Motor Conduction Velocity Studies in Patients with Leprosy Reaction Treated with Thalidomide and Other Drugs[1, 2]

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Thalidomide treatment of patients suffering from leprosy reaction (LR) was introduced in 1964 ([3]). This therapy has a striking, often dramatic effect upon the neuritis of LR, as manifested by disappearance of the neuralgic pain within 24 to 48 hours and a relative decrease of the nerve swelling within five to 10 days ([4, 5, 6]). Both pain and nerve swelling are subjective indicators of nerve damage, and as such, difficult to assess and measure.

In order to evaluate the effects of various therapies upon peripheral nerve inflammation under more objective conditions, motor conduction velocity tests (MCV) were carried out at various intervals.

MATERIALS AND METHODS

Four male and two female patients with lepromatous leprosy underwent dermatologic, neurologic and MCV examinations while in LR. Their ages ranged from 19 to 55 years. The disease was detected from two to 24 years ago. All the patients were receiving sulfone therapy. They were hospitalized during the investigation.

These six patients suffered from 17 LR which were either spontaneous or a result of discontinuation of therapy. The diagnosis of LR was based on the presence of at least two of the following signs: dermalgia, erythema nodosum-like or erythema multiforme-like lesions, orchitis, iritis or iridocyclitis, myalgia, neuralgia, and neuritis of polyneuritis. The main neurologic manifestations of LR were acute pain along long peripheral nerves and swelling, mostly of the ulnar nerve. During LR, the patients received, in addition to sulfone, thalidomide, prednisone, analgesics or placebo.

Ninety-six MCV examinations were carried out at various time intervals, which were determined according to the clinical conditions (Table 1). Thirty-five MCV were performed while the patients were receiving thalidomide, 24 MCV during prednisone therapy, nine during analgesic administration and six during placebo treatment. MCV was also performed on each patient while the disease was inactive and an additional 16 examinations were carried out after the clinical signs of LR had completely disappeared. Although both the median and common peroneal nerves were also examined, the present report will deal mainly with the ulnar nerve since it exhibited the most constant signs of damage.

The technic of MCV was as follows: a coaxial needle electrode was inserted in the most distal muscle of the nerve to be examined (in this case the abductor digital quinti) and the nerve was stimulated from at least two points. The distal point was just above the medial aspect of the wrist (for the ulnar nerve) and the proximal about five centimeters above the olecranon process. The impulses were supramaximal and graded at one per second in order to avoid undue pain or discomfort. The signal and response were visually displayed on an oscilloscope provided with electronic storage, linked to a tape recorder for reproduction of results, and to a digital computer of

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TABLE 1. *Leprosy reactions and motor conduction velocity in relation to therapy.*

Therapy	No. of LR	No. of MCV
Thalidomide	6	36
Prednisone	6	24
Analgesics	3	9
Placebo	2	6
TOTAL	17	74
Inactive state	—	22[a]
TOTAL	17	96

[a] Six MCV examinations before and 16 after the leprosy reaction.

average transients for accurate, exact measurement of the delay period. In order to circumvent possible errors of technic or vacillations, 20-30 nerve stimulations were given for each test. The velocity was calculated from at least two delay (proximal and distal) periods. All the MCV examinations were carried out by the same investigator (A.M.), using the same technic. The temperature in the laboratory was kept as stable as possible, with a maximal fluctuation of 5°C which, according to Henriksen ([2]), corresponds to a variation of velocity of not more than 12 meters/second. In order to avoid any bias, the MCV investigator did not have any information about the clinical or bacteriologic status of the patient, or of the therapy. On the other hand, the clinicians were not provided with any MCV results until all the investigations were completed.

RESULTS

In each of the six leprosy patients under investigation, both ulnar nerves were examined before, during and after LR. Of the 12 ulnar nerves, nine had initially normal MCV (Fig. 1), consistently above 60.0 m/sec ([1]), while three had abnormal conduction (18, 30 and 35 m/sec. respectively) on repeated examinations (Figs. 2, 3). A variation of at least ± 5.0 m/sec. was considered necessary for the definition of either amelioration or deterioration of motor conduction (MC).

During LR, providing no therapy other than sulfones had been administered, the MC decreased markedly, and gradually, to 0-18 m/sec. within one to four days after the appearance of pain, in both the previously normal and damaged nerves. This decrease of MC was observable almost from day to day.

In LR treated with thalidomide (up to 400 mgm./day) there was an arrest of the progress of the nerve lesion in the first 24 to 48 hours; within the next one to seven days the MC showed a clear tendency to return to the pre-LR levels and, except in one case, did so within ten days. In this one case, the MC returned to the pre-LR value only after two weeks. Whenever thalidomide was continued for protracted periods of time (up to 30 months) no recurrence of LR was observed and repeated MCV showed normal values.

The LR group treated with prednisone (15-25 mgm./day) exhibited clinical and MCV arrest of the nerve lesion within four to five days the MC returned to normal values within one week in one patient and within three weeks in the other five. No deterioration of the MCV was observed for as long as the steriod therapy was continued at the same dosage.

In the three cases treated with analgesics and the two with placebo, the MC became progressively worse until a certain level was attained and then remained unchanged. A similar response was seen in the cases without any treatment. Table 2 illustrates the MCV follow-up in one case in which the two types of therapy were used.

DISCUSSION

From the neurologic point of view, nerve pain is the first sign of LR. It may be widespread, or localized along one or more of the peripheral nerves, especially the ulnar. For our studies, onset of pain was essentially considered as the beginning of the nerve lesion in LR. It is also of interest that, insofar as therapy had any effect, the pain was the first symptom to diminish and eventually disappear. The second clinical neurologic sign was swelling of the nerve trunk, or further swelling if nerve thicken-

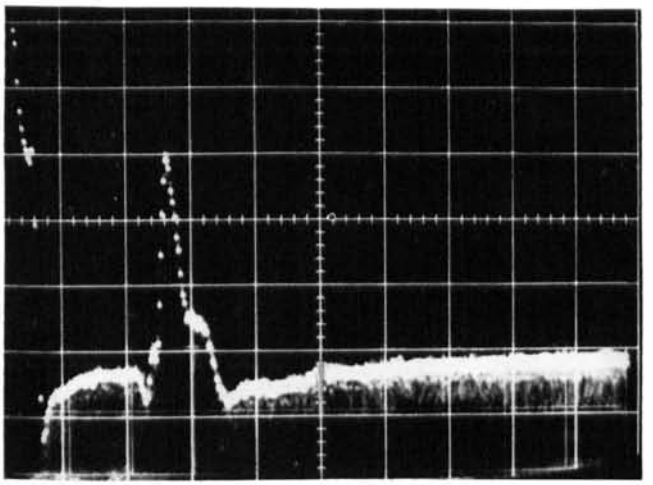

FIG. 1. Computerized average of 30 stimulations of right ulnar nerve. Stimulation given at proximal point 36 cm. distant from the receiving electrode. Calibration 25 micro V. and five m.sec. per square. Delay of motor conduction 8.5 m.sec. (normal).

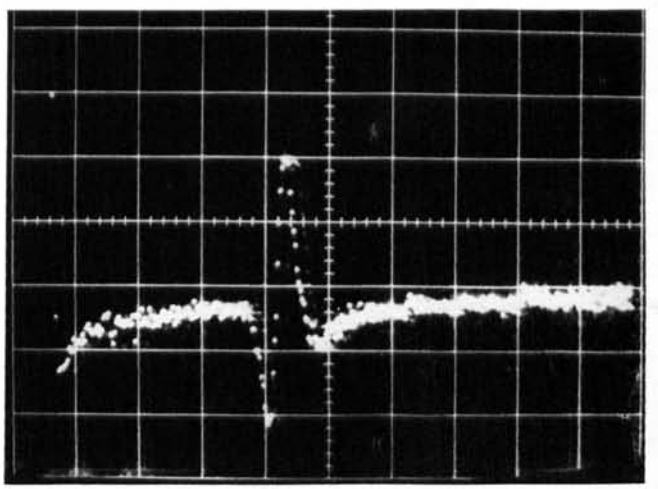

FIG. 2. Computerized average of 30 stimulations of right ulnar nerve. Stimulation given at proximal point, 38 cm. distant from the electrode placed in the abductor digiti quinti. Calibration 250 micro V. and five m.sec. per square. Delay of motor conduction 15 m.sec. (prolonged).

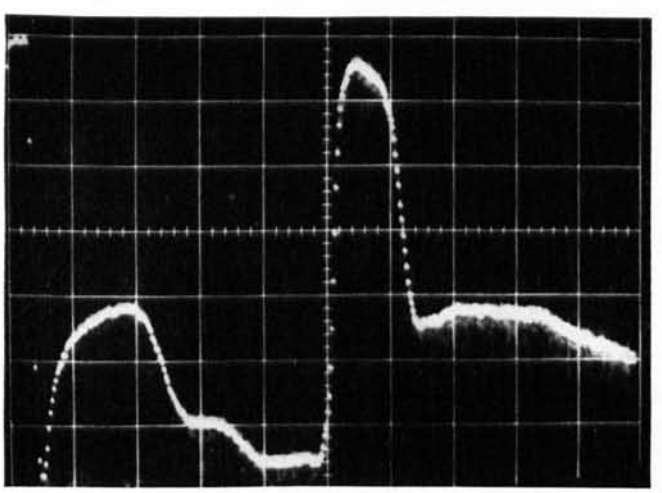

FIG. 3. Computerized average of 25 stimulations of right ulnar nerve. Stimulation given at proximal point, 32 cm. distant from the receiving electrode. Calibration 250 micro V. and five m.sec. per square. Delay of motor conduction 22 m.sec. (severely prolonged).

TABLE 2. *Motor conduction—three consecutive leprosy reactions in one patient.*

Date	MCV from ulnaris		LR	Therapy[a]
	Rt.	Lt.		
Oct. 10, 1967	65 m/sec.	60 m/sec.	Absent	
Oct. 29, 1967	30 "	35 "	Present 48 hrs	Thalidomide 400 mgm./d
Oct. 31, 1967	63 "	60 "	Absent	Thalidomide 400 mgm./d
Nov. 9, 1967	66 "	58 "	Absent	
Dec. 12, 1967	35 "	28 "	Present 48 hrs	Prednisone 20 mgm./d
Dec. 18, 1967	40 "	N.O.[b]	Present	Prednisone 20 mgm./d
Dec. 20, 1967	46 "	48 "	Absent	Prednisone 20 mgm./d
Jan. 12, 1968	52 "	56 "	Absent	
Jan. 30, 1968	32 "	26 "	Present 48 hrs	Placebo
Feb. 1, 1968.	27 "	22 "	Present	Placebo
Feb. 5, 1968	25 "	20 "	Present	Thalidomide 400 mgm./d
Feb. 7, 1968	44 "	46 "	Present	Thalidomide 400 mgm./d
Feb. 9, 1968	58 "	62 "	Absent	Thalidomide 300 mgm./d

[a] In addition to sulfone.
[b] Not obtainable.

ing was already present. This sign, however, tended to decrease, if at all, only long after all other manifestations had already receded. Other neurologic signs, such as sensory loss, motor deficit or loss of tendon and periosteal reflexes, were not constant and became manifest only in the later stages of LR.

Both pain and nerve swelling, the two constant features of neurologic LR, are obviously highly subjective signs and, for all practical purposes, impossible to measure and quantitate. On the other hand, MCV is determined by an electric instrument which allows, within certain limits of exactitude and reliability, measurement of conduction (or delay) of impulses and determination of the trend of the nerve lesion, thereby permitting objective assessment of drug effects.

The MCV may be influenced by a variety of extraneous or intrinsic factors (e. g., temperature, perspiration, emotional condition of the patient, unwarranted movement of the stimulator, inexact measurement of the distance between the stimulator and the receiving electrode, etc.). However, it seems to us that certain basically simple, previously mentioned, precautions will help to eliminate, at least in part, these sources of error.

From the chronologic point of view, MC became clearly affected in all the cases approximately 48 hours after the appearance of pain. It should be mentioned that this finding was noted only in the ulnar nerves. In quite a number of instances the MC of the median and common peroneal nerves became decreased only a week or more after the onset of LR. This possibly corroborates the clinical impression that the ulnar is the most vulnerable long peripheral nerve.

No clear relationship between the MCV and nerve swelling during LR, with or without treatment, was noticed although the number of cases examined was obviously too small for statistical evaluation.

The cases treated with analgesics or placebo, behaved exactly like those without any therapy, and showed a MC which became progressively slower, until a certain level was reached, and then became stationary. The same process occurred in both the nerves that were normal and those that were already damaged before LR. In some

of the ulnar nerves MC became unobtainable, while in others it only diminished (the delay became prolonged) to a pathologic level. It would seem that the nerve lesion is not of the same degree in all LR, though it is very difficult to determine beforehand to what extent the LR will progress, even in repeated LR in the same patient. The factors that determine the extent of neurologic damage in each LB and each nerve are not known.

In LR treated with steroids, the MC levelled within four to five days after the onset of nerve deterioration, after which a gradual, relatively slow, return to pre-LR vaues occurred within one to three weeks. This clearly indicates that prednisone has a marked, but slow, effect upon LR nerve lesions. It is also of interest that a too early or abrupt reduction or discontinuation of prednisone produced an almost immediate reappearance of LR.

In contrast, thalidomide had a rapid, sometimes dramatic, effect upon pain, which completely disappeared within one or two days after the initiation of therapy. The MC levelled off in one or two additional days and, with one exception, returned to pre-LR values within one week. A slow decrease of thalidomide, on the other hand, did produce a LR. This would seem to indicate that both prednisone and thalidomide have a suppressive effect upon the neurologic manifestations of LR, with the latter being faster and more potent. It has also been demonstrated that MCV is a reliable, objective tool for the evaluation of nerve trunk lesions and their response to drug therapy.

SUMMARY

Six patients with lepromatous leprosy had 17 leprosy reactions of which six were treated with thalidomide, six with prednisone, three with analgesics and two with placebo.

Ninety-six motor conduction velocity tests were carried out, before, during or after leprosy reaction.

It has been demonstrated that both thalidomide and prednisone have a suppressive effect upon the neurologic manifestations, thalidomide being faster and more potent.

The motor conduction test has been shown to be a reliable indicator of the progress of nerve lesions and for the assessment of drug effects.

RESUMEN

Seis enfermos con lepra lepromatosa tuvieron 17 reacciones leprosas, de las cuales 6 fueron tratadas con talidomida, 6 con Prednisona, 3 con analgésicos y 2 con placebo. Se realizaron 96 tests de velicidad de conducción, antes, durante y después de la reacción leprosa. Se demostró que la talidomida y la Prednisona tuvieron efectos supresivos sobre las manifestaciones neurológicas; la talidomida fué más rápida y potente. El test de conducción motora se mostró como un indicador fiel de los progresos de la lesión nerviosa y para la evaluación de los efectos de las drogas.

RÉSUMÉ

Six malades atteints de lèpre lépromateuse ont présenté 17 accès de lèpre; 6 de ces accés ont étè traités par la thàlidomide, 6 par la prednisone, 3 avec des analgésiques et 2 avec un placebo.

En outre, 96 tests de rapidité de transmission motrice on été exécutés avant, pendant et aprés les accés.

Les auteurs ont montré que la thalidomide et la prednisone ont un effet suppressif sur les manifestations neurologiques, la thalidomide étant plus rapide et plus puissante.

Il a été montré que le test de conductivité motrice était un indicateur fidèle des progrés des lésions nerveuses et permeittait d'évaluee l'effet des médicaments.

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