

*Original article*

# Clinical characteristics predicting erythema nodosum leprosum (ENL) among patients with multibacillary leprosy (MBL) in Sarawak

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## Abstract

**Objective:** To determine the clinical features predicting erythema nodosum leprosum (ENL) in a non endemic leprosy area. **Methods:** Twenty newly diagnosed patients with MBL attending the skin clinic, Sarawak General Hospital from 1992 to 2007 were analyzed. They were divided into 2 groups, one with ENL and one without. Analysis of the presenting clinical features was done to determine the risk factors for ENL. Chi square and student *t* test was used for statistical analysis. Level of significance was set at 0.05. **Results:** ENL was present in 40 % patients, all with lepromatous leprosy (LL). Clinical features that were seen more frequently in patients developing ENL include earlobe thickening (100 % cf. 25 %,  $P=0.00$ ), loss of the lateral third of the eyebrows (75 % cf. 16.7 %,  $P=0.02$ ) and mean bacteriology index (BI) (5.1 cf. 2.9,  $P=0.03$ ) and mean morphological index (MI) (17.8 cf. 7.0,  $P=0.02$ ). Number of thickened nerves (mean 2.5 cf. 1.4,  $P=0.12$ ), number of skin lesions (mean 19.4 cf. 10.9,  $P=0.15$ ) and duration of illness (mean 15.3 cf. 12.8 months,  $P=0.68$ ) did not predict ENL development. **Conclusion:** Finding LL patients with thickened earlobes, loss of lateral third of the eyebrow, high BI and MI should alert treating clinician to the possibility of ENL in a non endemic leprosy area.

**Keywords:** Leprosy; Erythema nodosum leprosum (ENL); Multibacillary leprosy

## INTRODUCTION

Erythema nodosum leprosum (ENL) or type 2 leprosy reactions is a systemic inflammatory reaction to the deposition of extravascular immune complexes affecting many organs characterized by painful, tender, erythematous papules and nodules on the skin<sup>[1]</sup>. Pioneering work by Wemambu et al showed deposition of immunoglobulins and complement in the blood vessel walls, considering ENL a manifesta-

tion of Arthus phenomenon<sup>[2]</sup>. However, recent studies have challenged this concept<sup>[3,4]</sup>. ENL is seen among patients with multibacillary leprosy (MBL) mainly in those with lepromatous (LL) and borderline lepromatous (BL) leprosy. Higher antigen load in these patients is postulated to enhance antibody production<sup>[5]</sup>. In Ethiopia, ENL was seen in 0.8 % of BL patients at diagnosis, 1.1 % in the first year and 0.8 % in the second year. Among LL patients it was seen in 2.8 % at diagnosis, 5.5 % in the first year, and 2.8 % in the second year<sup>[6]</sup>. In Hyderabad, India, the overall prevalence of ENL was 24 %, 49.4 % among cases of LL and 9 % among cases of BL leprosy<sup>[7]</sup>.

ENL can be accompanied by constitutional symptoms and involvement of the nerves, eyes, liver,

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spleen, joint, bones, lymphatics, testicles, heart, and kidney<sup>[5,8]</sup>. Early treatment of ENL can usually prevent these disabling morbidities. Identifying clinical features that can predict development of ENL is crucial to preempt the treating clinician of the possible development of ENL. This can allow earlier treatment to prevent these disabilities.

In Sarawak, East Malaysian Borneo, leprosy was once a common disease until its elimination in 1994, with less than 1 in 10 000 populations contracting the disease since then<sup>[9]</sup>. Currently sporadic cases of leprosy are seen among the Penan communities and the Indonesian immigrant workers<sup>[10]</sup>. In the capital city of Kuching, leprosy is hardly seen nowadays.

Here, a retrospective study is done to determine the clinical characteristics of newly diagnosed patients with MBL that predict development of ENL, in the skin clinic, Sarawak General Hospital between 1992 and 2007. This aim of this study is to determine the risk factors predicting ENL in a non endemic leprosy area. Identifying these risk factors will allow the clinician in this area, where leprosy is rarity, to actively anticipate the development of ENL.

## MATERIALS AND METHODS

A retrospective review of all the newly diagnosed MBL patients in the skin clinic, Sarawak General Hospital from its inception in 2002 until 2007 was undertaken. Data regarding the baseline demographics, clinical characteristics and slit skin smear results on initial presentation, and the presence of ENL, its treatment and outcome were retrieved from the case folders in the skin clinic.

Clinical characteristics on initial presentation retrieved from the case folders included numbers of skin lesions, numbers of thickened nerves, durations of skin lesions prior to presentation, earlobe thickening and loss of lateral third of the eyebrows. The skin lesions consist of erythematous macules, papules, patches, plaques and nodules with or without loss of sensation. The thickened nerves were the superficial nerve palpated by the dermatologist on initial presentation and included ulnar, median, radial cutaneous, greater auricular, lateral popliteal and posterior tibial nerves. Earlobe thickening is the presence of indurated and nodular earlobes on palpation.

All the slit skin smears utilized 6 sites, 1 on each earlobe and 4 on the skin lesions on the body. Bacteriologic index (BI) is a logarithmic scale from 1 to

6 quantifying the density of *Mycobacterium leprae* in the smear. It is calculated by averaging the results from all the 6 sites. Morphological index (MI) is the percentage of regularly stained bacilli signifying the percentage of live bacilli in the smear. It is also the average from the 6 sites.

All the patients with MBL based on WHO classifications in this study were also classified based on the Ridley-Jopling classification as mid borderline (BB), BL and LL<sup>[11,12]</sup>.

The data collected was divided into two groups: with and without ENL. Statistical analysis was done utilizing SPSS version 15 in the clinical research centre (CRC), Sarawak General Hospital comparing these two groups. Chi square test was utilized in non parametric data whereas the student *t* test for comparisons of means was used in the parametric data. Level of significance was set at 0.05.

## RESULTS

There were 20 new patients diagnosed with MBL from 1992 to 2007. Of these, 8 (40%) had ENL. All the patients who developed ENL were from the LL group. Of those who did not develop ENL, 10 had BL and 2 had BB. Males constituted majority of cases with 62.5% ( $n = 5$ ) in the ENL group and 83.3% ( $n = 10$ ) in the non ENL group.

Mean age of the ENL cases was ( $38.1 \pm 18.2$ ) years. The youngest patient was 19 years old on presentation and the eldest 66 years old. Those with non ENL had a mean age of ( $38.8 \pm 23.4$ ) years, with the youngest being 12 and eldest 94 years old. There was no statistical significant difference between the ENL group and the non ENL group in terms of mean age at presentation.

Table 1 depicts the differences in the clinical characteristics of MBL patients with and without ENL. Based on the clinical findings of MBL patients in initial presentation, it was noted that those who developed ENL had more skin lesions (mean 19.4 cf. 10.9,  $P = 0.15$ ) and more thickened nerves (mean 2.5 cf. 1.4,  $P = 0.12$ ) although the differences were not significant. Earlobe thickening and loss of the lateral third of the eyebrows were seen more frequently in those with ENL at the initial clinical examination ( $P < 0.05$ ). All the patients with ENL had earlobe thickening, whereas only a quarter of those without ENL had this finding ( $P = 0.00$ ). Loss of the lateral third of the eyebrows was seen in three quarters of those with ENL compared to only a

sixth of those without ( $P=0.02$ ). Those who developed ENL also had their skin lesions slightly longer before presenting to the medical personnel (mean 15.3 months) compared to those without (mean 12.8 months) although it did not have statistical difference ( $P=0.68$ ).

Based on the slit skin smear at initial presentation, patients with ENL was noted to have significantly higher BI score (mean 5.1 cf. 2.9,  $P=0.00$ ) and MI score (mean 17.8 cf. 7.0,  $P=0.02$ ).

Among MBL patients, there was a weak positive correlation between number of skin lesions and thickened nerves on presentation with BI (Figure 1 and 2). More MBL patients with ear lobe thickening and loss of lateral third of the eyebrows had BI 4 or more (Table 2). However, when compared with

those without these signs, there were no statistical significant differences ( $P=0.07$ ).

Among the patients with ENL, 50% had ENL at diagnosis, 1 had it within 6 months of treatment and 3 had it on the second year of treatment. All the patients were given oral prednisolone to control the type 2 reactions. Mean duration of prednisolone administration was 30.25 months ranging from 4 to 48 months. One patient had combination of prednisolone, azathioprine and thalidomide to control her disease. One patient in the ENL group died during treatment for his ENL. He died of sepsis secondary to his immunosuppressive medications. No death was reported in the non ENL group during the treatment period of 2 years and the surveillance period of 10 years.

**Table 1** Differences of clinical characteristics of MBL patients with and without ENL.

Risk factors	Present (n = 8)	Absent (n = 12)
Age (mean ± SD)	38.1 ± 18.2	38.8 ± 23.4
Male Sex	5 (62.5 %)	10 (83.3 %)
No. of skin lesions on presentation (mean ± SD)	19.4 ± 14.3	10.9 ± 5.3
No. of thickened nerves on presentation (mean ± SD)	2.5 ± 1.3	1.4 ± 1.6
Duration of skin lesions before diagnosis (mean ± SD)	15.3 ± 9.7	12.8 ± 14.3
Earlobe Thickening	8 (100.0 %)	3 (25.0 %)
Loss of lateral third of eyebrow	6 (75.0 %)	2 (16.7 %)
MI (mean ± SD)	17.8 ± 10.8	7.0 ± 8.2
BI (mean ± SD)	5.1 ± 0.7	2.9 ± 1.9

**Table 2** Relationship of loss of eyebrow and earlobe thickening with BI.

BI	Loss of eyebrow		Earlobe thickening	
	Yes (n = 8)	No (n = 12)	Yes (n = 11)	No (n = 9)
< 4	1	5	2	6
≥ 4 *	7	7	9	3

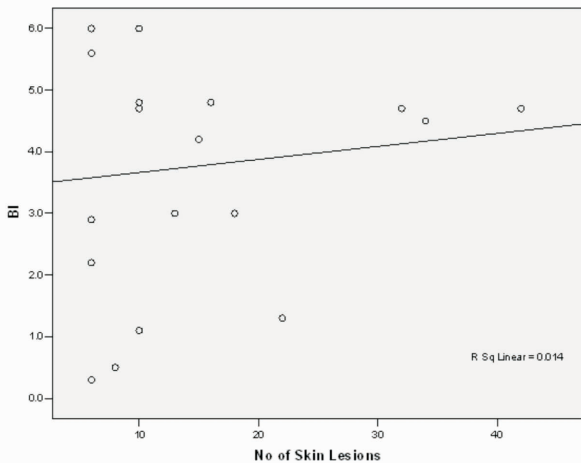
\* BI ≥ 4 = BI score of 4 or more

## DISCUSSION

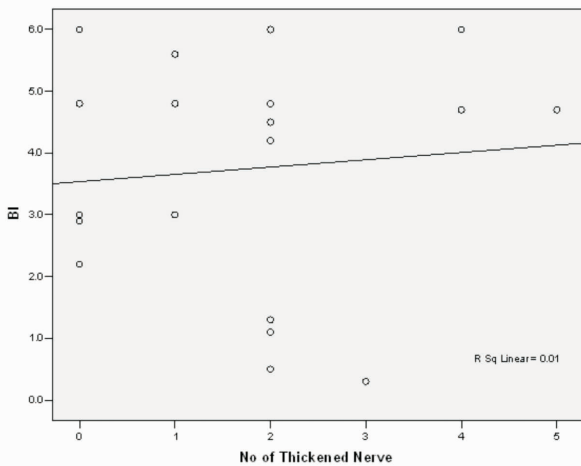
Development of ENL is associated with higher antigen load<sup>[5]</sup>. Antigen load is measured by the BI. There is a direct positive relationship between antigen load and BI. Most studies have concluded that a higher BI is associated with the development of ENL<sup>[13-16]</sup>. Some have concluded that a BI of greater than 3 is associated with ENL, while others have found a BI of at least 4 to be linked with the development of ENL. Serological study had noted that a high BI is associated with high serum IgM antibodies

against *Mycobacterium leprae*-derived phenolic glycolipid I. These antibodies are postulated to be involved in the pathogenesis and propagation of ENL<sup>[17,18]</sup>. In the current study, it was also noted that MBL patients who developed ENL in Sarawak had higher mean BI than those who did not develop the reaction.

In this study, a higher mean MI was noted in the ENL group. A higher MI translates to a higher burden of living bacilli. This will allow a higher proportion of intact living bacilli to be disrupted during treatment with multiple drug therapy. It is these disrupted bacilli that will activate the complement components that are important in development and propa-



**Figure 1** Relationship between number of skin lesions on presentation and BI.



**Figure 2** Relationship between number of thickened nerves on presentation and BI.

gation of ENL<sup>[19]</sup>.

It was noted that patients with thickened earlobes and loss of the lateral third of their eyebrow in this study had a higher BI, although it did not reach statistical significance ( $P = 0.07$ ). Thus, it can be concluded that these signs are associated with higher BI. This explained the finding that those patients with these signs were more likely to develop ENL. An active search for these two simple signs is essential, as they are easily detected during routine examination.

A Brazilian study had observed that ENL occurred more frequently in LL leprosy patients with disseminated lesions<sup>[13]</sup>. Similarly, in Nepal, presence of extensive skin infiltration was associated with ENL<sup>[14]</sup>. Here, it was noted that patients who developed ENL had a higher number of skin lesions on

presentation. However, it did not reach statistical significance. It was also noted that there was only a slight positive correlation between number of skin lesions on presentation with BI. This may explain the poor correlation between number of skin lesions and development of ENL in this study. A slight correlation between number of thickened nerves on presentation and BI was also noted. Again, this translates to a poor correlation with development of ENL. Thus, it was concluded here that the higher number of skin lesions and thickened nerves were not risk factors for development of ENL in Sarawak.

ENL is reported to occur in 20 % of patients with LL and 10% with BL<sup>[8]</sup>. In this study, all the LL patients developed ENL. None of patients with BL developed this reaction. This was very interesting as it implied that by having LL, patients are deemed to have ENL. However, due to the small sample size, this finding needs to be validated by a statewide study with good sample size.

In Nepal, an inverse relationship was noted between the occurrence of ENL and age. Nepalese patient older than 40 were at significantly decreased risk of ENL<sup>[14]</sup>. The average age of patients with ENL in this study was 38.1 years. This was far older than other studies<sup>[7,20]</sup>. Moreover, 3 of the 8 patients with ENL were over 40 years old. For those without ENL, only 50 % were over 40 years old. Thus, in Sarawak, ENL occurred at a older age than leprosy patients from endemic countries.

A third of Nepalese patients had ENL before treatment, a third within the first 6 months of treatment and another third after 6 months of treatment<sup>[14]</sup>. In contrast, ENL in India and Ethiopia occurred mostly during the second and third year after commencement of treatment<sup>[15,16]</sup>. Here, half of the patients presented with ENL prior to treatment. This might be due to prior ingestion of antibiotics before proper treatment that might kill the leprosy bacilli contributing to ENL before presentation to the skin clinic.

ENL was reported elsewhere to be more common in females<sup>[15,21]</sup>. However, in this study, male preponderance was noted. Among the patients with leprosy attending skin clinic, Sarawak General Hospital, men outnumber women at 3: 1<sup>[22]</sup>.

Limitations of this study are the small number of patients with MBL seen in the 15 years period and

the retrospective nature of the study. The small number of patients had affected the statistical power of this study. By being a retrospective study, certain important data were not recorded on the case folders, limiting the variables for analysis.

In conclusion, clinical characteristics predicting ENL among MBL patients attending the skin clinic, Sarawak General Hospital include LL, thickened earlobes, loss of lateral third of the eyebrow and higher BI and MI at initial presentation. Hence, by determining these clinical features, clinician can preempt the occurrence of ENL and institute treatment early to prevent morbidities and mortality associated with this condition.

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