

Morbidities & Mortality in Erythema Nodosum Leprosum: A Hospital based study in Western Odisha, IndiaDebabrata Nayak¹, Sibasish Patro², Nikhil Ranjan Das³, Subhasree Madhual⁴, Sambit Ranjan Dalei⁵¹Assistant Professor, Department of Dermatology, Pandit Raghunath Murmu Medical College, Baripada, IND²Associate Professor, Department of Dermatology, Saheed Laxman Nayak Medical College, Koraput, IND³Assistant Professor, Department of Dermatology, Saheed Laxman Nayak Medical College, Koraput, IND⁴Assistant Professor, Department of Dermatology, Institute of Medical Sciences & SUM Hospital, Bhubaneswar, IND⁵Assistant Professor, Department of Dermatology, Fakir Mohan Medical College, Balasore, IND

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Abstract

Background: Erythema nodosumleprosum is a chronic recurrent multisystem immune complex mediated reaction of leprosy which primarily affects skin, nerve and other organ systems of the body. The morbidities are very high due to its chronic and recurrent nature and involvement of various organs of the body. The mortality associated with ENL is underscored due to its chronicity and usually patients are lost to follow up. There is paucity of data regarding morbidity and mortality in ENL in existing literature. So the present study was conducted among the patients of ENL regarding morbidity and mortality in a tertiary care hospital present in an endemic zone.

Method: It was a prospective hospital-based study was carried out for 3 years from 1st September 2014 to 31st August 2017. Demographic details, clinical features, comorbidities and systemic association were collected from 137 diagnosed patients of ENL. Laboratory investigations, slit skin smear of AFB and histopathological investigations were also done.

Result: Majority of the patients were males 109 (79.5%) and belonging to lower socioeconomic status 75 (54.8%). Most of the patients (70%) belong to age group of 21-40 years with a rural background (89.8%). Pain was the most common morbidity (92%) and arthritis being the most common association (76.6%). Psychological stress was one of the important morbidities (62.8%) in ENL patients. 14 patients died during this study period.

Conclusion: Most of the patients were males (79.5%), in their 3rd decade of life (37.9%) and belong to lower socioeconomic status (54.8%). Recurrent pain (92%) and fever (88.3%) were most common morbidities and arthritis (76.6%) being the most common systemic involvement. Data from this study will be helpful for early effective management of reactions of leprosy to reduce the morbidity, mortality and research cum prevention strategy at various levels.

Categories: Dermatology**Keywords:** prospective study, leprosy reaction, western odisha, mortality, morbidities, erythema nodosumleprosum

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Introduction

Leprosy is a chronic infective granulomatous inflammatory disease affecting the skin, superficial peripheral nerves and other organs. It is caused by Mycobacterium leprae, an obligate intracellular parasite. The clinical spectrum and histopathologic variations of the disease depend on the host immune status. The patients with high cell mediated immunity (CMI) present in tuberculoid pole whereas with low CMI load present in the lepromatous

pole. Most often insidious course of leprosy is interrupted by acute leprosy reactions, which are immune mediated complications. Those play significant roles in the morbidity & mortality of the disease. Reactions in leprosy comprised of Type 1 or reversal reaction, type 2 or erythema nodosumleprosum (ENL) and Lucio phenomenon. The type 1 reaction is a delayed hypersensitivity reaction, whereas type 2 leprosy reaction or erythema

nodosumleprosum is a Type 3 hypersensitivity reaction mediated by immune complexes deposition. Cytokines like Interleukin-6 (IL-6), Interleukin-8 (IL-8), transforming growth factor beta 1 (TGF- β 1), TNF alpha and IL-1 beta play key roles in pathogenesis of ENL. ENL presents in various forms like acute, recurrent or chronic forms. Its incidence among leprosy cases varies from about 10% in borderline cases to as high as 50% among lepromatous leprosy patients. [1] Overall incidence of ENL among MB cases was found to be 8.9% in one Indian cohort. [2] Clinical manifestations may include fever, arthritis, subcutaneous erythematous tender nodules, synovitis, lymphadenopathy, neuritis, iridocyclitis, epididymo-orchitis, hepatitis, glomerulonephritis etc. Risk factors for development of type 2 reaction include infection, anemia, pregnancy, lactation. All these morbidities usually occurring in young patients restrict their ability to work and provide their families with financial supports.

There are very few published studies examining the relationship between leprosy reactions, its morbidities and death. The western part of Odisha used to be an endemic region for leprosy for a long time and in some of the districts, the prevalence is very high even in the post-elimination era. Majority of the population belongs to agricultural and low income background; where job related migration and access to treatment facilities are scarce predisposing them to leprosy and therefore ENL. The present study was carried out to find out morbidities & mortality among the patients of ENL in this endemic area of Western Odisha, India.

Materials and Methods

It was a hospital based prospective study undertaken by department of Dermatology, Venereology and Leprology at VSS medical college and hospital, Burla, India. The study was conducted after due approval from institutional ethical committee (IEC/IRV-60/13 dated 25/11/2013). Total 137 patients of ENL were enrolled in the study using following criteria.

Inclusion Criteria

All patients diagnosed with leprosy attending the OPD and indoor presenting with erythema nodosumleprosum from 1st September 2014 to 31st August 2017 were included in study.

A patient was clinically diagnosed as ENL and included in the study when he/she presented with brightly erythematous, slightly raised nodules or plaques of variable sizes which were of acute onset, evanescent and appearing in crops. The lesions were warmer than the surrounding skin, tender than normal skin and blanched with pressure. They were often associated with various constitutional signs and symptoms like pain, fever, arthralgia, malaise

and headache. Bullous and necrotic lesions were also been presented.

Exclusion Criteria

All patients with erythema nodosumleprosum not giving consent for clinical and histopathological examinations, digital photographs and not adhering to proper treatment were excluded from study. Also, the patients presenting with fever, pain, multiple tender erythematous lesions seen in various other conditions like erythema nodosum, erythema induratum, papulo necrotic tuberculides, drug reaction, SLE and vasculitis were excluded from the study.

Study Tool

A data extraction sheet was prepared as per the study needs. It included 4 sections, i.e. patients' demographic details, complete history, clinical / dermatological findings and laboratory/ histopathological investigations.

Demographic details: Detailed information in all patients regarding demographic details such as (age, sex, residence, occupation, educational status, socioeconomic status) was recorded.

History: Duration of HD and ENL, number of episodes of ENL, Past history of treatment for Hansen's disease, ENL or any other co morbidities, family history of leprosy and presence of any history of significant health problems other than Hansen's disease were noted properly.

Clinical/dermatological finding: All cases in the study were subjected to detailed general and systemic examinations. Proper dermatological examination was done in all cases to determine status of Hansen's disease, nerve involvement and for diagnosis of erythema nodosumleprosum. Other areas of skin, nail, hair, mucous membrane and lymph nodes were also examined to rule out abnormalities or coexisting dermatoses. **Lab investigations:** Investigations like CBC, RFT, LFT, FBS, PPBS, routine and microscopy examinations of urine and stool, slit skin smear for AFB and histopathological study were conducted in all cases.

Data Collection Method

The data of 137 patients of ENL were recorded from 1st September 2014 to 31st August 2017 in a data extraction sheet. The study variables such as demographic details, complete history, clinical/dermatological findings and laboratory examination reports were recorded for all patients of ENL. Laboratory investigations were done to establish various systemic involvement like arthritis, glomerulonephritis and co morbidities like diabetes mellitus, hypertension, co-infections, stress and social stigma. The death reports of all 14 patients and their probable causes (though not directly related to ENL) during these 3 year follow up period were noted.

Data Analysis

At the end of 3 years of collection of data, all the collected data were cleaned, compiled and tabulated as per the study objectives. Data were analyzed with the help of IBM SP.

SS Statistics, version 21.0 (IBM Corp., Armonk, NY). All the descriptive data were presented with frequency and percentage.

Results

During this study period, 1972 cases of leprosy patients had reported to this tertiary care hospital, out of which 242 (27%) were in leprosy reactions. 105 (5.32%) patients had type I reaction and 137 (6.95%) had type II reaction (ENL).

Majority of patients were males (79.5%) with male to female ratio 3.8:1. Most of the patients (70%) belong to age group 21-40 years, mean and median age of the patients found to be 33.5 year and 35.6±4.3 year respectively. 123 (89.8%) patients were from rural area and 14 (10.3%) from urban area. Majority (54.8%) of the patients belong to lower socioeconomic status. 48 (35%) patients were found to be illiterate.

Table 1: Demographic details of ENL patients (n=137)

Characteristic	Number	Percentage
Gender		
Male	109	79.5
Female	28	20.5
Age Distribution (in years)		
0-10	0	0
11-20	9	6.5
21-30	52	37.9
31-40	44	32.1
41-50	20	14.5
51-60	7	5.1
>61	5	3.6
Residence		
Rural	123	89.8
Urban	14	10.3
Socioeconomic status		
Upper	4	2.9
Upper middle	9	6.5
Lower middle	17	12.4
Upper lower	32	23.3
Lower	75	54.8
Educational status		
Illiterate	48	35
Had received Primary education	37	27
Had Secondary education	39	28.5
Had received Higher education	13	9.5

Pain was the most common morbidity observed in 126 (92%) patients followed by fever in 121(88.3%) patients.

Table 2: Morbidities of ENL

Sl. No	Morbidities	Number of cases
1	Pain	126 (92%)
2	Fever	121 (88.3%)
3	Recurrent Nodules with Ulceration	111 (81%)
4	Motor Impairment	24 (17.5%)
5	Deformity	14 (10.2%)

Arthritis, being the most common systemic association found in our study in 105 (76.6%) patients followed by peripheral edema in 45(32.8%) patients and glomerulonephritis in 37(27%) patients.

Table 3: Morbidities due to systemic involvement in ENL

Sl. No	Morbidities	Number of cases
1	Arthritis	105 (76.6%)
2	Peripheral Edema	45(32.8%)
3	Glomerulonephritis	37(27%)
4	Orchitic	8 (5.8%)
5	Lymphadenitis	13 (9.4%)
6	Ocular changes	10 (7.2%)
7	Hepatitis	12 (8.7%)

During the course of treatment 12 (8.7%) patients had diabetes mellitus, 8 (5.8%) patients had hypertension and 12 (8.7%) patient had xerosis of skin.

Table 4: Morbidities due to treatment of ENL

Sl. No	Morbidities	Number of cases
1	Diabetes Mellitus	12 (8.7%)
2	Hypertension	8 (5.8%)
3	Cushingoid features	3 (2.1%)
4	Xerosis	12 (8.7%)
5	Pigmentation	8 (5.8%)
6	Hypersensitivity reaction	4 (3%)
7	Sensorineural Impairment	5 (3.6%)

Psychological stress was one the important morbidity evaluated in this study in 86 (62.8%) cases. Apart from this, there was social stigma in 35 (25.6%) cases, co-infection in 46 (33.6%) cases and neuritic pain in 98 (71.5%) cases.

Table 5: Other morbidities of ENL

Sl. No	Morbidities	Number of cases
1	Psychological stress	86 (62.8%)
2	Social stigma	35 (25.6%)
3	Neuritic Pain	98 (71.5%)
4	Co-infection	46 (33.6%)

About 35.7% patients had presented to this tertiary care hospital in their first episode of ENL. Moreover 47 patients had reported to our hospital for the first time after more than four episodes of ENL.

Table 6: Number of ENL episodes experienced by patients

Number of ENL episodes	At Presentation	During follow up
Single	49 (35.7%)	36 (26.3%)
Second	25 (18.3%)	43 (31.4%)
Third	8 (5.8%)	14 (10.2%)
Fourth	6 (4.4%)	3 (2.1%)
More than four	47 (34.3%)	41 (30%)

42 (30.7%) cases had two nerve involvement followed by 25 (18.2%) cases who had more than 3 nerve involvement.

Table 7: Nerve involvement in ENL

Number of Nerves Involved	Number of cases
1	22 (16%)
2	42 (30.7%)
3	25 (18.2%)
4	8 (5.8%)

During this follow-up study, 14 patients died. Out of which the death of 8 patients was due to septicemia, four patients due to cardiac failure and two patients due to renal failure. However, the death of all these patients may not be directly related to ENL.

Table 8: Mortality in ENL (n=14)

Sl. No	Morbidities	Number of cases
1	Septicemia	8 (57.1%)
2	Cardiac Failure	4 (28.6%)
3	Renal Failure	2 (14.3%)

Discussion

The WHO launched 'Towards zero leprosy: global leprosy (Hansen's disease) strategy 2021–2030' aligned to the neglected tropical diseases road map 2021–2030. The Strategy calls for a vision of zero leprosy: zero infection and disease, zero disability, zero stigma and discrimination and the elimination of leprosy (defined as interruption of transmission) as its goal [3]. In India, in the year 2021-22 the prevalence rate of Leprosy was found to be 0.45/10,000 population [4].

The incidence of ENL in patients with multibacillary leprosy is up to 24%. ENL can occur before, during or after MDT treatment, but it is most common in the first 6 months of treatment. ENL is a severe, chronic and recurrent reaction and variable opinions are available for the management of this severe reaction. Steroids have been predominantly and extensively used for the treatment of ENL and also for prevention and treatment of nerve function impairment [5]. Frequently, it is difficult to control cases of ENL with prescribed dose of steroid (prednisolone 40 mg/day). Many patients develop new ENL lesions and there is the chance of steroid dependency in some situations when the steroids are tapered.

This prospective study was conducted in a tertiary care hospital of Western Odisha from 1st September 2014 to 31st August 2017. In our study ENL was more prevalent (137/242=56.61%) than the reversal (Type I) reaction (105/242=43.38%) which was similar to the study conducted by Motta AC et al where ENL was more prevalent (63.9%) as compared to type I reaction (36.1%) and also study done by Nery ZA et al, where reversal reaction occurred in 45% cases and ENL occurred in 55% cases [6,7]. This could be due to severity and chronic nature of the diseases and in addition to that a hospital-based study.

Among 137 patients of ENL, males outnumbered females. Results shown by various studies i.e. Motta et al in 2012 (68%), Walker et al in 2014 (73.68%), Prasad et al in 2013 (68.18%) were comparable to our study where 79.5% were males [6,8,9]. The reason could be early health seeking behavior among male patients and various social factors.

In this study, most of the patients belong to 21-40 years age group (70%). Comparable results were also obtained by Prasad et al in 2013 (mean age 40±13.6) and Walker et al in 2015 ENLIST group (median age 32 year), which could be attributed due to prolonged incubation period of the disease and increased immunological competence in the middle age group [9,10].

In the study conducted by Guerra JG et al in 2004 in endemic area of central Brazil near about 30% of ENL patients were found to be illiterate, which was

almost analogous in the present study (35%) [11]. In our study majority of cases had 81% nodular and necrotic lesions which finding was consistent with the study of Walker et al 2014 [8].

Various precipitating (Risk) factors associated with the development and severity of ENL like high BI, family history of contact, co-infection, HIV, pregnancy, Lactation and lepromatous leprosy were major contributors as reported by various workers such as Voorend CGN et al, Pocaterra et al, Manandhar et al, AMFES cohort study and Kumar B et al. Among these high BI was predominant finding [12-16]. Similar findings were also obtained in the present study such as family history of contact, HIV, Lactation, Co-infections, anemia, Stress and high BI (being the highest in 22.68% cases). In the study conducted by Motta AC et al, 39.1% of cases exhibited different co-infections which was comparable to our study where co-infections was seen in 33.6% cases [6].

Most of the studies about ENL had reported various systemic associations like arthritis, glomerulonephritis, hepatitis, lymphadenitis, orchitis in moderate to high proportion of cases (Walker et al in 2014 and Prasad et al in 2013) [8,9]. Arthritis was the most common association in 76.6% of cases followed by peripheral edema (32.8%), glomerulonephritis (27%) and hepatitis (8.7%) in our study. These similar systemic associations had also been reported by Vengadkrishnan et al in 2004 & Mendiratta et al in 2014 [17,18]. The severity of these systemic findings had major proportion of morbidities and disability among the ENL patients of our region. About one third of cases had some morbidity like diabetes mellitus, hypertension, xerosis, pigmentation due to treatment related causes. These findings could be due to the result of long-term corticosteroid and MDT therapy.

In our endemic zone nearly one third of patients who came for 1st time consultation when 1st episode of ENL had occurred. However, almost similar percentage of patients had reported for the 1st time after 4th episodes ENL. The rationale behind these observations might be changing socio-economic and educational status in rural area which reflects their prompt health seeking behaviour. However, stigma associated with leprosy still obstacle the patients to attend the health care centre in early stage. Multiple episodes of ENL (≥ 4 episode) in an Indian and other foreign hospital-based study as reported by Voorend CG et al in 2013 were found to be 23.5% and 24% respectively, however in the present study it was found to be 38.7% which could be attributed to multiple risk factor associated with the disease [12]. The psychological stress was one of the major contributors of morbidity due to the chronic and recurrent nature of ENL which was reflected in our study (62.8%). This stress might be due to the long-term corticosteroid therapy, social

stigma and disability. Nerve involvement is an important finding in leproreactions which was reflected in our study of multiple peripheral nerve involvement (30.7% cases of 2 nerve involvement). In present study nerve enlargement and palsy were seen in 17.5% of patients. These findings of our study showed the importance of nerve examination and early treatment of ENL. During follow up of ENL patients over a period of 3 years 14 patients (10.2%) died of various causes though not directly related to ENL. Mortality associated with ENL were also reported in Walker et al in 2014 [8].

Conclusion

Our study findings suggested that suffering from the ENL in terms of morbidities & mortality are still high even after the post elimination era. Most of the ENL patients were males (79.5%), in their 3rd decade (37.9%) of life and they belong to lower socioeconomic status (54.8%). Recurrent pain (92%) & fever (88.3%) were most common morbidities & arthritis (76.6%) being the most common systemic involvement. In addition to that psychological stress (62.8%), social stigma (25.6%) & treatment related morbidities were also contributing major impacts on this disease. Larger multicentric community-based study may be recommended for the grey area of this neglected disease. Data from this study will be helpful for early effective management of reactions of leprosy to reduce the morbidities, mortality & research cum prevention strategies at various levels.

Limitations: This was a prospective single centre study with small sample size conducted in leprosy endemic zone of western Odisha. Multicentric field-based studies should be carried out to reveal the actual morbidities & mortality.

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