Update on Diabetic Neuropathy – Speakers' Panel

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Question: I was quite interested to see your remarks on axonal atrophy, because in the animal literature, axonal atrophy is well recognized. Yet, axonal atrophy is not well recognized in diabetic patients. I wondered if you could comment on that?

Dr. Anders Sima: It is certainly very difficult to identify axonal atrophy, particularly in human diabetic nerves, unless you have age-matched control nerve biopsies to examine. Certainly, there are situations in human diabetic neuropathy in which neuropathy affects mainly small-sized fibers. In these situations, there may be a relatively greater loss of smaller fibers than of larger fibers. Consequently, if axonal atrophy is determined from the average of nerve fibers, the value may be skewed by the presence of more large fibers. So I think it is very important to subclassify the fibers that are measured, at an early stage, before too much regeneration has taken place. The most accurate way to determine axonal atrophy is by calculating axonal area over myelin thickness expressed as the number of myelin lamellae.

Question: If the hypothesis is that the axoglial dysjunction is a prominent pathological finding, how would you expect this to be reflected in different patterns of electrical abnormalities?

Dr. Anders Sima: Under controlled conditions in the animal model, early events are paranodal swelling, causing inactivation of the sodium pump, and sodium accumulation but without structural abnormalities. I'm sure that this is a pure metabolic abnormality. It leads to conduction block in large, myelinated fibers, when they are examined in single-fiber, voltage-clamp studies. Using the same technique axoglial dysjunction is associated with decreased Na^+-permeability and subthreshold Na^+ currents at the node.

Dr. Eva Feldman: What you might expect as a result of failures occurring at all nodes is that the fiber does not conduct the action potential. Perhaps the small improvement in conduction velocity that we see early, within three to six months, is because of recovery of various nodes that allows improved function. However, I think the pathology of the human nerve is primarily that of fiber loss, which is more important than the nodal abnormalities. Regardless of these nodal abnormalities, the primary event is loss of neural fibers, producing associated electrical changes (loss of amplitude with secondary slowing of conduction velocity). Quite some years ago it was reported that you could see improvements in nerve conduction velocity of 5 to 10 m/sec in diabetic patients. I have not seen this level of improvement in my patients. However, I would assume that some of these patients had primarily nodal abnormalities that were reversible. In the usual human situation, you see loss of nerve fibers more than nodal abnormalities as reflected by the electrical studies.

Question: You showed several different potential causes of diabetic neuropathy. Do you have an opinion as to which one might be most important in the pathogenesis of diabetic neuropathy?

Dr. Anders Sima: It is certainly very difficult to say. I think the more recent studies that are looking into blood flow and oxygen tension within the endoneurium are very interesting. However, I wonder whether alterations in blood flow or oxygen tension can be directly responsible for axonal loss, because if you look at these nerves from a structural point of view at that early stage, there is no axonal loss. It may be that the effect of hypoxemia is similar to that of hyperglycemia; in effect, accumulated hypoxemia, with or without hyperglycemia, may produce effects that lead to progressive axonal loss. It may be very difficult to discriminate between these two mechanisms, other than to look at different models of diabetic neuropathy. For instance, a hypoxemic and galactosemic model may be studied to determine if synergistic or additive effects are occurring. Our knowledge is rapidly progressing as we learn more and more about the vascular story, which I think is more functional than structural, at least at an early stage of the disease. Recent results on capillary closure indicate that this mechanism may not be so important to the pathogenesis of diabetic neuropathy. I think what happens metabolically is much more interesting than are the effects on the endothelial cells. I think some interesting developments regarding the pathogenesis of diabetic neuropathy are ahead of us.

Question: In that experiment you showed, it was interesting that, in the presence of an ARI (aldose reductase inhibitor), there seemed to be an improvement that one would expect to see with euglycemia. So, did you try ARI's in the controls?

Dr. Anders Sima: We were involved with Dr. Yagihashi in an *in vivo* study, where we treated control animals with an ARI. And indeed there was a significant, although small, increase in the frequency of regenerating fibers compared with nontreated controls. This is an interesting concept, because it raises the question as to whether this represents a separate effect of ARI's in addition to their effects on the polyol pathway.

Dr. Eva Feldman: Dr. Bril, did you average the sural nerve amplitudes on those regression analyses that you showed? And do you routinely do that?

Dr. Vera Bril: They were averaged and we routinely average sural amplitudes. When responses are in the 1- or 2-microvolt range, I don't think you can do sural responses accurately without averaging. Having done many nerve conduction studies and having observed the manner in which a noisy baseline provides a

very high amplitude on one sweep, and then half the amplitude or less on the very next sweep, I find it inaccurate and misleading to do these measurements without averaging the sensory potentials. Although this statement is particularly apt in a patient population, the value of averaging applies to a normal population.

Question: In the data you presented on tolrestat, the change in nerve conduction velocity was about 1 m/sec. Are there any other pharmacologic agents that will produce that magnitude of change in nerve conduction other than tight insulin control?

Dr. Vera Bril: Other treatments for diabetic neuropathy have shown promising effects in preliminary studies. A multicenter study from Italy using acetyl-L-carnitine (Alcar) in a group of diabetic patients showed similar results, but the preliminary results from this study have not been replicated yet. Previously, various other pharmacologic agents have shown promising preliminary findings, but these results have not borne up with repeated studies. For example, gangliosides worked well in Italy but were ineffective in North America. Alcar has shown positive effects in early studies, but these results need to be confirmed. So there are treatments for diabetic neuropathy, other than ARI's. However, it is likely that tolrestat will be the first agent to become clinically available. The current study will show correlations of structure with function and perhaps some clinical changes. It will be finished next year. The results from this study will be available far in advance of other trials using ARI's or other agents.

I think everyone would agree that euglycemia is the optimal therapy for diabetic complications. Everyone should have as goals euglycemic control, the prevention of diabetes, and the complete cure of diabetes. I challenge Dr. Boulton and all diabetologists to improve diabetic control in their patient population. In fact, whenever diabetic patients are referred to me for problematic diabetic neuropathy, I send them back to the diabetologist, with the famous words, "Improve their glycemic control". However, we all know that euglycemia is not easy to accomplish and in fact is very difficult to achieve. Consider that the most stringent efforts to achieve optimal control as in the Diabetes Control and Complications Trial (DCCT) are labor-intensive, costly, and difficult to implement and even then do not achieve an average normal glycated hemoglobin for even half of the patients. Despite the outstanding efforts by the DCCT, a sizable proportion of patients in both treatment arms still developed neuropathy.

In summary, I think the future is very optimistic for pharmacological interventions in diabetic neuropathy. The most promising area seems to be metabolic intervention to protect the nerve from hyperglycemia or the metabolic consequences of hyperglycemia, using ARI's or other new agents such as Alcar.

Dr. Vera Bril: I attended the American Diabetes Association presentation of results from the DCCT and recall that Dr. Douglas Greene presented data showing that patients who had neuropathy or evidence of neuropathy at baseline were excluded from this analysis. I think as many as 39% of patients on entry had some abnormality indicative of neuropathy. Can you comment on the effect of excluding these patients on the results of the DCCT?

Dr. Eva Feldman: That was true for the nerve conduction studies, although I don't know if that included patients with abnormal clinical exams. At baseline, patients who had more than two abnormal nerve conductions were excluded from the DCCT. I did not elaborate on that point because I don't know if there were patients in the DCCT who had an abnormal neurologic examination but fewer than two abnormal nerve conductions. I don't know if those patients were maintained in the cohort for the DCCT.

Dr. Vera Bril: I had the impression that this cohort of patients was excluded, which would indicate that the prevalence of neuropathy in this particular population was quite strong.

Question: I have a question about footwear. What do you do before you make custom-built shoes? Is there a special type of shoe that you recommend, or do you use the classic leather shoe?

Dr. Andrew Boulton: That is a good question, because we talk about the science of footwear design. However, it is not a science, but rather an art. We are only now entering the days of proper, computerized design and manufacture of footwear.

For most patients, the training shoe is very good, cosmetically attractive, and acceptable to the patient. In most patients, an excellent pair of shoes with protective hosiery constitutes good training footwear. A custom-designed pair of shoes can cost £300 to £400, or nearly $1,000. And we need to be sure that custom-designed shoes are really needed, because the extra-depth shoes cost only about $150 to $200. I believe that most patients can be fitted with the extra-depth shoe, which gives more room for claw toes and room for an insole.

For those who need custom-designed shoes, production is still done manually by creating a mold of the foot. But, we are slowly moving forward. I was speaking just last Saturday at the Foot Council of the American Diabetes Association, and I indicated to the audience that good in-shoe pressure measurement devices are now coming onto the market. I'm sure that these devices will have a major impact in helping to design appropriate footwear scientifically. So, to answer the question, in most patients, extra-depth shoes or a trainer can be used rather than custom-built shoes. The design and fitting of custom-molded shoes is still an art, but by the end of the decade it should have progressed to a science.

Question: When do you use commercially available socks, should they be wool or cotton?

Dr. Andrew Boulton: Well, because the foot is usually dry, I don't think it matters that much. The sock that I referred to is a good sports-tennis sock. It is the closest to the experimental sock, which is not yet on the market. A good tennis sock protects against high pressures to the metatarsal heads. Good tennis hosiery is quite acceptable to patients because it is trendy to wear white socks and trainers.

Question: What is the cumulative risk of developing a foot ulcer over the lifetime of a diabetic patient?

Dr. Andrew Boulton: I don't think I can answer that. There are too many variables. In the patient with detectable neuropathy, the risk is about 5% per year, whereas in the patient with no detectable neuropathy, the risk is less than 1% per year. But I cannot say over a patient's lifetime, because we don't know. I am certain that there is a genetic component to the pathogenesis of neuropathy, but we do not know who is at risk until they are diagnosed. So we have to treat all as being at risk for developing neuropathy and thus assess them regularly in order to determine whether they have moved into a risk category.

Question: Could you please comment on testing sensation in the patient with diabetic neuropathy?

Dr. Andrew Boulton: We use the Weinstein monofilaments, which are available in gradings of 4, 5, and 6, corresponding to 1, 10, and 50 grams. A patient who cannot perceive grade 4 or 5 does not have normal sensation, and we put such a patient into the high risk category. This is similar to not being able to feel the vibrating 128 Hz tuning fork over the great toe, which patients find easier to judge. I think if a patient has any sensory loss, then that patient must be placed into a high-risk category. So we use a 128 Hz tuning fork or the biothesiometer. I don't think it is necessary to use all these tests, because you can spot an at-risk foot within a minute in the clinic.

Question: There may not be an easy answer to this, but when faced with an inherited form of neuropathy, do you know, relative to the diabetic population, what is the relative risk of development of an ulcer?

Dr. Andrew Boulton: I have a number of patients with leprosy, which is much more similar to diabetes. It's more global and is characterized by small-fiber neuropathy. I think that the risk is higher with larger-fiber dysfunction. And the best correlate in the first study we did was vibration perception, which was a better correlate than thermal testing. I don't think I can answer the question. But I have a feeling that the risk is much higher for diabetic patients, because they have a combination of neuropathy and Charcot arthropathy which puts them at high risk with very high foot pressures. We've never looked at any inherited sensory neuropathies, although the neurologists in Manchester are very interested in that area.

Question: Did you look at any patients with high foot pressures who were not diabetic?

Dr. Andrew Boulton: We looked at a comparable group of patients with rheumatoid disease, who had very high foot pressures—higher than the diabetic patients. Although patients with rheumatoid disease can get a neuropathy, they still have protective sensation. Not one ulcer occurred in the rheumatoid disease group. So it is not high pressure alone, but high pressure plus insensitivity that causes ulcers.

Question: One thing I don't remember from your diagram was the presence or absence of the flare response to injury. Would you comment on the correlation between the presence or absence of flare in patients with foot ulcers?

Dr. Andrew Boulton: This was described in the *Journal of the Neurological Sciences* just a few years ago. Obviously, any foot ulcer must end up being a failure of the macrovasculature. Now, the flare response, of course, is a neurological reflex. We haven't looked at the flare response ourselves, but, certainly, it does correlate with risk of foot ulcers.

There are abnormalities of macrovascular circulation, which are well described. There are present very early in type 1 diabetes. I think that these clinically undetectable, macrovascular abnormalities, together with increased pressure, lead to skin breakdown. Using laser-Doppler fluorometry, we showed that the hyperemic response was delayed in the neuropathic foot. Recovery of normal blood flow does not occur between footsteps, which probably leads to the repetitive stress and the skin breakdown.

Question: Specifically talking about the microvascular, as opposed to the macrovascular changes that occur in diabetic neuropathy, can you separate the effect of microvascular disease in the diabetic foot, as opposed to, for example, the inherited neuropathic foot from the actual effects of the neuropathy? Although you can show that there is a very strong association with neuropathy, presumably the neuropathic foot also has microvascular disease.

Dr. Andrew Boulton: There are two schools of thought. Some have suggested there is no such thing as macrovascular disease in the diabetic foot and that the cause is microvascular disease followed by blood flow abnormalities. What I think is happening is that arteriovenous shunting occurs through diseased capillaries. We've done biopsies and shown these abnormalities. For example, in small vessels in the nerve, we've seen membrane hyperplasia, obstructed lumen, platelet debris, and other changes. So it's a multifactorial effect, and you can't divorce microvascular disease from the neuropathy. I don't know how you could separate the effects, because we don't have sensitive enough techniques.

Acknowledgement

The Speakers' Panel was recorded and summarized by Dr. Anders Sima.