An Evaluation of Sural Nerve Biopsy in Leprosy[1]

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Sural nerve biopsy has been found to show evidence of activity in some cases of borderline and lepromatous leprosy which have been inactive by the usual criteria for several years. Though it possesses no advantage over skin biopsy in the average case, it may be useful for evaluation of a progressive neural deficit in an apparently inactive case or for study of the morphologic changes in the nerves of patients with leprosy.

The current criteria at Carville for classifying a case of leprosy as inactive have been employed for many years with essentially no change. They include 12 months of negative skin scrapings from multiple sites, followed by one or more skin biopsies negative for acid-fast bacilli, and no clinical evidence of activity such as progressive neural deficit or reaction. While these criteria may be satisfactory from a public health point of view, they are inadequate insofar as the patient's long-term prognosis is concerned for two reasons. First, relapse has often been observed at Carville and elsewhere (1) in patients with inactive borderline (intermediate) or lepromatous leprosy who for one reason or another stop taking the sulfones entirely or take them only irregularly. Occasionally it is seen even in those who, insofar as it can be ascertained, have faithfully continued such therapy prophylactically. On the other hand, some patients in the same category who stopped therapy shortly after their disease became inactive have steadfastly refused to reinstitute therapy, or take sulfones only sporadically, and are still inactive many years later. Unfortunately, no consistent clinical or histopathologic differences have been found which might distinguish these individuals from those who reactivate. Secondly, months or years after a case of leprosy appears to have become inactive we have occasionally observed development of a progressive neural deficit. Often this occurs in an area where none had existed previously and in spite of the fact that no evidence of reactivation has appeared in the skin. Since only a relatively small portion of the total skin area can be sampled by scrapings or biopsy, and the nerves are usually not evaluated at all, regions of continued low grade activity are undoubtedly missed at the time the patient's disease is declared "inactive." These areas may be the source of the problems noted above and for this reason we have begun looking for other means to evaluate the bacterial status of our patients at a time when they meet all the usual criteria of negativity.

One such approach is nerve biopsy. Nerves are usually involved early in a case of leprosy and experience at Carville over the last 20 years with nerve biopsies obtained either at autopsies, or in the course of various surgical procedures where nerves are exposed, indicates that bacilli can occasionally be found in nerves from patients whose disease has been inactive for many years. Unfortunately, most nerves are unsuitable for routine biopsy because of their relative inaccessibility or the presence of important motor or sensory fibers that would be permanently damaged by the procedure. The sural nerve, however, has been used extensively for evaluation of a number of peripheral neuropathies (2) because of its accessibility and because no major motor or sensory deficits are likely to occur as a result of the procedure.

We therefore began a series of sural nerve biopsies in leprosy patients to determine whether this offered a more sensitive criterion of negativity than routine skin scrapings and biopsy. It was, of course,

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necessary to obtain nerve segments from a number of patients with active leprosy to determine both the frequency of sural nerve involvement in the various types of leprosy and also the degree to which the activity in the nerve corresponded to that in the skin at the time of biopsy.

MATERIALS AND METHODS

Fifty-nine sural nerve biopsies were obtained over a two-year period from 53 patients, 50 of whom had either tuberculoid, borderline (intermediate) or lepromatous leprosy. Table I shows the total number of patients in each group and the activity status of their disease at the time of biopsy. In the "not leprosy" group are three patients on whom biopsy was done in the course of a diagnostic workup where leprosy was a part of the differential diagnosis. None of these was shown to have leprosy by this or other procedures, and the biopsy did not help establish a diagnosis except in a negative sense. Eleven excisions were done at autopsy on leprosy patients who died of causes not directly related to leprosy, and some of the remainder were obtained during the course of corrective foot surgery. Both sural nerves were usually obtained at autopsy. This accounts for the difference between the patient and biopsy totals. All but six of the 50 leprosy patients showed pre-existing sensory deficit in the area innervated by the sural nerve so that a segment of the nerve could be removed rather than just a fascicle as has been done by others (2). Routine biopsy was accomplished through a small incision along the posterolateral ankle under local anesthesia. The procedure involved very little morbidity, since the incisions healed readily in most cases, and no increase in the preoperative neural deficit was noted.

TABLE 1. *Diagnoses in the 53 cases under study.*

Diagnosis	Active	Inactive
Lepromatous leprosy	21	17
Borderline leprosy	2	4
Tuberculoid leprosy	0	6
Not leprosy	0	3

RESULTS

Table 2 lists the findings in the 56 sural nerve biopsies performed on leprosy patients. Here the term "active" leprosy means that skin scrapings and/or skin biopsy were still positive for acid-fast bacilli, and "inactive" leprosy refers to the patient having met the criteria for inactive disease mentioned at the beginning of this article. The average case in the latter group had been inactive for seven and a half years. Sural nerve biopsy was considered positive if acid-fast bacilli were found and negative if they were not. An infiltrate typical of the type of leprosy each patient had was also noted in all but one of the "positive" nerves, the exception being a nerve which had become fibrotic in a borderline (intermediate) case. The finding that seven of 32 cases (22%), with leprosy inactive for an average of five and a half years by the usual criteria, had positive sural nerve biopsies is of interest. The average Bacterial Index (BI) was 1.4 in the nerves obtained from these patients. The degree of activity observed in the nerves was also compared to that in the skin of all patients with active disease. Considering the 31 cases who have either "active" leprosy or a positive sural nerve biopsy, the average BI in the skin

TABLE 2. *Results of sural nerve biopsy.*

Classification	Active leprosy and positive sural biopsy	Active leprosy and negative sural biopsy	Inactive leprosy and positive sural biopsy	Inactive leprosy and negative sural biopsy
Lepromatous	18	4	5	17
Borderline	0	2	2	2
Tuberculoid	0	0	0	6

biopsies was 2.8 and in the nerves 2.9 If only the 18 cases with both "active" leprosy and a positive sural nerve biopsy are used in the calculation, the average BI was 4.1 in the skin and 4.4 in the nerves.

DISCUSSION

The results of this study indicate that leprosy bacilli can readily be found in the nerves of a significant number of leprosy patients whose disease is inactive by the usual criteria. The average BI of 1.4 in these cases, however, indicates that they are usually present in only small numbers and in most instances the bacilli were all nonsolid-staining (Morphologic Index, or MI = 0). Furthermore, there were nearly an equal number of cases (6) where the sural nerve biopsy was negative while the patient's leprosy was still active with an average BI of 2.1 found on skin biopsy. Thus, sural nerve biopsy in this group of patients has proven no more useful or reliable than our previous criteria for negativity. Whether those who have a positive nerve but negative skin biopsy are more apt to have a reactivation of their disease, or to suffer further nerve deterioration than those who had a negative nerve biopsy can only be determined after a prolonged period of observation. The relatively small number of microorganisms present in these nerves, and their presumably nonviable state (MI = 0) in most instances makes such a correlation seem unlikely, but all of these cases will be periodically reevaluated with this possibility in mind.

Though it cannot be recommended as a routine procedure, there are instances where sural nerve biopsy may be useful. If a progressive neural deficit occurs in an apparently inactive case, such biopsy may indicate whether this is due to reactivation or continued activity of the leprosy evident only in the nerve, or to progressive fibrosis of a previously damaged nerve. One of our cases did present such a problem. The patient had lepromatous leprosy, and her skin scrapings had been negative for just over a year when she stopped taking DDS although she had been advised to continue it for life. One year later she returned for a routine checkup and was noted to have increased sensory loss over the forearms though her skin was still negative on scrapings and biopsy. Her sural nerve, on the other hand, showed a typical lepromatous infiltrate with BI of 2 and an MI of 1 per cent. We recognize, of course, that the pathologic changes observed in the sural nerve could be different from that in the nerves of the arms, but in a few lepromatous cases studied at autopsy the degree of activity in the various superficial nerves was usually similar. Also of interest is the finding that the patient had no sensory loss in the area innervated by the sural nerve. Indeed, the three lepromatous cases in the group under study without sensory loss in the sural distribution all had positive sural biopsies indicating, as one might expect, that a lack of clinical involvement does not necessarily indicate an absence of infiltration in the nerve. The average BI in the nerve specimens from these three cases was 4.2 so that the lack of clinical involvement is not due only to minimal infiltration.

One result of this study has been the close correlation. between the degree of activity observed in the skin and that seen in the nerve. Even in those cases where either the nerve or skin was negative, the BI of the active segment was usually only in the 1 to 2 range, and over-all the average BI's from both sources were nearly identical as noted above. With a few major exceptions, this correlation held for each patient individually as well as the group as a whole so that the nearly identical averages are not just fortuitous and the activity in the nerve does indeed seem to mirror that in the skin.

In view of the findings in the present study, we are continuing to utilize sural nerve biopsies both for evaluation of cases with progressive neural deficits and for study of the morphologic changes accompanying nerve involvement in leprosy.

SUMMARY

Fifty-nine sural nerve biopsies have been performed on 53 patients, all but three of whom had leprosy. Though seven of 32 cases with inactive leprosy had bacteriologically positive sural nerve biopsies, the over-all findings in the nerve correlate very closely with those in the skin. Sural nerve biopsy, therefore, appears to offer no better

criteria for establishing inactivity in leprosy patients than evaluation of the skin by scrapings and biopsies as is currently done. It, however, can be useful in the evaluation of cases with inactive disease where a progressive neural deficit develops, or for study of the morphologic changes in the nerves of patients with leprosy.

Whether patients with inactive leprosy but positive nerve biopsies are more likely to have their disease clinically reactivate than those with negative nerve biopsies can be determined only after follow-up over a period of many years.

In lepromatous cases, the close correlation between the degree of activity observed in the skin and nerve biopsies seems to hold whether or not the nerve is clinically involved as evidenced by sensory loss in the area it innervates.

RESUMEN

Se tomaron 59 biopsias de nervio de pantorrilla en 53 pacientes, de los cuales todos menos tres tenían lepra. Aunque siete de 32 casos con lepra inactiva tenían biopsia de nervio de pantorrilla bacteriológicamente positiva, la mayoría de los hallazgos en nervio correspondían estrechamente con los resultados en piel. La biopsia de nervio de pantorrilla, por lo tanto, no parece ser un mejor criterio para determinar inactividad en pacientes con lepra que la evaluación de piel por medio de frotis o biopsias como se hace corrientemente. Sin embargo, puede ser útil para la evaluación de casos con enfermedad inactiva en los cuales se desarrolla un deficit neural progresivo o para el estudio de los cambios morfológicos en los nervios de pacientes con lepra.

Si los pacientes con lepra inactiva pero que presentan biopsias nerviosas positivas tienen mayores probabilidades de que su enfermedad se reactive clínicamente que los que tienen biopsias nerviosas negativas sólo se podrá determinar después de seguir estos pacientes durante un período de muchos años.

En los casos lepromatosos, la estrecha relación entre el grado de actividad observado en las biopsias de piel y nervio parece conservarse ya sea que el nervio esté o no comprometido clínicamente, compromiso que se evidencia por pérdida de la sensibilidad en el área que inerva.

RÉSUMÉ

Cinquante-neuf biopsies du nerf sural ont été pratiquées chez 53 malades dont tous, à l'exception de 3, avaient la lèpre. Malgré que sept de 32 cas souffrant de lèpre inactive aient présenté des biopsies nerveuses bactériologiquement positives au niveau du nerf sural, les observations globales au niveau des nerfs présentent une corrélation fort étroite avec les observations relevées au niveau de la peau. Dès lors, la biopsie du nerf sural ne semble pas constituer un meilleur critère pour établir l'état d'inactivité chez des malades atteints de lèpre, que l'évaluation de la peau par frottis et par biopsie telle que l'on la pratique généralement. Cette méthode peut toutefois être utile pour procéder à l'évaluation de cas présentant une maladie inactive, chez lesquels un déficit nerveux progressif se développe; elle peut également être utile pour étudier les modifications morphologiques survenant au niveau des nerfs chez les malades atteints de lèpre.

Quant à savoir si les malades prèsentant une lèpre inactive, mais avec des biopsies nerveuses positives, sont plus enclins à souffrir d'une réactivation clinique de leur maladie que les sujets avec biopsie nerveuse négative, constitue un problème qui ne pourra être résolu qu'après que la surveillance des malades ait été poursuivie pendant de nombreuses années.

Dans les cas lépromateux, la corrélation étroite notée entre le degré d'activité observée au niveau de la peau et les résultats des biopsies nerveuses semble indépendante de l'atteinte clinique du nerf, telle qu'elle peut être mise en évidence par la perte de la sensibilité dans la région inervée.

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