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Reversal Reaction: The Prevention of Permanent Nerve Damage Comparison of Short and Long-Term Steroid Treatment [1]

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Nerve damage leading to permanent disability is one of the major hazards in leprosy. In borderline (BT, BB, BL) leprosy such damage usually develops during a "reversal" reaction ([13]). When this happens the nerve trunks at specific sites become swollen and tender and show deterioration of function, which is usually rather gradual, taking weeks or even months to become irreversible, but the damage may also occur overnight. The reversal reaction can occur both before and after antileprosy treatment has been initiated ([12]).

The mechanism of nerve damage in reversal reaction is not yet fully understood, but it is thought to be related to immune processes ([2, 13]). Patients with borderline leprosy are able to develop cell-mediated immunity (CMI) towards *M. leprae* antigens and it seems likely that an increase in *M. leprae* antigens, either due to a multiplication of *M. leprae* or due to a breakdown of dead and dying bacilli within nerves, can trigger this response. The nerve is then invaded by inflammatory cells and there is an increase in the permeability of the vascular wall of the intraneural blood vessels, resulting in interstitial edema with impaired nerve function and possibly structural nerve damage (demyelinization). If the interstitial edema gives rise to raised intraneural pressure ([2, 11]), the likelihood of permanent damage is even greater. Intraneural granuloma formation and the organization of intraneural inflammatory exudate into fibrous tissue will cause irreversible damage.

In the management of the leprosy patient with reversal reaction, it is essential to stop and to reverse the nerve damage. Many treatment regimes have been tried and claimed to be more or less successful ([2-4, 14, 16, 19]). However, prednisolone with its dual action seems, to date, to be the drug of choice ([6, 10, 19]). Prednisolone both suppresses the CMI and decreases the inflammatory processes, thus decreasing compression and encouraging remyelinization in the nerve. When given for a longer period of time it may improve nerve recovery by preventing scar formation in the nerve.

Testing of voluntary muscle power with the Voluntary Muscle Test (VMT) has been used for many years in the Addis Ababa Leprosy Hospital to assess the extent of nerve damage in leprosy ([5, 9]) and to monitor the response to treatment. However, since 1974 prednisolone has been used in higher dosage and for longer periods in the management of neuritis than formerly. This paper reports the results of treatment of reaction with neuritis in borderline leprosy, comparing patients treated between 1968 and 1974 with those treated between 1974 and 1978, using serial VMT results as the indicator of response to treatment.

PATIENTS AND METHODS

Patients treated in the period 1974–1978 were selected from those attending the Addis Ababa Leprosy Hospital. All were clinically, and the majority also histopathologically, classified as borderline (BT, BB, BL) according to criteria described by Ridley and Jopling ([15]). The patients were considered to be in reaction when there were raised swollen skin lesions, tender nerves, or when

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there was evidence suggesting recent deterioration in nerve function.

The patients received prednisolone, 30-40 mg daily in a single morning dose for two weeks; thereafter the dose was slowly reduced over a period of 4-18 months. The antileprosy treatment (DDS, 50-100 mg daily) was continued. Assessments of nerve function (including sensory testing and motor nerve conduction velocity measurements in addition to VMTs) were performed regularly (at the beginning of the antireaction treatment weekly, later monthly, bimonthly and every six months). When the dose of prednisolone was lowered too rapidly, deterioration in the nerve function parameters was visible within a few weeks and the prednisolone dose was corrected. Patients were only admitted to the hospital for initiation of treatment; they were discharged as soon as steroid therapy could be lowered below 25 mg prednisolone daily (usually after about one to two months in the hospital).

Patients treated in the period between 1968 and 1974 who developed reaction or neuritis were usually managed in a "neuritis clinic"; serial VMTs were used to monitor the response to treatment. Case records of patients registered in this clinic were reviewed and those with borderline leprosy and a reversal reaction who had sufficient numbers of VMTs performed to enable proper analysis were included in the study. The duration and dosage of antireaction treatment were recorded, together with any available clinical information.

The VMT was used to compare the effect of treatment in the two groups of patients. As usually performed, this test shows the power of different muscles on a 0-5 scale (a completely paralyzed muscle scoring 0; full power 5). For this study, however, the scoring system was reversed and the "VMT-deficit" scored. Thus: full power = no deficit = 0; complete paralysis = total deficit = 5. The full system is shown in Table 1.

TABLE 1. *Scoring of VMT-deficit.*

VMT-deficit
0 = normal range, normal resistance
1 = normal range, reduced resistance
2 = normal range, no resistance or reduced range, slight resistance
3 = reduced range, no resistance
4 = no joint movement but a muscle flicker
5 = muscle paralyzed

For the ulnar nerve, three muscle groups were graded: the *abductor digiti minimi,* the first dorsal interosseous muscle and the lumbricales III and IV. The result of the weaker of the last two muscles was added to the result of the *abductor digiti minimi* and the first dorsal interosseous muscle. The maximum VMT-deficit for an ulnar nerve was therefore 15.

For the median nerve, the *abductor pollicis brevis* muscle was graded together with the *opponens pollicis* and the lumbricales I and II muscles. The result of the weaker of the last two was added to the results of the *opponens* and *abductor pollicis* to give the VMT-deficit for the median nerve (maximum 15).

The overall VMT-deficit was obtained by adding the VMT-deficits of both ulnar and median nerves together. Complete bilateral ulnar and median palsy thus gave the maximum score of 60 points. When the function improves, the score is reduced.

RESULTS

Table 2 compares the prednisolone dosage received by the two groups of patients. Those treated before 1974 received a much lower dosage after the initial one to two weeks, and the prednisolone was discontinued much sooner, though a few patients had repeat courses. A further difference in management was that DDS treatment was stopped for a period (and almost always reduced to low dosage thereafter) in the pre-1974 patients.

Table 3 shows that the number of patients who became worse after one month of treatment was much greater in the 1968-1974 treated patients. It seems clear that the process of nerve damage was not arrested by the short period of high dose prednisolone treatment used at that time. When a higher dosage was given for a longer period, as in 1974-1978, very few patients deteriorated after treatment was initiated and none after the first three months.

TABLE 2. *Clinical management of the trial patients.*

Period	Prednisolone dosage per day (mg)		
	Patients treated 1968-1974		Patients treated 1974-1978
	Regime A	Regime B	
Week 1	45-60	15	30-40
Week 2	20	10	30-40
Week 3	10	10	25-35
Week 4	5	5	25-35
Month 2	5	5	20-30
Follow-up	A few patients received 2-3 additional course of regime B, otherwise no prednisolone was administered.		Gradual reduction of dosage: periods of follow-up treatment were: BT cases 3-8 months BB cases 4-12 months BL cases 4-18 months
DDS dosage			
Whole trial	Discontinued for week 1-2, often low dosage thereafter.		Continued at 50-100 mg daily throughout the trial period.

TABLE 3. *Results of treatment of trial patients.*

Time at which maximum nerve damage was observed	25 patients treated 1968-1974	23 patients treated 1974-1978
Start or after one month	8	19
At three months	6	4
At 6-12 months	11	0

Figure 1 shows the average VMT-deficit during and after antireaction treatment. The period 1968-1974 is compared with 1974-1978. In severe reaction (initial VMT-deficit > 12) during the period 1968-1974, there was no improvement of the mean in the first half year after the beginning of antireaction treatment, though there was a gradual improvement thereafter, starting at the time when the reaction might be expected to subside spontaneously. During the 1974-1978 period, on the other hand, there was improvement from the start of antireaction treatment onwards, continuing for over two years.

Patients with mild neuritis (initial VMT-deficit < 12) in the period 1968-1974 showed no improvement from their treatment. Indeed, their mean VMT-deficit after a three year follow-up period was greater than that of patients with severe neuritis treated after 1974. The patients with mild neuritis treated between 1974 and 1978 were completely relieved.

DISCUSSION

Many methods have been used to measure and assess nerve involvement in leprosy. Voluntary Muscle Testing (VMT) has been used in leprosy for a long time ([5]). Motor Nerve Conduction Velocity (MCV) has proved its value ([8,10]), and more recently Sensory Testing (ST) has been reintroduced ([9]).

Using the above-mentioned parameters, Naafs and Van Droogenbroeck ([11]) developed an objective method for assessing nerve involvement, the Nerve Deficit Index

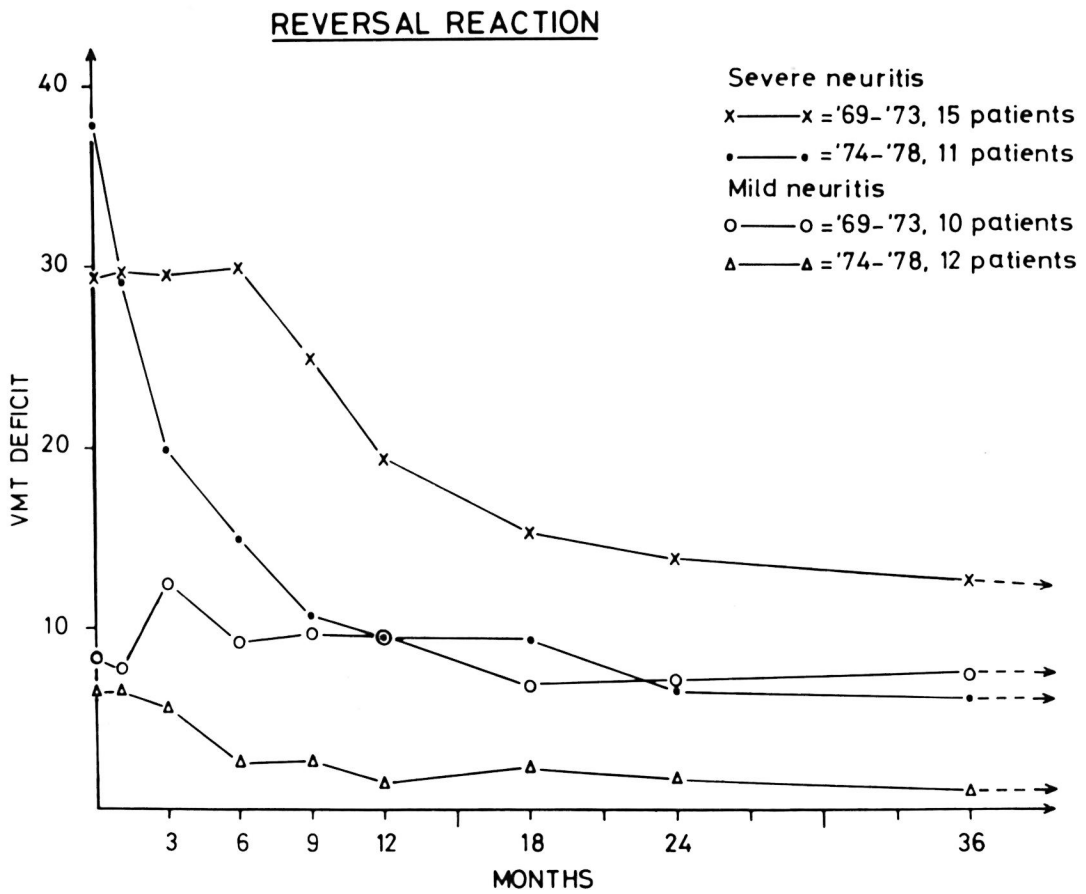

FIG. 1. Improvement of borderline patients with neuritis during a three year follow-up period. Short-term steroid treatment compared with prolonged steroid treatment.

(NDI), which expresses numerically the degree of nerve damage. With this method the dose and the length of the antireaction treatment for an individual patient can be determined.

Before 1974 the NDI was not used, but careful VMT assessments were done for patients in reaction. In order to compare the results of treatment regimes before 1974 with those presently in use, the VMT, which is one of the parameters in the NDI, was used. The VMT had already proved to be a reliable parameter in assessing the degree of nerve damage ([9]).

The effectiveness of prednisolone in the treatment of reversal reaction is well known ([3, 6, 17, 19]). However, duration and dosage of the drug is not yet well defined. With the help of the NDI it was possible to adjust the prednisolone treatment for the individual patient in the 1974-1978 period.

It was not possible to reverse the overall VMT-deficit within three months in only 4 of the 23 patients treated in this period (Table 3), though in these patients the reactional symptoms (active erythematous skin lesions, rheumatic pain and nerve tenderness) were settling. In two of these patients the nerve damage persisted and did not improve at all. It is possible that in these patients and in these nerves the antireaction treatment was begun too late and it may well be that these patients could have benefited by surgical decompression of the nerves in addition to steroid therapy. This has been performed on similar cases with encouraging results ([18]).

It may be concluded from the treatment results in the period 1968-1974 that despite ineffective antireaction treatment but with more or less effective chemotherapy, the reaction settles by itself after six to nine

months. It seems that within this period effective chemotherapy, together with the body's ability to dispose of *M. leprae* antigens, diminishes the amount of *M. leprae* antigens to a level below the "threshold" needed to give rise to a damaging reaction. This is in agreement with earlier findings that no reversal reaction was observed in BT and BB patients after half a year of antileprosy treatment ([12]). It also explains why the prednisolone dosage in the period 1974-1978 could slowly be reduced in the course of antileprosy treatment.

The fact that DDS was continued in full dosage during the antireaction treatment after 1974 did not seem to have any effect upon the severity of the reaction, contrary to the view of some leprologists ([1,7]).

The antireaction treatment in BT patients can be shorter than in BL patients, probably because of the lower antigenic load of BT patients. The average duration of about six months is only slightly longer than the period described by Consigli *et al* ([3]) who especially studied BT patients.

In the past four years more than 300 patients with neuritis caused by reversal reaction have been treated with the prolonged steroid treatment here described. No major side effects were encountered, especially no "steroid dependence." About 1% to 2% of the patients developed active pulmonary tuberculosis. However, this is approximately the prevalence of this disease among the general population in Ethiopia. The use of steroids in patients with chronic ENL was more hazardous; 10% to 20% developed active pulmonary tuberculosis (unpublished observations). However, the question here remains whether tuberculosis predisposes to ENL or was the result of the steroid treatment.

The prolonged steroid regime as here presented has been shown in this study to be more effective than a short-term steroid regime and it has been without serious side effects in Ethiopian borderline leprosy patients. The differences in the results obtained by the different treatment regimes cannot be explained by differences in the composition of the patient groups treated. There were no significant differences between the groups with respect to sex, age, type and duration of leprosy, nor in the type and the duration of the reversal reaction before antireaction treatment.

It is now clear that when a reversal reaction is detected in time (within three to four months), the patient can be assured that he will not become crippled. This should increase his trust in his doctor and his compliance with the treatment prescribed, which is essential for any leprosy control scheme. Methods of applying these encouraging results to rural leprosy control programs deserve careful consideration.

SUMMARY

Borderline leprosy patients with a reversal reaction were studied and short-term steroid treatment compared with prolonged steroid treatment using voluntary muscle testing (VMT) to assess the results. Prolonged steroid treatment was shown to be superior to short-term treatment and free of harmful effects. It is concluded that with the described antireaction treatment, permanent nerve damage can be prevented, provided that the reversal reaction is detected in time (within 3-4 months).

RESUMEN

Se estudió el efecto del tratamiento con esteroides durante periodos cortos de tiempo en comparación con el tratamiento esteroidal prolongado en pacientes con lepra intermedia (borderline) en reacción reversa. Los resultados se valoraron por la "prueba de los músculos voluntarios" (PMV). Se demostró que el tratamiento prolongado con esteroides es superior al tratamiento de corto tiempo, además de estar libre de efectos colaterales indeseables. Se concluye que el tratamiento antireaccional descrito, puede prevenir el daño nervioso permanente siempre y cuando la reacción reversa sea detectada a tiempo (dentro de los primeros 3 a 4 meses).

RÉSUMÉ

Des malades lépreux du groupe "borderline" qui ont présenté des réactions d'iversion ont fait l'objet de cette étude. Deux traitements aux steroides ont été comparés en employant les tests musculaires comme paramètres: un traitement à court terme et un traitement prolongé. Il est apparu que le traitement de longue durée était supérieur au traitement plus court. Nos résultats permettent de conclure qu'un traitement antiréactionnel bien conduit est en mesure de prévenir des dommages nerveux permanents, pourvu que la réaction d'inversion soit détectée à temps (en dedans les 3 à 4 mois).

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REFERENCES

1. BROWNE, S. G. Treating HD today and tomorrow. The Star **36** (1977), No. 7, pp 2-3.
2. CARAYON, A. Gamme lésionnelle des névrites Hanséniennes. Med. Trop. **36** (1976) 41-61.
3. CONSIGLI, C. A., BIAGGINI, R. and VASQUEZ, C. El tratamiento de la reacción leprosa con prednisona. Leprologia (Buenos Aires) **3** (1958) 16-20.
4. GARRETT, A. S. Hyalase (hyaluronidase) injection for lepromatous nerve reaction. Lepr. Rev. **27** (1956) 61-63.
5. GOODWIN, C. S. The use of the voluntary muscle test in leprosy neuritis. Lepr. Rev. **39** (1968) 209-216.
6. JONQUIERES, E. D. L. Control de las reacciones leprosas tuberculoide con Prednisona. Communicacion previa. Semana Med. **111** (1957) 313-317.
7. JOPLING, W. H. Any questions: dapsone in leprosy. Trop. Doct. **4** (1974) 140.
8. MAGORA, A., SHESKIN, J., SAGHER, F. and GONEN, B. The conduction of the peripheral nerve in leprosy under various forms of treatment. Int. J. Lepr. **38** (1970) 149-163.
9. NAAFS, B. and DAGNE, T. Sensory Testing: a sensitive method in the follow-up of nerve involvement. Int. J. Lepr. **45** (1977) 364-369.
10. NAAFS, B., PEARSON, J. M. H. and BAAR, A. J. M. A follow-up study of nerve lesions in leprosy during and after reaction using motor nerve conduction velocity. Int. J. Lepr. **44** (1976) 188-197.
11. NAAFS, B. and VAN DROOGENBROECK, J. B. A. Decompression des névrites réactionnelles dans la lèpre: Justification physiopathologique et méthode objectives pour en apprécier les resultats. Med. Trop. **37** (1977) 763-770.
12. NAAFS, B. and WHEATE, H. W. The time interval between the start of antileprosy treatment and the development of reactions in borderline patients. Lepr. Rev. **49** (1978) 153-157.
13. PEARSON, J. M. H. and ROSS, W. F. Nerve involvement in leprosy. Pathology. Differential diagnosis and principles of management. Lepr. Rev. **46** (1975) 199-212.
14. RAMANUYAN, K. A note on the use of intraneural corticoids in acute leprous neuritis. Lepr. India **36** (1964) 261-264.
15. RIDLEY, D. S. and JOPLING, W. H. Classification of leprosy according to immunity, a five group system. Int. J. Lepr. **34** (1966) 255-273.
16. SEPATRA, G. C. and SHARMA, D. R. Intraneural cortisone and priscol in treatment of leprosy. Lepr. India **36** (1964) 264-268.
17. TIO, T. H. Neural involvement in leprosy. Treatment with intraneural injection of prednisolone. Lepr. Rev. **37** (1966) 93-97.
18. VAN DROOGENBROECK, J. B. A. and NAAFS, B. Etude comparative d'une série de nerfs lépreux décomprimés chirurgicalement par rapport aux nerfs controlatéraux non opérés. Med. Trop. **37** (1977) 771-776.
19. WATERS, M. F. R. Treatment of reaction in leprosy. Lepr. Rev. **45** (1974) 337-341.