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Original Article

A prospective study of clinical profile of type 2 lepra-reaction, clinical responses to treatment with thalidomide and seroprevalence of HIV in reactional patients

Lokanatha K[1], Dennis Henry[2], Priya KS[1], Vishal Methre[1]

[1] Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road, Bangalore, Karnataka, India.
[2] Usha Memorial Skin and Eye Hospital, Kududand, Bilaspur H O, Bilaspur-Chhattisgarh, India.

Abstract

Objective The purpose of the present study is to know the prevalence of components of Type2 lepra reaction, clinical response to Thalidomide for Type 2 reaction during Acute Therapy Period and sero prevalence of HIV in the reactional patient.

Methods All patients were hospitalized and Thalidomide capsules 100mg three times a day for seven days were given under supervision. The clinical response assessment was made and recorded for the following clinical parameters at 48 hours, 98 hours and on the 7th day. Fever, malaise and anorexia, ENL count, arthritis/ arthralgia, orchitis, nerve tenderness.

Results Among the 52 patients of type 2 lepra-reaction patients, 27 patients fulfilled the selection criteria to observe the clinical response to thalidomide during the Acute Therapy Period (ATP). There were five female patients (18.5%). The total no of males was 22 (81.5%). Among the total 27 patients, 23 (85.2% patients showed partial improvement and 4 (14-8%) patients showed striking improvement at 48 hours. At 96 hours the number of partial improvement group patients decreased to 7 (25.9%) and the striking improvement group rose to 20 (74.1%) but no total response. On the 7th day, only one (3.7%) patient remained in the partial improvement group, while 21 (7.8%) were in the striking group. Five patients (18.5%) showed a total response to thalidomide.

Conclusion A total of 27 patients enrolled, on the seventh day, 5 (18.5%) patients showed complete clearance of reactional symptoms. 21(77.8%) patients showed 50 to 99% improvement. One (3.8%) patient showed only 25% improvement and was considered a treatment failure.

Key words
Leprosy; Lepra reaction.

Introduction

Leprosy is a chronic disease caused by Mycobacterium leprae. Ridley and Jopling (1962) were the first to suggest a subdivision of leprosy based on immunology and histology, in addition to the clinic bacteriological features i.e., Tuberculoid Leprosy (TT), Borderline Tuberculoid (BT), Mid-Borderline (BB), Borderline Lepromatous (BL), and Lepromatous Leprosy (LL).[1]

The term reaction describes the appearance of symptoms and signs of acute inflammation in lesions of a patient with leprosy. They represent episodes of acute hypersensitivity.[2]

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Address for correspondence
Dr. Lokanatha K, Senior Resident, Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road, Bangalore-560 074, Karnataka, India.
Email: dermalok0006@yahoo.co.in

In 1959 W.H. Jopling made an attempt to classify reactional leprosy and proposed the names type 1 and type 2 for the two major types of reactions, and using the term lepra-reaction to cover both types.[3]

Erythema nodosum leprosum or Jopling Type 2 lepra reaction is an immune-complex mediated inflammatory condition occurring most frequently in LL, less frequently in BL Patients which comprises of the eruption of crops of evanescent tender, red papules and nodules on the skin often involving other organs with systemic upset, which develop in few hours and lasts only a few days. Size varies from 2mm to 2cm. The papules are red to purple in light-skinned and dark-blue-red in dark-skinned patients. They are dome-shaped with ill-defined margins. Sometimes, the lesion can be more easily palpated than seen. They feel firm and frequently painful on palpation.

The purpose of the present study is to know the prevalence of components of Type2 lepra reaction, clinical response to Thalidomide for Type 2 reaction during Acute Therapy Period and seroprevalence of HIV in the reactional patient.

Methods

A descriptive prospective study of leprosy patients to know the clinical profile of Type2 lepra reaction between May 2008 and May 2009 and an open uncontrolled study for Response to treatment. (Thalidomide for ENL) after acquiring clearance from the ethics committee (RRMCH-IEC/184/2020-2021). The inclusion criteria were all newly diagnosed cases of leprosy who were on anti-leprosy treatment and RFT Cases (old cases) presenting with ENL Lesions with or without systemic involvement like fever, malaise, arthritis, iridocyclitis, orchitis.

All patients were hospitalized and Thalidomide capsules 100mg three times a day for seven days were given under supervision. The clinical response assessment was made and recorded for the following clinical parameters at 48 hours, 98 hours and on the 7th day.

1. Fever
2. Malaise and Anorexia
3. ENL count
4. Arthritis / Arthralgia
5. Orchitis
6. Nerve tenderness

Results

The leprosy patients registered were 5283. Among these 260 were new leprosy cases. During this one-year study period, 52 patients met the selection criteria for Type 2 lepra-reaction. There were 25 Borderline lepromatous and 27 lepromatous leprosy cases none of which were HIV positive.

There were 11 females and 41 males. The age group ranged from 21 to 60. The most common age group affected was 20 to 49 with 44 patients. It was followed by the age group of 50 to 69 years, which together constituted 15.3%

The minimum number was 13 and maximum was 178. The mean, median and mode were 71, 70 and 88 respectively. The higher median values (178 and 163) of ENL were recorded in disseminated form, followed by the upper and lower limbs and face (median 138). 13 patients (25%) had a median value of 85 in the age group 20-49. Seven patients each (13.3%) had a median value of 18 and 40 in the same age group respectively. Over the upper and lower limb and face the most occurred median value of ENL was 85 (13 Patients) followed by 60 (6 patients). Over the upper limb and face 18 was

the most occurred ENL (7 patients).

Among the 52 patients of type 2 lepra-reaction patients, 27 patients fulfilled the selection criteria to observe the clinical response to thalidomide during the Acute Therapy Period (ATP). There were five female patients (18.5%). The total no of males was 22 (81.5%).

Among the total 27 patients, 23 (85.2% patients showed partial improvement and 4 (14-8%) patients showed striking improvement at 48 hours. At 96 hours the number of partial improvement group patients decreased to 7 (25.9%) and the striking improvement group rose to 20 (74.1%) but no total response.

On the 7th day, only one (3.7%) patient remained in the partial improvement group, while 21 (7.8%) were in the striking group. Five patients (18.5%) showed a total response to thalidomide **(Table 1)**.

Out of 27 patients, 10 patients (37.0%) had severe degree fever, 8 (29.6%) had mild and moderate. On the 7th day, however, only 2 (7.4%) continued to have an intermittent mild-degree fever **(Table 2)**.

7.4% had moderate to severe tenderness of a single nerve 7 (25.9%) and 3 (11.1%) had moderate to severe and 12 (44.4%) had mild to moderate tenderness for the first two days of therapy at 96 hours however no patient had a sever tenderness but on 7th day only 6 (22.2%) had mild tenderness **(Table 3)**.

Of the total 27 patients, 17 (63.0%) experienced moderate arthralgia, while 2 (7.4%) had severe arthralgia, and 5 (18.5%) had mild arthralgia. Lastly, 3 (11.1%) patients did not report any arthralgia **(Table 4)**

Table 1 Response to thalidomide.

Response	*48hrs No. (%)*	*96hrs No. (%)*	*Day7 No. (%)*
Total	0 (0)	0 (0)	5 (18.5)
Striking	4 (14.8)	20 (74.1)	21 (77.8)
Partial	23 (85.2)	7 (25.9)	1 (3.7)

Table 2 Response to fever.

Degree of Fever	*Day 1*	*48H*	*96H*	*Day7*
No Fever	1 (3.7%)	7 (25.9%)	15 (55.6%)	25 (92.6%)
Mild	8 (29.6%)	10 (37.0%)	12 (44.4%)	2 (7.4%)
Moderate	8 (29.6%)	10 (37.0%)	0	0
Severe	10 (37.0%)	0 (0%)	0	0
Total	27	27	27	27 (100.0%)

Table 3 Response to nerve tenderness.

Nerve Tenderness	*Day 1*	*48H*	*96H*	*Day7*
No	15 (55.6%)	14 (51.9%)	15 (55.6%)	21 (77.8%)
Mild	3 (11.1%)	7 (25.9%)	7 (25.9%)	6 (22.2%)
Moderate	7 (25.9%)	5 (18.5%)	5 (18.5%)	0
Severe	2 (7.4%)	1 (3.7%)	0	0
Total	27	27	27	27

Table 4 Response to arthritis.

Arthralgia/Arthritis	*Day 1*	*48H*	*96H*	*Day7*
No	3 (11.1%)	3 (11.1%)	3 (11.1%)	10 (37.0%)
Mild	5 (18.5%)	7 (25.9%)	12 (44.4%)	16 (59.3%)
Moderate	17 (63.0%)	16 (59.3%)	12 (44.4%)	1 (3.7%)
Severe	2 (7.4%)	1 (3.7%)	0	0
Total	27	27	27	27

Table 5 Response to orchitis.

Orchitis	*Day 1*	*48H*	*96H*	*Day7*
No	16 (72.7%)	17 (76.7%)	19 (85.7%)	21 (95.3%)
Mild	3 (13.8%)	3 (13.8%)	2 (9.2%)	1 (4.6%)
Moderate	2 (9%)	2 (9%)	1 (4.6%)	0
Severe	1 (4.6%)	0	0	0
Total	22	22	22	22

Table 6 Response to anorexia.

Malaise and Anorexia	*Day 1*	*48H*	*96H*	*Day7*
No	0	0	1 (3.7%)	13 (48.1%)
Mild	1 (3.7%)	4 (14.8%)	13 (48.1%)	13 (38.1%)
Moderate	16 (59.3%)	23 (85.2%)	13 (48.1%)	1 (3.7%)
Severe	10 (37.0%)	0	0	0
Total	27	27	27	27

Table 7 ENL count changes.

Change in ENL count	*Day 1*	*48H*	*96H*	*Day7*
25% reduction	0	22 (81.5%)	6 (22.2%)	3 (11.1%)
50-99% reduction	0	5 (18.5%)	21 (77.8%)	9 (33.3%)
Complete reduction	0	0	0	15 (55.6%)
Total	27	27	27	27

Out of the total participants, only one individual (3.7%) reported moderate pain on the 7th day, while the remaining 16 reported mild pain.

Out of the cases observed, 5 individuals (23.6%) exhibited mild to moderate orchitis, while 1 individual (4.7%) showed severe symptoms. However, within 48 hours, all 5 cases of mild to moderate orchitis had progressed to a moderate degree. By day 7, only one individual was still experiencing mild symptoms of orchitis **(Table 5)**.

On the first day, all patients experienced varying degrees of malaise and anorexia, ranging from mild to severe. However, within 48 hours, the number of patients with severe malaise and anorexia decreased from 10 (37.0%) to 0.

By day 7, only 1 (3.7%) patient had moderate symptoms, while most patients, 13 (48.1%), only experienced mild symptoms. Additionally, 13 (48.1%) patients were completely free of symptoms by this point **(Table 6)**.

Within 48 hours, a significant reduction of 25-50% was observed in 22 individuals (81.5%), while 5 individuals (18.5%) showed an even greater reduction of 50-99%. By the 7th day, a remarkable 55.6% of individuals (15) had achieved a complete reduction in ENL count, while 33.3% (9 individuals) enjoyed a reduction of 50-99%, and 11.1% (3 individuals) achieved a reduction of 25% **(Table 7)**.

Discussion

The wide geo-prevalence of ENL with high rates in Asia and Brazil and probably lower rates in Africa are more severe in Caucasians and Mongolians than in Negroes. The frequency of ENL appears to be lower in patients on MDT compared with patients on dapsone monotherapy.[4]

The published data shows that the reaction frequency is higher in hospital-based studies than in field-based studies. i.e., 31.3% and 5.7%, respectively.[5] A retrospective study of clinic-based Indian patients from 1990-2000 found the overall prevalence was 24%, a rate of almost 50% in lepromatous and 9% in borderline

lepromatous cases.[6]

The most prevalent were 21-49 years old with male dominance. Multiple episodes are more common with erythema nodosum leprosum. 43.5% and 56.5% had single and multiple episodes respectively.[7] However, a study in Thailand showed ENL occurring at the same frequency in both sexes.[8]

With respect to age, adults are more frequently affected than children and the aged due to a higher absolute incidence of LL leprosy in this period of life.[9] Some studies have shown that ENL is more frequent among patients in the 20-to-40year age group.[10,11]

ENL occurs before, during or after leprosy treatment. A study carried out in Southeast Asia revealed that more than 50% of LL patients developed ENL by the year's end of treatment with sulfone.[12]

The majority of ENL reactions started in the 2nd and 3rd years after the start of MDT. The rate was 6.9 episodes per 100 people yearly.[1,2] The cohort study in India reported the occurrence of reaction in 1.1 % of patients after MDT, most within the first three years.[14]

In many countries, thalidomide is restricted to physicians and pharmacists registered with the STEPS program for thalidomide education and prescribing safety.[15] In Mumbai, the Leprosy Project offers free thalidomide to patients. Alternatively, access to thalidomide is available through CLRTI in Chennai. Given the historical context, prescribing thalidomide requires extreme caution. With its increased availability in India, careful monitoring is essential.

Obtaining written, informed consent is crucial. Patients need to be informed about potential adverse effects, must not share the medication, and female patients are required to use two forms of contraception (one highly effective and one barrier method) and must not donate blood. Since the effects of thalidomide on sperm production are unknown, male patients should also use barrier contraceptives.[15]

Thalidomide is contraindicated[15,17] in cases of drug sensitivity, pregnancy, and severe existing peripheral neuropathy. It should be used cautiously in patients with liver dysfunction, kidney dysfunction, neurological disorders, gastrointestinal issues, hypertension, and hypothyroidism.

Therapy should be withheld or discontinued if the patient does not understand or follow the instructions, if a pregnancy test is positive, if paraesthesia develops, if there is a reduction in sensory nerve action potential by more than 40%, or if the absolute neutrophil count drops below 750/mm^3.[15]

Conclusion

A significant proportion of patients developed extra-cutaneous manifestations. Hence management of Type 2 lepra reaction needs a multispecialty and multidisciplinary approach.

In our open uncontrolled study to know the clinical response of Thalidomide, a total of 27 patients enrolled after informed written consent. On the seventh day, 5 (18.5%) patients showed complete clearance of reactional symptoms. 21(77.8%) patients showed 50 to 99% improvement. One (3.8%) patient showed only 25 % improvement and was considered a treatment failure.

Hence it can be concluded that with our observation Thalidomide is effective in alleviating the ENL reactional symptoms during the acute therapy period.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Author's contribution

LK: Substantial contribution to study design, manuscript writing, has given final approval of the version to be published.

DH: Substantial contribution to acquisition of data, manuscript writing, critical review, has given final approval of the version to be published.

PKS: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

VM: Substantial contribution to acquisition of data, critical review, has given final approval of the version to be published.

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