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Systemic Manifestations of Leprosy: A Comprehensive Epidemiological Study from Eastern India

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Abstract

Background: *Leprosy is a chronic infectious disease primarily affecting skin and peripheral nerves. Involvement of various other systems has been well documented in the literatures, but all the studies date back to the pre-elimination era. India achieved leprosy elimination as a public health problem in 2005. But, as a country, India still has the highest burden of cases worldwide. In India, Odisha is among the seven states where the disease is still highly prevalent. Thus, this study was undertaken to assess the prevalence of systemic manifestations of leprosy.*

Materials and Methods: *The aim of this study was to assess the prevalence of systemic involvement in leprosy and to compare the prevalence of systemic involvement among various types of leprosy. A total of 218 new cases of leprosy were included and were divided into 6 groups, namely indeterminate leprosy, borderline tuberculoid leprosy, mid borderline leprosy, borderline lepromatous leprosy, lepromatous leprosy and pure neuritic leprosy. The clinical features and investigation findings of various system involvements in all groups were recorded and compared.*

Results: *Out of a total of 218 new cases, most commonly involved system was nose and paranasal sinuses and the least commonly involved was male reproductive system. Features of various system involvement were more common in the multibacillary group except, involvement of musculoskeletal system, which was more commonly involved among patients of paucibacillary group. This points to the fact that higher bacillary load correlates with higher incidence of systemic involvement.*

Conclusions: *Systemic involvement, as evident from our study, is more common in the lepromatous end of the disease spectrum and during reactional states. Features of various system involvements were more common in the multibacillary group, except involvement of musculoskeletal system, which was more commonly involved among the paucibacillary patients. Systemic involvement in post-elimination era is not significantly different from that of previous studies, which is a matter of concern.*

Introduction

To describe leprosy, Vagbhatha in 600 BD used the term "Kushnati" which means "eating away" in Sanskrit.[1] Leprosy, also known as Hansen's disease, is a chronic granulomatous infection caused by the bacterium Mycobacterium leprae, a slow-growing obligate intracellular bacterial pathogen. It is one of the oldest and yet incompletely understood disease. Armauer Hansen, who discovered M. leprae, once commented "there is hardly anything on earth, or between it and heaven, which has not been

regarded as the cause of leprosy; and this is but natural, since the less one knows, the more actively does his imagination work."[2]

Truly, as a disease, leprosy involves not only the skin and nerves, but almost all organs of the body. Systemic involvement is more obvious in the cases towards the lepromatous end than those towards the tuberculoid pole. The factors which aid dissemination of the disease include: (i) bacteremia resulting in bacterial colonization of small blood vessel endothelium, (ii) filtration of bacilli in the reticulo-endothelial system, (iii) predilection of the bacilli for cooler sites, (iv) advanced lepromatous infections with heavy or prolonged bacteremia which induces lesions even at less favoured sites like the adrenals, bones and skeletal muscle and (v) immune complex deposition. Some or all of the above factors contribute to make leprosy a systemic disease.

Systemic manifestations occur mostly towards the lepromatous pole and the number of such patients is very small. Also, the smoldering nature of the infection and lack of symptoms mask these occurrences. The patients rarely ever present with symptoms pertaining exclusively to the involvement of internal organs, though most of them are found to be affected at autopsy/necropsy in lepromatous leprosy.

Though leprosy mainly affects skin and the nervous system; involvement of other systems does occur. The systemic involvement in leprosy is significant, because it provides a source for the persistence of M. leprae which may be responsible for relapse even after adequate therapy.[1] The incidence of various systemic manifestations needs to be studied in greater details.

Even though different aspects of leprosy have been widely studied, the systemic involvement of leprosy still requires more exploration in a state like Odisha. The present study is designed to study the systemic manifestations throughout the spectrum of leprosy as well as leprosy in reaction. This study aims at finding out the incidence of the systemic manifestations throughout the disease spectrum of leprosy. All the available studies are timed in the pre-elimination era. Thus, the status of systemic involvement needs to be studied. Systemic involvement in leprosy is significant because it provides a source for the persistence of M. leprae, which may be responsible for relapses even after adequate therapy. This persistence may not alter the course of treatment or produce any systemic effects or symptoms, but this becomes important during reactional states since complications may arise secondary to the involvement of various organs. Early diagnosis of systemic involvement and timely institution of treatment may prevent the damage and disability and thereby decrease the stigma associated with the disease.

Place of study: Department of skin & V.D., S.C.B.M.C.H.

Study population: all new patients attending Skin & V.D. O.P.D. having features consistent with leprosy (WHO criteria) [3] after obtaining proper consent

Period of study: June 2015 to Nov 2016

Ethics - The study was approved by the Institutional Ethical Committee, S.C.B.M.C.H., and Cuttack under registration ECR/84/Inst/OR/2013 and IEC/IRB No: 333/20/10/16.

Sample size: all patients meeting the inclusion criteria who presented during the study period were included and at the end, a total of 218 patients were recruited.

Inclusion criteria

- All new cases of leprosy (including those patients who had reactional state during presentation) presenting at the O.P.D. and referred from other departments

Exclusion criteria

- All cases suffering from known hepatological and renal diseases
- All known cases of alcoholic liver diseases, viral hepatitis, pulmonary tuberculosis, H.I.V. or addiction to drugs.

Study design: A hospital based cross sectional study was conducted on all new leprosy cases, who presented at the Out Patient Department of Skin & V.D. and referred from other departments of S.C.B medical college. Detailed history was taken. The diagnosis was made as per the WHO definition (1998) [3] i.e. a person having one or more of the following features:

- Hypopigmented or reddish skin lesion(s) with a definite loss of sensation.
- Involvement of peripheral nerves as demonstrated by definite thickening with loss of sensation.
- Skin smear positive for AFB.

After initial screening, thorough clinical evaluation was done. All clinically confirmed cases of leprosy (except previously treated, on MDT therapy or having known systemic diseases) were enlisted. During the course of enlistment, an informed consent was taken and only those who gave consent were included in the study. Slit skin smear for AFB and histopathological examination of tissue biopsy was done to confirm the diagnosis. The patients were grouped into various categories as per the well-established Ridley and Jopling criteria. [4]

Required investigations were sent to the regional diagnostic centre and microbiology department. Detailed history of patients, specific features of leprosy and features of systemic involvement were noted and recorded in case record form. The results of investigations were also noted. Clinical photographs were taken. Childhood leprosy cases i.e. age less than 14 years were also included.

Anaemia was defined as per WHO recommendation i.e. hemoglobin concentration below 11g/dL. [5] Leukocytosis was defined as a white blood cell count greater than 11,000/mm^3. [6]

Statistical analysis: The data obtained was tabulated in Microsoft Excel worksheet. Descriptive statistics with mean, frequency and percentages were computed.

Results

The aim of this study was to assess the prevalence of systemic involvement in leprosy and to compare the prevalence of systemic involvement among various types of leprosy. A total of 218 new cases of leprosy were included and were divided into 6 groups, namely IL, BT, BB, BL, LL and PNL. The clinical features and investigation findings of various system involvement in all groups were recorded and compared.

- Most common type of leprosy was borderline tuberculoid type, least common was indeterminate type.
- Proportion of lepromatous leprosy was high (32.56%).
- During presentation, 30 cases (13.76%) had type 1 reaction and 32 cases (14.68%) had type 2 reaction.
- Percentage of slit skin positive cases was 36.69%.
- Childhood leprosy was higher (9.63%).
- Among these patients, borderline tuberculoid was the most common type of leprosy, and mid borderline type was least common. There were no cases of borderline lepromatous and pure neuritic leprosy group.
- Haematological system and musculoskeletal system were the only two systems found to show features of involvement in children.
- Out of a total of 218 new cases, most commonly involved system was nose and paranasal sinuses (18.81%), and involvement was more common in the lepromatous group.
- Involvement of nose and paranasal sinuses was most common in the lepromatous leprosy group (73.17%). Pure neuritic leprosy and indeterminate leprosy groups showed no abnormality.
- Involvement of nose and paranasal system was more common during type 2 lepra reaction.

- Haematological (11.93%) system involvement was in the form of anaemia (5.96%), leukocytosis (8.26%) and neutrophilia (9.17%)
- Leucocytosis (77.78% in LL and 94.44% in type 2 reactional state) and neutrophilia (80% in LL and 95% in type 2 reaction state) were more common in lepromatous leprosy group and during type 2 reation.
- Ophthalmological involvement (16.05%) was in the form of supraciliarymadarosis (11.01%), lagophthalmos (5.50%), corneal opacity (2.29%), corneal ulceration (1.38%), conjunctivitis (3.67%)
- Supracilliary madarosis and conjunctivitis were common during type 2 reaction, where as lagophthalmos, corneal opacity and corneal ulceration were more common during type 1 reaction
- Musculoskeletal system (10.55%) involvement was in the form of muscle atrophy (9.63%), foot drop (1.83%), resorption of digits (6.88%), osteolysis and fracture (3.67%)
- Muscle atrophy was more common with type 1 reaction, but osteolysis and fracture and resorption of digits more common with type 2 reactional states.
- Renal system (7.79%) involvement was in the form of albuminuria (7.34%) and hematuria (4.59%).
- Both findings were more common in lepromatopus leprosy group and during type 2 reactional states.
- Derangement of liver function was seen in 1.83% cases, all of which were of multibacillary category.
- The least commonly involved was male reproductive system gynaecomastia (0.91%), testicular atrophy (0.91%) and decreased level of testosterone (0.46%). All these cases were of lepromatous leprosy type.
- Features of various system involvement were more common in the multibacillary group except, involvement of musculoske-letal system, which was more commonly involved among patients of paucibacillary group. This points to the fact that higher bacillary load correlates with higher incidence of systemic involvement.

Table 1: Distribution of study population showing Summary of Systemic involvement:

Systems Involved	PB	MB	Total(218)
Nose &Paranasal sinuses	3(7.32%)	38(92.68%)	41(18.81%)
Renal system	0	17(100%)	17(7.79%)
Ophthalmological system	12(34.28%)	23(65.71%)	35(16.05%)
Haematological system	5(19.23%)	21(80.77%)	26(11.93%)
Musculoskeletal system	22(73.33%)	8(26.67%)	30(13.76%)
Hepatological system	0	4(100%)	4(1.83%)
Male reproductive system	0	2(100%)	2(0.92%)

Features of various system involvement were more common in the multibacillary group except involvement of musculoskeletal system, which was more commonly involved among paucibacillary group.

Discussion

Among 218 recruited new cases of leprosy, majority of the patients were of the borderline tuberculoid (BT) category (109 i.e. 50%), followed by lepromatous leprosy (LL) (71 i.e. 32.56%), borderline leprosy (BL) (15 i.e. 6.88%), pure neuritic leprosy (PNL) (15 i.e. 6.88%), mid borderline (5 i.e. 2.29%), indeterminate leprosy (3 i.e. 1.37%) as shown in Table no.1

The mean age of presentation was 33.78(±13.2) years and the male: female ratio in our study was 1.87:1.

A total of 28.44% cases presented in reaction, 30 cases (13.76%) were having type 1 reaction and 32 cases (14.68%) had type 2 reaction during presentation.

In our study, 133 cases were of multibacillary type (61.01%) and 85 cases were of paucibacillary type (38.99%).

Slit skin smear for AFB is an important method for diagnosis. In our study, 138(63.30%) cases were smear negative and 80(36.7%) cases were smear positive for AFB.

Though majority patients were adults, 21(9.63 %) were children. The mean age among childhood

leprosy cases was 10.81(±2.6) years. Among childhood cases, 6 cases were of multibacillary type (28.57%) and 15(71.43%) were of paucibacillary type. Male: female ratio was 1.62:1. Fourteen cases were of borderline tuberculoid type, three cases were of lepromatous type, three were of indeterminate type and one case was of mid borderline type. Three cases had type 1 reaction and one case had type 2 reaction during presentation. Four cases had anaemia, of which 2(50%) were of borderline tuberculoid type. Total five cases had peripheral nerve enlargement, of which 3 cases were of borderline tuberculoid type. Three cases had muscle atrophy with clawing, one each of borderline tuberculoid, mid borderline and lepromatous type.

Ocular lesions of leprosy may be classified into four categories: (i) lesions following direct invasion of eye by M. leprae; (ii) secondary lesions following granulomatous infiltration of contiguous structures; (iii) secondary lesions following granulomatous infiltration of fifth and seventh cranial nerves; and (iv) inflammatory reactions secondary to sensitization of ocular tissues to M. leprae antigens and formation of intraocular immune complexes. The reported prevalence of ocular complications varies from 6% to 96%.

In our study, ocular involvement (35/218 i.e. 16.05%) was in the form of supracilliary madarosis (24/218 i.e.11.01%), lagophthalmos (12/218 i.e.5.50%), conjunctivitis (8/218 i.e.3.67%), corneal opacity (5/218 i.e. 2.29%) and corneal ulcer (3/218 i.e. 1.38%). Daniel E et al reported lagophthalmos (4.20%), corneal opacity (10.5%) and cataract (12.6%). [7] In the lepromatous group of patients (BL and LL), having a higher number of mycobacteria may be a risk factor for the development of lagophthalmos and orbicularis oculi muscle weakness. In our study, lagophthalmos was more common among borderline tuberculoid type (11/12 i.e.91.67%), and supracilliary madarosis was more common in lepromatous group (21/24 i.e. 87.50%) and type 2 reaction (12/24 i.e. 50%). Conjunctivitis was more common in lepromatous group (6/8 i.e. 22.86%) and during type 2 reaction (7/8 i.e. 87.5%). In our study, the prevalence of lagophthalmos is higher, as we have included the patients in tuberculoid pole along with lepromatous cases, and the incidence of type 1 reaction is higher in patients of tuberculoid pole. The prevalence of corneal opacity in our study is much lower in our study, as all types of leprosy cases were included, whereas Daniel et al recruited only lepromatous cases.

The lesions of the skeletal system are very important for they lead to the most dreaded facet of leprosy-deformities and disabilities. The bone changes may be specific or nonspecific. [8] Specific: when they occur due to direct invasion by M. leprae. Nonspecific: when they are affected indirectly. The nonspecific involvement is more common and includes osteomyelitis, osteoporosis, atrophy and absorption of the bones. They result from the impairment of sensations, repeated trauma, trophic changes and restricted movement of the muscles.

In our study, musculoskeletal system involvement (30/218 i.e. 13.76%) was in the form of muscle atrophy (21/218 i.e. 9.63%), foot drop (4/218 i.e. 1.83%), osteolysis and fracture (8/218 i.e. 3.67%) and resorption of digits (15/218 i.e. 6.88%). Muscle atrophy was more common in borderline tuberculoid (8/21 i.e. 38.09%) and pure neuritic leprosy group (7/21 i.e. 33.33%) as compared to lepromatous (4/21 i.e. 19.05%) and mid borderline (1/21 i.e. 4.76%).

Leprosy confines itself mainly to the upper part of the respiratory tract while the lower respiratory tract and lungs appear to escape. The nose is the portal of entry for M. leprae and is the earliest site of involvement in lepromatous leprosy. Edema and mucosal thickening are the main findings seen commonly in the anterior aspect of the inferior turbinate and nasal septum. [9] Chronic rhinitis can occur. Though not discernible during examination, in a study, a standardized test for odour showed lower scores for smell as compared to controls, indicating leprous affection of the first cranial nerve, which could be reversed by therapy. An

important clinical clue is to ask for a history of epistaxis, which is often passed off by the patient as an unrelated occurrence. The combination of anterior nasal spine collapse and septal destruction causes total collapse of the nose.

Impairment of olfaction has been described secondary to atrophic changes in the nasal mucosa with blunting of the olfactory nerve endings. This involvement has varied in different Indian series from 4% to 42%. [10]

In our study, 41/218 i.e. 18.81% patients showed involvement of nose and paranasal sinuses. Most common finding was stuffiness of nose (38/218 i.e. 17.43%), out of which 27/38 i.e. 71.05% were of lepromatous leprosy group. The least common finding was depression of nasal bridge 3/218 i.e. 1.38%. Involvement of nose and paranasal sinuses was more common in the lepromatous leprosy group and along with type 2 reaction. The prevalence of nasal and paranasal sinus involvement in our study is almost similar to the studies from the pre-elimination era, which is alarming, as nose and paranasal sinuses act as the portal of entry and exit the lepra bacilli.

Involvement of the liver is through hematogenous spread and has been noted in both tuberculoid and lepromatous leprosy. The involvement is dependent upon severity of the lesions on skin, and the frequency and intensity of bacteremia. Hepatic dysfunction can also occur. Jaundice occurring in erythema nodusum leprosum reaction and prolonged jaundice in lepromatous leprosy has been reported.

Robins et al reported that there were no changes in transaminases and alkaline phosphatase activities in the untreated patients.[11] Pacin et al found raised enzymatic activity of GOT, GPT and alkaline phosphatase with no changes in turbidity tests and bilirrubinemia, in all reactional patients.[12] The study by Swathi et al revealed minimal derangement in hepatic function in leprosy patients. [13]

In our study, 4/218 i.e. 1.83% had deranged liver function tests. All these cases were of lepromatous leprosy group. 50% presented in type 2 reaction state.

Therefore, monitoring of liver function tests is very important to assess the functional status of the liver before administration of therapy in leprosy.

Renal involvement in leprosy is quite a frequent finding. Functional abnormalities have been found to be more common than the histopathological changes. These include proteinuria, microscopic hematuria, granular, hyaline and red blood cell casts; and the biochemical aberrations, like increased serum urea, serum creatinine, altered distal tubular functions and reduced glomerular filtration rate.

In our study, a total of 17/218 i.e. 7.79% cases had renal involvement. 16/218 i.e. 7.34% had albuminuria and 10/218 cases i.e. 4.59% had hematuria. Both findings were more common in lepromatous type (albuminuria 15/16 i.e. 93.75% and hematuria 10/10 i.e. 100%) and during type 2 reaction (albuminuria 12/16 i.e. 75% and hematuria 10/10 i.e. 100%).

Hematuria has been described in leprosy, mainly in the virchowian form and during erythema nodosum state, even in the absence of evident glomerulonephritis. [14] Microscopic hematuria is found in 12-16% of cases, which is higher than what is found in the general population (0.5-2%). [15,16,17] This complication can disappear after a few months of specific treatment. [18] Proteinuria has been described in several studies and its prevalence varies from 2.1 to 68%, and it is also more frequent in the multibacillary forms. [15,19,20, 21,22]

The prevalence of renal involvement in our study is comparable to previous studies.

Experimental studies have suggested that reticuloendothelial system gets involved early in the course of the disease. Clinically appreciable enlargement of lymph nodes is uncommon in leprosy, except during reactions. The involvement is seen in the form of mild to moderate enlargement of the regional lymph nodes which do not show any suppuration or matting. In

tuberculoid leprosy, only the regional lymph nodes draining the affected cutaneous area are involved, while in lepromatous leprosy the involvement is more widespread and generalised affecting, even the visceral nodes, if the concerned organ has leprous involvement, e.g. hepatic lymph nodes and splenic hilar lymph nodes, in hepatic and splenic affection, respectively. The size of the glands was found to be proportional to the duration of the disease.

Nail changes in leprosy are generally nonspecific and nails may appear dystrophic. The changes are seen in both paucibacillary and multibacillary disease, but are much more frequent and extensive in the latter. The affection of nails has been attributed to many factors that include neuropathy, trauma, vascular changes and infections. [23, 24] In a large series of 300 patients, the changes noted were longitudinal melanonychia, longitudinal ridging and subungual hyperkeratosis. [23] The nonspecific nail changes of chronic disease, such as striae, pitting, leukonychia, Beau's lines, and in advanced disease with the absorption of fingers, anonychia can be seen.

In our study, nail dystrophy and dermatophyte infection were the two most common nail abnormalities, and these findings were more common in the lepromatous leprosy group.

Lower levels of haemoglobin, a raised erythrocyte sedimentation rate, lower serum iron levels and lower levels of serum albumin are often observed. These abnormalities (not usually severe enough to warrant any special attention) are seen more towards the lepromatous pole of the spectrum.

In our study, 13/218 i.e. 5.96% had anaemia, 18/218 i.e. 8.26% showed leucocytosis and in 20/218 i.e. 9.17% patients had neutrophilia. All these findings were more common in the lepromatous leprosy group and during type 2 reaction.

In our study, nose and paranasal sinuses was the most commonly involved system (41/218 i.e. 18.81%) and male reproductive system was least commonly involved (2/218 i.e. 0.92%). Other systems which were found to be affected were renal (17/218 i.e. 7.79%), ophthalmological (35/218 i.e. 16.05%), haematological system (26/218 i.e. 11.93%) and musculoskeletal system (30/218 i.e. 13.76%), hepatological (4/218 i.e. 1.83%) as shown in Table no 1.

Features of various system involvement were more common in the multibacillary group except involvement of musculoskeletal system, which was more commonly involved among paucibacillary group.

Taken individually, it is seen that almost every system is involved in multibacillary forms of leprosy, though in practice, the classification and treatment of disease is based on a thorough examination of the skin and peripheral nerves. The importance of systemic evaluation assumes significance in reactional states when many systems can be noticeably affected. Some of these can have very atypical presentations, simulating other immune-complex diseases, like systemic LE, characterised by malar flush, alopecia, skin eruptions, fever and joint pains. Such patients may have ANA; anti-single stranded DNA, anti-neutrophil cytoplasmic antibodies and positive RA factor [25], but are negative for anti-double stranded DNA antibodies [26]. They are thought to result from stimulation of B-cells by antigenic complexes of M. leprae plus autologous tissue. [27]

Leprosy is not a fatal disease, but it is a chronic and crippling disease, if not diagnosed and treated early. Most of the systemic complications and their disfiguring sequelae can be prevented by early diagnosis and treatment. [28]

Limitations of our study

The current study, being a hospital based study, does not reflect the actual prevalence of the disease in the community. To determine the actual prevalence in the community, a multicentre study needs to be undertaken. A larger study population would allow the determination of statistical correlation between different groups.

Conclusion

Systemic involvement, as evident from our study, is more common in the lepromatous end of the disease spectrum and during reactional states. Features of various system involvement were more common in the multibacillary group, except involvement of musculoskeletal system, which was more commonly involved among the paucibacillary patients. Systemic involvement in post-elimination era is not significantly different from that of previous studies, which is a matter of concern.

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