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ORIGINAL ARTICLE

A Twenty Five Year Retrospective Study on the Clinico-Histopathological Correlation of Hansen's Disease, Trends, Dynamics of the Spectral Rami and Psycho-Temperamental Incline, in a Tertiary Care Hospital in South India

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Abstract

Background: Leprosy is an ever challenging, chronic infectious disease, caused by *Mycobacterium leprae*. The variations in clinical forms of leprosy depends on several factors namely nutrition, immune status of the host and bacillary load. Histological diagnosis of leprosy is more specific in typing the disease when compared to clinical diagnosis. This retrospective study was aimed to find out the clinico pathological correlation of various spectrum of Hansen's disease and to estimate the value of histopathology for the diagnosis and appropriate planning of treatment. **Materials and Methods:** All clinically diagnosed cases of leprosy enrolled in the leprosy register between January 2001 to December 2025 were analysed retrospectively. Clinical diagnosis was correlated with that of histopathological diagnosis. **Results:** A total of 975 cases were enrolled, of which biopsy was done in 612 cases. There were 437(71.4%) males and majority of patients were in the age group of 21- 30 years (30.1%). Clinically the most common type was BT with 53.6% (328) followed by BL 19.1% (117), LL and IL each 9.50% (58). Mid borderline was diagnosed only in 9(1.5%) out of 612 cases. Histologically also the most common type was BT (55.4%) followed by IL (17.3%). The overall concordance rate was 67.48%. Correlation was maximum in BT (79.57%) followed by IL (70.68%), LL (63.79%), HL (61.1%), BL (45.29%), BB (11.1%) and least in TT (9.2%). **Conclusion:** Histopathology should be preferably done in all cases of leprosy for better correlation which inturn helps in management of such cases in post elimination era.

Keywords: Leprosy, *Mycobacterium leprae*, projected bias, Ridley-Jopling classification, Histopathology

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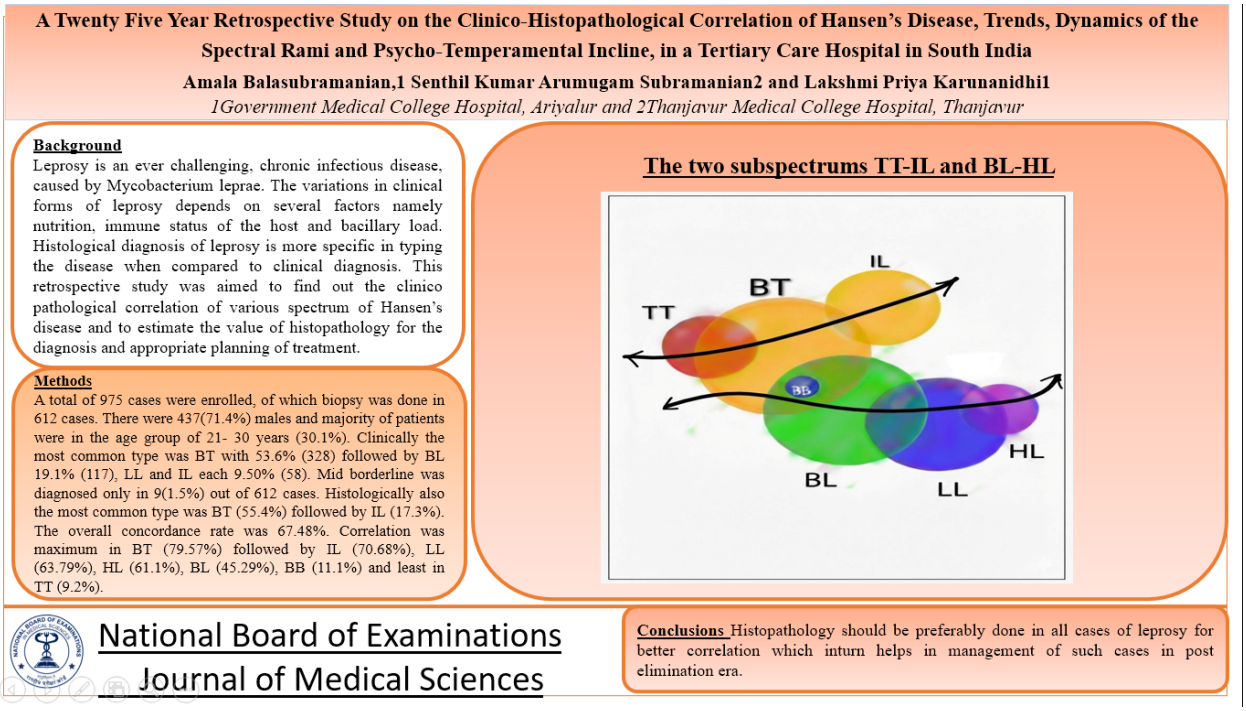
Graphical Abstract



Introduction

Leprosy, also known as Hansen's disease, is a curable, chronic granulomatous infectious disease caused by *Mycobacterium leprae*. It mainly affects peripheral nerves and skin but can affect any other site such as the eyes, bones, mucous membranes, testes and internal organs and produces a spectrum of clinical types depending upon the immune status of the host [1–3]. Hansen's disease causes bodily disability of multiple forms along with commensurate and reciprocal psychological morbidity, resulting in fear and stigma of the highest proportions [4–6].

Since the days of antiquity leprosy had been documented in literature. The New Testament talks of the socially ostracised patients and a model destigmatisation campaign for the public view. Tamils had classified leprosy into *to̲lunōy* (etymology from *to̲lu,* a cattle manger or stall; and *tolumarai,* a disease with round patches all over the body of cattle), *peruñco̲rikku̲rai* (a virulent form of leprosy with eruptions, probably Erythema Nodosum Leprosum), *perunōy* (features similar to rinderpest a disease of the cattle), *veppu* (appearance similar to a type I lepra reaction), *a̲linōy* (resorption of bones), and *kārakku̲rai* (black, necrotic autoamputation), in Cankam literature like *Maturaikkāñci:69* and *Kalittokai:65,* two millennia ago. Aretaeus of Cappadocia, the celebrated Greek physician also described the clinical features including leonine facies of *elephantos*, in the second century CE. Leprosy had been mentioned as *rai/kattai* in Japanese literature including Nihon Shoki Chronicles, and as *líkþrá* in Old Norse-Icelandic texts.

The disease spectrum has been characterised in a number of classification systems, among which Ridley-Jopling classification is most widely used. According to this classification, leprosy has been divided into Tuberculoid (TT), Borderline tuberculoid (BT), Mid borderline (BB), Borderline Lepromatous (BL), and Lepromatous (LL) based on clinical, bacteriological, immunological and histological criteria [7]. Indeterminate leprosy (IL) denotes lesions not localizable on the Ridley-Jopling range of spectrum due to absence of distinctive discerning characteristics, especially histopathologically than clinically. In 1982, World Health Organization (WHO) proposed simplified classification of pauci and multibacillary leprosy based on clinical features and bacteriological index to facilitate diagnosis and treatment of leprosy in the field [8]. According to this classification, IL, TT, and BT cases were included under paucibacillary (PB) treatment regimen, and BB, BL, and LL cases of leprosy were included under multibacillary (MB) treatment regimen. In addition to classical types of leprosy, a new variant of leprosy has been described by Wade in 1960, known as "histoid leprosy" [9]. Initially it was reported in multibacillary patients, who were on irregular or inadequate dapsone monotherapy, but later de novo cases were also reported. Sehgal has reported that histoid leprosy has a distinct position in the leprosy spectrum and that it might not be considered as a variant of LL [10].

Though Government of India declared leprosy eliminated from India in January 2006, still it is considered as a serious public health problem with social stigma. Clinical diagnosis in some leprosy cases can be difficult which leads to occurrence of resistant cases if inadequately treated. Skin biopsies play an important role in confirming the clinical diagnosis and helps in classifying different types of leprosy for proper treatment [6]. This study had been done to find out the concordance between the clinical and histopathological diagnosis in cases of leprosy using Ridley- Jopling scale.

Materials and Methods

This retrospective study was conducted in leprosy patients, who attended the Dermatology Department, in a tertiary care hospital at south India between the period of January 2001 to December 2025. After Institutional Ethics Committee approval, all the newly diagnosed untreated cases of leprosy were selected regardless of their age, sex, occupation and socioeconomic status by consecutive sampling. Clinical diagnosis was made based on history and clinical examination. Skin biopsies were obtained from the lesions processed and stained with Haematoxylin and Eosin. Ridley-Jopling classification was followed in both clinical and histopathological diagnosis. Patients with Indeterminate leprosy (IL) and histoid leprosy (HL) were also included in the study for purpose of analysis. Histopathological evaluation included changes of epidermis, involvement of sub-epidermal zone, neurovascular bundle and adnexae, density of lymphocytes, epithelioid cells and formation of granuloma, other cellular elements and the presence of bacilli [7]. Statistical analysis was done using SPSS version 17. Slit skin smear (SSS) results were

not included in this study because it was not done uniformly for all patients at the time of diagnosis.

Results

About 975 leprosy patients who were clinically diagnosed during the study period and 363 were excluded as biopsy was not done due to various reasons and remaining 612 patients were included as biopsy was performed in these cases. Among them 437 (71.40%) were males and 175(28.60%) were females with male to female ratio of 2.4:1. Age group of the patients ranged from 4 to 81 years with the mean age of 34.5 years. Majority of patients were in the age group of 21-30 years (30.10%) and least affected were less than 10 years (3.43%) (Table 1). Clinical presentation of various types of leprosy cases is shown in Table 2. Table 3 shows histopathological distribution of cases.

Correlation of clinico histopathological diagnosis is shown in table 4. Overall concordance of diagnosis was observed in 67.48% of cases. As chance is not corrected for in an analysis of the similarities between the proportions presence or absence of agreement, it is a weaker measure. Kappa is the statistic of choice as it incorporates calibration for chance and is helpful in quantifying group-variability between the objectively clinico-morphological and the tissue-based histopathological diagnoses. In essence, it implies the frequency of similar interpretations in these two diagnostic modalities. Kappa value of this study was 0.503, indicates the poor strength of agreement and P value was <0.001 hence, this study is more significant.

Table 1. Age distribution of the leprosy cases

Age group(years)	No. of cases	Percentage
0 - 10	21	3.43%
11 - 20	77	12.58%
21 - 30	184	30.10%
31 - 40	146	23.90%
41 - 50	94	15.40%
51 - 60	56	9.20%
> 60	34	5.60%

Table 2. Clinical presentation of leprosy cases

Clinical types	No. of cases	Percentage
Tuberculoid leprosy (TT)	24	3.90%
Borderline tuberculoid leprosy (BT)	328	53.60%
Mid borderline leprosy (BB)	9	1.50%
Borderline lepromatous leprosy (BL)	117	19.10%
Lepromatous leprosy (LL)	58	9.50%
Indeterminate leprosy (IL)	58	9.50%
Histoid leprosy (HL)	18	2.90%

Table 3. Histopathological distribution of leprosy cases

Histopathological types	No. of cases	Percentage
Tuberculoid leprosy (TT)	17	2.80%
Borderline tuberculoid leprosy (BT)	339	55.40%
Mid borderline leprosy (BB)	7	1.10%
Borderline lepromatous leprosy (BL)	71	11.60%
Lepromatous leprosy (LL)	50	8.20%
Indeterminate leprosy (IL)	106	17.30%
Histoid leprosy (HL)	22	3.60%

Table 4. Clinico-histopathological correlation

Clinical diagnosis	No of cases	Histopathological diagnosis							CPC%
		TT	BT	BB	BL	LL	IL	HL	
TT	24	**9**	11	0	0	0	4	0	9/24 (9.2%)
BT	328	7	**261**	4	2	0	54	0	261/328 (79.57%)
BB	9	0	5	**1**	3	0	0	0	1/9 (11.1%)
BL	117	0	45	1	**53**	9	7	2	53/117(45.29%)
LL	58	0	1	1	10	**37**	0	9	37/58(63.79%)
IL	58	1	16	0	0	0	**41**	0	41/58(70.68%)
HL	18	0	0	0	3	4	0	**11**	11/18(61.1%)
TOTAL	612	17	339	7	71	50	106	22	**413/612(67.48%)**

CPC: Clinico pathological correlation

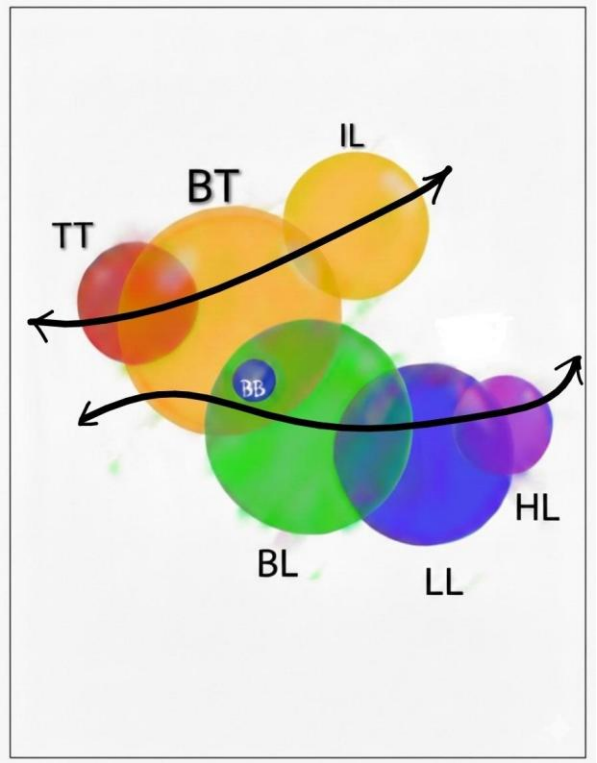


Figure 1. The two subspectrums TT-IL and BL-HL, and overlapping from clinicohistopathological correlation

Discussion

Leprosy, a chronic granulomatous infectious disease, still continues to be a serious health problem with prevalence rate of 0.57 per 10,000 in India, as per National Leprosy Eradication Programme Annual Report: 2024-2025. Accurate classification of leprosy is needed as the disease manifests in different clinicopathological forms. In the present study, presentation of leprosy was found to be slightly more prevalent in males (71.40%) than in females, with male to female ratio of 2.4: 1. These finding correlates with other studies conducted by Gridhar et al. (77.6%), Bhushan et al (72.34%), Kakkad et al. (82%) & Bijjaragi et al. (64.3%) [11–14]. This male preponderance is due to various socio-cultural factors like poor knowledge, illiteracy and strong tradition leading to under reporting of leprosy in females due to gender bias.

Majority of cases were seen in the age group of 21-30 years. Age of the youngest patient was 4 years and oldest was 80 years. These results were also similar to other studies conducted by Bijjaragi et al., Tiwari et al and Banushree et al. [4,14,15]. Children below 10 years of age were only 3.43%, which revealed that there might have been mis diagnosis in this group and many may not be attending the hospital.

In our study the common type of leprosy both clinically and histopathologically was BT (53.6%). Borderline group constituted the major spectrum (74.2%), which included BT, BB, and BL and is similar to findings of other authors namely Shivaswamy et al. 2012, Manandhar et al. 2013 and Rizvi et al. 2015 [16-18]. Maximum clinico-histopathological correlation was observed in BT (79.57%) followed by IL (70.68%), LL (63.79 %) and HL (61.10%), BL (45.29%), B (11.1%) and TT (9.2%). When we considered LL and HL together as one group, the concordance was maximum i.e., 80.26% which because of their stable histopathology and similar results were reported by Mathur et al. (95%), Mohan et al. (97.2%), Moorthy et al. (80%) and Kakkad et al. (93.3%) [13,19–21]. In this study kappa value was 0.503, which indicates the poor strength of agreement. Overall Clinico-pathological concordance of this study was 67.48%, which was also similar to other studies. Pandya et al., reported a concordance of 58%, Tiwari et al. 54% and Manandhar et al., reported the least concordance of 45.33% [15,17,22]. Expectation of some discordance between morphological and diagnostic histological findings is reasonable as the determinants upon which the histopathological typification is founded are clearly defined and delineated with precision, while only the external presentation of the dermatological lesions direct the clinicomorphological stratification [23]. Typical microscopic pathological findings have been noted to be preceded by clinical signs in early subjects occasionally. A high probability of incongruence between the morphological and histological results exists in the event of very early tissue biopsies. As dissonant variance is founded upon the loci of the lesion sampled in the time period of the research, serial tissue sampling from the very loci or from adjacent lesions ought to be evaluated for consistency of diagnoses.

In the present study, 106 cases were diagnosed as IL histologically, whereas only 58 of these cases were clinically considered. Four cases of TT, 54 cases of BT and 7 cases of BL were histologically diagnosed as IL. This high percentage of IL noted histologically could have been due to immunological difference in the host response. The diagnosis of IL also depends on many factors such as age of the lesion, nature and depth of biopsy, quality of sections and number of sections examined.

Out of 24 clinically diagnosed TT cases, histologically minor disagreement (difference of one group e.g. TT-BT) was seen in 11 cases. This could have been due to BT and TT often overlap clinically, histologically and immunologically but differ only in some features, e.g. erosion into the epidermis with absence Grenz zone in TT. Both TT and BT are under paucibacillary group hence, these minor disagreement does not affect the chemotherapy and outcome of the disease.

Among the patient classified clinically as BT, 4 cases were mid borderline (BB) and 2 cases were BL histologically. According to WHO classification, BB, BL and LL cases were included under multibacillary group. Without a biopsy if we had started on WHO Paucibacillary treatment only on the basis of clinical diagnosis, there might have been a chance for relapse as the treatment would have been inadequate. Similarly in 117 cases of BL, 45 cases were histologically BT which showed only Paucibacillary regimen of 6 months was sufficient in these patients. These patients also would have been overtreated with one more additional drug and for six more months which was not needed.

Surprisingly out of 58 cases of LL one case turned out to be BT histologically. This is very vital because of the lesser rate of transmission of BT and also for treatment aspect. Out of 9 clinically diagnosed cases of BB, 5 were BT and 3 were BL histologically, which was a minor disagreement of difference in one group. It was anticipated because mid borderline leprosy is immunologically least stable type of leprosy. When we considered TT and BT together as one group, and also LL and BL together as other group, concordance was maximum *i.e.* 81.8% for TT-BT group and 72% for BL-LL group.

Projected bias perspective and other inferred dynamics of the spectral pattern

The results of the study provide us a glimpse of restricted directional tendency of the BT-LL core of the histopathological spectrum and its ramification. The following inferences highlight on the dynamics of the spectral pattern, and the almost fixed localized pockets of confluence within the subspectrums TT-IL and BL-HL.

a. Inadvertent bias or psycho-temperamental inclination can not be completely ruled out as it is a retrospective study. Assuming synchronicity, when both methods of diagnosis were compared in the clinicopathological correlation, diagnosis in the clinically diagnosed TT group appears 45.8% (11/24) negatively biased (false negative for BT) against a clinical BT diagnosis; 55.6% (5/9) in the BB

group, 38.5% (45/117) in the BL group, 27.6% (16/58) in the IL group were similarly biased against BT diagnosis. Otherwise, about 16.5% (54/328) in the BT group were in turn biased against a clinical IL diagnosis. This implies a possibility of an average of 41.9% negative bias in diagnosing BT among all other clinically diagnosed subtypes, thus more BT were being diagnosed clinically as other subtypes.

b. It is evident that there is overlapping of clinical diagnosis between the subtypes within BT subspectrum (TT, BT and IL), and between the subtypes within LL subspectrum (BL, LL and HL) over the course of illness. In case of asynchronicity (undetermined in this study due to incomplete data on the time interval) with varying intervals between clinical diagnosis at index visit and last confirmatory biopsy, the above overlaps may be implying a possible graded progression and occasional regression within the two corresponding subspectrums in due course. It also unmasks an one-to-one overlapping of diagnostic features exclusively between BT-BL (Figure 1).
c. This correlation statistically proved IL to be a part of the BT spectrum (requiring PB regimen) as there is no apparent exclusive overlap (i.e. not involving a BT overlap) between IL and the LL subspectrum.
d. Statistically it appears there is no true BB subtype, as its frequency distribution is inconspicuous caught deep within the multiple overlaps of other (primary) subtypes.
e. No significant difference (χ^2=4.505, p=0.60) was found between the distribution of cases in various subtypes in both clinical and histopathological groups.

Positive psycho-temperamental inclination in beneficiary and benefactor

The annual prevalence rates of leprosy in India have been found almost static over the past decade around 0.57±.10 per 10,000 [24]. Reasons may include among others, the shift from vertical to integrated implementation of the eradication programme and surveillance, and apparently increasing ignorance and minimization of the seriousness of the complications even among literates that has led to frequent delay in availing preliminary medical consultation. The latter is a major contributory factor in the recent higher incidence of grade 2 deformity (G2D) at index diagnosis, and increased incidence in paediatric age group (10-23% of new cases and more MB proportion). This is more glaring when compared to the flattening of the adolescent and young adulthood peak in the age-specific incidence of the still fatal tuberculosis caused by another bacteria of the same mycobacterium genus. Compounding psychiatric morbidity to the locomotor and/or sensory disability and targetted incentivization can help propagate community awareness on the seriousness and the availability of more deserving support from government social welfare institutions.

Suggested future directions for India

1. To begin with, the annual declaration of the prevalence rates of leprosy in India should list state-wise rates ranking them

along with the rates of the world countries, to increase the objectivity, and set more aggressive goals and revamp the protocols. Understanding the true position of states like Odisha, Andhra Pradesh and Tamil Nadu on the global ranking list and comparing them on par with the ranks of countries like Netherlands, Brazil and Austria, will motivate and help sustain the drive effectively.

2. Providing adequate and appropriate disability certification and benefits should encourage caregivers for drug adherence and nutrient-rich diet, in turn reducing dropouts and community carrier states, and promoting safe palliative care. Disability percentage increment accounting for the secondary depression and other psychiatric conditions over and above the estimated locomotor disability, would provide better incentive that the patients deserve.
3. Use of Artificial Intelligence driven schematics especially "an AI with a psyche," would help devise strategies to track down isolated pockets to defuel continued transmission, to overcome mass screening challenges, to enforce statutory Post Exposure Prophylaxis, and establish simultaneous parallel, competing, multidimensional programmes to completely eliminate the bacteria in the environment, and even theorize a possible elusive new intermediate animal host.
4. Reviving of house-to-house surveillance and routine skin smear examination of the bygone era, use of screening tools like WHO-Skin NTD app, novel drugs like bedaquiline and telacebec, and trials of leprosy vaccines should be applied in the field.

Conclusion

Leprosy, though considered to be eliminated from India, is not eradicated completely and still prevalent in various parts of India and other countries. A gold standard for the diagnosis of leprosy cannot be established since the clinical features varies with immune status of the host. However, skin biopsy is a useful tool in confirming the clinical diagnosis and hence correlation of clinical and histopathological examination along with bacteriological index should be carried out in all cases to determine the spectrum of leprosy which inturn helps in initiation of multidrug therapy and elimination of the disease.

Limitations

Our study is a record based, retrospective study. A prospective study may give better concordance. Bacteriological index was not included in this study and inter-observer variations regarding the clinical and histopathological observations exists.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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