Leprosy and neuropathy seen from the perspective of a surgeon

A hanseníase e a neuropatia através da perspectiva de um cirurgião

Frank Duerksen[1]

Already A. Hansen[1] described in detail the nerve pathology in leprosy. The basic histologic changes in the different types of neuropathy are well documented. We still don't know what those histopathological pictures mean in relation to that nerves function. We don't even know for sure how the *Mycobacterium leprae (M. leprae)* gets into the nerve and why it likes Schwann cells so much.

Surgeons have already attempted to improve the outcome of leprosy neuropathy in the 1930's[2].

By definition, leprosy is a neurological disease. Most impairments, disabilities and handicaps that patients with leprosy have to face, are related to the neuropathy. The standard prevention of nerve damage is early diagnosis and aggressive treatment of the neuropathy with corticosteroids and multidrug treatment (MDT).

In spite of all conditions being ideal, thousands of patients are left, after cure, with permanent nerve impairment. It is well known that nerve damage occurs before, during and even after cure.

We still do not know enough about the intrinsic factors acting in leprosy neuropathy, but there are several facts that are evident. The process of nerve lesion is very different in Lepromatous leprosy (LL) as compared to Tuberculoid and different again in Borderline cases. Reactive stages like Erythema Nodosum Leprosum (ENL) and Reversal Reactions (RR) damage the nerves acutely in different ways again. Most cases of neuropathy will respond positively to corticosteroid treatment but some will progress and cause permanent nerve damage, in spite of correct medical treatment.

In non complicated Lepromatous leprosy the fine subdermal network of nerves is destroyed by the lepromatous granuloma. The result is glove and stocking type of loss of sensation, as well as sensory loss and autonomic nerve dysfunction in large areas of the body. We do not know if corticosteroids can avoid this neuropathy, but early diagnosis and MDT will prevent serious loss of nerve function.

In the nerve trunk millions of *Mycobacterium leprae* are scattered around in every compartment and layer of the nerve with initially no apparent tissue reaction from the nerve. There is usually some edema. But in time proliferation of fibroblasts will create diffuse scarring in the nerve and finally complete fibrosis and loss of all nerve function. This process may take many years to complete and is seen in almost every peripheral nerve from near the spine to periphery. There is some evidence that early MDT and long term corticosteroids may delay or prevent some nerve damage[3-11].

In Tuberculoid leprosy there is a violent reaction of the cellular immune system trying to destroy the *M. leprae*, and if present in the nerve trunk a large tuberculoid granuloma may develop[12]. Clinically there will be an enlarged nerve, sometimes with drainage of necrotic nerve tissue through a fistula in the skin. It is important to remember that initially only a small part of the nerve is affected, either one fascicle or a localized area in the epineurium. As the abscess grows, it will compress healthy fascicles, cause local ischemia and eventually spill over to other fascicles. Corticosteroids and MDT have only a preventive role but are ineffective in treatment of the abscess.

The Borderline patient is the one with the most severe and diffused neuropathy, combining high levels of cellular immunity and with diffuse fibrosis, both at increased levels of activity[13]. There is no doubt that adequate MDT and long term corticosteroids are effective in these cases but it is this group of patients that very often ends up with diffuse, severe, permanent nerve function loss in spite of receiving the best possible treatment by the most experienced clinicians[14,15].

To make matters even worse, we have the reactive stages. In ENL or type II reaction there are diffuse, localized areas of

Correspondence: Frank Duerksen, MD. Department of Surgery, Section of Orthopaedics, Health Sciences Centre, AD4 – 820 Sherbrook St. Winnipeg, MB, Canada R3A 1R9. Phone: (204) 787-2395. fduerksen@hsc.mb.ca

[1] MD. FRCS©. Associate Professor or Surgery, University of Manitoba, Winnipeg, Canada. Honorary consultant in Rehabilation to Instituto Lauro de Souza Lima – Bauru – SP. Brasil.

immune complex deposits in the nerve, causing destruction of axons and acute edema. Complete loss of nerve function can occur in a matter of days. Usually there is good response to treatment with MDT, thalidomide and corticosteroids. A complicating factor is that this type of reaction may become subintrant with less positive response to subsequent treatment. Complications from long term, high dose corticosteroids are seen in some of these patients.

In reversal reaction (RR or type 1 reaction) there is a sudden awaking of the cellular immune system with marked enlargement and edema of skin and mucosal lesions caused by tuberculoid or mixed granulomas[16,17]. Almost always several nerve trunks are also involved in this reactive process. Paralysis may happen over night. Fortunately most patients with RR respond well to treatment with corticosteroids but the process may also become subintrant. In this group of patients complications from corticosteroid treatment are also seen because of the need of high dosis and long term treatment[18,19].

In all these scenarios described severe pain is part of the picture at some stage. This pain may become very disabling[20]. But a large number of patients will not feel any pain, while their nerves are destroyed. This is known as silent neuropathy[21,22]. I would like to stress the importance of regular nerve function monitoring, at diagnosis, regularly during treatment and for 2-3 years after discharge.

Another factor common to all types of neuropathy is the presence of edema. If the nerve is already affected by the specific leprosy lesion, with axons destroyed, demyelinization with fascicles destroyed etc. and we add the factor of edema, there will be an increase of endoneural tissue pressure and subsequent occlusion of veins and eventually arteries. The end result is ischemia. The nerve tissue does not tolerate ischemia well. With edema there will be enlargement of the nerve. If there is fibrosis of the epineural (outer envelope of the nerve) this nerve enlargement will rapidly cause an internal compartment pressure increase and again: ischemia[13, 23-28].

If there is an anatomical band or constricting structure around the enlarged nerve, there will be external compression and again the end result will be ischemia.

Fibrosis of the nerve will prevent gliding and stretching with joint motion. A nerve that is stretched suffers the exact mechanism of ischemia as by compression. This is probably the explanation why the ulnar nerve is the most often affected nerve in leprosy. This nerve has to glide and stretch when flexing the elbow.

Clinically it is evident that enlarged nerves are typically compressed in specific sites of the body where an external anatomical structure does not allow expansion. So we see this in the face as the upper branch of the facial nerve crosses the zygoma, the ulnar nerve at the medial epicondyle area, the median nerve at the wrist in the carpal tunnel, the common peroneal nerve at the knee level around the neck of the fibula and the tibialis posterior nerve at the ankle in the tarsal tunnel. Each site has primary and secondary compressive structures.

Lundborg[29] in his book "Nerve Injury and Repair" writes about the double crush syndrome. When a nerve has an intrinsic pathology like diabetes or leprosy, compression of the nerve will cause a greater degree of damage. This is also true for a nerve that has pathology at different levels including reverse double crush factor. These factors are all present in leprosy neuropathy.

Looking over this dismal picture of different mechanisms of nerve damage in leprosy and with the clinical experience of so many permanently damaged nerves, surgeons have looked at the compression factor and decided to decompress nerves[30-32]. The sites of compression are well known and the surgery is usually easy and can be done will local anesthesia. A very heated debate between surgery and no surgery proponents has been present since the early 60's[33-36]. It is true as in many other areas in leprosy, that no really valid controlled trials to show the effectiveness or not of surgical decompression are available. At most it is circumstantial evidence. This is not the place to discuss all the papers published. It would take many pages. Probably the best conducted study is the one published by Ebenezer et al[37]. Most trials of treatment of Leprosy Neuropathy relied on a point system, adding sensory and motor points. An improvement of 2 points is considered significant. But clinically this might not mean much. For example improving from 0 to 2 in motor power will not produce function, but is counted the same as improving from 3 to 5, which is a very significant difference[38-40].

There is no doubt that in general nerves will improve after surgery since compression is a major factor. Pain is a symptom that is improved in almost all variations of technique. But for how long? Pain may recur later[20]. Surgery is only a brief intervention on a longterm progressing neuropathy.

To complicate matters further we find proponents of simple external decompression, of single or multiple epineurotomies and even some that attempt to free each fascicle using the operating microscope by internal neurolysis[41-44]. I would definitely not agree with this last approach because the microcirculation is destroyed and a scarred and fibrosed nerve is most often the end result, 6-8 months after the initial neurolysis.

The goal of the epineurotomy (opening longitudinally the nerve sheath or epineurium) is to decompress the closed compartment of tthe nerve trunk. Only when the fibrosis is not severe, does one see fascicles extruding. This is greatly appreciated by the surgeons. If fibrosis is intense, no evidence of release of internal pressure is seen.

With the ulnar nerve there is the question of various methods of anterior transposition and the possible ischemia in the nerve caused by the dissection needed in order to move the nerve[45-47].

Where do I stand in this minefield?

Lundborg[29] and others have compared nerve compression to nerve transection, since the localized ischemia will eventually destroy all nerve elements if the compression is strong enough and when sustained for a period long enough.

Compression is an important component in leprosy neuropathy. Surgeons can do something about nerve compression.

1. I indicate urgent surgery with wide opening of nerve abscesses. Only very gentle scraping of necrotic tissue should be done since normal compressed fascicles may be damaged by the debridement. In a nerve with a tuberculoid abscess there are usually fibers with neuropraxia degree of damage. They will recover within hours or three weeks. Some fibers may have suffered axonotmesis and will recover partially over a long period of time, probably a year. Some fibers may be completely destroyed and never recover (neurotmesis). The recovery of compressed fascicles will depend on the degree of compression and the duration.

2. In a Lepromatous patient with progressive neuropathy that does not improve after 4 weeks of medical treatment (this is arbitrary) a decompression of the affected nerve is indicated. Expected recovery is poor, since the intrinsic pathology of the nerve is great and the compression factor might be only minimal. Pain is most often relieved.

3. In Borderline patients presenting with neuropathy, even if it is not progressive, after a 4 week trial of MDT and corticosteroids (l mg x Kg of weight) and no improvement, decompression of the nerves most severely involved is indicated. I also mildly agree with surgeons that decompress all nerves.

4. Patients with ENL. If treatment with Thalidomide and corticosteroids does not control pain and/or loss of function, decompressing nerves involved with 2mg/Kg of corticosteroids coverage is indicated. This high dose of corticosteroids is necessary because there is a danger of the patient developing necrotizing ENL. Re-operations are most frequent in this group and in group 5 and are usually rewarding.

5. The same for reversal reaction (RR).

6. Tibialis Posterior Nerve (Tarsal Tunnel). This is a special situation. Often this neuropathy is silent. The result of loss of function of the tibialis posterior nerve is plantar ulcer and Charcot foot. For these reasons I agree with many colleagues that at the first signs of local pain or loss of sensation in the plantar aspect of the foot, a full decompression of the tarsal tunnel is indicated. The added benefit of improved perfusion of the foot is well known.

So far I have given strong indications for external decompression of nerves in various clinical settings in the course of the disease known as leprosy and its neuropathy.

Some surgeons perform prophylactic nerve decompression on all nerves at the time of diagnosis. No long term follow-up for this approach (as for any other) does exist to my knowledge. But knowing that in leprosy all stages of neuropathy present edema in the nerve, it makes some sense to decompress them. Especially in Borderline cases. I do not perform prophylactic nerve decompressions, but I also have no arguments against them. We have to remember that the intrinsic pathology is very complicated and significant and that we have really no way to surgically change that.

For any situation it is essential to have adequate monitoring of nerve function, a trained surgeon, good operating room conditions and proper anesthesia. This is not kitchen surgery as I have seen it done in some places.

We need urgently controlled studies to answer many questions: long term follow-up after nerve release. Is it necessary to repeat the surgery later? Will that help? Is epineurotomy helpful? Is surgery helpful during reaction? Should the ulnar nerve be transposed anteriorly if it is fibrosed? Which technique should be used? Is prophylactic surgery of any value?

I believe that Brazil is in a unique situation to conduct randomized controlled trials to answer some basic questions about treatment of Leprosy Neuropathy.

I know we have the knowledge and expertise available to answer at least the basic question in regards to the role of surgery in Leprosy Neuropathy. Many have expressed this same view, but nothing seems to get off the ground. But going further, there are still so many unanswered questions that only astute clinical and basic researches can answer. Before leprosy drowns in a sea of new and lethal viral diseases, we hope that some light is directed at the central problem in Hanseniasis and Leprosy: the neuropathy!

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