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Original Article

Risk Factors for Erythema Nodosum Leprosum: A Case Control Study in a Tertiary Hospital of Western Odisha, India

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Erythema nodosum leprosum (ENL) is a serious, often recurring and disabling, immunologically mediated reaction occurring in leprosy which often requires hospitalization. There are published several studies of ENL, but systematic studies regarding the risk factors associated with ENL in the post elimination era are few. The aim of the study was to determine the risk factors associated with ENL in a tertiary care centre in Western Odisha. This is a case control study involving 292 patients of leprosy who attended the Dermatology OPD of this tertiary care centre. These constituted 97 patients with ENL and 195 patients without ENL who attended the OPD during this period. Detailed history, clinical examination, slit skin smears were done. These included gender details, age, area of residence (rural/urban), education and socioeconomic status. The most common subtype of leprosy observed in ENL was lepromatous leprosy followed by borderline lepromatous type. Patients diagnosed with initial high BI and lepromatous leprosy were found to be significant risk factors for development of ENL. Skin diseases, Anaemia and Diabetes Mellitus were found to be more prevalent in ENL patients.

Keywords : Erythema Nodosum Leprosum, Risk Factors, Western Odisha, India

Introduction

Leprosy, an ancient disease, is still associated with fear, stigma and social discrimination due to its chronicity and associated disabilities & deformities. It is caused by *Mycobacterium leprae*, an obligate intracellular parasite, which affects the skin, peripheral nerves, and other organs of the human body (Lockwood 2004). Leprosy is usually linked with poverty and is often observed in the economically productive age group (20 to 60 years), more in males which may be related to social factors and health seeking behaviour of the population, illiteracy, job related migration, overcrowding, malnutrition,

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repetitive trauma and poor knowledge of the curability of the disease and available treatment facilities may also be some of the contributing factors towards the chronicity of disease and development of ENL. Contact history of leprosy in the family is an important risk factor found for the incidence of leprosy but its association with ENL has not been properly investigated. Various comorbidities observed may be a chance finding or may be related to the treatment of ENL (long and intermittent H/O taking steroids) such as acne, dermatophytic infections, diabetes mellitus etc.

Leprosy disease manifests in a wide clinical spectrum which extends from the tuberculoid pole to the lepromatous pole, and also includes the Indeterminate and Neuritic types of the disease. The clinical manifestations depend basically on the cell mediated immunity (CMI) of the host, bacillary load of the organism, which contribute and determine the clinical manifestations, presentation and morphology of the disease (Boggild et al 2004). In some cases, the course of the disease is often interrupted by events of acute inflammation, or "reactions". These 'reactions' are immunologically mediated which may occur before, during or following the completion of multidrug therapy (MDT) (Pandhi & Chhabra 2013). It usually occurs during the course of treatment but can occur before treatment as a presenting symptom complex or even after completion of treatment and in longstanding standing untreated cases. Leprosy reactions are the major cause of nerve function impairment as well as involvement of organ systems which lead to leprosy associated disabilities and the resulting physical, mental and economic consequences (Walker et al 2014). Therefore, there is an urgent need to diagnose and provide prompt treatment to the affected patients (Kahawita et al 2008).

Erythema nodosum leprosum (ENL) or Type-2 lepra reaction is a manifestation of type-III hypersensitivity response, wherein, antigen-antibody immune complex formation occurs in response to the presence of the leprosy bacillus and /or its products and these are deposited in the skin and other tissues of the host. It has been reported that ENL affects about 50% of patients with lepromatous leprosy (LL) and 10% of borderline lepromatous (BL) patients (Walker et al 2014). It often presents with appearance of painful skin nodules, fever, with and without nerve involvement and neuritis, often associated with lymphadenopathy, joint pains and arthralgias, which may be serious, difficult to manage and often requires hospitalisation (Levy et al 1973). These episodes are usually abrupt and unpredictable, and exacerbations and remissions are commonly seen.

India achieved elimination of leprosy as a public health problem (prevalence less than 1/10,000) at the end of 2005. Afterwards the programme was merged with general health system leading to issues of competing priorities and diluted/ weakening expertise among caregivers. During the post elimination era, with widespread availability of MDT but lack of a vertical programme and dwindling expertise in leprosy, timely diagnosis and management of leprosy cases especially having reactions assumes immense importance. As the situation will be different in various geographical settings, an attempt has been made to conduct a systematic study regarding the risk factors associated with ENL in this area of Western Odisha so that area specific research and intervention strategies could be worked out.

Material and Methods

After due approval of the protocol by the Ethical Committee of the institute, this study was conducted in the Department of Dermatology

and Venereology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla from November 2013 to October 2015. The participants were informed in detail about the study. A total of 292 clinically diagnosed cases of leprosy who attended the department of Skin and VD during the above period and agreed to be a part of the study after reading the participation information sheet, were enrolled for the study after obtaining their written consent. All cases enrolled into the study were subjected to clinical examination (general and systemic), dermatological examination and investigations like complete blood count, urine and stool (routine and microscopic examination), renal function tests, liver function tests and fasting glucose level. Slit skin smear for acid fast bacilli (AFB) was done from lesions and four other areas. Histopathological study of lesions was done in doubtful cases. Ninety- seven patients presented with ENL (33.2%), while the other 195 leprosy patients gave neither history nor presented with ENL (66.8%). The results were tabulated and analysed utilizing Chi square test. A p value of equal to and < 0.05 was considered statistically significant.

A detailed history of all patients regarding demographic details such as age, sex, educational status (revised Udai Pareek scale - Holyachi & Santosh 2013), socioeconomic status (Kuppuswamy scale - Bairwa et al 2013), literacy status, area of residence, duration of leprosy 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 taken and recorded.

Complete clinical examination (general and systemic), dermatological examination and investigations like complete blood count, urine and stool-routine and microscopic examination, renal function tests, liver function tests and fasting glucose level were carried out. Slit skin smear for acid fast bacilli (AFB) was done from lesions as well as four other areas. The bacillary index of the smears was graded as per Ridley's logarithmic scale. Histopathological study of lesions was done in doubtful cases.

Results

The demographic characteristics of all 292 patients attending the facility are depicted in Table 1. Male predominance was seen with a male female ratio of 4.38 vs. 1.6. Majority of the patients were from rural background and belonged to lower socio-economic status. The mean age was found to be 34.7±11.31 years in the patients with ENL and that of the rest was 35 years respectively. Most of the patients attending the OPD facility were in the age group of 21-40 years.

Sixty-five (68.4%) out of 97 patients in the ENL group were literate and had received some education. Although the literacy rate in the non ENL patients was 83% this difference was not statistically different. Rather more percentage of patients were highly literate in the ENL group (9/97). The mean duration of Hansen's disease was found to be 19.14 ±18.40 months and 5.48 ±3.12 months respectively in the ENL group as compared to non ENL group. Respectively, indicating a long-standing illness in the ENL group.

About (23/97; 23.7%) patients with ENL had yet to be started on MDT while the rest 76.3% were on MDT. On the contrary, 123 patients out of 195 (63.1%) patients of leprosy without ENL were not on any anti leprosy treatment. This is a huge number who had not received MDT even on this day, indicating a huge reservoir of infected untreated cases. Among the 74 patients

Table 1 : Showing the demographic and other characteristics of patients (N=292).

Demographic profile	ENL Cases		Other cases without ENL		Statistical correlation
	N	%	N	%	P value
Gender/ Sex					
Male	79	81.44	120	61.5	Male preponderance significant 0.001 in the ENL group
Female	18	18.56	75	38.5	
Residence					
Rural	84	86.6	150	76.92	0.051 (insignificant difference among the groups)
Urban	13	13.4	45	23.08	
Education qualifications					
Illiterate	32	32.99	33	16.92	
Had received Primary education	27	27.84	79	40.51	
Had Secondary education	29	29.89	76	38.97	
Had received Higher education	9	9.2	7	3.59	
Age grouping in years					
<11	0	0.00	10	5.13	0.000 (significant difference in this age group)
11-20	6	6.19	15	7.69	
21-30	37	38.14	24	12.31	
31-40	31	31.96	69	35.38	
41-50	16	16.49	28	14.36	
51-60	5	5.15	30	15.38	
>60	2	2.06	19	9.74	
Socioeconomic status					
Upper	1	1.03	0	0.00	0.000(s)
Upper middle	5	5.15	25	12.82	
Lower middle	14	14.43	37	18.97	
Upper lower	22	22.68	13	6.67	
Lower	55	56.70	120	61.54	
Occupation					
Farmer	42	43.29	117	59.39	
Independent profession	10	10.30	28	14.36	
Business	4	4.12	6	3.07	
Labourer	33	34.02	28	14.36	
None	8	8.28	16	8.20	

who reported with ENL and were on treatment 25 (33.8%) of them were on corticosteroids for variable durations during their course of treatment. During treatment of ENL, all patients were taking Clofazimine.

Table 2 summarises the details of the clinical subtypes of all leprosy patients both with ENL and those with no ENL enrolled in the study.

The most common clinical subtypes of observed in the study was LL in ENL patients (74.2%) while it was BT leprosy (43.6%) in the non ENL patients (Table 2**).** The distribution of skin lesions is depicted in Table 3**.** Many of the ENL patients had neuritis. Out of 13 cases of PNL with ENL, 2 patients had polyneuritic leprosy whereas the rest were mononeuritic leprosy. Highly bacillated cases were higher in proportion in cases with ENL (Table 4).

Table 2 : Showing the clinical subtypes of leprosy in patients.

Clinical subtypes of Leprosy patients	ENL Cases (97)		Non ENL cases (195)	
	N	%	N	%
TT (Tuberculoid leprosy)	0	0	0	0
BT (Borderline tuberculoid)	0	0.00	85	43.59
BB (Borderline borderline)	1	1.03	9	4.62
BL (Borderline lepromatous)	11	11.34	39	20.00
LL (Lepromatous leprosy)	72	74.23	52	26.67
PNL (Pure neuritic leprosy)	13	13.40	10	5.13

Table 3 : Showing the distribution of skin lesions in patients.

Clinical subtypes of Leprosy patients*	ENL Cases (97)		Non ENL cases (195)	
	N	%	N	%
Upper limbs	82	84.54	67	34.36
Lower limbs	73	75.26	78	40.00
Face	28	28.87	57	29.23
Trunk	75	77.32	113	57.95

*It may be noted that lesions occurred simultaneously in more than 1 site in several patients

Table 4 : Showing the Bacillary Index (BI) of patients.

BI*	ENL Cases (97)		Non ENL cases (195)	
	N	%	N	%
0	7	7.21	70	35.90
1+	12	12.37	22	11.28
2+	15	15.46	34	17.44
3+	13	13.40	33	16.92
4+	50	51.55	36	18.46

* As per Ridley's logarithmic scale.

Table 5 : Showing the incidence of co-morbidities in patients.

Comorbidities	ENL Cases (97)		Non ENL cases (195)	
	N	%	N	%
Acne	8	8.25	5	2.56
Dermatophytosis	25	25.77	6	3.08
Hypertension	7	7.22	5	2.56
Alcoholic liver disease	9	9.28	7	3.59
Chronic duodenal ulcer	1	1.03	0	0.00
Chronic Kidney Disease	1	1.03	0	0.00
COPD	4	4.12	1	0.51
Diabetes Mellitus	11	11.34	7	3.59
Type 1 reaction	0	0.00	11	5.64
Total*	66	68	42	21.5

*Some of the patients were simultaneously suffering from more than one co- morbidity

Table 6 : Showing other risk factors for ENL.

Comorbidities	ENL Cases (97)		Non ENL cases (195)		P value
	N	%	N	%	
Anaemia	17	17.5	18	9.2	0.04
Stress	14	14.4	9	4.6	0.003
Upper respiratory tract Infection	6	6.18	3	1.5	0.03
Family H/O leprosy	5	5.15	7	3.6	0.52
Total	42	43.2	37	18.9	

Table 5 shows the occurrence of co-morbidities in the patients enrolled in the study.

The prevalence of anaemia, stress, upper respiratory tract infections and history of leprosy in other family members has been represented in Table 6.

Among all cases of ENL enrolled into the study, a high bacillary index of 4+ was observed to be associated with highest incidence of ENL (Table 4). About 24% of all ENL patients had some significant co-morbidity. Diabetes mellitus (11.34%) followed by hypertension (7.21%) were the most observed co-morbidities (Table 5). Dermatophytosis (25.7%) and acne (8.25%) were the common dermatological findings in patients of ENL. In the non ENL group, type 1 reaction (5.64%) was most observed co-morbidity followed by diabetes mellitus (3.59%) and alcoholic liver disease (3.59%). TB disease was not observed in any of the patients in the study.

Discussion

In our study a male preponderance was noted in both the groups (97 patients of ENL versus 195 having no history of ENL). This is similar to previous studies done which have also reported that more than half of the cases involved were

males (Motta et al 2012, Walker et al 2015, Guerra et al 2004, Prasad et al 2013). The rationale behind the observation might be conventional social norms and gender specific health seeking behaviour.

In the current study mean age was 34.70 ± 11.31 years with a median of 35 years in patients of ENL, while it was 38.76 ± 15.36 years and 36 years respectively in non ENL leprosy population studied. This finding is also consistent with various other studies carried out and reported by various researchers (Pocaterra et al 2006, Walker et al 2015, Guerra et al 2004, Prasad et al 2013). However, ENL was not observed in children of less than 11 years of age in the present study.

Lepromatous leprosy is a much-recognized risk factor for ENL. In present study, majority of the cases i.e. patients of ENL belonged to the LL subtype (74.22%) +11.34% in BL and PNL (13.4%) i.e. pure neuritic leprosy. As compared to this, in leprosy cases without ENL, the BT subtype was most frequently seen. This finding matches with the reported results (Prasad et al 2013, Patel et al 2020, Tiwary et al 2011, Mahajan et al 2003, Singh et al 2009). Though, there was multiple nerve involvement in ENL, and nerve involvement per se couldn't be elicited as a significant risk factor.

A high BI>4 has been universally accepted as a risk factor for the development of ENL. In our present study, also, we found that in people without ENL, about 64% of patients had BI of 1+ and more. In contrast, a high BI of 4+ was seen in about half of the patients with ENL (51.54%). Out of 97 ENL patients, 38 (39.17%) patients had completed their course of MDT. Walker et al (2015) and Guerra et al (2004) have reported similar results. This finding stresses upon the importance of estimation of BI in all cases of ENL, particularly in institutional set up. This also reflects that as the bacillary load takes a longer time to come down even after completion of one year course of MDT, ENL continues to occur and must also be looked for and treated in patients who have completed MDT.

In an earlier study (Motta et al 2012), coinfections were observed in 60.3% of ENL patients and these had considered them to be a possible risk factors to develop ENL. In the present study, dermatophytosis (25.7%) and acne (8.25%) were the common dermatological afflictions observed in patients of ENL, as compared to other leprosy patients without ENL. Diabetes mellitus (11.34%) and hypertension (7.22%) were the common systemic comorbidities observed by our group in the investigated population. In the non ENL group both diabetes mellitus and alcohol addiction were observed in 3.59% subjects of this group. Long term corticosteroid therapy in ENL could be one of the contributing factors to the high incidence of diabetes co morbidity. Papang et al (2009) observed that 19% patients of leprosy had developed steroid induced diabetes mellitus. Another study reported that 13.3 % of leprosy patients were diabetic and 37.7% were prediabetic (Saraya et al 2012). These findings may have been a *de novo* development or consequent to prolonged steroid therapy and need to be studied in larger population.

In the current study, about 80% patients of ENL had arthritis. Peripheral oedema (29.89%), glomerulonephritis (29.89%), lymphadenitis (7.21%), ocular changes (8.24%), hepatitis (9.27%) and orchitis (5.15%) were other systemic associations observed in ENL patients. Our observations were like those reported by previous studies on ENL (Walker et al 2015, Dutta 1979, Prasad et al 2013).

A few studies have implicated stress - both psychological and physical, and co-existing infections as contributors; however, more evidence is needed to come to a definite conclusion. In the current study, 17/92 patients

of ENL were anaemic as opposed to 18/195 patients of non ENL group (p=0.04). Stress was also more often observed in the ENL group as compared to 9/195 leprosy patients without ENL, which is highly significant (p=0.003). Also, in our study, upper respiratory tract infection was found to be one of the significant triggering factors of ENL. Six patients of cases had URTI while only 3 patients of controls showed symptoms of URTI (p = 0.03).

Though there is a high association of family history of contact with development of ENL, it was found not significant (p=0.52) in our study. This could be due to small sample size.

Our study was conducted in a tertiary care centre that caters to the poorer sections of society particularly tribals and others who have lagged in terms of proper nutrition, education level, socioeconomic status, and access to the hospitals. The late consultation in tertiary care medical facilities, delayed diagnosis, poor treatment compliance, and could also be playing a role, all play a role to the development of multiple episodes of ENL. Improved socioeconomic condition and education in this predominantly rural area would have possibly changed the health seeking behaviour, but this should be properly studied and more needs to be done in this regard so that more patients come forward earlier for treatment.

A small sample size and relatively smaller study period were the limitations of our study. For strengthening the programme more studies also need to be undertaken at population level as patients reporting to a tertiary care centre may be different than at community level. Experiences from other districts / states may be useful to understand the risk factors if any for the development of ENL.

Conclusions and way forward

Our findings suggest that in this area a typical ENL patient is a male in his fourth decade from rural areas belonging to lower socio-economic status. This could be related to gender-related differences in health seeking behaviour particularly in rural areas. Moreover, inadequate access to health facilities could have resulted in this finding. All of these suggest that a lot is yet to be done for leprosy and therefore ENL in rural and economically backward areas. As expected, warmer body area such as the face was relatively spared as compared to the trunk and extremities. The higher incidence of ENL among lepromatous leprosy cases with a high bacillary index was also along the expected line. Apart from this, anaemia, upper respiratory tract infection and stress also had contributory roles in triggering episodes of ENL. Early diagnosis and management of precipitating factors can help improve the general wellbeing of patients, impair recurrence and hence, chronicity of the disease. Many of the cases had concomitant dermatophytic infections and diabetes mellitus. This is suggestive of adverse effects of long-term systemic steroid in patients of ENL. The information derived from this study would be useful in developing research cum intervention strategies specific to adjoining areas catered by our tertiary care centre.

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