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Original Article

# Thalidomide in Severe Erythema Nodosum Leprosum (ENL) - Our Experience in Chronic, Recurrent and Steroid-Dependant Cases

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In India, Leprosy is still an important health problem. In the Indian context, there are about 15-20% of leprosy patients come with erythema nodosum leprosum (ENL) as their first presentation. Due to its prolonged course, ENL has a detrimental impact on quality of life (QoL) and is the commonest reason for admission to the hospital. Apart from physical disabilities, ENL causes financial problems for patients and their families as young patients are more often affected, leading to their inability to work and loss of jobs. Early diagnosis and prompt treatment can reduce disability and deformity. Among the various treatment modalities available, steroids and thalidomide are the most effective drugs for ENL. The aim of this research work was to study the demographic and clinical profile of ENL patients with the objective to evaluate the therapeutic response and recurrence rate observed in ENL patients treated with steroids or thalidomide; and to assess the role of thalidomide in chronic, recurrent and steroid-dependent cases of ENL. A longitudinal observational study was carried out at Civil Hospital Ahmedabad from June 2016 to May 2019, comprising type 2 reaction patients. Of 467 total leprosy patients treated during this period, 224 (48%) had either type 1(90) or type 2 (134) lepra reactions. Patients with mild to moderate ENL were given tablet prednisolone 1mg/kg/d followed by tapering by 5mg every two weeks while patients with severe, chronic, recurrent and steroid-dependent ENL were started on thalidomide 400mg followed by tapering by 100mg every four weeks along with prednisolone with the same dose as above. Out of 134 ENL patients, 57 (42.5%) presented with type 2 reaction at 1st visit before starting multi-drug therapy (MDT), 54 (40.2%) after initiation of MDT while 23 (17.1%) after MDT completion. Among 82 patients on prednisolone, 12 (14.6%) patients had recurrence at two months, 18 (22%) at three months, 8 (9.7%) at six months and 5(6.1%) after six months of treatment. Among 52 patients with severe ENL on thalidomide, 5 (9.6%) patients had recurrence at two months, 2 (3.8%) at six months of treatment. Thalidomide decreases the recurrence rate with steroid dependency and helps to limit steroid side effects.

**Keywords:** Type 2 reaction, Erythema Nodosum Leprosum (ENL), Thalidomide, Steroids, Recurrent ENL, Chronic ENL, Steroid-dependent ENL

## Introduction

Leprosy, a chronic granulomatous infection caused by *Mycobacterium leprae*, is still one of the leading causes of physical disabilities and social stigma in India. Earlier, the standard multi-drug therapy (MDT) for Leprosy included

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rifampicin and dapsone for six months in patients with paucibacillary (PB) and three-drug regimen rifampicin, dapsone and clofazimine for 12 months in multibacillary (MB) leprosy patients. However, in 2018 to simplify the treatment, to avoid repercussions of misclassification of patients in either group and for better outcomes in PB patients, WHO amended the guidelines where the same three-drug regimens is recommended to all leprosy patients for 12 months in MB and six months in PB leprosy (WHO 2018). Nevertheless, a significant proportion of patients develop leprosy reactions which are immune-mediated complications of Leprosy leading to neuritis; hence, Leprosy associated disability, so it is crucial to treat them early and appropriately. From field-based studies in India and Brazil, the incidence of ENL in all leprosy patients was found to be 1.2% and 4.5% in MB patients, while it was 13.7% in MB patients from hospital-based studies. According to Voorend & Post (2013) the incidence of ENL in LL leprosy and BL leprosy is 15.4% and 4.1%, respectively.

Type 1 Reaction is a type 4 hypersensitivity reaction that affects borderline Leprosy where patients experience inflammation in pre-existing Leprosy skin lesions along with neuritis (Walker & Lockwood 2008). Type 2 Reaction, i.e. Erythema nodosum leprosum (ENL), is a complex immune syndrome which complicates mainly lepromatous Leprosy (LL, 50%) & rarely borderline leprosy (BL, 10%) patients and characterized by fever, malaise, and crops of painful erythematous nodules (Lockwood 2004, Pocaterra et al 2006). Other organ systems can also be affected in type 2 reaction leading to iritis, neuritis, rhinitis, arthritis, dactylitis, lymphadenitis, orchitis, hepatitis, peripheral oedema, and renal impairment (Walker et al 2014). In most of cases, ENL usually occurs during the course of antileprosy treatment, while in some instances, it may occur before Leprosy is diagnosed and treatment is started and in some after completion of multi-drug therapy (Shaw et al 2000).

ENL is usually a chronic condition with a relapsing and remitting course that may last for several years (Walker & Lockwood 2006). Due to its prolonged course, ENL has a detrimental impact on quality of life (QoL) as reported by Levy and is the commonest reason for admission to the hospital (Yap et al 2016, Levy et al 1973). Other consequences include economic trouble for patients and their families as young patients are more often affected, leading to inability to work (Pocaterra et al 2006, Chandler et al 2015). It can also increase the risk of death in patients (Walker et al 2014, Davison & Kooij 1957). Treatment requires prolonged immunosuppression where options available are corticosteroids, clofazimine and thalidomide either alone or in combination and other immunomodulatory agents like apremilast, non-steroidal anti-inflammatory drugs (NSAIDs), pentoxyphylline, colchicine, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, minocycline, thalidomide analogues, intravenous immunoglobulins, TNF-α inhibitors including biologicals, plasma exchange and immunotherapy (Bhat & Vaidya 2020). In ENL, recurrences are quite problematic, requiring high dose and longer duration of steroid therapy leading to varying degrees of side effects such as an increase in blood sugar, hypertension, osteoporosis, increased risk of infections and much more, thereby increasing morbidity and mortality (Walker & Lockwood 2006, Schreuder & Naafs 2003). The long-term administration of steroids can lead to steroid dependence in these patients. In the immunopathogenesis of ENL there is a role of T cells (Negera et al 2017) and macrophage dysregulation with the over-production of the cytokines like TNF-α; (Haslett et al 2005) a known pyrogen signifying the role of

thalidomide in ENL. Thalidomide is highly effective for the acute inflammation and in maintaining long term immunosuppression with fewer side effects (Teo et al 2002). So it is an ideal drug in the cases of recurrent and steroid-dependant ENL. As we already know about the efficacy of thalidomide in ENL, yet some physicians have curtailments on starting it due to cost-issues, availability issues and especially in females due to its teratogenic side effects due to which WHO recommends strict medical supervision on using thalidomide. We conducted an observational study to find our the demographic and clinical profile of ENL patients, to understand as how the ENL patients with different severity respond to steroids or thalidomide and to study the role of thalidomide in recurrent, chronic and steroid-dependent cases of ENL.

## Materials & Methods

This longitudinal observational study was carried out at Civil Hospital Ahmedabad, Gujarat from June 2016 to May 2019, where cases diagnosed with mild, moderate and severe ENL were recruited (Guerra et al 2002). Approval from the Institution Ethics Committee was obtained (Ref no. EC/certi/25/2016) and informed consent was taken from patients for the data and clinical pictures. Patients with mild to moderate ENL were given oral steroids while the ones with severe, recurrent, chronic recalcitrant and steroid-dependent ENL were treated with oral thalidomide.

**Inclusion criteria were:**

- Patients with mild, moderate and severe ENL.

  * *Mild ENL*: less than ten painful nodules per body segment involved, Moderate: 10 to 20 ENL nodules per body segment; Severe: more than 20 ENL nodules per body segment involved (Guerra et al 2002).

- *Acute ENL*: a single episode lasting less than 24 weeks.
- *Recurrent ENL*: a second or subsequent episode of ENL occurring 28 days or more after stopping treatment for ENL.
- *Chronic ENL*: ENL occurring for 24 weeks or more during which a patient has required ENL treatment either continuously or where any treatment-free period had been 27 days or less.
- *Steroid dependence*: recurrence of symptoms upon discontinuation of steroids or even when steroid doses are tapered gradually (Walker et al 2015).

**Exclusion criteria were:**

- Reproductive age group females.
- Patients with previous intolerance to thalidomide.
- Concurrent use of drugs that may potentiate somnolescence.
- Patients at risk of thromboembolism.

A pre-designed proforma was used to collect the baseline data [including patient demographics, disease-specific parameters like duration, type of leprosy as per Ridley-Jopling classification, the incidence of reactions, possible precipitating factors for reactions, treatment history, relevant past and family history]. A detailed muco-cutaneous and neurological examination to ascertain the type of Leprosy, type of reaction, its severity or any deformity was performed. Systemic examination to discover lymph nodes, bones, joints involvement, or organomegaly if present. Apart from the routine investigations [complete blood count, renal function test, liver function test, urine routine, random blood sugar, chest X-ray], slit skin smear (SSS) for acid-fast staining of bacilli (AFB) was done from skin lesions, ear lobes by slit and scrape method every

six months. SSS were graded as per Ridley logarithmic scale. In every patient, punch biopsy was taken to confirm the diagnosis and special investigations [electromyography (EMG) and nerve conduction velocity (NCV) studies] done as indicated. Patients with mild and moderate ENL were started on oral prednisolone, while ones with severe ENL were given tablet thalidomide. Patients were started on thalidomide after written, well-informed consent and counselling as per the system for thalidomide education and prescribing safety (STEPS) protocol (Zeldis et al 1999). Male patients were advised to use a barrier contraceptive method at the initiation of treatment and up to 1 month after the completion of treatment.

As per our institutional protocol, after appropriate medical clearance & informed consent, patients with severe ENL were prescribed thalidomide 400 mg at night to avoid sedation, followed by tapering by 100 mg every four weeks along with prednisolone 1mg/ kg/ d followed by tapering by 5 mg every two weeks and mild to moderate ENL patients were started on prednisolone 1mg/ kg/ d followed by tapering by 5 mg every two weeks (WHO guidelines, n.d., Azhary et al 2017). The patients were kept on monthly follow up to look for the disease progression and adverse effects. Patients were further evaluated for numbness, tingling, burning over palms, soles to rule out thalidomide induced sensory loss or Leprosy induced neuritis and weight gain, dyspepsia with regular monitoring of blood sugar and blood pressure to look for steroid induced side effects.

***Statistical analysis:*** The data were entered in a spreadsheet and then described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations were done using SPSS (Statistical Package for the Social Science) version 21.

## Results

Among the 467 leprosy patients registered during this duration, 224 (48%) patients presented with signs and symptoms of lepra reactions where 90 (40.2%) had Type 1 reaction and the remaining 134 (59.8%) had Type 2 reaction. Out of the 134 patients with ENL, as per severity assessment, 82 (61.2%) had mild to moderate reaction so were started on steroids, and the remaining 52 (38.8%) patients had a severe reaction with ulcerative lesions in 18 (34.6%) patients. These severe ENL patients were further classified as acute ENL in 6 (11.5%), chronic in 30 (57.7%) and recurrent ENL in 16 (30.8%) (Table 1).

***Demography:*** Among the 134 patients of ENL, the M: F ratio of 2.9:1 with 100 (74.6%) males and 34 (25.4%) females. The mean age overall was 36.62 11.2 years (range 11-70 years), with the largest group in 31-45 years (42; 31.3%) (Table 1).

The majority of these patients belonged to endemic zones of Leprosy in India. 94 (70.1%) were from Gujarat, 10 (7.4%) were migrants, 11(8.2%) came from Madhya Pradesh, 8 (6%) from Uttar Pradesh, 7 (5.2%) from Rajasthan and 4 (3%) from Maharashtra.24 (18%) patients had a positive family history.

***Risk factors:*** Intercurrent infection constituted the major risk factor (94; 70.1%) followed by surgical stress (11; 8.2%), physical stress (9; 6.7%), mental stress (8; 6%), idiopathic (6; 4.4%) and trauma (5; 3.7%).

***Symptomatology:*** Among the 134 patients, 84 (62.7%) patients had lepromatous leprosy and 50 (37.3%) had borderline leprosy. Fifty-seven (42.5%) patients present with reaction at first visit before starting MDT, 54 (40.2%) developed reaction after initiation of MDT while 23 (17.1%) patients had reaction after completion of MDT

**Table 1 : Demography and clinical features of patients with ENL**

| Characteristics | | ENL Patients |
|---|---|---|
| Mean age (in years) | | 36.62 ± 11.2 |
| M:F ratio | | 2.9:1 |
| RJ classification | BL | 50 (37.3%) |
| | LL | 84 (62.7%) |
| Bacteriological index | <4 | 88 (65.7%) |
| | ≥ 4 | 46 (34.3%) |
| ENL presentation (n=134) | Before MDT | 57 (42.5%) |
| | During MDT | 54 (40.2%) |
| | After MDT | 23 (17.1%) |
| Severity (n=134) | Mild | 35 (26.1%) |
| | Moderate | 47 (35.1%) |
| | Severe | 52 (38.8%) |
| ENL presentation type (n=52) among severe ENL cases | Acute | 6 (11.5 %) |
| | Chronic | 30 (57.7%) |
| | Recurrent | 16 (30.8%) |
| Cutaneous lesions (n=134) | Nodular | 116 (86.5%) |
| | Ulcerative | 18 (13.5%) |

Abbreviations used : RJ classification = Ridley-Jopling classification, BL = Borderline leprosy, LL = Lepromatous Leprosy, MDT = Multidrug therapy, ENL = Erythema nodosum leprosum.

(Table 1). Mean duration of ENL was 26.5 4.8 months (range 3-240 months). The number of recurrent ENLs ranged from 3-10 episodes. Most common presenting complaints were painful skin lesions (116; 86.5%), fever (85; 63.4%), joint pain (73; 54.4%), epistaxis (29; 21.6%), slippage of footwear (27; 20.1%) and pedal oedema (24; 17.9%) (Table 2).

***Examination findings:*** On cutaneous examination, the most common findings were nodular lesions in 116 (86.5%) and ulcerating lesions in 18 (13.5%) patients. Systemic examination revealed lymphadenopathy in 102 (76.1%), orchitis in 2 (1.5%) and gynecomastia in 1 (0.7%) (Table 2).

Among nerves, the ulnar nerve (108; 80.5%) was most commonly involved, followed by lateral popliteal (55; 41%) and greater auricular nerve (46; 34.3%) (Table 3). Grade 3 nerve involvement was seen in 15.7% of patients, grade 2 in 44.4% and the rest of 39.8% had grade 1 neuritis.

Patients had a varied range of deformities; the most common was a trophic ulcer in 5 (3.7%), claw hands in 3 (2.2%), lagophthalmos in 2 (1.5%), foot drop and saddle nose in 1 (0.7%) each.

***Laboratory findings:*** On routine investigations, anaemia was found in 26 (19.4%) patients with normal values of all laboratory parameters in others.

Majority (88; 65.7%) patients had bacteriological index (BI) up to 4+ and 46 (34.3%) had BI ≥ 4. The mean BI was 3.9 (range 0.46 to 5.33) (Table 1).

Skin biopsy done in all showed positive clinico-pathological correlation in 114 (85%) patients.

**Table 2 : Associated clinical features**

| Associated clinical feature | Number of patients (%age) (n=134) |
|---|---|
| Fever | 85 (63.4%) |
| Joint pain | 73 (54.4%) |
| Epistaxis | 29 (17.9%) |
| Slippage of footwear | 27 (20.1%) |
| Pedal oedema | 24 (21.6%) |
| Others | |
| 1. Sensory symptoms | 90 (67.1%) |
| 2. Motor symptoms | 18 (13.4%) |
| 3. Orchitis | 2 (1.5%) |
| 4. Lymphadenopathy | 7 (5.2%) |
| 5. Gynecomastia | 1 (0.74%) |
| 6. Neural pain | 34 (25.3%) |

**Table 3 : Neural involvement seen in ENL patients**

| Nerves involved | | Number of cases (%age) (n=134) |
|---|---|---|
| Ulnar nerve | Bilateral | 72 (53.7%) |
| | Unilateral | 36 (26.8%) |
| Lateral popliteal nerve | Bilateral | 29 (21.6%) |
| | Unilateral | 26 (19.4)% |
| Greater auricular nerve | Bilateral | 11 (8.2%) |
| | Unilateral | 35 (26.1)% |
| Supra clavicular nerve | Bilateral | 5 (3.7%) |
| | Unilateral | 9 (6.7%) |
| Infra-orbital nerve | Bilateral | 2 (1.4%) |
| | Unilateral | 5 (3.7%) |
| Supra-orbital nerve | Bilateral | 2 (1.4%) |
| | Unilateral | 4 (3%) |
| Posterior tibial nerve | Bilateral | 5 (3.7%) |
| | Unilateral | 5 (3.7%) |

***Treatment given:*** Out of 134 patients with type 2 reaction, 82 patients of type 2 reaction with mild reaction were given Tab. Prednisolone 1mg/ kg/ d followed by tapering by 5mg in every two weeks, among them 12 (14.6%) patients had recurrence at two months follow up, 18 (22%) at three months, 8 (9.7%) at six months and 5(6.1%) after six months (Table 4). So 43 (52.4%) patients had a recurrence on steroid tapering, and in them dose of steroids had to be increased (Figs. 1 and 2).

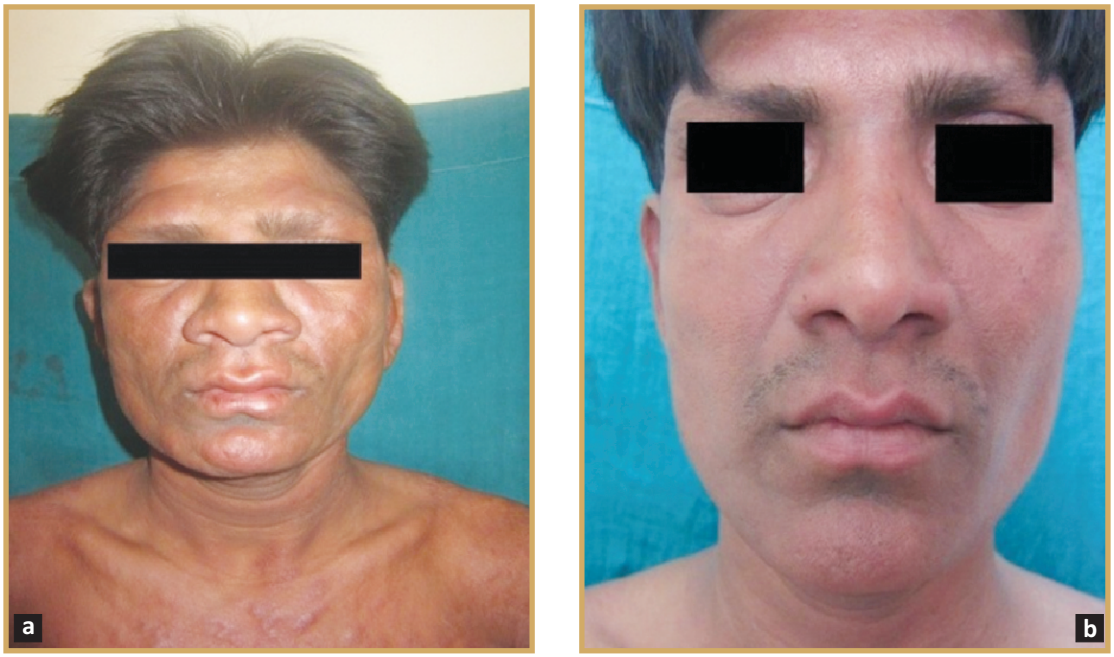


**Fig. 1 (a and b) : Pre and Post-treatment clinical photograph of a patient after 2 months of prednisolone showing improvement but with persistent induration.**

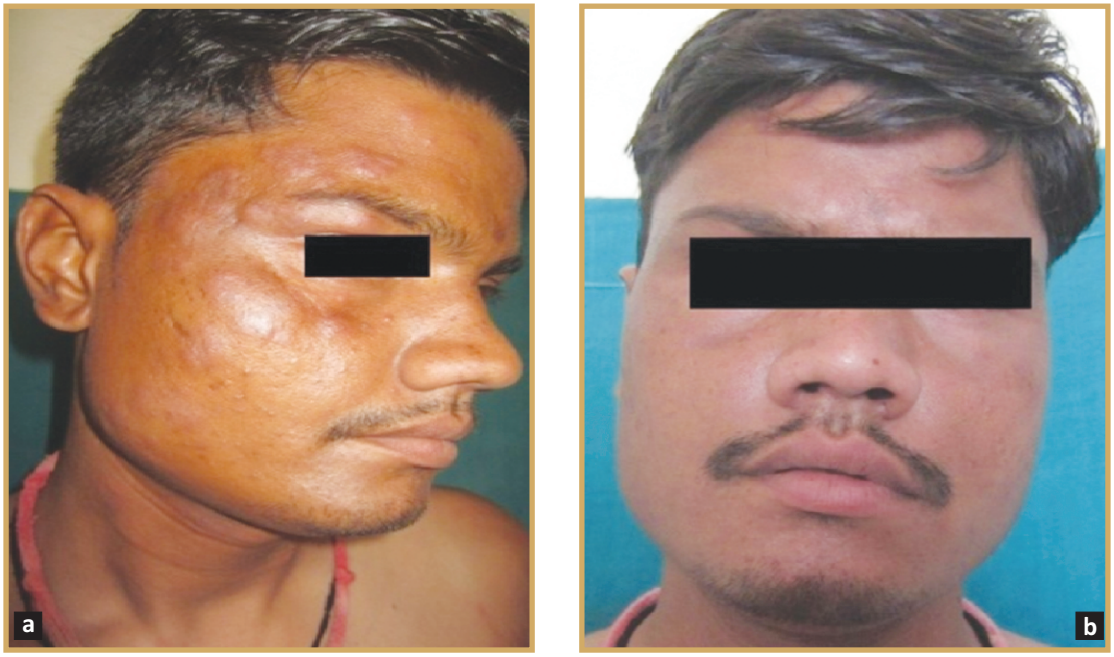


**Fig. 2 (a and b) : Pre and Post-treatment clinical photograph of a patient after one and half month of prednisolone.**

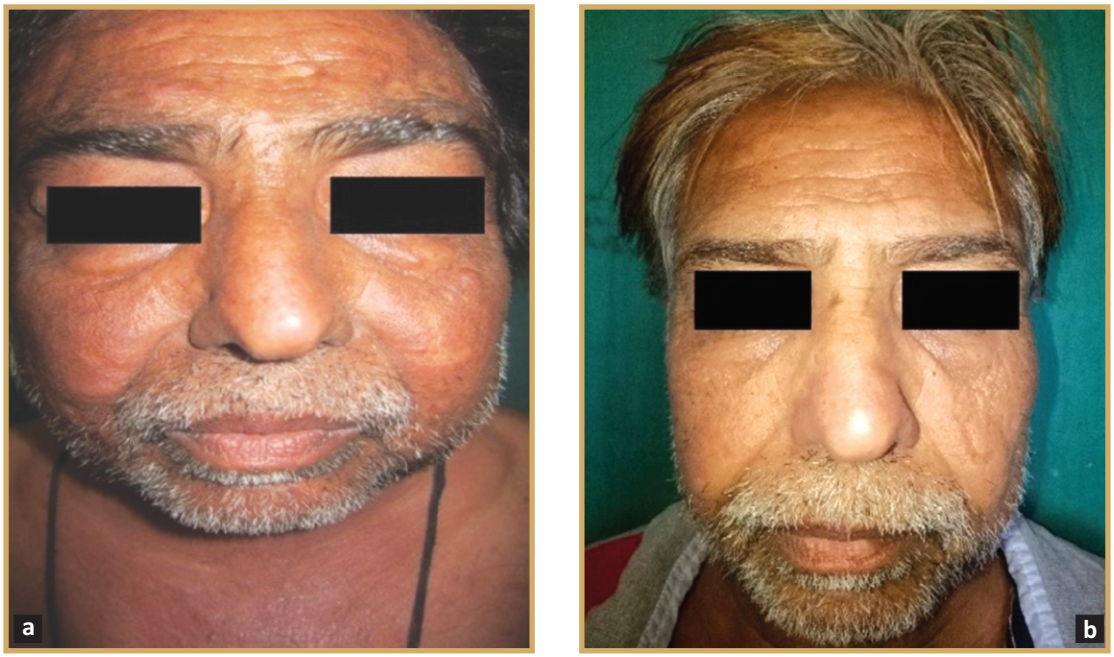


**Fig. 3 (a and b) : Pre and Post-treatment clinical photograph of a steroid dependent patient showing marked improvement after 3 months of thalidomide and prednisolone.**

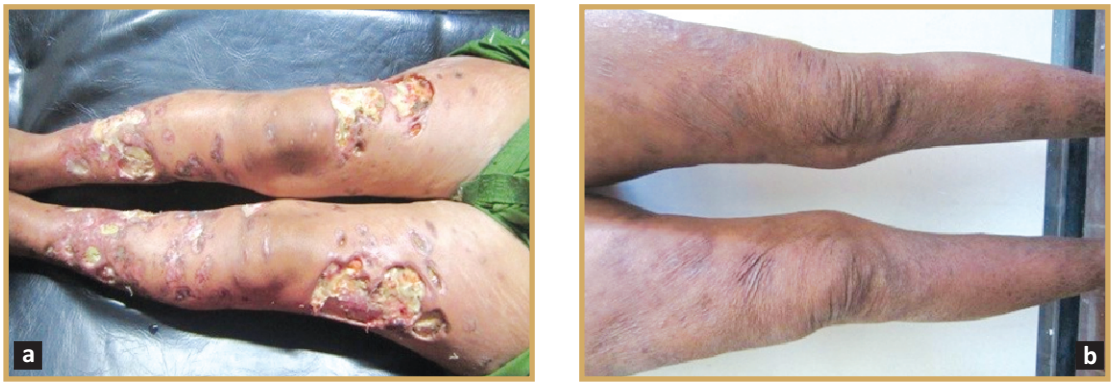


**Fig. 4 (a and b) : Pre and Post-treatment clinical photograph of a patient with ulcerative form of ENL after 2 months of thalidomide and prednisolone showing complete clearing of lesions.**

Fifty-two patients with severe and recurrent type 2 reaction were given tab. thalidomide 400 mg followed by tapering by 100 mg every four weeks along with tab. prednisolone in the same dose as above (Fig. 3). Forty-five (86.5%) patients were already on steroid treatment from outside with steroid-dependency in 35 (77.8%) of them and were given thalidomide, to which they responded beautifully. The patients with ulcero-necrotic ENL also responded very well to thalidomide, with no

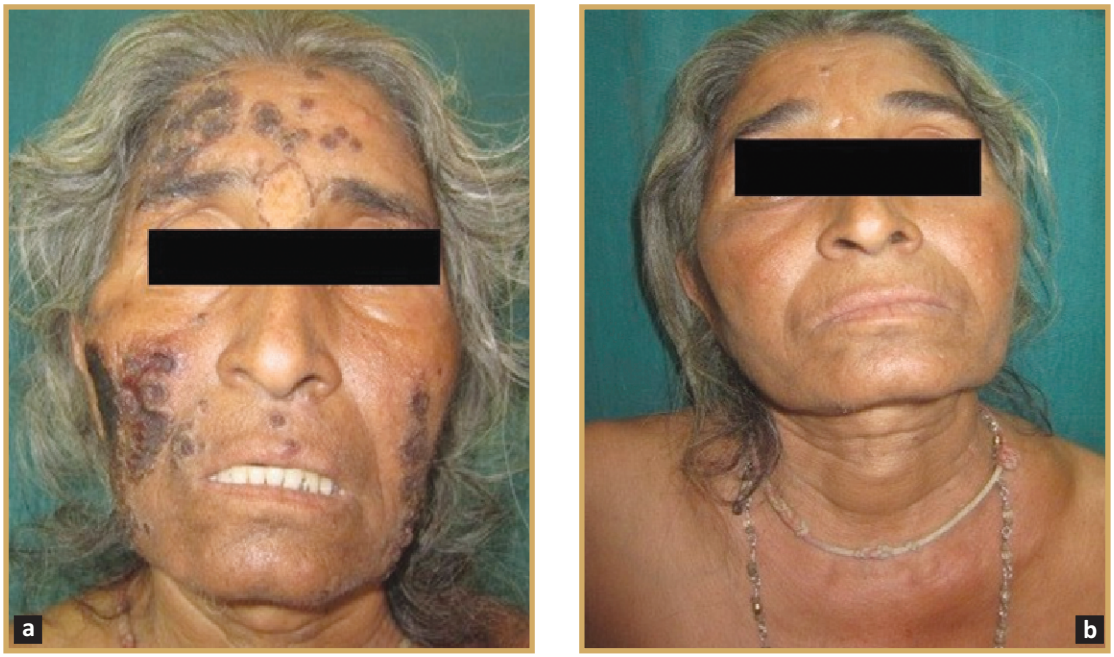


**Figure 5 (a and b) : Pre and Post-treatment clinical photograph of same patient with ulcerative form of ENL showing complete resolution after 2 months of thalidomide and prednisolone.**

**Table 4 : Clinical response to steroids and thalidomide**

| Treatment duration (in months) | Improvement (%age) | | Recurrence (%age) | |
|---|---|---|---|---|
| | Steroid (n=82) | Thalidomide (n=52) | Steroid (n=82) | Thalidomide (n=52) |
| ½ | 57 (70 %) | 47 (90.3%) | - | - |
| 1 | 71 (86.6%) | 52 (100 %) | - | - |
| 2 | 68 (82.9 %) | 47 (90.3%) | 12 (14.6%) | 5 (9.6%) |
| 3 | 52 (63.4 %) | 47 (90.3%) | 18 (22%) | - |
| 6 | 44 (53.6 %) | 45 (86.5%) | 8 (9.7%) | 2 (3.8 %) |
| After 6 months | 39 (47.5 %) | 45 (86.5%) | 5 (6.1%) | - |

recurrences throughout the follow-up period (Figs. 4 & 5).

Five (9.6%) patients had recurrence at 2 months, 2 (3.8%) at 6 months (Table 4). So only 7 (13.4%) patients showed recurrence after thalidomide therapy in spite of the severe and recurrent nature of reactions. These results show that thalidomide treatment is useful for preventing the recurrence of ENL symptoms.

At the end of the study, 39 (47.5%) of steroid

group patients with mild to moderate ENL and 45 patients (86.5%) of thalidomide group patients with severe ENL were in remission. Treatment duration for the steroid group ranged from 6 months to 30 months, while that of thalidomide group was two months to 18 months.

***Side-effects:*** Patients on steroids showed majority of side-effects like weight gain (30; 36.5%), acneiform lesions (24; 29.2%), increased bacterial and fungal infections (18; 22%), diabetes (5; 6.1%), hypertension (4; 4.9%) and gastric ulcers (2; 2.4%) while fewer and mild side effects such as drowsiness (10; 19.2%), pruritis (5; 9.6%), constipation (3; 5.7%) and pedal oedema (3; 5.7%) were seen in patients on thalidomide.

## Discussion

Nowadays, the interest of physicians has been shifted to management of leprosy reactions from Leprosy as they, specially ENL lead to more disability compared to underlying Leprosy (Levy et al 1973). In Ethiopia, it was found that almost 1/3$^{rd}$ of ENL patients suffered for more than two years (Saunderson et al 2000)[7] and in India, it was around 18.5 months (Pocaterra et al 2006; Bhat & Vaidya 2020). A systemic review documented that about 30-50% of ENL patients had moderate to severe form of ENL (Voorend & Post 2013). Management of ENL is itself a significant issue where the main aim is to control inflammation, pain and more importantly, to prevent the recurrence. The recurrence of ENL is seen in around 64.3% of patients, with 15.1% having more than four episodes (Kumar et al 2004). This study describes epidemiology, clinical-investigative profile of ENL and its response to steroid or thalidomide, recurrences and adverse effects observed along with the role of thalidomide in recurrent, chronic and steroid-dependent cases of ENL.

There are varied treatment options available for ENL, which includes corticosteroids, thalidomide, clofazimine, pentoxyphylline, apremilast, NSAIDs, colchicine, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, minocycline, thalidomide analogues like supidimide, revlimid and actimid, intravenous immunoglobulins, biologicals like infliximab & etanercept, plasma exchange and immunotherapy using *Mycobacterium w* vaccine (Bhat & Vaidya 2020). Tenidap, a newer NSAID with significant anti-TNF-α properties can also play an important role against ENL (Bhat & Vaidya 2020). But thalidomide and systemic corticosteroids are still the two most effective and most studied drugs, while other drugs are slow and not very effective in severe ENL (Kaur et al 2009).

Corticosteroids are considered the first-line treatment of ENL. They offer rapid control in inflammation, easily available, cost-effective and can be used with other drugs in various combinations and dosages. Corticosteroids effectively halt the manifestations of ENL with the restoration of the functional and neural impairment impressively. Each subsequent episode of ENL requires a higher dose of steroids and, upon withdrawal, results in recurrence (Kaur et al 2009). In our study, steroid dependence was observed in 77.8% of patients and in an analysis by Upputuri et al, it was seen in 89.10% of patients (Upputuri et al 2020) in comparison to 80% in the study by Darlong et al (2016).

Thalidomide is a steroid-sparing drug effective in treating ENL and provides a rapid anti-inflammatory effect, yet has not been used to its full capability due to several reasons like risk of teratogenicity, neuropathy, poor availability and cost (Walker et al 2007). Cost is one of the most important limiting factors in developing countries like India. Along with it there are certain other issues like debatable dosage and duration of

thalidomide, usually, a dose of 100 to 400 mg/day is employed and is adjusted according to severity (Penna et al 2005).

The patients included had a mean age of 36.62 11.2 years which concurs with Upputuri et al (2020) and Adhe et al (2012) where the average age was 34 and 39 years, respectively. In the present study, M:F was 2.9:1 likewise, in a 5-year analysis, it was 2.3:1 Upputuri et al (2020), while Kumar et al (2004); reported M:F ratio of 1.5:1 and Adhe et al (2012) reported it as 1.8:1.

A significant number of patients (57; 42.5%) present to us with type 2 reaction directly; likewise Lockwood (1996), noted type 2 reaction in a high percentage of their patients (41.3%) at the time of presentation and Kaur et al (2009) reported 33.3% such patients. It is obvious that many patients seek treatment only when they get frightened by the sudden development of lesions, particularly over the face, or painful symptoms of neuritis due to reaction.

In the present study, thalidomide was started at the dose of 400 mg OD for a month followed by tapering by 100 mg every four weeks. This regimen was different from the one given by Upputuri et al, where thalidomide was started at the dose of 300 mg OD for a month and then reduced slowly by 100 mg each month as a fixed-dose regimen for two months and then tapered depending on the clinical response of the patient Upputuri et al (2020), Nidhi et al (2009) who started with 300 mg OD for 1-2 months followed by a fixed dose of 200 mg for two months and then 100 mg for two months and then tapered based on patients marked clinical improvement. Kaur et al (2009) used thalidomide at a dose of 300 mg OD for one week, which was gradually reduced by 50 mg every two weeks.

As mentioned earlier, a greater frequency of adverse effects was observed in the cortico steroid group, which is in agreement with other studies Kaur et al (2009). The most common adverse events associated with thalidomide were drowsiness, constipation, pruritis and pedal edema similarly; Kaur et al (2009) reported somnolescence as the most common side effect in thalidomide group followed by pruritis and constipation. Upputuri et al (2020) and Parikh et al (1986) observed pedal edema as the most common side effect in their patients. The cause of pedal edema can be stasis of blood in the extremities, and it usually occurs at high doses of thalidomide (Upputuri et al 2020). Peripheral neuropathy, a most severe side effect to occur, has been reported in 1–70% of patients (Stirling 1998)' while no similar case was observed in our study similar to Kaur et al (2009) where no patient had the side-effect of peripheral neuropathy. Another study reported peripheral neuropathy and deep vein thrombosis (DVT) as the most common adverse events (Drummond et al 2019). In our study, none of the patients had DVT similar to that reported in the study by Upputuri et al (2020) and Darlong et al (2016).

In the present study, although the groups were non-comparable we observed severe ENL patients on thalidomide showed early recovery with lesser relapses similarly, a comparative study between 3 groups found a lower recurrence rate in the thalidomide alone group, followed by the prednisolone plus thalidomide group during the 20-week treatment period (Kar & Gupta 2016). Kaur et al (2009), too in their randomised study, showed excellent clinical response with thalidomide. In another study comparing the efficacy of thalidomide and pentoxifylline in 44 ENL patients, response to thalidomide was significantly better than to pentoxifylline (Sales et al 2007).

In the present study, seven (13.4%) patients on thalidomide had a recurrence, 5 (9.6%) at two months and 2 (3.8%) at six months of tapering

thalidomide; they were restarted on the same dose of thalidomide and are now in remission while 43 (52.4%) patients in steroid group had relapses as soon as tapering was started and had to increase steroid doses in them.

Patients with recurrent ENL also responded well to thalidomide. In the present study recurrence rate after thalidomide was 13.4%; likewise, ENL recurrence was observed in 16.2% of patients in the study by Upputuri et al (2020), while another study reported only 6% rate of recurrence post thalidomide (Kaur et al 2009).

To conclude, we experienced thalidomide to be very effective in the management of severe cases with necrotic lesions, chronic, recurrent and steroid-dependent cases of ENL. Thalidomide decreased the recurrences to a large extent too. So this study fills in the known role of thalidomide in controlling ENL by inducing a fast and effective response with minimal adverse effects. Still, there are a few limitations that have to be taken into account, like it is not readily available, teratogenicity, and cost, making its continued administration over a long duration not possible in the developing countries with maximum case load of Leprosy. So these had to be looked into as thalidomide is well tolerated and offers an effective treatment of this severe condition, which makes it worthy to perform further studies with large patient populations to compare the effects of thalidomide with other drugs for ENL and to establish safe regimens of thalidomide. Thorough counselling to the patient to follow STEPS and use dual contraceptives to avoid pregnancy is of paramount importance. USA based Celgene Corporation has developed two thalidomide analogs, Revlimid, and Actimid which are anti-myeloma agents and can also be used to treat ENL (Kaplan 2000). Other non-teratogenic analogs of thalidomide such as supidimide have also been tried for the treatment of ENL with success. These thalidomide analogues would be a welcome addition in the management of ENL.

Study limitations include the non-comparative groups as it was only an observational study where routine treatment protocols were followed, so the groups could not be compared at various parameters like disease duration, severity, and treatment duration and response rate.

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