patients who have type 2 diabetes. In many or most of them, the cause is related to being overweight and other lifestyle factors that can be addressed in several ways. So I would give you the unconventional answer that the best treatment or the most effective treatment overall for diabetic neuropathy could very well end up being gastric bypass or other treatments to reduce excess weight.

On the other hand, if it turns out that the cause of your neuropathy is that you have celiac disease and are not aware of it, then the best treatment for your neuropathy is probably going to be to go on a gluten-free diet. And one of the reasons why I've become so interested in autoimmune causes of small-fiber neuropathy is because, again, the evidence [is] suggesting that this is a more common cause than currently appreciated, but also it's eminently treatable. There are so many immunotherapies that have been developed to treat other types of autoimmune neuropathies and other autoimmune conditions, [so] patients who have autoimmune causes of neuropathy have very realistic prospects for disease-modifying or potentially curative treatments.

RELIEF: That is encouraging. In the second part of our podcast, let's shift a little bit to talk about fibromyalgia, which, of course, is a condition that many people struggle with. The way it relates to our discussion is [that there is] evidence emerging that small-fiber neuropathy may play a role in certain pain conditions like fibromyalgia, whose causes have remained unclear. What is fibromyalgia, and how have doctors and researchers thought about it historically in terms of its causes?

Anne Louise Oaklander: You're asking all the right questions. The reason why fibromyalgia is so pertinent to a discussion of small-fiber neuropathy is that many of those symptoms that I mentioned to you above that are coming out as symptoms of small-fiber polyneuropathy are also symptoms of fibromyalgia. Remember I told you that fatigue and reduced endurance is the most common symptoms that patients complain of, as well as chronic widespread pain, both on the surface of their skin and within, [as well as] difficulty thinking [and] concentrating. This equally describes fibromyalgia.

So fibromyalgia is a syndrome. I'm going to spend a minute on this because I think it's a very important point. A syndrome is a collection of symptoms that is common enough to get recognized by doctors as a distinct clinical entity—and fibromyalgia is one of those. Fibromyalgia, in fact, turns out to be hugely common, and epidemiologic studies have shown that it affects anywhere from 1 to 5% of the population of countries all around the world. So that's a staggeringly common medical condition. But, it is a condition.

The problem with the condition, and the problem that fibromyalgia has had so far, is that, as you mentioned, there's really been no information about what the underlying cause might be. In fact, [there is also a lack of information about] what cells are involved, and where the damage comes from. Because of that—because of that lack of information—unfortunately in the past, a lot of fibromyalgia was attributed to psychological causes or neurosis. I can understand how that came about. A lot of patients who have these kinds of chronic debilitating conditions do become depressed or anxious, and so I think that the depression and anxiety have more recently been shown to be consequences of the fibromyalgia or the chronic pain. But in the past, I think doctors may have assumed that the depression or the anxiety somehow brought the patient to make up or exaggerate symptoms, including chronic pain and fatigue. Fortunately, more recent studies have shown that's dead wrong.

Another reason that might have played into this is that fibromyalgia is far more common in women. Women make up about 75 to 80% of fibromyalgia patients around the world. In contrast, physicians historically have been 75 to 80% men. And so perhaps there might have been some tendency to think that these women were somehow psychologically predisposed to this. The problem with attributing something to psychological causes is that [it] leaves you with psychiatric treatment as the main thing you can offer to patients. Now I'm a big fan of psychiatric treatment, and I offer this readily to my patients who need it, and I've certainly even sought it out myself when needed. But unfortunately, it doesn't address underlying non-psychiatric causes. And what's been coming out in research is that there's quite a bit of overlap between small-fiber neuropathy and fibromyalgia.

RELIEF: Could you describe some of your studies that look at the issue of the presence of small-fiber neuropathy in adults with fibromyalgia?

Anne Louise Oaklander: Let me start with our pediatric study, because that was really the first study that we published on this and what got us into thinking about fibromyalgia.

This 2013 study, which I published with Max Klein, with whom I work at Mass General, was published in the journal *Pediatrics*, and the title of it is "Evidence of Small-Fiber Polyneuropathy in Unexplained Juvenile Onset Widespread Pain Syndromes." We studied patients who had fibromyalgia and similar syndromes who had the onset of their illness before the age of 21. I'm not a pediatrician, but I have to say in retrospect, that turned out to be a wonderful cohort, the youngest patients to look at. The reason is that, using the objective tests for neuropathy that we mentioned above—skin biopsy, nerve biopsy, and autonomic function testing—we were able to diagnose definite small-fiber neuropathy in 59% among this group, out of 41 patients, and probable neuropathy in another 17%. So the vast majority of this cohort of 41 young patients who had fibromyalgia or similar labels ended up having objective evidence of small-fiber polyneuropathy.

I've got to tell you, we had a hard time getting this published because what we were saying was so unusual, that we had identified an objective test for a neurologic disease that might be the cause of symptoms. Because fibromyalgia was the most important or the most common label that these young patients had, we decided to do as a next step a more rigorous prospective study, meaning we recruited people, not patients. We recruited members of the public by advertisements to the public, who had this label of fibromyalgia. And for the next study, we included adults, not just younger people.

We also really bent over backwards to make sure that these people really truly had fibromyalgia. So we applied the American College of Rheumatology diagnostic criteria for fibromyalgia. And, we made any subject submit a note from their doctor to attest to the fact that they really, truly did have this label of fibromyalgia. What that study showed was even more unexpected. It showed evidence that 41% of these card-carrying fibromyalgia patients had skin biopsies that diagnosed them with small-fiber polyneuropathy.

We didn't want to rely just on the skin biopsies. We felt it was very important to look at patient symptoms and to look at their neurologic exams as well. And so we applied validated questionnaires for symptoms of small-fiber neuropathy and also a validated examination, the Utah Early Neuropathy Scale, to these patients. And not only the skin biopsies, but the exam for neuropathy and the questionnaire for neuropathy, all showed that small-fiber neuropathy was present undetected among the patients with fibromyalgia at much higher levels than in control subjects. So this was a prospective controlled study that provided very hard evidence that almost half of patients with fibromyalgia met the best available diagnostic criteria for small-fiber [neuropathy].

Again, [we had] difficulty getting this published, because I think there have been so many papers purporting to find different causes of these syndromes, [so] the journals have become a little bit wary about this. But there was a very interesting development, which is that the same kinds of studies started coming in from other labs as well. In 2013, there were also very strong studies from the lab of Claudia Sommer in Germany, and the group of Jordi Serra. These are independent groups—I didn't know they were working on this, [and] they didn't know I was working on it. They used different methods than we used. They studied different groups of people. But all three of these studies came to the same conclusion, which is that there was considerable overlap between fibromyalgia and small-fiber polyneuropathy.

I should mention that since 2013, there's actually been about a dozen more followup studies. And indeed, this has been of interest to the press. *Scientific American Mind* published an article about this, which I think has been translated into other languages around the world, looking at the implications of these findings, since fibromyalgia is so very, very common.

RELIEF: It's great to see the progress in trying to find the underlying basis for fibromyalgia and answering some of the questions that people have had. Speaking of questions, what are the most important questions that remain in terms of understanding the role of small-fiber neuropathy in pain conditions, whether it's fibromyalgia or other pain conditions?

Anne Louise Oaklander: I think that small-fiber polyneuropathy is extraordinarily common and probably becoming more and more common as more people develop diabetes, or are treated with cancer chemotherapy, or have HIV; even the treatments used for HIV can cause it. So small-fiber neuropathy really needs to become part of common medical awareness and also part of the public's awareness so that patients can seek help. Chronic pain is one of the most common symptoms of small-fiber neuropathy, and it's horribly debilitating. I think for that reason we need to define more clearly which are the chronic pain conditions that may have a substantial contribution from small-fiber neuropathy so that we can quickly diagnose those patients, do the right test to figure out the cause, and get them sent off to more effective treatments than just pain relievers.

I think that the discovery of small-fiber neuropathy underlying some of these conditions also has implications for the rest of the chronic pain patients who will turn out not to have

small-fiber neuropathy—who test negative for it. The reason is is that there's no one cause of chronic pain in all patients. It's a mixture of causes in different patients. I think by siphoning out the patients who do have neuropathy, it will also help the remaining patients, who after all appear to be the majority. 60% of the fibromyalgia patients studied do not appear to have small-fiber polyneuropathy. But we think that pulling out the 40% is going to help the remaining 60%, because once those with small-fiber polyneuropathy are pulled out of the mix, and researchers are able to go back and look at the other 60%, we are really hoping that this will allow other underlying causes to emerge more clearly, once we simplify the mix. Then those patients who may have completely different conditions, [such as] rheumatoid arthritis, or dermatomyositis, for instance, will more easily get the correct diagnosis and the correct treatment for them.

RELIEF: It seems like you're very optimistic that progress is being made and will continue to be made on these questions. Is that accurate?

Anne Louise Oaklander: Yes—there's been tremendous scientific progress made; it's continuing to be made. Our group has a number of federally-funded research grants to study small-fiber polyneuropathy. We're even beginning to consider moving into clinical trials for small-fiber neuropathy, which have really not been done outside of the context of diabetic neuropathy. So patients do need to hang on, and the landscape is evolving.

But I'd like to end by asking your listeners to consider what they might be able to do to help progress advance even more rapidly. Again, I think we scientists are actually doing quite a good job in research labs around the world at making these advances. The bottleneck right now as I see it is actually disseminating this information to other physicians and other medical specialties, and also disseminating it to the public. So science journalists such as you, Neil, I think are just carrying the torch right now, playing the critical role. And I hope that if any of your listeners can think of any connections that they might have to other writers, to authors, to people who might spread the information about neuropathy, that really is what's critically missing right now. There's no patient support organization. There's no fundraising organization. So we really need [those] who are affected by this or who know people who are affected by it to step up and partner with the physicians and with the scientists in the way they have for other better-known diseases.

RELIEF: That's a great note to end on. Dr. Oaklander, thank you so much for being here today. It's really been wonderful to speak with you, and I know I am and our audience is really looking forward to following your research in this area to see what the future brings. So thank you so much.

Anne Louise Oaklander: And thanks again to you, Neil, thanks to RELIEF, and thanks to all your listeners.