Problems in the management of leprosy reactions: A study of 31 patients

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Introduction

Leprosy, which had been a major cause of nerve damage and disability worldwide, is now being considered a disease under control by the WHO. The global burden of the disease has decreased since 1981, the year of introduction of Multi Drug Therapy (MDT)[1]. In 2005 there were 296,499 new cases of leprosy reported worldwide, the majority of them from India and Brazil[2].

With the introduction of MDT, treatment of leprosy per se has become successful, leaving leprosy reactions as the major challenge for the clinician. There are mainly two types of reactions, type 1 (reversal) reaction and type 2 (erythema nodosum leprosum ENL) reaction. In addition to this, the entity of mixed reaction has also been discussed recently.

The incidence of leprosy reactions, especially ENL, has fallen with the introduction of MDT, possibly due to the combined bactericidal effect of rifampicin and the anti-inflammatory effect of clofazimine[3]. Even though many studies had been done on the epidemiology of reactions, studies during the post-MDT era are less well documented.

WHO has laid down guidelines on the treatment of leprosy reactions[4,5]. Even though a standard regime of prednisolone is supposed to be effective in the management of reversal reactions and even NSAID's are recommended as first-line therapy in ENL reactions, in our experience, steroid dependence as well as the need for better second-line medications are problems for the clinician managing ENL reactions.

We have also found out that even though there are many studies on the epidemiologic characteristics of leprosy reactions there are only a few studies/ articles on the long-term outcome and management of leprosy reactions.

Deformities and nerve function impairment are a major cause for concern in leprosy. Many studies have shown that even though leprosy has been controlled as an infectious disease, the morbidity due to deformities is still a major problem[6,7,8,9].

In Sri Lanka, the Central Leprosy Campaign (CLC) has played a monumental role in bringing leprosy under control. It was responsible for the MDT treatment as well as deformity and disability care, which were carried out through a force of well-trained medical officers and Public Health Inspectors (PHII).

With the achievement of elimination level in 1990's, the management of leprosy has been integrated into the general health care services since 2001. Dermatologists serving in all major hospitals now have more opportunities of managing patients with leprosy. The dermatology unit at the National Hospital of Sri Lanka (NHSL) alone has treated more than 600 leprosy patients since late 2001.

At the dermatology unit NHSL, we have come across many patients with reactional leprosy whose management has been complicated by steroid dependence, need for second-line therapy and the occurrence of deformities. This fact, and the scarcity of literature on the management of leprosy reactions, especially in the Sri Lankan setting, led us to study leprosy reactions in detail.

Methods

The study was carried out at the Dermatology Unit, National Hospital of Sri Lanka (NHSL) over a period of one year from 1st June 2004 to 31st May 2005.

This is a descriptive study. All the patients who were on treatment for leprosy reactions at the beginning of the study and all new patients who were diagnosed to have lepra reactions and started on treatment during the period of study were enrolled. Only those who had documented evidence of follow up for at least 6 months were included in the final analysis.

All the patients were interviewed and examined by the chief investigator at enrolment. A comprehensive data sheet dealing with all the aspects of the study was filled for each patient. All the patients were managed by the same investigator during the follow up visits.

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All the details pertaining to previous treatment and clinical events were extracted from the patients' notes.

Demographic data and data on the treatment and side effects were tabulated. Suitable statistical methods were used.

Results

31 Patients were included in the final analysis. There were 18 males and 13 females. Mean age at enrolment was 40.32 years (range 19 to 76 years). 32.26% of them belonged to the 21 – 30 year category. When age at onset of leprosy was considered, equal numbers (19.35%) belonged to 3 age groups, <20, 21 – 30, 31 – 40 years. All the patients were diagnosed to have multibacillary (MB) leprosy.

Type 1 reactions were seen in 7 (22.6%) patients, while 17 (54.8%) had type 2 (ENL) reactions. 7 patients were diagnosed to have mixed reactions. The majority of all types of reactions were diagnosed within 6 months of starting MDT. 2 patients with ENL had initially presented with overt ENL before features of leprosy had become evident. Documentation for follow up was available for a mean duration of 27 months (range 6 – 78 months).

The commonest clinical features were appearance of new lesions, fever, numbness and oedema of extremities. Involvement of both skin and nerves was seen in 71% of type 1, 53% of ENL and 100% of mixed reaction patients. The majority (53%) of patients with type 1 reaction had only one episode of reaction during the period of follow-up, while 57% with ENL and 53% with mixed reaction had more than 5 episodes.

Even though reactions are classified into 3 types, we identified several clinical patterns, which occurred within these categories. ENL reaction occurring while on treatment and going on with several relapses was the commonest clinical pattern occurring in 10 (32.2%) patients. Late type 1 (reversal) reaction occurred in only one patient, while late ENL was seen in 5 (16.1%) patients.

All the patients were treated with multibacillary (MB) therapy. Dapsone could not be continued in 6 patients due to haemolysis or hypersensitivity. Two of them were treated with ofloxacin instead. In 18 patients (58%) MDT had to be continued beyond the standard 12 months. The maximum duration of MDT was 24 months.

Prednisolone was the standard first-line therapy in all the patients. The maximum daily dose of prednisolone used to control reactions ranged from 15 to 80 mg. The mean duration of therapy was 17 months (standard deviation 13 months), with a range of 1 – 50 months. 20 patients were treated with prednisolone alone, while in 60% of them the duration of therapy was less than 12 months. Of the 11 patients who needed second-line drugs, 10 (91%) had to be given prednisolone beyond 12 months. 11 patients were dependent on prednisolone for relief from reactional symptoms, 3 of them needing daily doses as high as 15-20 mg for effective control of symptoms.

The commonest second-line drug used was clofazimine, which was used in all 11 patients in that category. 4 patients were treated with azathioprine and/or pentoxifylline for effective control. Combination therapy was successful in one patient only, in whom all reactional therapy could be tailed off without relapse of symptoms.

Only 30% (n=9) of the patients could be tailed off reactional therapy during the period of study. They included 4 patients with type 1 reaction, 3 with ENL and 1 patient with mixed reaction who responded to prednisolone.

The commonest adverse effects due to therapy were pigmentation and dry skin attributable to clofazimine, which was seen in 26 (84%) of the patients. Serious problems like hypertension and diabetes mellitus were uncommon.

Only 23% (n=7) patients recovered without any deformity. Persistent numbness was the commonest deformity occurring in 22 (71%) of the patients, while trophic ulcers were seen in 11 (36%). 3 patients ended up with nerve palsies, involving ulnar and common peroneal nerves.

Discussion

31 patients were included in the final analysis. There was a slight male preponderance (58% males, 42% females) in this sample. When we considered the age at onset of leprosy, 3 age groups, <20, 21 – 30 and 31 – 40 years, included the same percentage of patients, which was the highest also. According to the literature, onset of the disease in the 2nd decade of life is a risk factor for the development of ENL[10]. As this study was carried out at the NHSL, which caters to adult patients only, we may have missed a percentage of patients in the second decade of life. But this study also shows that leprosy reactions are commoner in the productive age groups, thus leading to considerable loss of working and earning capacity.

All the patients in this sample had the multibacillary type of leprosy. Usually paucibacillary (PB) leprosy is commoner than MB leprosy, but the recent trend in Sri Lanka has been towards the detection of more MB cases. Another reason for this may be that NHSL being a tertiary care hospital attracting more complicated cases.

Leprosy reactions have conventionally been classified into 2 types, type1 (RR) and type 2 (ENL). In addition to this, mixed reaction, where features of both RR and ENL occur in the same patient either at the same time or at different times has been described[11]. This is not an entity recognized by the WHO.

54.8% of the patients had ENL while only 22.6% had type 1 reactions. Previous study in Sri Lanka by Ragunathan et al reported 80% type 1, 14% ENL and 6% mixed reactions[11]. In the ENL group there was one female patient with ulcerative ENL and another young female with histoid leprosy.

Our study was a retrospective study, which recruited patients who are already on treatment, thus including more ENL and mixed reactions that have a long drawn-out course. We may have missed a percentage of patients who had been successfully treated for type 1 reactions and released from treatment. The percentage of mixed reactions also has shown an increase from 6% in 1994 to 22% in 2004/5[11].

22.6% of all types of reactions were diagnosed at presentation. This figure is lower than the figures reported in other studies (30.9 – >50%)[12, 13, 14]. 43% of type 1 reactions were diagnosed at registration and 72% were diagnosed within the first 6 months of therapy. This is comparable to other studies.

Out of the ENL cases 18% presented with the reaction, 29% were diagnosed during the first half of therapy, while a similar percentage was diagnosed after completion of therapy. According to a study done in Chandigarh, India, the majority of ENL occurred in the 2nd and 3rd years after starting of therapy[12]. The total percentage of 47% diagnosed within the first 6 months of therapy is comparable to the previous Sri Lankan figure of 54%[11]. The majority (43%) of mixed reactions were first diagnosed during the first 6 months of treatment.

Only one patient had a late type 1 reaction, while 29% of ENL patients had late reactions. This figure cannot be compared with the previous studies, as we have not calculated the incidence of late reactions in comparison to the cases of leprosy.

The majority of patients, both type 1 and ENL, had involvement of both skin and nerves. All the patients with mixed reaction had skin and nerve involvement. 19% of patients with type 1 reaction had nerve involvement only, thus highlighting the importance of a thorough neurological examination at all times of follow-up.

In the type 1 category just over 50% patients developed only one episode of reaction during the period of follow-up. 43% had more than one episode (recurrent RR). The majority (53%) of patients with ENL had more than 5 recurrences during the period of follow-up while only one patient was fortunate to have a single episode of reaction. In the mixed category too the majority developed more than 5 episodes. Recurrence of type 1 reactions was seen in 9.7% and 33% of patients in 2 previous studies[12, 15]. Our figures are higher than this. 64% of patients in the Chandigarh study had recurrences in ENL, 31% of them having more than 5 episodes[12]. In our study the respective figures stood at 94% and 53%.

In the patient group with type 1 reactions, only one recovered without deformity, while 3 recovered with deformities. 2 patients had recurrent type 1 reaction and 1 had a late type 1 reaction. The typical ENL reaction with recurrences was the commonest clinical pattern including nearly one third of patients.

The two patients, who had features of ENL before features of leprosy became obvious, need special mention.

A 30 year old female, who had presented with features of erythema nodosum in her first pregnancy, had been on varying doses of prednisolone for over 4 years. She had been seen by several dermatologists, undergone skin biopsies which showed vasculitis and panniculitis, without features of leprosy and been dependent on prednisolone 15 mg daily. She had defaulted treatment for 6 months and presented to us with features of both leprosy and ENL complicating the first trimester of pregnancy. By this time skin smear was positive and skin biopsy was also supportive of the diagnosis.

The second patient, a 65 year old man had been repeatedly treated at a medical unit for fever, erythematous nodules and lymphadenopathy with a diagnosis of "drug reaction". A lymphoreticular malignancy was suspected and lymph node biopsy was suggestive of leprosy. The only clues to suggest leprosy that he had were a long-standing peripheral neuropathy and acquired ichthyosis of the dorsa of feet, which can be easily missed by a non-dermatologist. Both these patients developed frequent recurrences and which were poorly responding to prednisolone.

Two of our patients underwent pregnancy during the period of study. One was the above-mentioned female who presented to us at 6 weeks of pregnancy, who was managed with MDT and prednisolone throughout the pregnancy. The other, also a long-standing leprosy patient, was managed with low doses of prednisolone during the pregnancy. Both had a successful pregnancy outcome and delivered healthy babies at term.

11 (36%) patients needed second-line therapy. All were given clofazimine (100-300mg daily) while azathioprine at a dose of 50mg daily was used on 4 patients and pentoxifylline (1200mg daily) on two.

The latter 2 patients were given all 3 second-line drugs, but only one of them responded to therapy and could be tailed off drugs. Current literature on the treatment of reactions recommends the use of clofazimine[16, 17], azathioprine[18] and pentoxifylline[19, 20, 21] in addition to thalidomide which is considered to be the gold standard[22, 23]. Thalidomide was not available in Sri Lanka during the period of this study. At present thalidomide is being used in severe reactions in a limited number of patients with many precautions.

77% of the patients had some form of deformity due to the disease. The incidence of deformities in this study is higher than that reported in other studies from India, Thailand and Brazil (23-28%)[7, 9, 14]. The only study that came close to this figure was the AMFES in Ethiopia, where nerve function impairment was detected at first presentation in 56% of the patients[6]. The occurrence of disability in Sri Lankan patients with leprosy reactions seems to be unacceptably high.

Conclusions

Leprosy reactions are clinically complex, with repeated episodes and varying clinical combinations. The epidemiological characteristics of reactions are comparable to other studies carried out in the region. In contrast with other studies type 2 reactions were the commonest entity, with a considerable percentage of mixed reactions. Recurrences in both type 1 and ENL were higher compared to available literature.

Treatment of reactions is complex, needing prolonged therapy with high-dose steroids. Steroid dependence is seen in more than one third of patients. More than 35% of patients need second-line therapy. Complete response to second-line therapy is rare.

Serious adverse effects due to therapy are rare. The commonest are benign reversible effects.

Deformities occur in more than 75% of patients, which is unacceptably high in comparison to the other countries of the region.

Recommendations

A larger, prospective study, with a longer period of follow-up should be carried out on Sri Lankan patients with leprosy reactions. This study should focus more on the treatment response and the incidence of deformities.

According to this study the incidence of deformities in Sri Lankan patients is high in comparison to other countries of the region. More emphasis should be given to education of health care personnel, especially doctors, on the detection of early NFI, management and prevention of disabilities and deformities.

As late reactions and recurrences were seen in a considerable number of patients, continued surveillance of leprosy patients after release from therapy is advisable.

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