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Treatment of Neuritis in Borderline Leprosy with Rifampicin and Corticosteroids —A Pilot Trial

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Upon the premise that rifampicin in conjunction with corticosteroids may be of value in the treatment of neuritis in borderline leprosy, a full-scale trial was planned. But the rapid appearance of an increasing peripheral neuropathy in three of the patients made cessation of the trial imperative. The combination of clofazimine with a similar scheme of administration of corticosteroids was found to produce far superior results even after rifampicin had caused an exacerbation of the neuritis.

Introduction

Rifampicin is the only antileprotic drug which has a bactericidal effect (Shepard *et al.*, 1971; Shepard, 1974), producing a much more rapid reduction in the Morphological Index than any other drug (Rees *et al.*, 1970).

Research into the pathology and especially the immunopathology of Type I reaction has as yet failed to provide basic understanding of its etiology. It is generally held that Type I reaction in borderline leprosy is a cell mediated allergic response (Type IV Gell and Coombs) related to the amount of antigen produced and released by the mycobacteria, or by macrophages in the process of digesting *Myco. leprae*.

Theoretically two conditions might be considered as possibly responsible for Type I reactions:

1. A sudden change in the cellular immune response itself, independent of the alteration of antigen presented by the bacilli. As yet there have been no controlled trials that give conclusive evidence that *Myco. leprae* itself, its antigens or antileprotic treatment have a direct immunotoxic effect on the cellular immune response. On the other hand, there are no studies to prove that antileprosy therapy does not increase the immune response, but there is a great body of clinical experience to suggest that effective therapy does in fact increase the immune response.

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2. A change in the total amount of antigens. An increase in the number of disintegrating *Myco. leprae* results in an increased release of antigens. This may be a result of treatment with bacteriostatic drugs, or simply be due to an increase in the cellular immune response. It may be that the degenerate bacilli release an increased amount of antigen, inducing a hypersensitive cell mediated immune response. Or it may be that antigens responsible for this type of reaction originate from *Myco. leprae* that have been damaged, but not yet been killed by the treatment or the cell mediated immune response; rather than that they arise from dead *Myco. leprae.*

Since rifampicin is an effective bactericidal drug that reduces the Morphological Index to nil in about six weeks, as compared to other antileprotic drugs that take at least six months, one could expect:

(1) There may be a decreased amount of antigen released.
(2) With rapid killing of the bacilli there may be a shorter duration of the reactive phase.
(3) If rifampicin is active in the presence of corticosteroids, then suppression of reaction during treatment should cause less tissue damage.

Materials and Methods

Four patients with borderline leprosy were included in this trial. One had BL leprosy and three BT leprosy. All had moderate to severe reactions with neuritis of at least two peripheral nerve trunks. In each case one of these had to be an ulnar nerve. Two of the patients had had some previous treatment, and two none, as noted in the case histories. Every two weeks the patients were evaluated for possible changes in motor and sensory function of the ulnar nerve selected for evaluation, and this was taken as the parameter of clinical status of the reactional state. Motor and sensory function of these nerves were standardized and quantified so that a follow-up of each patient was possible, as well as to make a comparison among the various patients.

All patients received treatment according to the following schedules:

A. Rifampicin 600 mg daily during the trial period.
B. Prednisone was given according to the following scheme:
   Prednisone 10 mg 4 times daily × 7 days.
   10 mg 2 times daily × 7 days.
   10 mg once daily × 7 days.
   10 mg on alternate days × 14 days.
   This scheme had to be altered for three of the four patients to meet individual requirements for severe reactions.
C. Analgesics were used as indicated to control pain in nerves.
D. All patients received optimal physical therapy twice daily during the trial period.

Individual Patient Reports

No. 1 M.M. 73/207 Male, age 33 years, a patient with BL leprosy with no evidence of peripheral neuropathy clinically, was given dapsone in small doses for six months. After having had 100 mg per week for three weeks he suddenly developed bilateral ulnar and median paralysis. He was then begun on the trial

routine and improved so that very quickly the median paralysis was completely reversed. Because of this initial improvement he was continued on rifampicin and steroids for a total of 10 weeks. There was further reduction in the extent of anaesthesia, but no change in the ulnar paralysis. At the end of 10 weeks the active process seemed to have subsided and there was no evidence of further improvement so he was started on standard dapsone therapy and referred to out-patient care and lost to follow-up.

No. 2 P.T. 74/146 Female, age 26 years. This patient had BT leprosy in reaction, no previous treatment. On admission the patient had enlarged and painful ulnar nerves, incomplete ulnar anaesthesia, and motor weakness in both ulnar nerves. After a month of treatment on the above scheme there was an increased extent of anaesthesia and complete motor paralysis of both ulnar nerves with continued swelling and pain in the ulnar nerves proximal to the elbow. Rifampicin was stopped and treatment continued with clofazimine, repeating the corticosteroid regimen of the trial schedule. At the end of 10 weeks there was complete return of function of the intrinsic muscles of the left hand, but the right hand remained paralysed. There was also a diminution of the area of anaesthesia in the ulnar distribution. The patient was then transferred to out-patient care.

No. 3 K.M. 74/177 Male, age 37 years. A patient with BT leprosy who had had two months of treatment with dapsone in an out-patient clinic with a maximum dose of 200 mg weekly, which had appeared to precipitate a severe ulnar neuritis in the left arm. The trial treatment was started, but in the third week the corticosteroid dose had to be increased again as there was an exacerbation of the neuritis. Before the completion of a full six weeks of treatment it was deemed essential to stop the trial and give clofazimine and corticosteroids, as the neuritis continued to get worse, with increasing paralysis and further extension of anaesthesia. After two months of clofazimine plus prednisone there was incomplete return of sensation in the ulnar distribution, but the residual ulnar paralysis remained stationary.

No. 4 N.S. 74/190 Female, age 23 years, a patient with BT leprosy in reaction having had no previous treatment. On admission the patient had large, painful ulnar and median nerves, with bilateral ulnar weakness and anaesthesia. There was an increase in the nerve deficit during four weeks of the trial treatment, most marked in the left hand. She was then treated with clofazimine, plus the trial dosage scheme of prednisone. After a further four weeks the area of anaesthesia was reduced and the right hand had returned to normal motor function with nearly complete return of lumbrical function in the left hand, but with residual weakness in the interossei. Except for the areas of the hand on which there are obvious skin lesions, there is normal sweat production, even in the ulnar distribution.

Biopsies of both skin and a portion of the radial cutaneous nerve were taken from this patient prior to treatment, after a month of the trial therapy, and finally after a month on clofazimine plus corticosteroids. Although changes could be seen in the process occurring in the nerve, there could be no definite correlation between the therapy and the histological picture seen.

Discussion

The anticipated improvement of neuropathy related to the reactional state in borderline leprosy when treated with rifampicin and corticosteroids was not

confirmed. It appears from the single BL patient that perhaps the use of rifampicin may be justified in the lepromatous half of the spectrum in conjunction with corticosteroid immunosuppression to control neuropathy. But the other three patients have provided unequivocal evidence that this method of management is not indicated in tuberculoid leprosy where there is potential danger of nerve damage.

It is interesting that although nerve damage was not reversed, there was in every instance a dramatic improvement in the appearance of skin lesions, leading to a type of resolution not previously seen in any other therapy. The lesions developed a much more clearly defined border, the elevated edge having a "hard" appearance much like that of a keloid. Central healing was rapid, with a rapid return of normal pigmentation.

Although a trial of this number of patients is insufficient to provide conclusive evidence of the result of the therapy, it would appear that rifampicin is contraindicated in the treatment of borderline tuberculoid leprosy.

One has to question if the increase of neuritis occurring with the use of rifampicin may be due to the sudden release of large amounts of *Myco. leprae* related antigens leading to the exacerbation of reaction. However, a similar result does not occur in Type II reactions as they do not seem to be at all exacerbated by the use of rifampicin, but rather to be somewhat suppressed.

Conclusion

From the results of this pilot trial of rifampicin and corticosteroids in borderline leprosy, it appears that this therapy is contraindicated in the presence of neuropathy. It has been shown that it has aggravated neuritis, leading to an increase in sensory and motor deficits.

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