“CLINICOPATHOLOGIC STUDY OF CHILDHOOD HANSEN’S DISEASE”

DISSERTATION

SUBMITTED FOR THE AWARD OF

M.D. DERMATO-VENERO-LEPROLOGY

BRANCH XII-A

TIRUNELVELI MEDICAL COLLEGE

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI , TAMILNADU.

APRIL 2013

CERTIFICATE

This is to certify that the Dissertation titled **"CLINICOPATHOLOGIC STUDY OF CHILDHOOD HANSEN'S DISEASE"** presented herein by **Dr. S.PRIYADHARSHINI** is an original work done in the Department of Dermato – Venero – Leprology, Tirunelveli Medical College Hospital, Tirunelveli for the award of the Degree M.D. Dermato – Venero – Leprology (Branch XII-A) under our guidance and supervision during the academic period of 2010 - 2013.

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This is to certify that the Institutional Ethical Committee of this College unanimously approves the Thesis /Dissertation/ Research Proposal submitted before this committee by Dr. S.PRIYADHARSHINI a **POST GRADUATE** in the Department of **DVL**, of Tirunelveli Medical College /Hospital, Tirunelveli titled **"CLINICOPATHOLOGIC STUDY OF CHILDHOOD HANSEN'S DISEASE"** registered by the IEC as 043/DVL/IEC/2011 dated: 15.12.2010. The Investigator is hereby advised to adhere to all the stipulated norms and conditions of this ethical committee.

Issued on this Date

15.12.2010

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DECLARATION

I solemnly declare that the dissertation titled "**Clinicopathologic study of childhood Hansen's disease**" is done by me in Tirunelveli Medical College hospital, Tirunelveli.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch XII-A) in Dermato-Venero-Leprology.

Place: Tirunelveli
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ABBREVIATIONS

MDT	-	Multi-Drug therapy
TT	-	Tuberculoid leprosy
BB	-	Midborderline leprosy
BTHD	-	Borderline tuberculoid Hansen’s disease
BLHD	-	Borderline lepromatous Hansen’s disease
LL	-	Lepromatous leprosy
SSS	-	Slit Skin Smear
WHO	-	World Health Organization
HLA	-	Human leukocyte antigen
PB	-	Paucibacillary
MB	-	Multibacillary
DDS	-	Diaminodiphenylsulphone (Dapsone)

CONTENTS

INTRODUCTION

Leprosy is one of the very old diseases to have afflicted man. After a great search for the etiology, it was attributed to a bacterium Mycobacterium leprae by Sir Gerhard Armauer Hansen in 1873 and he remarked wryly:

"*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 works* "

Leprosy is a disease with widely varied clinical manifestations and capable of affecting almost every organ of the body.The disease is considered important mainly because of its potential to cause permanent and progressive physical deformities.After a great struggle over many centuries, the disease has been brought under control. The credit goes to the advent of MDT therapy instituted from 1982. Most countries that were endemic for leprosy have achieved elimination. India achieved elimination in December, 2005.

Though there is a drastic decline in the prevalence of leprosy among the endemic countries, the fall in the new case detection rate is still stable or shows increasing trends. The total number of new cases detected during the year 2011-2012 was 1.27 lakhs and children contributed 9.7% (12,305) of the new cases.

Children are susceptible to leprosy as they are to many other diseases. Not all the hypopigmented skin lesions are due to leprosy. Children usually present with single hypopigmented patch especially over the face with intact or impaired sensation. Clinical features of leprosy among children are confusing and testing of sensation in them is difficult. Unless specifically looked for, the diagnosis may be missed and they will manifest in early adulthood with disabilities. The disease in children responds well to treatment if detected in early stages and the deformities can be prevented.

Above all, childhood leprosy is an indicator for assessing the endemicity of the disease. The high child case rate indicates the continuous spread of the disease in the community. It is also a measure of the efficacy of the control programme.

In view of the importance of detecting leprosy early among children, clinical and histopathologic profile of children who were diagnosed with leprosy at Tirunelveli medical college hospital were analysed in this study and the implications are discussed.

AIMS & OBJECTIVES

This is a prospective study done on childhood leprosy patients below 14 years of age at Tirunelveli medical college hospital with the following objectives

- To study the incidence of childhood leprosy in Tirunelveli district.
- To determine the age and sex distribution of the childhood leprosy cases.
- To study the various clinical presentations, histopathological features and SSS status among children.
- To study the incidence and pattern of nerve involvement, systemic involvement, reactions and deformity in the child cases of leprosy.
- To find out the PB and MB proportion of child cases.

REVIEW OF LITERATURE

DEFINITION:

Leprosy is a chronic granulomatous disease mainly affecting the skin and peripheral nervous system and is caused by the obligate intracellular organism Mycobacterium leprae [1].

Complications due to nerve damage can result in deformity and disability. Leprosy is a stigmatising disease. But, multidrug therapy (MDT) eliminates the infection and also has shown that the disease can be treated effectively and the disabilities can be prevented.

LEPROSY IN HISTORY:

As early as 300 BC, in Hellinistic culture, created by conquests of Alexander the great, Hebrew Bible was translated to Greek, 'lingua franca'. During this process, Hebrew word, reasonably transliterated as 'tsaraath', was translated as 'lepra'. But they didn't refer to the disease; it refers to any disease producing scaly lesions on skin. At some time later the word lepra came into vogue to refer to leprosy[2].

Leprosy is generally believed to have originated in Asia, and the earliest documentation of a disease mimicking leprosy comes from China and India during the early 6th century BC. Lowe recorded that in India, Leprosy was first described in the Susruthsamhita, written about 600 BC, and Chalmoogra oil was

used to treat Leprosy at that time[3]. Rastogi and Rastogi quote the Sanskrit word 'Kustha' as the original name in India for leprosy. In China, Pai-Niu, a disciple of Confucius suffered from a disease that resembled lepromatous leprosy and it was known as 'Lai, Li and Ta feng'. People believed that bones and skulls of Egyptian mummies could reveal even earlier evidence of the disease but it has not been fulfilled; the earliest paleopathological evidence to date is in mummies of the 2nd century BC[4].

The disease was probably carried from India to Europe in the 4th century BC by returning Greek soldiers from Asia, led by Alexander the Great. From Greece, leprosy slowly spread throughout Europe and in Western and Northern Europe, the disease was most active between 10th and 15th century BC. The first recognisable description of leprosy in Greece was written by Aretaeus of Cappadocia in the middle of 2nd century AD. Whether Alexander brought leprosy to Europe and the Near east from India or whether Persians had introduced it into Europe during their invasions are questions with no hope of answer [5] .

Noble families founded Leprosaria, hospitals for leprosy patients in twelfth and thirteenth centuries. Leprosy patients were legally considered as dead during that period and their heirs could inherit property.

Moller Christensen's (1961) works revealed that 80 % of the skeletons excavated in the cemetry of Lazar hospital at Naestved between 1250 and 1550

A.D. showed pathognomonic findings of leprosy. The Naestved study revealed that the sex incidence was equal and the majority of the leprosy cases had their onset in childhood [6.]

Carl William Boeck (1808 – 75) and Daniel Cornelius Danielssen (1818-94) are two of the most renowned leprosy experts of the nineteenth century who believed that leprosy was a congenital disease and not an infectious one.

Leprosy was conceived of as a punishment for sin. Thus the outward sign of Leprosy indicated a soul embroiled in sin.

EPIDEMIOLOGY OF LEPROSY:

Leprosy is considered important because of its potential to cause permanent and progressive physical deformities with serious social and economic consequences.

Despite the fact that M.leprae was discovered in 1873 by Sir Gerhard Henrik Armauer Hansen and so many researches all over the world since then, many of the epidemiological trends of leprosy are not clear still. In the classical epidemiological triad (agent factors, host factors, environmental factors) , apart from the agent M.leprae which is well described, the entry and exit of the organism from the host, its predilection for Schwann cells, the incubation period, are at best guesstimates. Children seem to be most susceptible to active infection by M. leprae but the disease manifests during adolescence or early

adulthood. The male to female ratio of leprosy in children is almost equal and is more towards males in adults[7].

GLOBAL SCENARIO:

WHA (World Health Assembly) set out the mission to eliminate leprosy in 1991. i.e. the prevalence of <1 per 10,000. The goal was achieved worldwide in 2000 except for 14 countries. The target was then reset for those countries to achieve elimination at their national level by 2005. India was one among those 14 and it achieved the goal of elimination by December, 2005[8].

Global statistics according to WHO report[9]:

No	WHO region	No.of new cases detected	
		2010	2011
1	African	25,345	12,673
2	American	32,740	36,832
3	South-east Asia	1,56,254	1,60,132
4	Eastern Mediterranean	4,080	4,346
5	Western pacific	5,055	5,092
		2,28,474	2,19,075

Progress since the introduction of MDT

The combination of clear objectives, a proper technology and an effective implementation lead to success in the control of leprosy. There are two important events that aided in decreasing the global load of leprosy in the past

two decades. The first event was in 1981, when a WHO study group on Chemotherapy for leprosy put forward the use of MDT for leprosy. The second event was in 1991, when the 44th WHA adopted a resolution to eliminate leprosy by 2000 [10].

The notable achievements after the introduction of MDT are:

- Almost 15 million patients with the disease were diagnosed and they were cured with MDT between 1985 and 2008 except for few relapses.
- Prompt case-finding and early treatment with MDT has reduced the disability due to the disease.
- The drugs for MDT are given free of cost in the endemic countries through WHO from the year 1995.

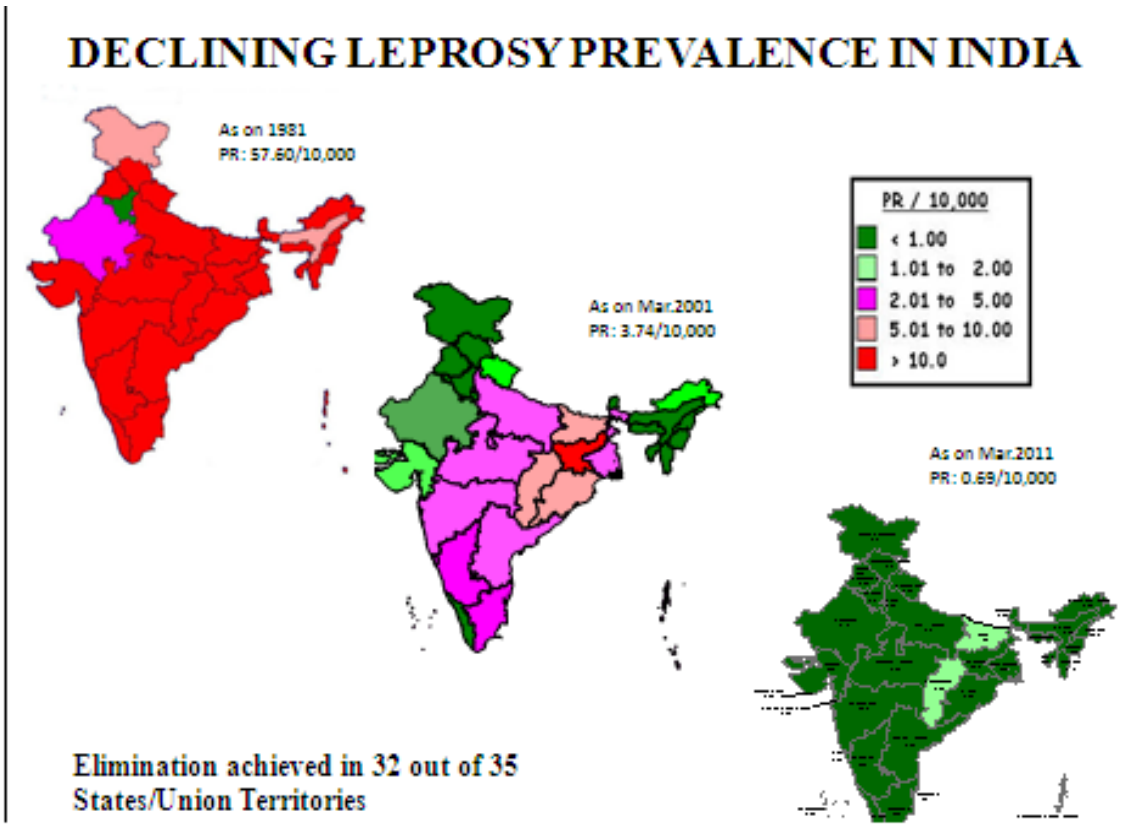
The number of new cases of leprosy reported to WHO was 2, 19,075 in the year 2011. The new case detection rates are the highest in India, Brazil, Nepal, Tanzania, Mozambique and Democratic republic of Congo, Angola, Madagascar and the Central African Republic. India constituted 73% of all the new cases across the world.

ABOUT NLEP:

The National Leprosy Eradication Programme is a Health Scheme sponsored by Central Government. The Deputy Director of Health Services (Leprosy)is the head of the Programme. He is under the administrative control of the Directorate General Health Services, Govt. of India. The formulation of plan is made by the central government and it is implemented at the state level. The Partners of this programme are WHO, The International Federation of Anti-leprosy Associations (ILEP) and few other Non-Government Organizations[12].

Milestones in NLEP

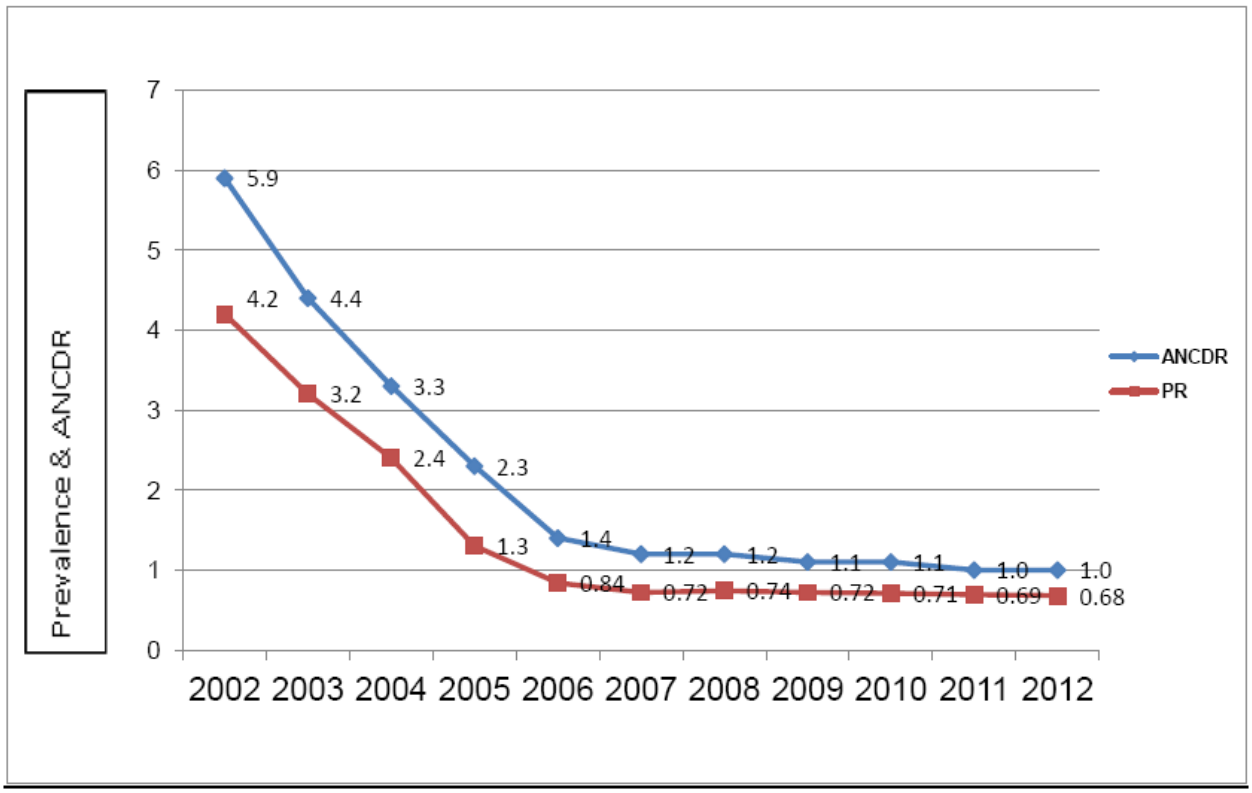
- 1955 - National Leprosy Control Programme (NLCP) launched
- 1983 - National Leprosy Eradication Programme launched
- 1983 - Introduction of Multidrug therapy (MDT) in Phases
- 2005 - Elimination of Leprosy at National Level
- 2012 - Special action plan for 209 high endemic districts in 16 States/UTs



Status in the Country:

At the beginning of the year 2011-12, there were 0.83 lakh leprosy cases on record as on 1st April 2011, with a prevalence rate of 0.69/10,000. Until then 32 States/ Union territories had attained elimination. About 530 districts (82.8%) out of the total 640 districts also achieved leprosy elimination by March 2011[13.]

Trend of leprosy Prevalence (PR) and Annual New Case Detection (ANCDR) over the last decade are indicated in the graph below:



The child case burden was greater than 10% of new cases detected in ten States/UTs namely (i) Andhra Pradesh 12.44%, (ii) Maharashtra 13.04%, (iii) Bihar 14.98%, (iv) Tamilnadu 11.56%, (v) Puducherry 14.29%, (vi) D&N Haveli 20.25%, (vii) Goa 12.50% (viii) Karnataka 10.76%, (ix) Kerala 11.61% and (x) Andaman & Nicobar Island 18.52%.

Among the 472 (11.56 %) child cases reported in Tamilnadu in 2011-12, 75 cases were PB cases and 397 cases were MB cases. The number of child cases reported with grade II deformity is 168 (35.59%).

AGENT FACTORS:

Leprosy is caused by Mycobacterium leprae. These are acid fast, straight / slightly curved rod shaped gram positive bacilli which can be seen single or as clumps or bundles on microscopic examination. They are slow growing bacilli and divide into two every 12 – 14 days. They do not produce toxins and have affinity for Schwann cells and cells of reticuloendothelial system. They can remain dormant in several body sites and tissues causing relapse. The organism is killed by boiling and autoclaving. Its susceptibility to air, cold, water, drying and disinfectants is uncertain[14].The bacilli can survive outside the human body for 2-9 days depending upon the environmental conditions. The bacillary load is highest in lepromatous cases [15]. The natural life span of the bacillus in human body is not known, but persisters have been isolated from patients even after 10 years [16.]

Mycobacterium leprae prefers cooler tissues like the skin, peripheral nerves, upper respiratory tract and testes and spares warmer areas. They are found in large quantity in the nasal mucosa and skin of earlobes, face and buttocks [17].

Number of antigens has been detected in M.leprae, the most significant of which is the Phenolic glycolipid-1 (PGL-1) detected on serological test. The disease can no longer be considered as confined to human, for naturally acquired leprosy has been reported in the armadillo, the chimpanzee and the

mangabey monkey. Successful transmission of M.leprae has been observed in experimental animals like nine-banded armadillo and nude mouse. M.leprae can also be grown experimentally by injecting them into the foot pad of mice. However, it has not yet been shown to grow in artificial media.

The genome of *Mycobacterium leprae was* sequenced in 2000. The organism seems to have undergone a reductive evolution with considerable reduction in the gene size compared with *M. tuberculosis*. Nearly 50% of the genome is occupied by pseudogenes [18].A better understanding of the genome of *M. Leprae* may give an insight into the mechanisms by which the organism evades immune surveillance and which metabolic pathways it requires in the host cells it infects to allow the development of techniques to culture the organism.

STRUCTURE OF M.leprae:

It is a rod shaped bacterium which is 1-8µm in length and 0.3µm in diameter, with parallel sides and rounded ends. Ultrastructural study reveals the bacterium has a cell wall, cell membrane, cytoplasm and a capsule. The cell wall is composed of the core, the inner leaflet and the outer leaflet. The core of the cell wall contains peptidoglycan, composed of alternating N-acetylglucosamine and N-glycolylmuramate linked by peptide cross-bridges, which are linked to galactan layer by arabinogalactan. Three branched chains of

arabinan are in-turn linked to the galactan, forming along with the peptidoglycan layer, an electron-dense zone around M.leprae. The inner leaflet is a pseudolipid bilayer. The outer leaflet is composed of intercalating mycolic acids and phenolic glycolipids (PGL)forming the electron-transparent zone. The predominant lipid in the cell wall PGL-1 gives immunological specificity. Recent studies show that PGL-1 is involved in the interaction of lepra bacillus with laminin of schwann cells, suggesting role for the lipid in peripheral nerve-bacilli interactions. The next layer is cell membrane which contains the two major polypeptides namely major membrane protein-I (MMP-I) and major membrane protein-II (MMP-II). The lepra bacillus has 3 major proteins in cytoplasmic extracts-a 28 kDa, a 17 kDa protein and a GroES heat shock protein. Outer to the cell wall the bacterium has a capsule which is composed of two major bacterial lipids namely 1.Pthiocercol dimycocerosate and 2. PGL-1, a specific glycolipid for M.leprae that is serologically active.

HOST FACTORS:

1. Age:

Leprosy is more commonly seen in the age group between 20 to 30 years. However, no age is exempt. In endemic areas the infection generally takes place during childhood though manifests later and in low endemic areas, the infection may occur in adult or later part of life. Increased proportion of child leprosy

cases in the population has epidemiological significance as it indicates presence of active transmission of the disease in the community. Age distribution of lepromatous cases generally shows that the disease has a later onset as compared with non-lepromatous cases.

2.Gender:

Though it affects both the sexes, males seem to be more commonly affected with a M: F ratio of 2:1.The gender difference is minimal among children below 15 years and more marked among adults. More number of male cases could be attributed to their greater movement for work and more susceptibility for contact. Males are also more active in reporting to health facility for seeking treatment for social reasons.

3.Migration:

Due to migration of population from rural to urban areas, leprosy cases have increased in urban areas in recent years. The population density is very high (10,000 to 15,000 per sq.km), most of the inhabitants are migrants from distant villages ,the hygiene and living conditions are poor, breathing space is greatly compromised .

Two types of leprosy carriage can be noted: a) the two way traffic, to and from the villages and slums, and b) one way from slums to middle class

localities where the population density and living conditions are different from those in slums.

4. Immunity:

Occurrence of the disease depends on the susceptibility or immunological status of the individual. Immunity to the organism is disease specific. Immunodeficiency states like HIV and congenital immunodeficiency disorders doesn't seems to increase the risk. Cell mediated immunity provides resistance to infection against M.leprae. Most of the early lesions in leprosy heal spontaneously. Such self-limiting lesions suggest innate or acquired immunity. Subclinical infections also contribute to development of immunity. Some amount of immunity also appears likely because of infections with other related mycobacteria[19]. There is a good evidence that BCG vaccine can provide some protection against leprosy particularly LL.

5.Familial clustering:

The occurrence of leprosy has been found more in certain clusters of communities and especially in family clusters. The community clusters can be explained in terms of environmental conditions like local mycobacterial flora to which all community people are exposed. But for the family clusters it becomes difficult to explain whether it is due to similar environmental conditions or due to the close familial (genetic) relatedness. Also it has been shown that the

probability of finding familial occurrence of leprosy is higher in families that include a lepromatous patient; than in those where it does not[20].

ENVIRONMENTAL FACTORS:

M.leprae survives well in humid environment. The bacilli survive for about 9 days in dried nasal secretions and for almost 46 days in wet soil at room temperature[21]. In leprosy endemic areas, the risk of developing the disease is more among the house hold contacts. The risk is increased by closeness and duration of contact. But all these factors would be operative only, if the exposed persons are genetically susceptible. This is supported by the observation that the rate of conjugal leprosy is generally low.

SOCIAL FACTORS:

Leprosy is a social disease and it produces physical and psychological stigma as a result of the permanent deformities and even the diagnosis itself produces social alienation. It is generally associated with poverty related factors such as overcrowding , lack of education, lack of personal hygiene ,lack of ventilation, etc. which favours the transmission of the disease. However, it may affect persons from any socio-economic group. Fear of leprosy, guilt, stigma and discrimination associated with the disease in the community and unfounded prejudices regarding leprosy forces a person to hide the disease and contribute

to delay in seeking treatment and thus promote worsening and transmission of the disease.

TRANSMISSION:

Source of infection:

Man is the only natural reservoir of M.leprae and the only source of infection is an untreated case of leprosy. Multibacillary cases particularly Borderline Lepromatous and Lepromatous Leprosy spectrum are the most important source of infection compared to paucibacillary cases. However, all leprosy cases should be considered as a potential source of infection. It is now evident that wild animals like armadillos, mangabey monkeys and chimpanzees show infections with M.leprae, but they don't seem to be a threat to humans.

Portal of Exit:

Respiratory tract especially the nose is the main portal of exit of M.leprae from the body of an infected person. Millions of bacilli are discharged from the nasal mucosa of the bacteriologically positive cases during sneezing. Patients with leprosy harbour most bacilli in their skin, but they are shed from intact skin in only small numbers. However, bacilli can be shed from broken skin and ulcers of untreated lepromatous cases.

Modes of transmission:

Various modes of transmission of leprosy are described but it is still not established with certainty that only one is the major mode or all of them contribute. The main likely modes of transmission are:

1.Inhalation(Droplet infection)

2.Contact

3.In utero transmission

4.Transmission through ingestion (Breast milk)

5.Inoculation following trauma

Portal of Entry:

Respiratory route is the major portal of entry for the bacilli. The possibility of infection through the skin, particularly broken skin cannot be ruled out.

INCUBATION PERIOD:

The incubation period is usually 3-5 years. But it may vary from few weeks to 30 or more years[22.]

IMMUNOLOGY OF LEPROSY:

Majority of the symptoms of leprosy are due to the immune response of the host to the organism, than due to the organism itself. We also know that the

individual differences in the immune activity to the bacillus are to a great extent controlled by genetic host factors.

Leprosy per se is not controlled by any HLA linked genes[23]. The susceptibility to certain types of leprosy, or, in other words, to different types of immunopathology certainly is linked to HLA and associated with several HLA alleles, particularly with HLA class II alleles. Examples are HLA-DR3 is associated with tuberculoid leprosy in some populations and HLA-DQ1 is universally associated with lepromatous leprosy[24].

Some of the recently identified genetic markers found associated with leprosy are [37, 38,39,40,41]:

No	Gene allele, Chromosomal location	Type of leprosy	Function of the gene
1	HLA-DRB1*1501, Ch.6p21	Multibacillary	To present peptides for immune response
2	HLA-DQB1*0601, Ch.6p21	LL,BL,TT	To present peptides for immune response
3	HLA-DQA1*0103, Ch.6p21	LL	To present peptides for immune response
4	HLA-DQA1*0102, Ch.6p21	BL	To present peptides for immune response
5	TNF-α 308A, Ch.6p21	Protection from LL,BL,leprosy per se	Associated with high cytokine secretion
6	PARK2/PACR Ch.6q25-27	Leprosy per se	Ubiquitin E3 ligase

The heat shock protein (hsp), a 65kDa M.leprae antigen is the one which is studied in detail. The T cell immune response to HSP is under strict control of HLA class II gene. Mosmann et al (1986) study in the mouse has described two helper T (Th) subsets differing in their lymphokine secretion profile. The first subset (Th1) secretes IL-2 and IFN-gamma and the second (Th2) one IL-4, but no IL-2 and IFN-gamma [25]. Comparing the cytokine production by T cells reaction with M.leprae antigens and non-mycobacterial antigens, the first produce a lot of IFN-gamma and no or very little IL-4 in contrast to the latter. Injection of IL-2 or IFN-gamma produced an increased cellular immune reactivity in LLHD patients with delayed type hypersensitivity reactions [2]. Since IL-10 has the ability to inhibit IFN-gamma and IL-2 production by Th1 cells (Fiorentino et al 1989, Vieira et al 1991), this can be utilized as an antagonist in the immunotherapy of DTH reactions in mycobacterial disease [27, 28].

The lymphocytes perform the central part in the specific immune response against Mycobacterium leprae. Although M.leprae can be engulfed by many host cells (notably Schwann cells), they are primarily taken up by specialized host cells termed professional phagocytes which include the polymorphonuclear granulocytes and members of the mononuclear phagocyte system. Presentation of peptides derived from proteins of M.leprae by class II expressing antigen-presenting cells (macrophages, Langerhans cells, dendritic

cells, activated epithelial cells) to CD4+ T cells represents the central part of cellular immunity in leprosy[29].

During persistent replication of M.leprae in the phagolysosome, the phagosomal membrane may become 'leaky', thus allowing transit of bacterial proteins into the cytoplasmic component to become cytoplasmic antigens. Antigen recognition represents an essential, though insufficient, step of T cell activation. In addition to this primary signal, a secondary or costimulatory signal is required which is delivered by interleukins [25, 30]. Primary activation of CD4 T cells requires factors provided by the antigen-presenting cells such as interleukin-1 (IL-1). At later stages, CD4 Tcell activation is further increased by IL-2. IL-2 which is produced by CD4 T cells and at least one additional factor (probably IL-6) provide costimulatory signals for CD8 Tcells. In the absence of costimulatory signals, T cells may be tolerized. In situ analyses revealed abundant numbers of IFN-gamma producing CD4 Tcells in tuberculoid lesions and in reversal reactions which are rare in lepromatous lesions[31]. CD4 T cells from tuberculoid leprosy patients produce high levels of IFN-gamma and IL-2 in vitro and hence belong to Th1 set, whereas T cells from lepromatous leprosy patients fail to produce these interleukins [32, 33, 34] . T cell numbers were reduced in lepromatous leprosy and the patients usually fail to respond to M.leprae antigens. In contrast to T cell functions, the antibody responses of both general and antigen specific type are enhanced in lepromatous patients. The

presence of antibodies along with the presence of high load of bacilli indicates that protection is not mediated by antibodies.

It is likely that macrophages are activated by IFN-gamma to inhibit the growth of M.leprae and perhaps even to kill them[35]. TNF probably synergises with IFN-gamma in macrophage activation [36]. Th1 cells which produce IFN-gamma and thus activate anti-mycobacterial macrophage function play the central part in acquired resistance against M.leprae.

CLASSIFICATION

Patients need to be classified in order to determine the appropriate treatment and also to predict the complications and prognosis.

There is a great need for understanding in the matter of evolving a common system of classification for general use. The well accepted classifications include Madrid, Indian classification, Ridley-Jopling, and WHO classification.

I.International classification at Madrid (1953)

It included two types and two groups. The term ‘Type’ denoted definite and typical clinical entities while the ‘Groups’ were less distinct non typical entities. The two types were lepromatous (L) and Tuberculoid (T); while two groups were ‘Indeterminate (I) and Borderline or Dimorphous (B). The morphological subtypes had been added up under each of these entities and

are called ‘varieties’.

1. Lepromatous Type (L)

Macular

Diffuse

Infiltrated

Nodular

Neuritic, pure (?)

2. Tuberculoid Type (T)

Macular (Tm)

Minor tuberculoid (Tt)

Major tuberculoid (TT)

Neuritic, pure (Tn)

3. Indeterminate Group (I)

Macular (Im)

Neuritic, pure (In)

4. Borderline Group (B)

Infiltrated

Though the classification was exhaustive, yet the pre-existing objections could not be done away with entirely.

II. Indian Classification:

This was drafted on behalf of the Indian association of Leprologists (IAL) at almost the same time as the Madrid classification (1953) but was accepted

and adopted in 1955. The main objection was that the classification was not entirely clinical and their applicability and usefulness at all levels of leprosy workers was doubtful. There were 6 categories namely:

1. Lepromatous (L)
2. Tuberculoid (T)
3. Maculoanasthetic (MA)
4. Polyneuritic (P)
5. Borderline (B)
6. Indeterminate (I)

II. Revised Indian Classification (1981)

A modification was made in the previous Indian classification. Maculoanasthetic leprosy (MA) was merged with tuberculoid leprosy (T). The resultant five group classification was called the New IAL classification of leprosy

1.Tuberculoid
2. Borderline
3. Lepromatous
4. Indeterminate
5. Pureneuritic

III. Ridley and Jopling Classification (1962)

Though the clinical manifestations of leprosy are numerous, patients can be classified along a clinical spectrum. It was perfectly done coincidentally, but

separately by Ridley and Jopling in the U.K. and by Leiker in The Netherlands in 1966. This classification is based upon the fact that bacteriological, immunological, histopathological and clinical features of leprosy are intrinsically interwoven. At one end of the spectrum is the tuberculoid (TT) leprosy patients with a relatively high CMI and on the other end are the lepromatous leprosy (LL) patients without any detectable CMI against the M.leprae.

The classification is as follows:

Tuberculoid (TT)

Borderline tuberculoid (BT)

Borderline Borderline (BB)

Borderline lepromatous (BL)

Lepromatous Leprosy (LL)

The advantages of this classification are that only it is easier to comprehend but it also helps to understand the disease in a better way. It also strengthens the polar and spectral concept. The main drawback is that there is no specific place for the indeterminate and pure neuritic leprosy in the spectrum.

IV.WHO classification (1982)

Paucibacillary

Less than 5 skin lesions

No nerve involvement or one nerve involvement

Bacterial index of 0

Multibacilliary

More than 5 skin lesions

More than one nerve involvement

Bacterial index ≥ 1+

Initially PB includes BI <2+ and BI =/> 2 in MB and it was Changed in 1988 to paucibacillary = bacterial index of 0; multibacillary ≥ 1+ by WHO Expert committee on leprosy 1988

CLINICAL FEATURES:

Clinical leprosy varies from the presence of an ill defined area of hypopigmentation that heals spontaneously to widespread involvement of peripheral nerves, eyes, bone, muscle and other tissues, with deformity and disability[42] . Clinical features of the disease in leprosy are more often the result of host response to the presence of the bacilli than of changes directly due to bacillary invasion [43].The explanation lies in the infected individual's immune status (resistance) against the organism, and the fact that it is not a question of bacterial strains of varying pathogenicity which has been confirmed by Rees[44].

It is worth remembering that a combination of skin and neural disorder is strongly indicative of leprosy, and the correct diagnosis can usually be made with the help of a pin and a scalpel [45].

EVOLUTION OF INFECTION AND ONSET OF DISEASE:

M.leprae is believed to enter the human host through the skin or the nasal mucosa. After a variable incubation period, in susceptible individuals a local lesion may be produced (primary lesion).Early single lesions in children are found mostly on the gluteal region, thighs, followed by those on the back and posterior aspects of the arms. In warm climates, children are scantily clad and microtrauma or insect bites may allow the entry of bacilli. Bacilli may get into the site of entry, they may spread via the lymphatics or there may be a bacillemia. Since the nerves offer a protected site, the bacilli lodging there as a result of the bacteremia escape elimination by the defense mechanisms of the body.

The onset is usually insidious so that it is difficult to time the sequence of events in the development of leprosy. Normally the incubation period is 2-5years. It tends to vary with the type of exposure. In child contacts of lepromatous leprosy patients, continuously exposed to infection, it ranges from 9 months to 6 years.

Duncan et al (1983) found that 2 of 38 babies born to active lepromatous mothers showed immunological evidence of infection by 6 months of age, and developed clinical leprosy at 12 and 17 months [46].

CASE DEFINITION:

At the 7th meeting of the WHO Expert committee on Leprosy in 1997, a case of leprosy was defined as an individual who has not completed the course of treatment and has one or more of the three cardinal signs.

CARDINAL SIGNS OF LEPROSY:

It is traditional to list these as:

1. Diminution or loss of sensation in a typical skin lesion, or in an area supplied by one of the peripheral nerves typically affected in leprosy;

2. Enlargement and / or tenderness in a peripheral nerve typically affected in leprosy, and

3. The finding of acid-fast bacilli in slit-skin smears.

FEATURES OF LEPROSY ACROSS THE SPECTRUM:

Indeterminate leprosy:

Indeterminate leprosy is the first sign of the disease in 20-80% of patients[47] .Indeterminate leprosy appears as one or a few slightly hypopigmented macules,1 or a few cm in diameter, with rather ill defined margins; in white skin they may be erythematous or coppery-red. The patient is usually a child .Usually there is nothing evident but a slight change in skin colour. Slight anaesthesia may be demonstrable but is usually absent. Smears

are negative, but occasionally a bacillus demonstrated within a cutaneous nerve .Lesions is common over the extensor surfaces of the limbs or buttocks or on the face. The scalp, axillae, groin and lumbar skin are usually spared[48].If the lesions are inconclusive, and histology is not available or inconclusive, a delay in the diagnosis for 3 months will allow one to keep the person free of stigma of diagnosis of leprosy. This type of leprosy may heal spontaneously, but about 30% progress to a determinate type, more often towards the lepromatous end of the spectrum [49].

Tuberculoid leprosy:

Tuberculoid leprosy affects skin and peripheral nerves. In contrast to the lepromatous type, the patient with tuberculoid leprosy is likely to report early for medical examination. Patient may present with neural symptoms, dermal symptoms or both. Neural symptoms consist of pain, loss of feeling, tinglings and muscle weakness or paralysis. Any of these may occur singly or in combination. Skin lesions are single or upto 3 in number. A dermal lesion of tuberculoid leprosy takes the form of a well defined plaque which may be anywhere on the skin apart from the warm areas such as the hairy scalp, axillae, groins and perineum. It is erythematous on a light skin, erythematous or coppery red on dark skin, and has a dry surface which is often irregular and sometimes scaly, with raised and well-defined edges and a tendency to central flattening. Hair growth is deficient or absent over the lesion, and the sensation is

blunted (Initially, the temperature is lost followed by light touch and pain), but it should be noted that it is quite difficult and may be impossible to demonstrate impaired sensation in lesions on the face because of the extensive sensory supply[50].Rarely the lesion is a macule, erythematous in light skin and hypopigmented in dark skin, with coppery or orange tint. Such macules are well demarcated and are dry; devoid of hair and hypoaesthetic. A thickened nerve is usually palpable in the vicinity of a tuberculoid lesion. A sensory nerve will be missed by the examiner if he does not run his finger lightly all the way around the edge of the lesion, for the thickened nerve is detected by feeling and not by sight. The extent of peripheral nerve involvement is minimal or nil. There may one or two in the area near a skin lesion. Nerve thickening may be smooth or irregular, and rarely a cystic swelling may be seen and felt in relation to a nerve – a cold abscess of nerve. Even rarer is calcification in a nerve.

In addition to testing tuberculoid lesions for sensory loss, a sweating test can demonstrate anhidrosis and a histamine test on a hypopigmented lesion shows absence of flare due to the invasion of afferent sensory nerve. Skin smears and nasal scrapings are negative [51] .The lepromin test is strongly positive.

True tuberculoid is usually an insignificant type of infection that will heal itself in a few months time without treatment[52].In the Saidapet study in India in which untreated children were followed up for 19 years from 1937-1956 , 88%

of major tuberculoid and 78% of minor tuberculoid lesions healed spontaneously. Only 1% downgraded to lepromatous leprosy[53].Tuberculoid leprosy seldom leads to peripheral nerve damage, nor to any disability, so one can say the prognosis is very good.

Borderline tuberculoid (BT)

Borderline tuberculoid is the most common type seen in children. The skin lesions of borderline tuberculoid retain more characters of tuberculoid leprosy. It may be present as macules or plaques or both. The number of lesions is greater than TT, up to 10 or 20 or more and it is asymmetrical. They vary in size and may be large enough to embrace the whole limb. Satellite lesions lie near the edges of larger lesions. Margins may be raised and well defined in part of a lesion, flat and vague in another. The margins may be wavy or have islands of extension. Hypopigmentation, dryness pebbling and scaling are less pronounced than in true TT, and there is less anesthesia in the lesions.

Peripheral nerve damage is widespread and severe. Peripheral nerve involvement is asymmetrical; may be irregularly enlarged, tender. Nodular thickening and frank abscess formation may occur. The striking feature of BT leprosy is the occurrence of high frequency of type 1 reaction. Nerve function may deteriorate rapidly and irreversibly leading to various deformities (Spontaneous or due to treatment / reactions). BT leprosy may present with large pale macules and multiple nerve involvement, it is sometimes called

maculoanesthetic or low resistant tuberculoid leprosy associated with liability to severe reaction.

Borderline Borderline (BB)

The most unstable form of the spectrum that is occasionally seen in children. The skin lesions are more in number but not as many as in lepromatous leprosy. There is often a tendency to symmetry. The skin lesions may be macules, papules or plaques or a combination of all. They vary greatly in size, shape and distribution and edges may be well defined in one area and vague in another area. Satellite lesions are common. Geographic appearance of lesions and lesions with ill-defined sloping outer margin and a punched out center with a very well demarcated raised edge (dough nut appearance) may characterize this spectrum. Nerve damage is variable. It may be asymmetrical multiple mononeuropathy if the patient is downgrading from BT to BB or may be symmetrical polyneuritis if the patient is upgrading from BL to BB. Glove and Stocking sensory loss is unusual.

Borderline lepromatous spectrum (BLHD):

There is numerous skin lesions not so well defined. They occur as slightly infiltrated macules with copper hue, round or oval about 2-3 cms in diameter, with bilateral but in not so symmetrical distribution with areas of apparently normal skin in between. With the disease progression, papules, nodules and plaques may develop with sloping margin which merge imperceptibly into

normal skin[54]. Signs of nerve damage start earlier than in LL (more common in cases downgrading from BB). Peripheral nerves become thickened and there is a tendency towards symmetry with corresponding anaesthesia and paresis. BL patients are more prone to develop type I and type II reactions, more commonly ENL reaction.

Lepromatous leprosy:

Lepromatous leprosy may be of subpolar type (LLs) in which the patients were earlier in the borderline phase or polar type (LLp) in which the patient has been lepromatous throughout. Clinical diagnosis is based on finding typical early lepromatous lesions in a patient who also has some typical lesions of borderline type and one or more thickened nerves, with or without evidence of nerve dysfunction. The main reason for this subdivision of lepromatous leprosy is that the LLs group can rapidly regain their lost cell-mediated immunity during an upgrading reaction. In other words, LLp is immunologically stable and LLs is not.

The signs of early LL that may precede the classical skin lesions by months or years are the nasal symptoms and oedema of the legs. Nasal symptoms include stuffiness, crust formation, and blood stained discharge. Oedema of the legs and ankle, always bilateral, is likely to be noted towards the end of the day, disappearing after a night's rest; becomes persistent and woody hard at a later stage. Oedema is due to a combination of gravity and increased

capillary permeability, and the latter is probably due to both leprous involvement of capillary endothelium and damage to autonomic fibres within dermal nerves controlling capillaries.

Multiplication and universal spread of the bacteria accounts for many of the features of the disease at the lepromatous pole. The early lesions of LL are small macules, innumerable in number, widely disseminated and distributed symmetrically. The edges are indistinct, their surface shiny and erythematous or hypopigmented. The early macules of LL are not anaesthetic. Lepromatous leprosy with infiltrated lesions presents as three distinct forms: diffuse, infiltrated and nodular forms. In the diffuse form, the skin has a shiny look with slight infiltration. Thickness of skin is most marked over the face especially over the forehead, earlobes, eyebrows, nose and malar surfaces. The earlobes are usually thickened and shiny. Thickening and nodulation of the earlobes is best appreciated by standing behind the patient. Loss of eyebrows is often a late sign of LL. Infiltrated leprosy is a more advanced stage of macular LL with easily visible infiltration which may be a sign of advancement of diffuse LL disease. Lesions are often shiny and succulent in consistency. Nodular leprosy is the result of progressive deterioration of the macular, diffuse or infiltrated forms of LL. In the early stage , the nodules appear first on the ears and later they may appear anywhere on the body . The infiltrated plaques accentuate the skin fold producing the classical leonine facies. The sensory loss is symmetrical and

gradually results in the typical glove and stocking anesthesia .Weakness usually start in the intrinsic muscles of hands and feet. The nerves are often not palpably enlarged and nerve conduction study may be normal early in the disease. The digits are swollen and tend to taper towards the tips, giving the hands and feet a characteristic appearance. Frequently the joints become swollen and angulated. Digits may shorten due to resorption of phalanges. It causes stuffy or blocked nose like that in coryza often followed by epistaxis. Oral mucosa may be involved in the form of nodules and plaques involving tongue and palate. Involvement of larynx can cause hoarseness of voice and stridor. Early eye involvement includes corneal anesthesia due to bacillary infiltration of corneal nerves and damage to the ophthalmic division of the trigeminal nerve. Hansen's disease is one of the causes of preventable blindness[55]. Other ocular manifestations include lagophthalmos,uveitis, corneal opacity, perforation, and blindness. LL does not remit naturally, though in few patients it burns out itself. Death occurs due to the secondary infection, amyloidosis leading to renal failure.

Pure neuritic leprosy:

It is one of the forms of leprosy that is difficult to classify, and finds a mere passing reference in Ridley-Jopling classification of leprosy. Wade, in 1952, was the first to recognize polyneuritic cases as a separate group[56] . Pure

neuritic leprosy may be an early form of leprosy in evolution in some patients, but in others it is a distinct presentation.

Pure neuritic leprosy constitutes 4.3%-10.7% in most Indian studies, with higher frequency in South India, where it constitutes up to 18% of new cases [57]. Males are affected more frequently than females and patients are most commonly in the age group of 20-40 years. They may have symptoms for a long time (2.5 – 3 years) before presentation [58]. Most of the patients present with sensory impairment, 5 – 10 % with nerve pain or deformity, and rarely as a nerve abscess. The deformity rate is up to 25-30%. The majority of cases are mononeuritic. The ulnar, median and lateral popliteal nerves are commonly involved. Cutaneous nerves like the sural, musculocutaneous, superficial radial and greater auricular nerves can be involved.

Pure neuritic leprosy can be diagnosed on the finding of a thickened nerve with sensory impairment, negative slit skin smears and the absence of skin lesions. A nerve biopsy is diagnostic and on histology the entire spectrum from TT to BL leprosy may be seen. A single thickened nerve that is firm in consistency with a strongly positive lepromin response indicates TT-BT leprosy. Abscess formation may be a presenting feature and suggests tuberculoid leprosy. If two or more nerves are thickened and the lepromin test is negative or doubtful, BL leprosy may be suspected and confirmed by a nerve biopsy.

Follow-up of patients with pure neuritic leprosy shows the development of skin lesions in 35% of cases over 3-5 years with or without treatment.

Histoid leprosy:

The term 'Histoid' was coined in the year 1960 by Wade[59].Histoid leprosy is a type of multibacillary leprosy, characterized by typical cutaneous and/or sub-cutaneous nodules and plaques over apparently normal skin characteristic histopathology and specific morphology of bacilli[60]. It usually occurs in patients on Dapsone for a long time and reflects initial improvement followed by a relapse. It also occurs in patients who have taken inadequate treatment. Some believe that it is due to the drug resistance to DDS, while others postulate that mutant organisms, that emerge from a predominantly sulphone susceptible bacterial population may be responsible [61]. Histoid leprosy is also reported in untreated patients [62]

It presents with 3-50 cutaneous or subcutaneous nodules over the extensor aspects of the extremities, back, buttocks and face[63]. Typical lesions are firm, reddish, or skin coloured, dome shaped or oval papules, regular in contour with shiny and stretched overlying skin. The surrounding skin is apparently normal. They may be localized to bony prominences such as around the elbows and knees. The nodules are erythematous and arise from apparently normal skin. On the face, they can be seen in groups on the mid forehead, cheeks, tip of the nose, and on the chin; the ears may not be affected. In a

widespread eruption, the mucosa of the oral cavity, hard palate and glans penis may be involved.

A slit skin smear from the lesions shows numerous AFB occurring in clusters, singly or tightly packed in macrophages. Most organisms are well preserved and are longer and have tapering ends when compared to normal lepra bacilli. Histopathologically, there are numerous, thin, spindle-shaped histiocytes with a moderate amount of cytoplasm and an oval, lightly stained nucleus. They may be tightly packed and arranged in whorls displacing the collagen bundles outwards forming a pseudocapsule. Histologically, it resembles neurofibroma.

REACTIONS IN LEPROSY:

Reactions in leprosy constitute the major complication of the disease which can lead to serious consequences like nerve damage and deformities. Leprosy reactions are immunologically mediated episodes of acute or subacute inflammation which interrupt the relatively uneventful usual chronic course of the disease affecting the skin, nerves, mucous membranes and other sites.

Type I reactions (reversal reactions):

Type I reactions usually occur in borderline leprosy (BT, BB and BL). It is mediated by type-IV (delayed type) hypersensitivity reaction. Patients may complain of burning, stinging sensations in the skin lesions. They may have

aches and pains in the extremities and of loss of strength and sensory perception. Increased inflammation of some or all of the pre-existing skin patches or plaques which become erythematous, swollen and may be tender. Necrosis and ulceration can occur in severe cases. Lesions desquamate as they may subside. Crops of fresh inflamed skin lesions in the form of plaques may appear in previously clinically uninvolved skin[64]. The pattern of these skin lesions are of upgrading nature clinically as compared to the existing skin lesions. Edema of the extremities or face, frequently accompanied by nerve involvement. Rapid swelling with severe pain, tenderness of one or more peripheral nerves is common at the site of swelling or along the course of the nerves. The peripheral nerve affected is usually close to the inflamed skin lesion or situated over the area innervated by the corresponding nerve. In severe form of type I reaction, nerve abscess may be formed. Tinel sign (i.e. the pressure exerted on the nerve gives distally a tingling pain) may be positive. Sometimes loss of nerve function occurs suddenly without other signs of inflammation, making it much less obvious – the so called 'silent neuritis'. i.e. without apparent neuritis, producing claw hand, foot drop or facial palsy. Due to strong DTH response in type I reaction, the positivity of lepromin will be stronger in BT and TTs and may become positive from earlier negativity in BB and BL.

Type II reactions (Erythema nodosumleprosum):

Type II reaction is an immune complex syndrome (antigen-antibody reaction involving complement). It is an example of type III hypersensitivity reaction (Gell and Coomb's classification) or arthus phenomenon. IgG, IgM, C3 and mycobacterial antigens are all identified at the site of ENL. The major clinical lesions on the skin are of erythema nodosum type; hence the term "Erythema nodosum leprosum"is used as an alternative term for type II reaction. These reactions mostly occur in the lepromatous (LL) and sometimes in Borderline –lepromatous (BL). Lepromatous leprosy patients with high bacillary load are more prone to get ENL. Risk factors include anti-leprosy treatment, BI >4+, patients of <40 years of age, inter current infections, trauma, surgical intervention and mental stress. In classical ENL reactions, no clinical change usually occurs in the original previous skin lesions of leprosy. There is sudden appearance of crops of evanescent (lasting for few days) erythematous tender papules, nodules or plaques variable in size. They are painful and tender to touch. The nodules are dome-shaped and ill-defined. The common sites of appearance of ENL are outer aspects of thighs, legs and face. These may be few or multiple. The fresh crops of ENL lesions usually appear in the evening when endogenous cortisol production is the lowest. After a period of 24-48 hrs. the lesions show a change of colour from red to bluish and brownish and finally dark and resolves without sequelae in a week or ten days. ENL lesions can be

vesicular, pustular, bullous, and necrotic and break down to produce ulceration, called as erythema nodosum necroticans. In some cases, the lesions may be hemorrhagic resembling Lucio phenomenon. The ENL lesions subside with desquamation or there may be peeling of the superficial skin. Pustular lesions scab or leave shallow ulceration followed by scarring of the involved skin. In type II reactions, the systemic symptoms like fever, malaise, prostration, head ache, muscle, joint and bone pain, usually confining to tibia are common, may precede the appearance of ENL. The associated features of type II reactions are myositis, arthritis, synovitis, rhinitis, epistaxis, laryngitis, iridocyclitis, glaucoma and painful dactylitis. There may be periosteal pain (particularly in tibia), generalized lymphadenopathy, acute epididymo-orchitis, nephritis and proteinuria, renal failure, hepatosplenomegaly and anemia.

LEPROSY IN CHILDREN:

Clinical presentation:

Leprosy in the child reflects to some extent all the aspects of disease in the adults; with some additional features of its own. The exposed parts in general and limbs in specific are the commonest sites affected [65].Children suffer from less severe disease form and their chances of developing deformities are also low, mainly due to less frequent involvement of nerve trunks. Though rare but when it occurs,the neuritis and the possibility of ensuing deformities in childhood leprosy is a compounded tragedy. Prevalence of various forms of

disease in children is mostly derived from hospital based studies. Borderline tuberculoid form is the commonest, the prevalence ranging from 55-78.7% of all child cases in various studies. Borderline lepromatous spectrum is seen in approximately 7.8 % while lepromatous leprosy rates are very low, ranging from 1.6 – 4.9% [66,67,68]. Prevalence of indeterminate leprosy in one study was estimated to be 10.1%.

The character of skin lesions found in children, as in adults, is determined by the type and stage of the disease. Most cases of childhood leprosy at diagnosis is indeterminate or at the tuberculoid end of the spectrum. The most common lesions of childhood leprosy in most series are hypopigmented macules and raised plaques. The indeterminate form is an early presentation of leprosy and it may progress to either spontaneous cure or one of the subpolar forms. The early single lesions in children are mostly found on the gluteal region, face, posterior aspects of arms and hands [69]. Slight sensory loss may be present and generally there is no peripheral nerve thickening. Any hypopigmented macule in the pediatric age group should arouse suspicion of leprosy.

Borderline tuberculoid leprosy in children form the most important part of the spectrum with regard to the number of patients seen and the severity of nerve damage. The lesions are greater in number than TT with less infiltration, less prominent margins and presence of satellite lesions. Damage to the nerves

is more widespread and severe. The most striking feature is the speed with which Type 1 reaction may occur. Nerve function may deteriorate rapidly and irreversibly. The cutaneous signs such as bilateral and symmetrical, innumerable , ill defined macular hypo anaesthetic lesions or diffuse infiltration of the face and earlobes and bilateral loss of eyebrows are uncommonly observed because of the rarity of BL and LL leprosy in children.

Pure neurtic leprosy presents with nerve involvement without any skin lesions and forms a small proportion of cases where leprosy is endemic. This form occurs less commonly in children than adults; and the nerve involvement is seen in approximately 20% of the cases.

Reactions are much less frequent in childhood than in adults. The lower prevalence of reactions and associated disabilities in children than the older group; is probably due to lower incidence of nerve involvement and lower prevalence of pure neuritic cases. Reaction is reported more frequently in hospital based studies, seen in approximately 25% cases [70,71,72].

Evolution:

The course of childhood Hansen's disease is unpredictable. Progression or regression of lesions is common, and the time course is variable. In children, spontaneous regression may occur in 33-75% of cases. The prognosis in children with leprosy on regular treatment is excellent.

Deformities:

Deformities occurring in children are most distressing both socially and psychologically, as they have to live their whole life with this stigma. Prevalence of deformities in India varies from 2.5 – 10.5%. The various factors responsible are increasing age of children, delay in accessing health care, more number of skin lesions, multibacillary disease, multiple nerve involvement and reaction at time of presentation and smear positivity. Children with thickened nerve trunk had 6.1 times higher risk of developing deformities as compared to those without nerve involvement. Majority of deformities are reported in upper limbs and only 10 % in lower limbs [73]. Importance of treating the disease and recognizing the complications early is important to prevent visible deformities.

LABORATORY DIAGNOSIS OF LEPROSY:

Early diagnosis of leprosy is very important, and cannot be over emphasized. In the recent past, the value of laboratory tests in the early diagnosis has been underestimated and hence underutilized. It is heartening to see that there is now an attempt to recognize the value and importance of laboratory tests in the diagnosis and classification of leprosy.

I.SLIT-SKIN SMEAR EXAMINATION:

Slit-skin smear technique was first developed by Wade and Rodriguez in 1927, described by Wade in 1935 and standardized by Cochrane in 1947[74]. Of

all the laboratory tests in leprosy service, the slit skin smear examination is the most simple and valuable one.

Role of Slit-skin smear examination:

Demonstration of acid-fast bacilli (AFB) in skin smear examination serves several purposes:

1. To confirm the diagnosis of leprosy,

2. To classify the disease,

3. To determine the infectivity of a patient,

4. To assess the progress of the disease,

5. To follow-up the patients on treatment.

When the technique was introduced, smears were obtained from multiple sites which included both ear lobes, both cheeks, forehead, chin, both buttocks and additional 6 suspicious sites. The number of sites is brought down to 4 without compromising the value of the test because of the risk of transmission of HIV and to minimize the trauma to the patient. Now the routine sites are: 1.right ear lobe, 2.right fore head, 3.chin, and 4.left buttock in men and left upper thigh in women. However, the active or suspicious lesion must be included, if the disease spectrum is closer to the paucibacillary side. In borderline leprosy, the bacterial load in different sites may vary considerably

and it is recommended that in such cases smears may be obtained from 8 sites to include 4 active lesions in addition to the 4 routine sites.

The smears are stained using modified Ziehl-neelsen method and examined using light microscope under oil immersion (100X). The Bacteriological index is calculated using Ridley's logarithmic scale as follows:

6+: Many clumps of bacilli in an average field

5+: 100 – 1000 bacilli in an average field

4+: 10 – 100 bacilli in an average field

3+: 1 – 10 bacilli in an average field

2+: 1 – 10 bacilli in 10 fields

1+: 1 – 10 bacilli in 100 fields.

Morphological index is calculated as a percentage of solid staining bacilli after examining 200 bacilli.

Ridley prefers his index termed SFG index in which bacilli are divided into three classes: 'Solid' (S), fragmented (F), granular (G).

II.NASAL MUCOSAL SMEARS:

In lepromatous leprosy, the involvement of the nasal mucosa is almost 100%. It has been reported that in a lepromatous patient about 10 million bacilli per day

can be collected from the nasal secretions[75]. The material is collected from the nasal blows first in the morning and is done very gently under the direct vision of the nasal cavity with good illumination. The mucosa is scraped with the blade and the material so obtained is processed similar to SSS. It is important to remember that nose may harbor acid fast saprophytes and therefore decolourisation should be done with an acid-alcohol decolourising solution. However, it is not used routinely.

III.SKIN BIOPSY & HISTOPATHOLOGY OF LEPROSY:

The histological features are particularly useful in the early stages when there is a sparsity of bacilli in skin smears. The histological changes in the skin in leprosy are protean and it is essential for a histopathologist dealing with skin biopsies from leprosy patients to be aware of these diverse manifestations. The special stains for AFB and nerve fibers further enhance the diagnostic yield.

A deeper biopsy specimen containing deep cutis and subcutis is needed for diagnosis of leprosy

(i)Hematoxylin – eosin stain:

Early / indeterminate leprosy:

There is accumulation of lymphocytes and macrophages particularly in the periappendageal and perineural region. There is a focal invasion of

lymphocytes into the lower epidermis and dermal nerves. Epitheloid granulomas are not formed. Schwann cell hyperplasia is a feature and it is highly subjective. The diagnosis lies on finding one or more acid-fast bacilli in the sites of predilection. The diagnosis can only be presumptive without demonstrating bacilli.

Tuberculoid leprosy:

Large epitheloid cells are present; arranged in granulomas. They surround the neural and vascular structures along with the lymphocyte collection at the periphery. Langhan's giant cells are absent. Dermal nerves are surrounded by dense lymphocyte collection and may be eroded.AFB is rarely seen.

Borderline tuberculoid leprosy:

Granulomas follow the neurovascular bundles and they infiltrate the appendages. They have peripheral lymphocytes. Langhan's giant cells are present; variable in number and are not so big in size. Granulomas are frequent along the vascular plexus that are superficial, but they usually do not infiltrate into epidermis. Erosion of nerves is typical. AFB is scanty. BI may be from 0 to 2. IHC with S-100 demonstrates the granuloma well.

Mid borderline leprosy:

Though the macrophages are activated to epitheloid cells, they do not localize to form distinct granulomas. The lymphocytes are scanty. Usually, Langhan's giant cells are not present. The BI is 3 or 4. There is a prominent dermal edema.

Borderline lepromatous leprosy:

There is a prominence of lymphocytes and some macrophages tend to get activated to form ill defined granulomas. Fibroblast proliferation especially in perineural region, forming an "onion-skin" appearance is typical. Foamy cells are not so prominent and there is no globi. BI is usually 4 to 5.

Lepromatous leprosy:

Usually, they have abundant cellular infiltrate and it is invariably separated from epidermis by a clear grenz zone of normal collagen. The epidermis is flattened. The infiltrate leads to destruction of skin appendages and may extend upto the subcutaneous fat. In early lesions, the macrophages tend to have abundant eosinophilic cytoplasm and they have a mixed population of both the solid and fragmented forms of bacilli. BI is high – 4 or 5 and they are packed like cigars. Lymphocyte infiltration is less, but there may be presence of plasma cells. With treatment and over time, bacilli degenerate and accumulate

within the macrophages – so called the Virchow cells – they have a foamy or vacuolated cytoplasm. When stained with Wade-fite stain, the bacilli are granular or fragmented and in chronic lesions, they are found as large basophilic groups. After treatment, the bacilli die rapidly and get fragmented within few weeks or months. But, it may take many years for the bacterial debris to get cleared by the macrophages. The antigens of M.leprae persist even longer and they are demonstrated by IHC staining.

(ii**) Job- Chako modification of Fite-Faraco Stain for M.leprae:**

AFB can be well identified using this stain.

(iii)Gomori- Grocott Methenamine Silver stain:

It has been found that Mycobacteria also take up the silver stain and appear black. Since the lipid coat of AFB is stained, even dead, fragmented and granular M.leprae(which usually do not take up the Fite'stain) can be visualized by using this method. The sensitivity is high but the specificity is very poor as the fibrous connective tissue and elastic tissue in the skin also take up the stain. So, this stain is useful in internal organ specimens and also in healed lesions of LL patients where the remnants may not be demonstrable using routine stains.

(iv)Fluorescent microscopy to detect M.leprae:

Fluorescent method of staining is more sensitive than other routine acid fast stains. In a study of 56 skin biopsies from early leprosy lesions, using slight modification of Kuper and May's method to obtain optimum fluorescence, 39 showed M.leprae compared to only 25 in section stained by Fite-faraco stain for M.leprae[76]. So far, it has not been widely used.

(v) Immunochemical staining to demonstrate Mycobacterial Antigens:

It has been reported that the identification of early lesions of leprosy is enhanced by using immunohistochemical staining to demonstrate M.leprae antigens[77,78]. The diagnosis of leprosy can be confirmed by finding the mycobacterial antigens by immunostaining using polyclonal BCG antibodies and the positivity rates are higher.

(vi) S-100 staining for Schwann cell:

In tuberculoid and borderline tuberculoid leprosy patients, it is used to demonstrate the active invasion and destruction of dermal and cutaneous nerves. The spindle- shaped schwann cell clumps may not be easily distinguished from the collections of epitheloid cells. S-100 stain which selectively stains the Schwann cells may be used to bring out the remnants of the destroyed nerves lying in tuberculoid granulomas[79]. It should be noted that S-100 also stains melanocytes, dendritic cells and the cells lining the sweat ducts.

IV.NERVE BIOPSY:

Used to diagnose pure neuritic cases. Usually, a sensory nerve is selected for biopsy. The suitable nerves include supraorbital branch of V th cranial nerve, a supraclavicular nerve, the greater auricular nerve in the neck, the radial cutaneous nerve at the wrist, a cutaneous nerve of the forearm or thigh, the sural nerve at the back of the leg or superficial peroneal nerve on the dorsum of the foot. The nerves usually chosen are sural nerve or radial cutaneous nerve.

The following stains are available for study in a nerve biopsy specimen.

1.Hematoxylin-eosin stain

2. Job-chako modification of Fite-faraco stain for AFB

3. Luxol fast blue stain for myelin

4. Bodian stain for axons

During histopathologic examination, when acid-fast organisms are demonstrated inside the nerves; or when granulomatous inflammation destroying the nerve parenchyma is seen, the diagnosis of leprosy is easily made.

The few other diagnostic tests which should be mentioned although they are not ordinarily done in routine practice are Histamine test and the sweat (Iodine) test.

V.CYTOLOGICAL DIAGNOSIS OF LEPROSY:

Singh et al found FNAC of skin lesions to be of value in the diagnosis of lepromatous leprosy. Aspirates of the nodules and plaques yielded cellular material and abundance of foamy macrophages and a few lymphocytes. Studies have also shown that FNAC is of value in pure neuritic leprosy also instead of nerve biopsy[80].

VI.SEROLOGICAL DIAGNOSIS:

Over the last 3 decades several workers have attempted the development of a specific serodiagnostic tests using M.leprae specific antigens and their epitope specific antibodies. The commonly used antigens of M.leprae are a 35 kDa protein, a 36 kDa protein, lipoarabinomannan and phenolic glycolipid-1 (PGL-1). Of all these, the PGL-1 based assay is most widely used and detects the anti M.leprae IgM antibodies. It is species specific and does not cross react with sera of the patients with M.tuberculosis, M.kansasii, M.avium and M.intracellulare. The types of serological tests used are radio immunoassay (RIA), monoclonal antibody inhibition test, and direct enzyme linked immunoabsorbent assay (ELISA). These tests can detect antibodies in serum; plasma, whole blood, and capillary blood collected and dried filter paper, but need time and expertise. The rapid and easy-to-use test suitable for use by peripheral health care workers include M.leprae particle agglutination test, a card test, a dipstick test, and a lateral flow test. The lateral flow test can detect

anti-M.leprae IgM antibodies in 10 minutes. Currently, the serological tests can neither distinguish between the past and current infection, nor they can distinguish between clinical and subclinical infection. The identification of new antigens in the future may lead to new applications for serological tests in leprosy [81,82].

VII. MOLECULAR DIAGNOSIS:

The information about molecular structure and functions has been used to develop molecular probes and assays for diagnosis and to assess disease activity in leprosy.

Conventional PCR, reverse transcriptase PCR and nested PCR are used to amplify different gene stretches of M.leprae. These assays are very sensitive (1 to 10 organisms) and exhibit a positivity of 60-75% in smear negative cases. Combined ethidium bromide staining of gels and hybridization further increases the sensitivity by 15%. Targeting M.leprae repetitive elements (RLEP) improves sensitivity. Effect of therapy is correlated with higher number of relapses. RT-PCR is more appropriate in differentiating late reactions from relapses. In situ protocols for PCR assays have overcome false positivity due to contamination in clinic or laboratory.

Molecular methods can help in rapid direct detection of drug resistance. Mutations in target genes can be identified by simple molecular approaches

such as line probe assays and sequencing which is the gold standard. Missense mutations within codons 53 and 55 of the sulfone resistance-determining region of folP1 result in the development of high level Dapsone resistance in M.leprae[83]. Mycobacterial resistance to rifampicin correlates with changes in the structure of the subunit of the DNA-dependent RNA polymerase, primarily due to missense mutations within codons of a highly conserved region of the rpoB gene referred to as the rifampicin resistance determining region[84,85]. Mutations within a highly conserved region of gyrA, the quinolone resistance determining region, are associated with the development of ofloxacin resistance in most of the resistant strains of Mycobacteria [86,87].

TREATMENT:

Until 1941, there was no truly effective medication for leprosy except for Chaulmoogra oil (Hydnocarpus) which was in use for centuries in India and China. Dapsone was first synthesized in 1908. Initially it was tried at doses similar to sulfonamides and withdrawn because of the toxic side-effect profile. Then, its derivative promin was tried followed by several other derivatives. Finally, in 1940, dapsone was tried at lower doses. To the surprise, it was very effective and since the early sixties, dapsone has continued to be the main weapon against leprosy. Clofazimine was found to have anti-leprosy effect in 1962. The potent bactericidal drug, Rifampicin was found to be effective in leprosy in 1970. However, until 1982, chemotherapy of leprosy relied almost

entirely on dapsone monotherapy. The main problems faced were drug resistance, bacterial persistence and defaulting.

WHO recommended multi drug therapy in 1982 for both PB and MB patients. The reasons for the introduction of MDT are:

- To reduce the incidence of post-treatment relapse
- To prevent drug resistance
- To reduce the side effects
- To increase the cost effectiveness
- To shorten duration of treatment

MDT is issued free in Blister packs with each pack contains drugs for 1 month. All we have to do is to decide which course of treatment (PB or MB) the patient needs based on WHO criteria and ensure if they are taking the drugs regularly.

TREATMENT REGIMEN FOR PB PATIENTS:

FOR ADULTS:

MDT FOR PB LEPROSY	
MONTHLY DOSE (supervised)	C.Rifampicin 600 mg
	T.Dapsone 100 mg
DAILY DOSE	T.Dapsone 100 mg

FOR CHILDREN:

PB-MDT		AGE <10 YRS	AGE 10-14 YRS
MONTHLY DOSE (mg)-supervised	C.Rifampicin	300	450
	T.Dapsone	25	50
DAILY DOSE(mg)	T.Dapsone	25	50

The monthly dose should be given under supervision. The course of treatment is given for 6 months. It must be completed within 9 months or less.

TREATMENT REGIMEN FOR MB PATIENTS:

FOR ADULTS:

MDT FOR MB LEPROSY	
Monthly dose (supervised)	C.Rifampicin 600 mg
	C.Clofazimine 300 mg
	T.Dapsone 100 mg
Daily dose	T.Dapsone 100 mg
	C.Clofazimine 50 mg

FOR CHILDREN :

MB-MDT		AGE <10 YRS	AGE 10-14 YRS
MONTHLY DOSE (mg)-supervised	C.Rifampicin	300	450
	C.Clofazimine	100	150
	T.Dapsone	25	50
DAILY DOSE(mg)	T.Dapsone	25	50
	C.Clofazimine	50(twice weekly)	50(alternate days)

The monthly dose is taken at the start of treatment (Day 1) and then every 28 days for 12 months. The daily dose is taken every day for 12 months. It must be completed within 18 months or less.

Earlier, MB patients were recommended to be treated for 2 years or till the skin smear becomes negative, whichever was later. In view of reported low relapse rates; recommendations were made to stop therapy after the completion of 24 monthly doses given in a maximum of 36 months. Then 2 years MDT also is considered too long from the operational point of view. In view of the changed definition of MB cases, low relapse rates, and demonstration that treatment with dapsone and clofazamine daily for 3-6 months was able to kill almost all viable bacilli- meaning that all spontaneously occurring rifampicin

resistant mutants are likely to be eliminated by this therapy-a treatment duration of 12 months has been recommended by WHO in 1997[88].

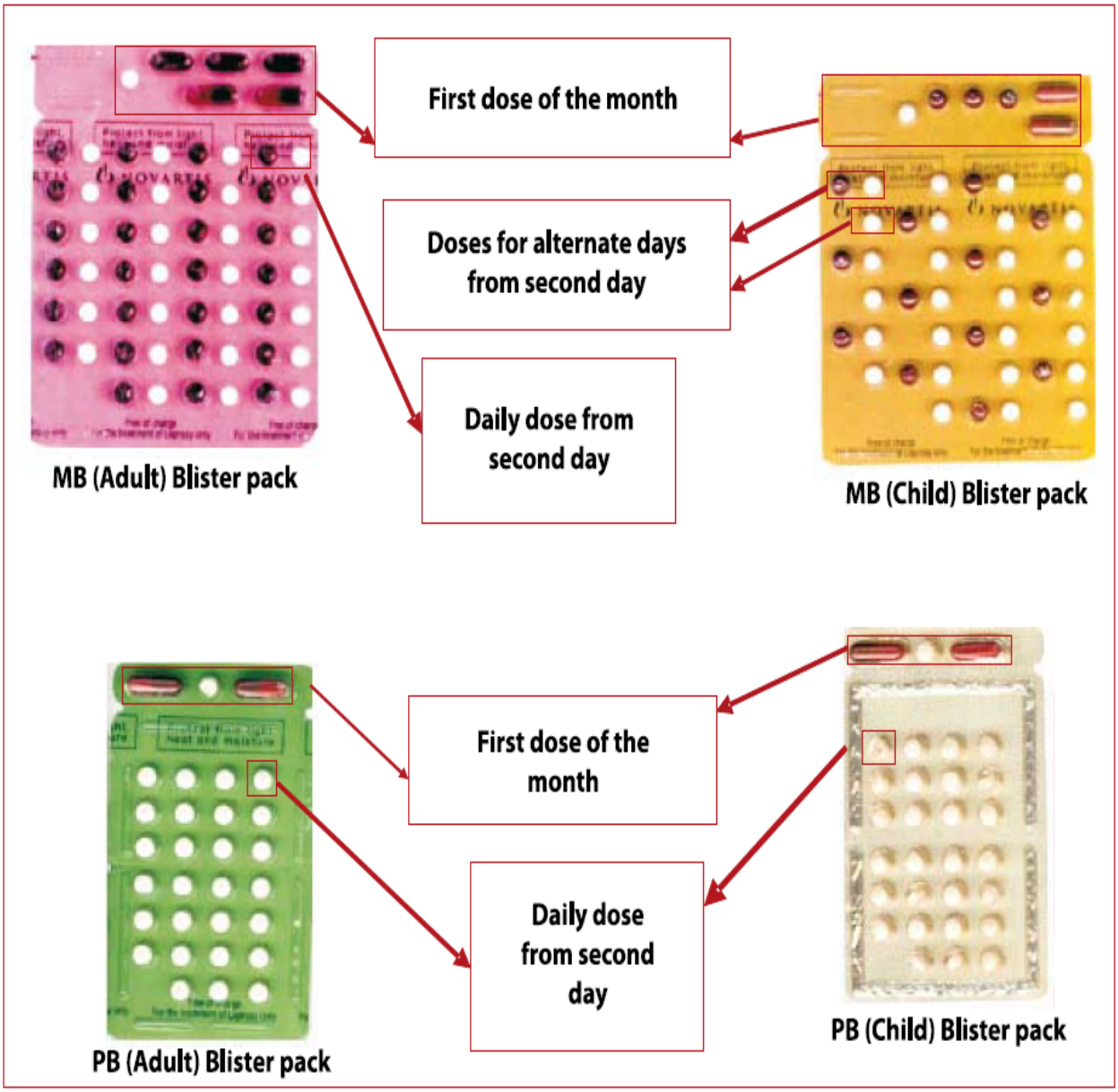
The newer drugs used in the treatment of Leprosy are Fluoroquinolones, Minocycline, Clarithromycin, Ansamycins (Rifabutin, Rifapentine, R-71-1, R-76-1), Fusidic acid,etc.

NEWER DRUG COMBINATION:

ROM therapy:

A single dose (Rifampicin, Ofloxacin and Minocycline) has been tried for single skin lesion (SSL). It has also been trialed for PB cases. Even this regimen has already been adopted and recommended by the National Leprosy Elimination Programme in India for single lesion but not recommended these days as relapses are beginning to be reported in patients treated with single dose ROM [89].

MDT- Blister packs



MATERIALS AND METHODS

INCLUSION CRITERIA:

1. Children aged 0 – 14 years

2. Both sexes

3. Cases who are newly diagnosed as Hansen's disease during the study period

4. Both the direct and referred cases from the PHC s, ULC s and other hospitals in Tirunelveli district.

EXCLUSION CRITERIA:

1. Children> 14 years

2. Children who have taken anti-leprosy treatment in the past in the form of monotherapy or as MDT.

Our study was a hospital based open prospective study conducted at Department of Dermatology in Tirunelveli Medical college hospital on Newly diagnosed childhood cases of Leprosy (includes the cases directly attending the OPD and those who are diagnosed in the field and referred to hospital) aged 0 – 14 years to study and analyse the clinical profile and Histopathology in every aspect during the period from September 2010 to October 2012.

A detailed history is elicited from the patient's attendant usually a parent regarding the presenting complaints, history and duration of the presenting illnesses, past history of similar and associated illnesses, family history of leprosy, treatment details including vaccination particulars especially of BCG, socio-economic status was taken

The complete physical examination was conducted including built. nourishment, lymphadenopathy, pedal edema, vital measures of pulse and blood pressure , examination of systems including cardiovascular , respiratory , central nervous system and per abdominal palpation was conducted. Gait, Facial features and visible deformity of leprosy if any were noted.

A thorough dermatological examination of the skin lesions regarding number of skin lesions, morphology , site , size , shape, colour,surface , margins , sensation , trophic changes viz. presence or absence of hair&sweating, satellite patches and lesional tenderness were recorded. Examination of the peripheral nerves done with palpation of supraorbital nerve, supra trochlear nerve ,infra orbital nerve, greater auricular nerve , supraclavicular nerve , ulnar nerve , radial nerve, median nerve , radial cutaneous nerve , lateral popliteal nerve , posterior tibial nerve and sural nerve were done to look for the enlargement , tenderness , symmetry, consistency , nodularity , abscess formation and noted.

Examination of the sensory system done along the course of the nerve and also for glove and stocking pattern with the modalities of temperature using

hot and cold test tubes , fine touch with a wisp of cotton , and pain with the help of a needle. Functions of the muscles of the forearm, hand, leg and feet were assessed by voluntary muscle testing (VMT). The six grades for VMT using Medical Research Council (MRC Scale) are as follows:

Grade 5: Normal power (with full resistance)

Grade 4: Muscle contraction against slight resistance but power subnormal

Grade 3: Movement possible without resistance

Grade 2: Active movement when gravity is eliminated

Grade 1: Flicker of movement

Grade 0: No movement

Genitalia of both the male and female patients were inspected and testicular size, consistency, sensation and tenderness if any were also noted.

Deformity was noted and graded using WHO grading.

Slit skin smear examination was done at our OPD using an 11 size blade and the smear is stained by modified acid fast stain. The smears were taken from 4 routine sites (Right earlobe, Right forehead, and chin, gluteal region in males and upper lateral thigh in females) and 2 – 4 from the lesions depending upon the patient

Bacteriological index was calculated using Ridley-Jopling scale.

Morphological index was also calculated as the percentage of solid staining bacilli, calculated after examining 200 red staining elements lying singly.

SSS repeated at 3 months, 6 months (in MB cases) and before RFT in all cases.

An elliptical incisional skin biopsy was taken from the skin lesion. The specimen was processed and stained with Hematoxylin and eosin and also with Fite - Faraco's method. The Histopathologic features in each case were noted.

The diagnosis of leprosy is made by correlating all the three features namely clinical features, SSS and HPE examination

Baseline blood investigations were done which included complete hemogram, Renal function tests, Liver function tests and Urine routine examination was done

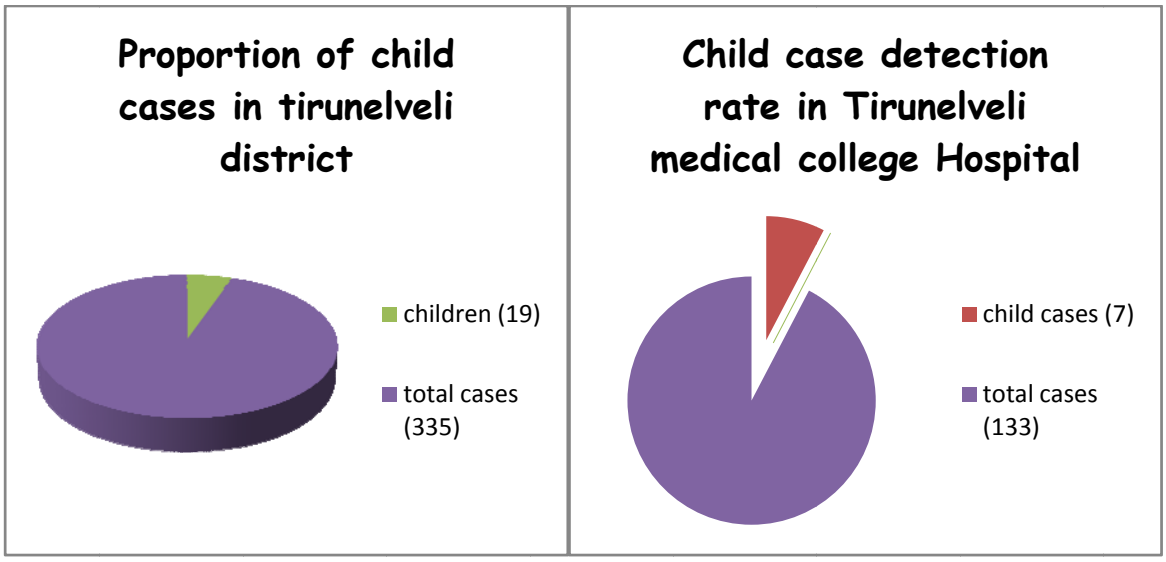
Patients were categorized into PB and MB based on WHO criteria and treatment was given with either Paucibacillary or multibacillary blister packs (fixed drug dosages and combinations available according to their age) provided free of cost to the patients under NLEP project.

The cases were followed up every 3 months to look for any new lesions, new nerve involvement and signs of reaction during treatment. Sensory testing and muscle power were assessed during every visit. Blood investigations were also repeated during each visit.

OBSERVATIONS AND RESULTS

The observations made in the study conducted in childhood Leprosy patients aged below 14 years are summarized in this section:

Chart 1: Proportion of child cases among the total cases of leprosy:



Total number of new cases during the study period in Tirunelveli district is 335 and the child cases among them are 19. The proportion of child cases in Tirunelveli district is 5.7%.

Total number of new cases detected in Tirunelveli medical college hospital is 133 and the child cases among them are 7. So, the child proportion among the new cases is 5.3% which is almost the same as the district statistics.

Of the total children analysed during the study period, 7 children(36.8%) were diagnosed in the hospital and 12 (63.2%) were detected in the periphery by means of school surveys and health camps.

Table 1: Comparison of Age Distribution with Gender :

Age in years	Male	Female	Total
0-5	0	0	0
6-10	5 (45.5%)	5 (62.5%)	10 (52.6%)
11-14	6 (54.5%)	3 (37.5%)	9 (47.4%)
	11	8	19

As depicted in Table 1 & chart 2:

Out of the total 19 children in our study, 10 children (52.6%) belong to the age group of 6-10 years and 9 children (47.4%) were in 11 to 14 years group .There were no cases detected below 5 years of age. Sexwise, 11 patients (57.89%) were males and 8 children (42.11%) were of female gender.

In the age group of 6 to 10 years , the number of males and females are equal whereas in higher age group of 11-14 years, there is a male preponderance.

CHART 2:

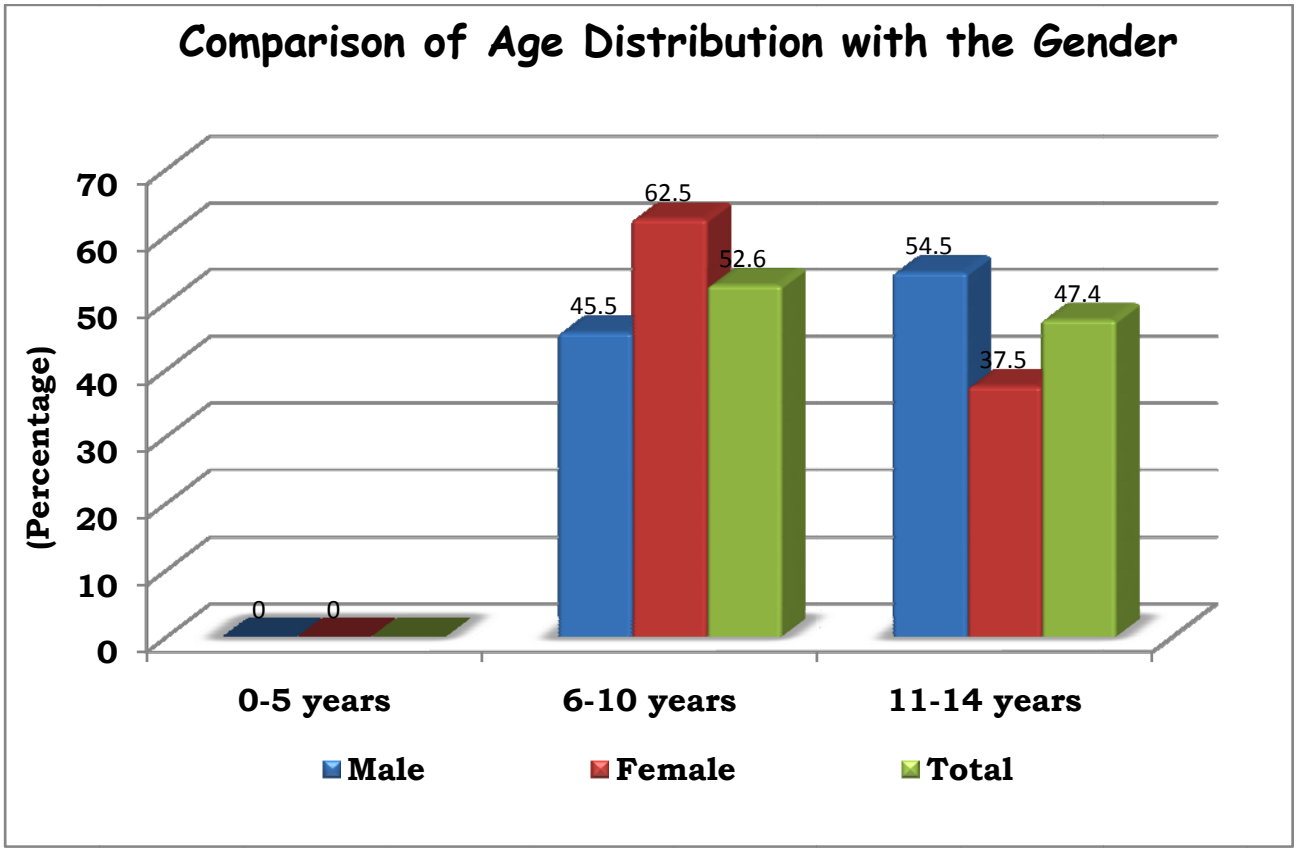

Comparison of Age Distribution with the Gender
(Percentage)
70
60
50
40
30
20
10
0
0
0
45.5
62.5
52.6
54.5
37.5
47.4
0-5 years
6-10 years
11-14 years
Male
Female
Total

Table 2: Comparison of presenting complaints of the study population with respect to gender :

Presenting complaints	Male n=11 (57.89%)		Female n=8 (42.11%)		Total	
	n	%	N	%	n	%
Deformity	1	5.3%	0	0	1	5.3%
Patches	2	10.6%	4	21.1%	6	31.6%
Screening	7	36.8%	4	21.1%	11	57.9%
Trophic Ulcer	1	5.3%	0	0	1	5.3%

Of the 19 cases in our study, 11 children(57.89%) were diagnosed during screening which includes both family screening of contacts of already diagnosed patients and also through other screening camps. Rest of the 8 children (42.11%) presented themselves to medical care , 6 children (75%) were brought with patches and 1 child (12.5%) with visible deformity and trophic ulcer each. [Depicted in table 2 & chart 3]

CHART 3:

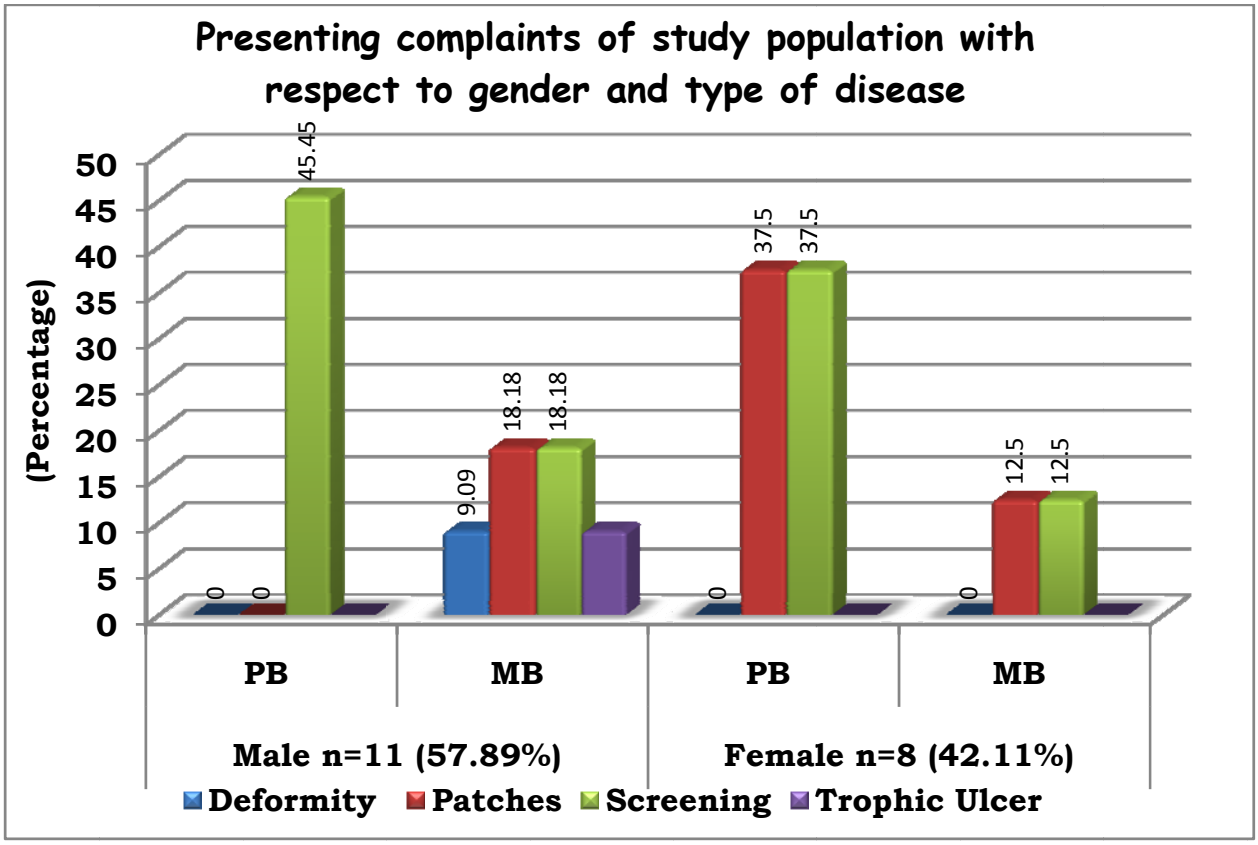

Presenting complaints of study population with respect to gender and type of disease
(Percentage)
50
45
40
35
30
25
20
15
10
5
0
0
0
45.45
9.09
18.18
18.18
0
37.5
37.5
0
12.5
12.5
PB
MB
PB
MB
Male n=11 (57.89%)
Female n=8 (42.11%)
Deformity
Patches
Screening
Trophic Ulcer

Table 3: Contact status of children with respect to gender distribution

Nature of Contact	No. of Patients			Percentage (%)		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
No	6	6	12	31.5%	31.5%	63%
Household contact	3	2	5	15.8%	10.5%	26.3%
Neighbourhood contact	2	0	2	10.5%	0	10.5%
Total	**11**	**8**	**19**	**57.9%**	**42%**	**100%**

Among the 19 children, 7 had a positive history of contact with known leprosy patients. They are analysed in table 3 & chart 4. Of these 7 children , 5 children had house hold contacts and 2 had contact with cases in the close neighbourhood (in the next house). Except for the 2 children who had a contact with the neighbourhood PB cases, all the other children's contacts were multibacillary cases . All were LLHD with highly positive smears.

CHART 4:

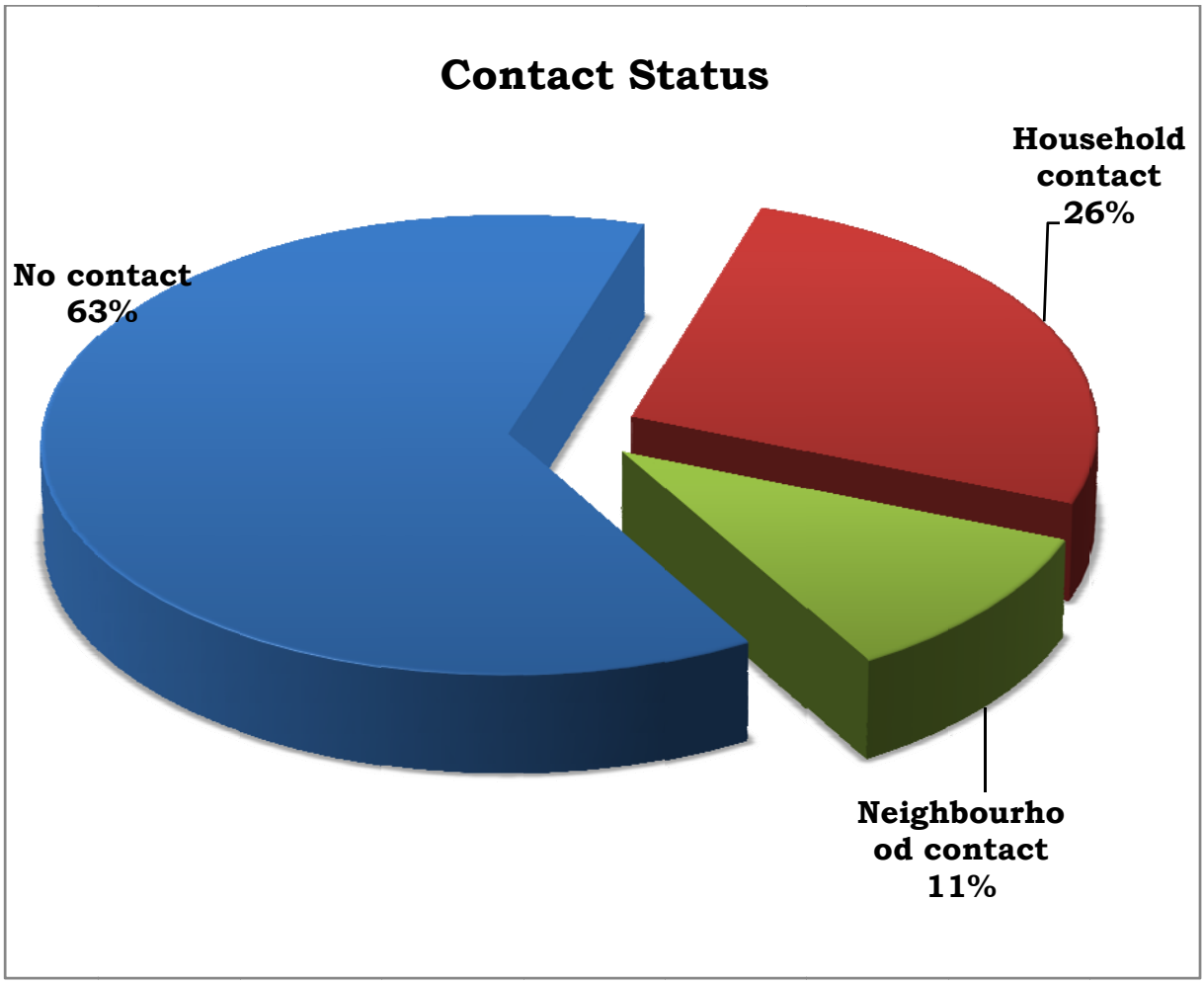

Contact Status
Household contact 26%
No contact 63%
Neighbourhood contact 11%

Table 4 : Analysis of the number of skin lesions at presentation:

No. of Skin Lesion	Male n=11 (57.89%)		Female n=8 (42.11%)		Total	
	n	%	n	%	n	(%)
1	8	42.1%	3	15.8%	11	57.9%
2-5	3	15.8%	1	5.3%	4	21.1%
>5	0	0	4	21.1%	4	21.1%

Regarding the number of skin lesions, majority of the patients (57.89%) had a single skin lesion. There are 4 children (21.1%) with 2 to 5 patches. The number of children with more than 5 patches were 4 (21.06%) in the study.

CHART 5:

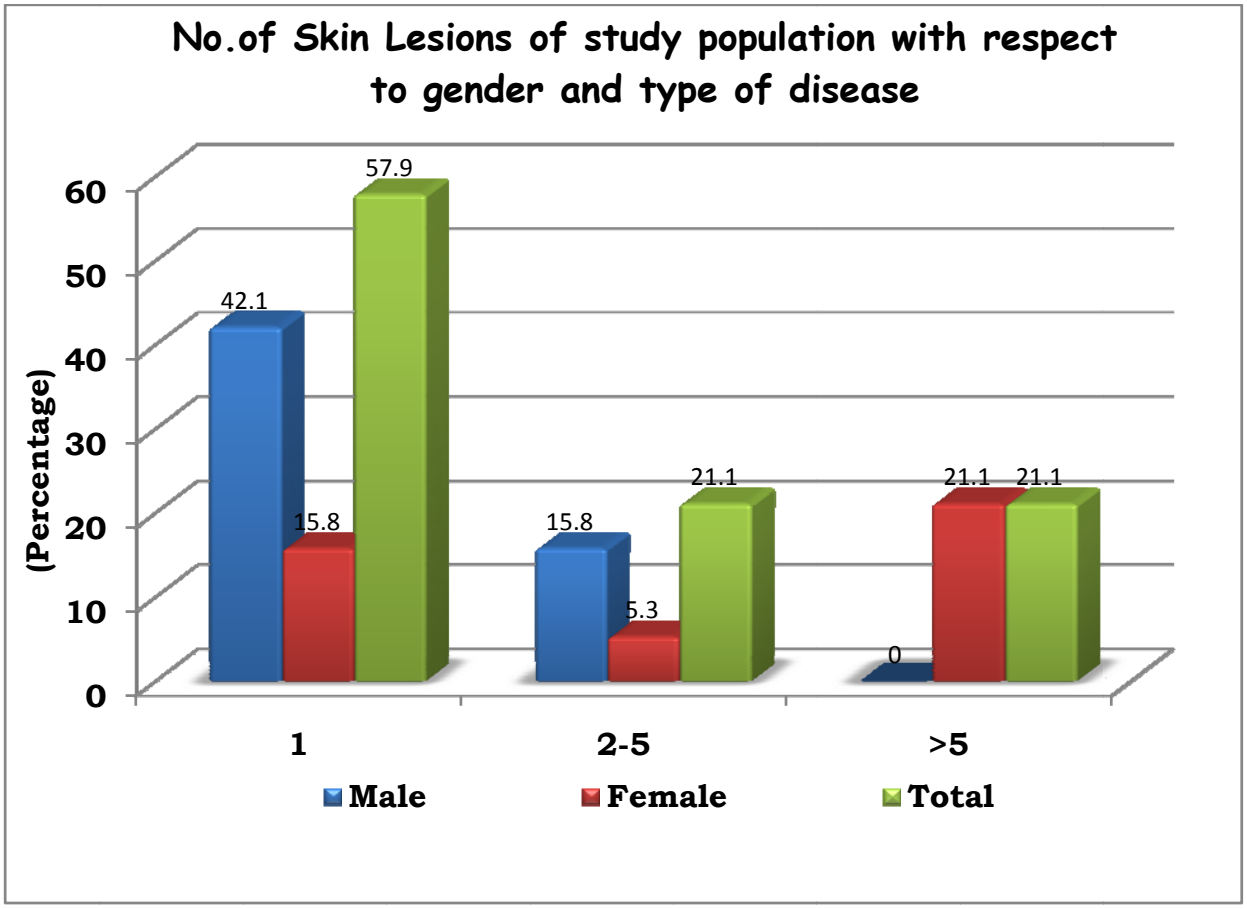

No.of Skin Lesions of study population with respect to gender and type of disease
(Percentage)
60
50
40
30
20
10
0
42.1
15.8
57.9
15.8
5.3
21.1
0
21.1
21.1
1
2-5
>5
Male
Female
Total

Table 5: Analysis of morphology of skin lesions at presentation:

Morphology	No. of patients			With nerve involvement N (%)
	Male	Female	Total (%)	
Single Patch	5	5	10(52.6%)	5(50%)
Multiple patches	3	2	5(26.3%)	2(10.5%)
Only Plaques	2	0	2(10.6%)	2(100%)
Patches & Plaques	1	1	2(10.6%)	1(50%)
Total	11	8	19	10(52.6%)

In the study, 16 children (84.21 %) had patches at the time of presentation. Of them, 10 children (52.6%) had single patch and 5 (26.3%) children had multiple patches. 50% of the children with single patch had nerve involvement. The plaques were the only morphology in 2 (10.6%) children and both had nerve involvement. Out of the 5 children (26.3%) with multiple patches, 2 had nerve involvement. Only 2 children had more than one morphology of lesions (Patches & Plaques).[Table 5 & chart 6]

CHART 6:

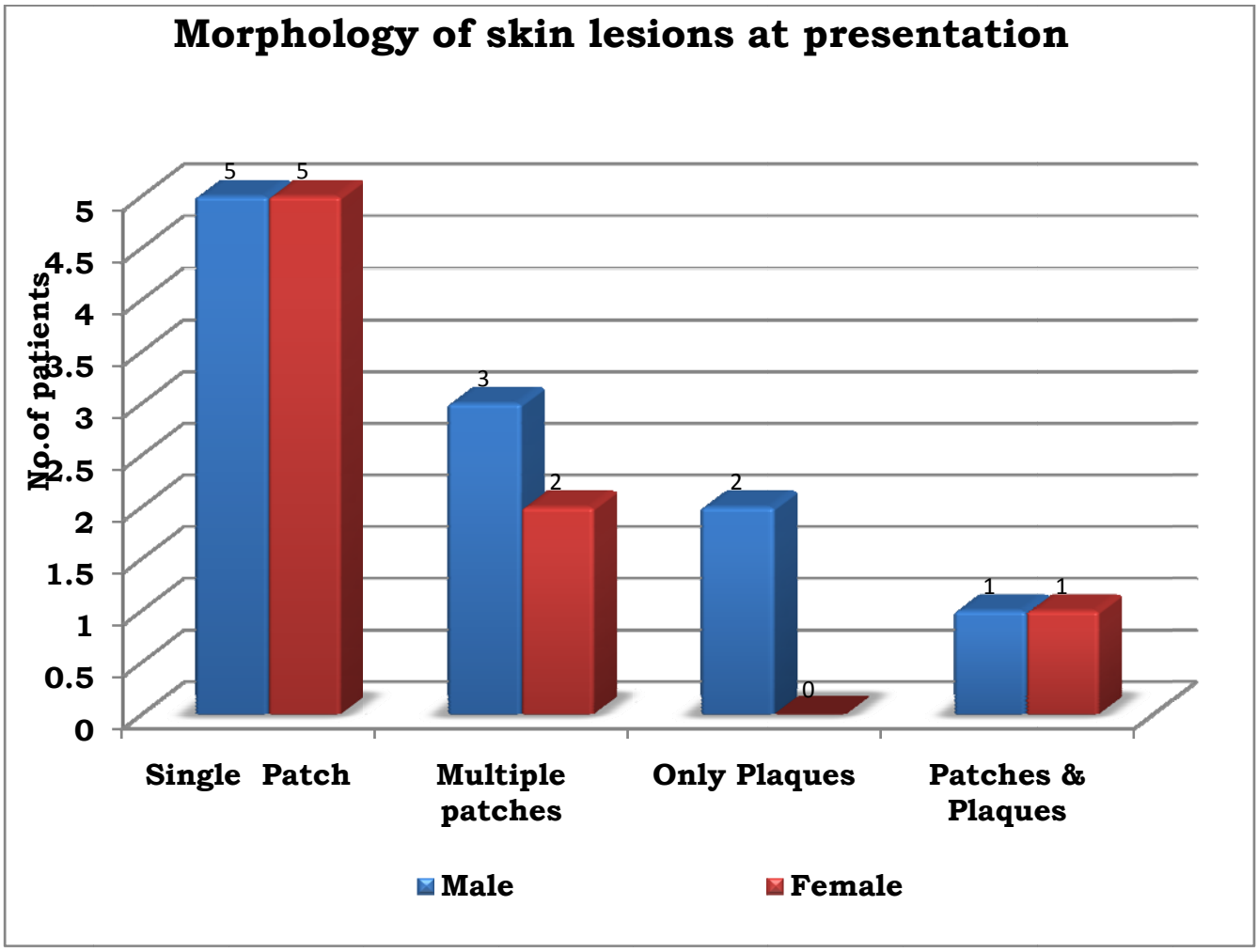

Morphology of skin lesions at presentation
No.of patients
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
5
5
3
2
2
0
1
1
Single Patch
Multiple patches
Only Plaques
Patches & Plaques
Male
Female

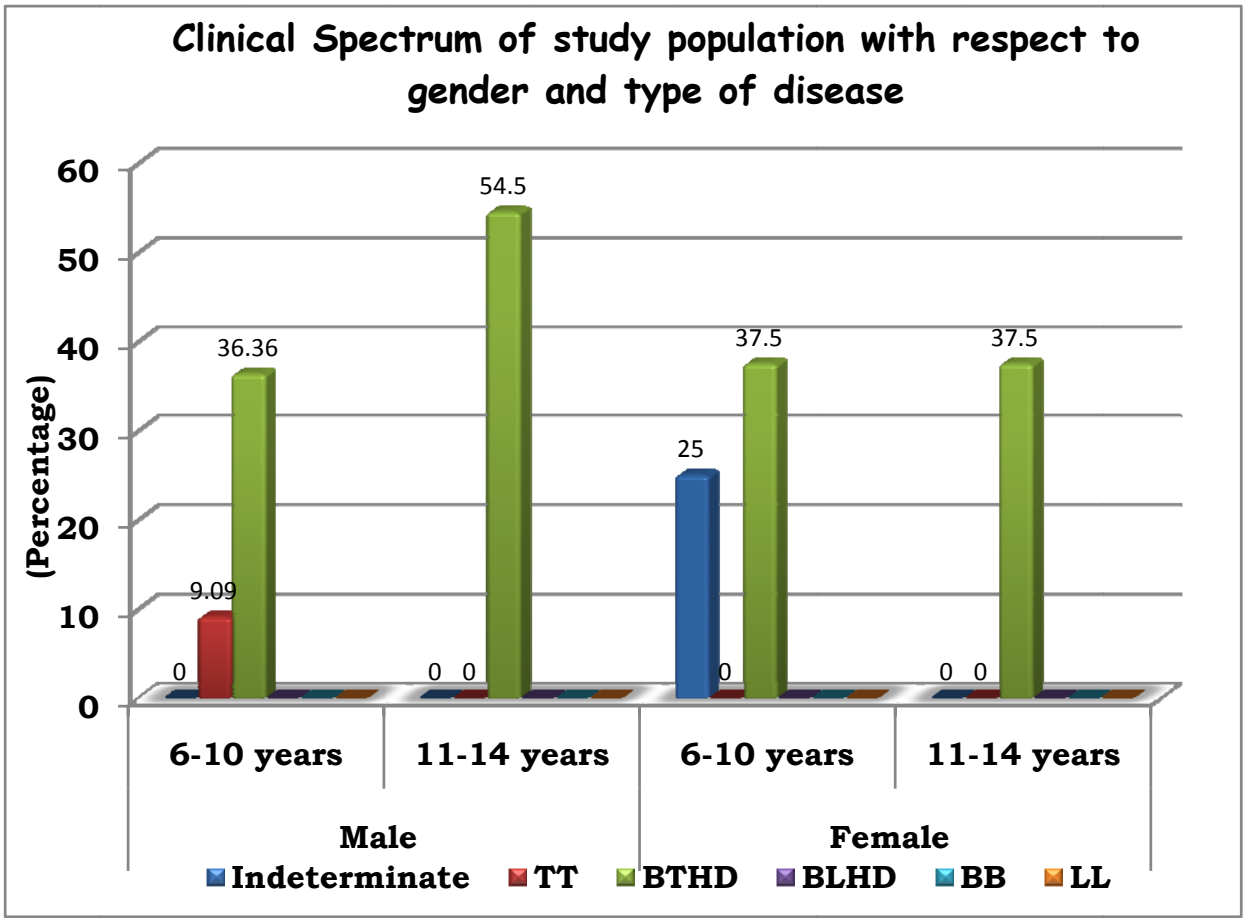
Table 6 : Analysis of clinical spectrum among children:

Clinical spectrum	Male n=11 (57.89%)		Female n=8 (42.11%)		Total	Smear status
	6-10 years	11-14 years	6-10 years	11-14 years		
Indeterminate	0	0	2 (25%)	0	2(10.5%)	N
TT	1 (9.09%)	0	0	0	1(5.3%)	N
BTHD	4 (36.36%)	6(54.5%)	3 (37.5%)	3 (37.5%)	16(84.2%)	N
BLHD	0	0	0	0	0	N
BB	0	0	0	0	0	N
LL	0	0	0	0	0	N

N= Negative.

Table 6 & chart 7 shows that the most common clinical spectrum in children is BTHD (84.2%) in this study followed by Indeterminate type (10.5%) and TT constitutes only 5.3 % of the children. There was no child with BB,BL or LL spectrum.

CHART 7:


Clinical Spectrum of study population with respect to gender and type of disease
(Percentage)
60
50
40
30
20
10
0
0
9.09
36.36
0
0
54.5
25
0
37.5
0
0
37.5
6-10 years
11-14 years
6-10 years
11-14 years
Male
Female
Indeterminate
TT
BTHD
BLHD
BB
LL

ANALYSIS OF NERVE INVOLVEMENT:

Among the 19 cases, 10 (52.6%) children had nerve involvement.

Table 7: Analysis of Pattern of nerve involvement in children with nerve involvement

No	Age/ Sex	No. of nerves	TRUNK NERVES					CUTANEOUS NERVES				Deformity
			Ulnar	median	Radial	LPN	PTN	STN	RCN	Sural	Others	
1	11/M	3	+ B/L	-	-	-	-	-	+ Lt	-	-	Lt.Ulnar claw
2	10/M	3	+Lt	-	-	+Lt	+Lt	-	-	-	-	Lt.Claw toes
3	8/F	6	+B/L	-	+B/L	+Lt	+Lt	-	-	-	-	-
4	12/F	1	+Lt	-	-	-	-	-	-	-	-	-
5	11/M	4	+Lt	-	-	+Lt	+B/L	-	-	-	-	-
6	9/F	2	+B/L	-	-	-	-	-	-	-	-	-
7	12/M	3	+Lt	-	-	-	+B/L	-	-	-	-	-
8	10/M	3	+Rt	-	-	-	+Lt	+Lt	-	-	-	-
9	10/M	1	-	-	-	+Lt	-	-	-	-	-	-
10	10/F	1	+Lt	-	-	-	-	-	-	-	-	-

Peripheral nerve enlargement was seen in 10(52.63%) children in the study[Table 7].The most frequently involved peripheral nerve trunk is Ulnar nerve; in 90 % of children with nerve involvement. The second common nerve affected is posterior tibial nerve and third being lateral popliteal nerve in this study.

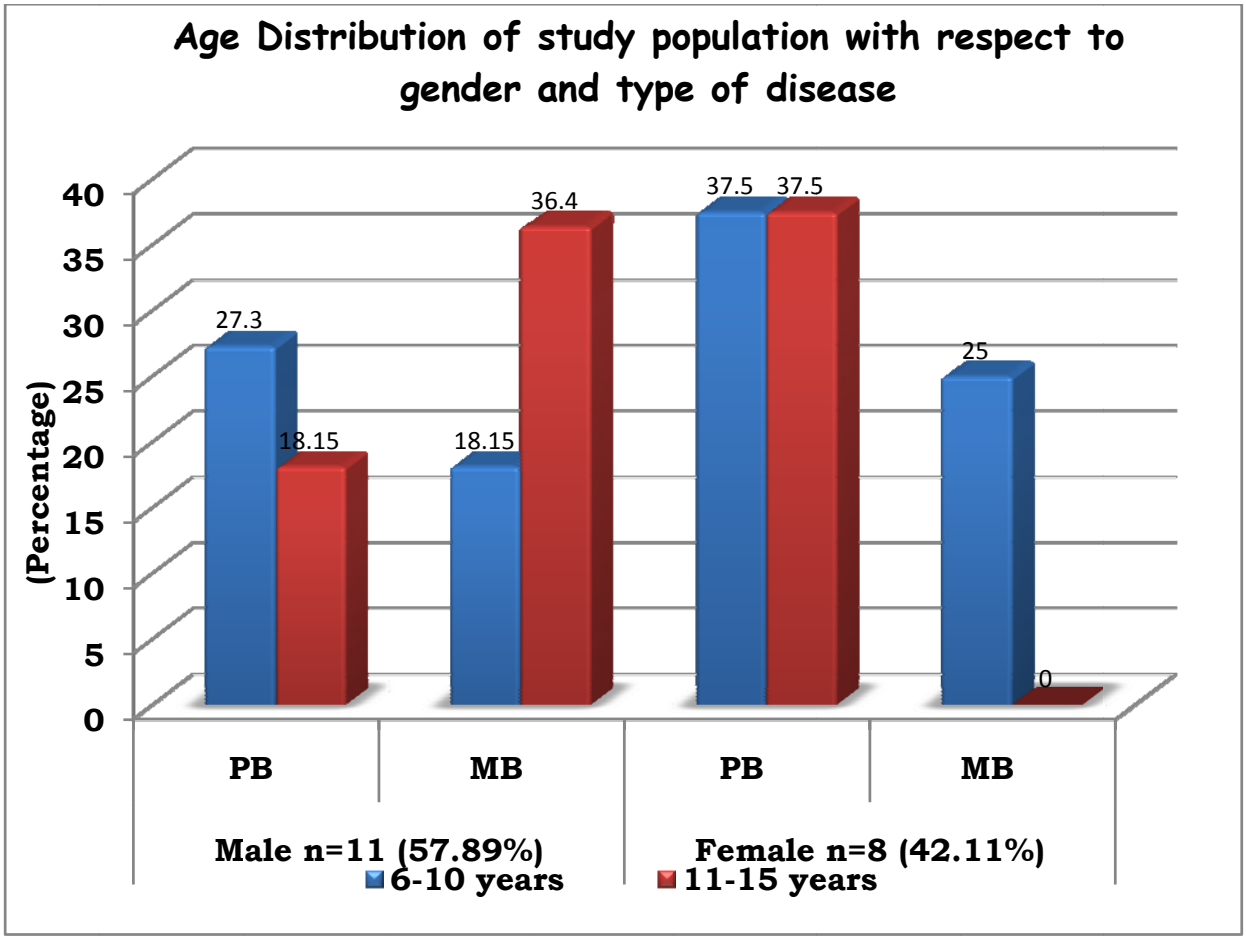
Table 8: Analysis of PB and MB proportion with respect to age and gender distribution of the children:

The total numbers of PB children are 11 (57.9%) and MB children are 8(42.1%)

Age	Male n=11 (57.89%)		Female n=8 (42.11%)	
	PB (n=5)	MB (n=6)	PB (n=6)	MB (n=2)
6-10	3(27.3%)	2(18.15%)	3(37.5%)	2(25%)
11-15	2(18.15%)	4(36.4%)	3(37.5%)	0

Table 8 & chart 8 depicts that the incidence of PB cases (57.9%) is more than the MB cases (42.1%) in the study. Among the male children, MB child constitutes 54.5% and PB child constitutes 45.4%. Whereas in females PB child cases (75%) clearly out numbers the number of MB Cases (25%)

CHART 8:


Age Distribution of study population with respect to gender and type of disease
(Percentage)
40
35
30
25
20
15
10
5
0
27.3
18.15
18.15
36.4
37.5
37.5
25
0
PB
MB
PB
MB
Male n=11 (57.89%)
Female n=8 (42.11%)
6-10 years
11-15 years

- SSS was negative in all the cases in the study.
- In this study, the histopathological examination was correlating with the disease per se in all the patients. The correlation between the clinical spectrum and the histopathology was done in all cases. Both the children with indeterminate type of leprosy had a correlating histopathology(100%) . The patient with tuberculoid type clinically did not show any evidence of well formed granuloma. The rest of the patients were of Borderline tuberculoid type. Among the 16 of them, one case showed well formed granuloma. Others showed scant periadnexal lymphohistiocytic infiltrates.
- No evidence of systemic involvement were noted during the study.
- Type I reaction was noted in a male patient with Borderline tuberculoid leprosy. Type II reaction was not encountered.
- Deformity was noted in two patients (10.5%). Both were male children. One had ulnar claw hand and the other child had claw foot.

DISCUSSION

The proportion of childhood leprosy among new cases in Tirunelveli district was 5.7% (19 children) during the period of study [Chart 1]. Of these 19 children, 7 children presented directly to the medical college hospital whereas remaining 11 were detected in the field through camps and referred to the medical college hospital.

Childhood leprosy was maximum in the age group of 6-10 years in our study[Table 1] which is consistent with the study of Selvasekar et al,1999[90] and Keelar et al, 1985[91]. Childhood leprosy was mostly seen in age group of 5 – 14 years in a study by Dayal et al, 1990[92].

Child cases in our study showed a slight male preponderance with the male to female ratio being 1.6 : 1 as shown in Table 2. Significant male preponderance was seen in studies done by Sandeep Sachdeva et al[93] ,2010(2:1) in Jawaharlal medical college at Aligarh and Singal et al [94] ,2011 in GTB hospital at Delhi. As per literature, there is a male preponderance in the disease in adults but the gender difference is least in children. This study correlates with the above fact. Males and females were equal in the age group of 6 to 10 years in the study but there was a male preponderance in 11 to 14 years age group.

In our study, the youngest case reported was a 7 year old male child comparable to the reports of 6 years in the studies conducted at Eastern Nepal

by Deb Burman et al[68],2003 and a peripheral hospital in Andhra Pradesh by AG Rao et al[95] ,2009.The disease in infants was very high before the advent of MDT. Brubaker et al[96],1985 reported 91 infants with leprosy from the records of US armed forces institute of leprosy and a correspondence survey. Many such reports had been made from India also with mother contacts in the last century. It has declined in the past decade since MDT is being given safely to the pregnant and lactating mothers. The incidence of leprosy in children of lower age groups including infants have decreased drastically now a days and only very few cases have been reported sporadically. Moorthy et al [97](2006) have reported leprosy in an 8 month old infant from Blue Peter research centre at Hyderabad. This reduction is the result of the effective national control programme .

Incidence rate among members of leprosy affected families living under the same roof has been shown to be higher than in the general population (Jesudasan et al 1984)[98]. In this study , 7 (36.8 %)children had a history of contact with Leprosy patients as shown in Chart 4. Of these, 5 children had history of family contact and the 2 others had contact in close neighbourhood [Table 3]. The family contacts were all at the higher spectrum in our study - fathers with LLHD under MB regimen. In a study done at Hyderabad by Jain et al(2002)[99] , history of contact was present in 38.8% of children with 95 % of them having index case in the family. 65% of the contacts were MB in that

study. In another retrospective study done at Jawaharlal Nehru medical college in Aligarh by Sachdeva et al[93],35% of children had house-hold contact with leprosy. All of them are invariably of MB type. Hence ,this study correlates well with the above mentioned studies.

Although a pivotal role of close contacts has been documented by several researchers, a few similar studies have shown that clinical leprosy develops only in susceptible persons after a contact with the patient. They opine that susceptibility is inherited and may be transmitted through successive generations without the appearance of clinical leprosy[93]. But the hereditary relationship within them were not clear. The chance of acquiring the disease is directly related to the closeness of the contact and the genetic relatedness between them. The possible reasons for the incidence among families may be chronic skin to skin contact, through droplet infection. HLA predisposition among families also contribute to the occurrence of disease. Whatever be the etiology this high level of family contact of the Hansen's disease in these children strengthens the necessity of strategy of screening children in leprosy affected households. There was no mother contacts in this study.

In this study, 11 children (57.89%) presented with a single skin lesion [Table 4]. It correlates with the previously published studies by Selvasekar et al[93], 1999, Nadkarni et al[100] ,1988& Kumar et al,1989[101] where single lesions were most frequently seen. The cutaneous signs like bilateral and innumerable

or diffuse involvement of skin uncommonly observed because of the rarity of BL and LL leprosy in children. There is no case of BB, BL or LL type in this study.

The morphology of the lesions had varied in different studies (Prasad et al,1998; Ganapthi et al,1976)[102,103]. Hypopigmented hypoanasthetic patches were the most common type of lesions in our patients (78.9%) similar to the study by AG Rao et al,2009 (68.8%)[95].

Borderline tuberculoid Hansen's disease is the most common type of leprosy in this study (78.94%) as shown in Table 6. Similar observations were noted in the studies by AG Rao et al,2009[95] (71.88%), Singal et al[94],2011 (70.3%) , Kumar et al,1989[101] (57.7%), and Jain et al ,2002[99] (66.3%).

More number of the skin lesions were on the exposed parts of the body, face, limbs in our study. Such observations were in concurrence with those noted by Jain et al [99](2002) , AG Rao et al[95](2009) and Sehgal and Chaudhary (1989)[104]. This can be explained by the fact that in warm climates, the children are scantily clad and microtrauma or insect bites may allow the entry of bacilli . The prolonged viability of M.leprae may facilitate such entry (Desikan and Sreevatsa ,1979).However majority of the lesions were observed on the gluteal region in a study by Ganapati et al (1976).

Peripheral nerve enlargement was seen in 10 (52.63%) children in the study [Table 7]. The study by Deb Burman et al [68],2003 had almost same statistics with the nerve involvement being 55%. Similar frequency of nerve involvement was documented by Kaur et al,1991(60%)[105]. Higher incidence was reported by Singal et al,2011[94] (70%). Of the 10 children , 3 (30%) had mononeuritic and 7 (70%) had polyneuritic involvement. Among the three mononeuritic cases, 2 had ulnar nerve involvement and 1 had posterior tibial nerve involvement.

The most frequently involved peripheral nerve trunk is Ulnar nerve in our study incident in 9 children (47.36% of the total children). Deb Burman et al[68], 2003 also reported Ulnar nerve as the most common nerve involved among children in his study. Many of the studies done previously have not discussed about the individual nerve involvement. Among the children with nerve involvement, Ulnar nerve was involved in 90%.The second common nerve affected is posterior tibial nerve and third being lateral popliteal nerve in this study.

Reactions in children is a rare entity. In our study, 1 child (5.26%) developed type I reaction. Most of the studies done in childhood leprosy reported comparable incidence. To state a few are the studies done by I Horo et al[106]2010 (4.63%), Sandeep Sachdeva et al[93],2010 (1.36%). There are no cases of type II reaction in our study.

Smear positive cases are considered as rare in children (Nadkarni et al , 1991; Keelar et al,1985). In our study no case was found to have positive slit skin smear [Table 6]. On contrary to our study, the manyother studies have shown significant positivity reports (AG Rao et al,2009[95] (25%) ; K Deb Burman et al[68],2003(30%).) The variation is due to more number of cases at the higher spectrum (BB,BL,LL) in other studies. In our study, only 1 child was in BL spectrum. All the other children were of I,TT and BT type and SSS may not always be positive in them.

The Histopathologic examination of the skin lesions was consistent with Hansen's disease in all of our patients (100%). The 2 children with Indeterminate type of leprosy had histopathologic features correlating with the diagnosis. Though all the other cases are of TT and BT type clinically, well formed granuloma was evident only in 2 cases. All the other cases had collection of macrophages and lymphocytes at the sites of predilection for Hansen's disease – in the perineural, peri-appendageal region. Altogether, this study showed a histopathological correlation in about 21% of cases. High correlation was observed in a study conducted by Singal A et al[94],2011. Few other studies had a relatively lower clinicopathological correlation which includes the study done by Bhushankumar et al,2000[67](60.6%) . Another study done by AG Rao,2009[95] et al showed comparable low correlation of 37.5%.

Deformities and disabilities are not so commonly encountered in children when compared to adults. In our study, 2(10.53%) of the children had grade II deformity [Table 7]. Similar incidence of deformity was reported in the study done by Kar and Job,2005[73] (10.5%) and Singal A et al,2011[94] (12.8%).The study done by AG Rao et al[95],2009 revealed a very low incidence of 3.12%.Both of the children were males in the study.

Based on WHO criteria, 8 children (42.10%) in our study were of the Multibacillary type of leprosy and 11 (57.89%) of our children were of Paucibacillary type as shown in Table 8. PB and MB cases were almost equal in our study. Deb Burman et al,2003[68] and Singal et al ,2011[94] showed similar observations where as the Paucibacillary leprosy was the commonest type in various studies (Prasad et al,1998[102]; Selvasekar et al , 1999[90] ; Kaur et al, 1991[105]). This may be related to the varying study period and sample size.

SUMMARY

The following are the implications derived from this prospective study done in the childhood Leprosy patients of age upto 14 years over a period of 2 years :

- The Incidence of childhood leprosy in Tirunelveli district is 5.7% in the study period.
- The most common age group affected is 6 to 10 years (52.63%). There was a slight male preponderance with male to female ratio being 1.6:1. The youngest case was a 7 year old male child.
- A significant proportion (36.84%) had contact with leprosy patients especially within the family.
- In this study, 47.4% of the children presented with only skin lesions and 53.6% with skin and nerve involvement. There was no case of pure neuritic leprosy.
- Histopathological examination was consistent with Hansen's disease in all the cases. Clinico-pathologic correlation was noted in 21% of children whereas others showed features of early Hansen's disease.
- Borderline tuberculoid type is the most common type noted. No cases of BB,BL or LL were encountered.
- The nerve involvement was seen in 52.6% of children. Ulnar nerve was the most commonly involved.

- Systemic complications were absent in the children in this study.
- Type I reaction was incident in 5.3% of children in the study period. There was no case with type II reaction.
- Grade II deformity was noted in 10.5% of children.
- In this study,57.9% of children were of Paucibacillary type and 42.1% were of Multibacillary type.

CONCLUSION

Leprosy continues to be an important health problem in children. Though the incidence of childhood leprosy has become low, considerable proportions of children are presenting to health care at a late stage with deformities which indicates reluctance either to come forward or an inadequate detection which may be related to unawareness. Deformities occurring in children are more distressing both socially and psychologically, as they have to live their whole life with this stigma. It is imperative that our goal should be to bring all cases of leprosy in children under treatment at the earliest possible stage. Childhood leprosy reflects the status of disease control in the community and in turn efficacy of the control programme .Awareness should be raised in the society by all means including the media and the health services. Parental education, counselling, screening of household contacts of leprosy patients and school surveys form an integral part of early detection and treatment to achieve the goal of eradication of leprosy.

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DISSERTATION PROFORMA

CLINICO-PATHOLOGIC STUDY OF CHILDHOOD HANSEN'S DISEASE

1. Patient name
2. Age
3. Sex
4. Father/guardian name
5. Address
6. Informant
7. Directly attending OP/Referred case
8. Referred from
9. Presenting complaints and duration
10. H/o Presenting illness:

    Elaborating the presenting complaint

    H/o Patch

    H/o sensory disturbance

    H/o muscle weakness

    H/o Pain along nerves

    H/o fever

    H/o Ulcers & blisters

    H/o joint pain

H/o Epistaxis

H/o Nasal stuffiness

H/o Slipping of foot wear

H/o swelling of hands and feet

H/o nodules over skin

H/o Pain in and around eyes

H/o Redness of eye

H/o Photophobia

10. Past History

H/o Antileprosy treatment

H/o juvenile diabetes

H/o Hypertension

H/o allergy / asthma

H/o contact with hansen's patient

11. Family History

H/o similar illness in other family members

H/o proved Hansen's disease patient in the family

12. Treatment History

13. Socio-economic History

Standard of living

Sanitation facility

No.of family members

Percapita income

14. General Examination

Level of conciousness / orientation

Whether the child is comfortable

Examination of physical signs

Anemia

Jaundice

Cyanosis

Clubbing

Generalised lymphadenopathy

BCG scar

Vital signs – PR

BP

RR

15. Examination of systems

Cardiovascular system

Respiratory system

Per abdomen

Central nervous system

16. Dermatological examination

I. Examination of patches:

Number

Size

Shape

Margin

Surface- sweating , dryness , hair loss

Symmetry of patches

Cutaneous nerves surrounding the patch

II. Examination of the Nerves ;

Nerves examined:

NERVE	RIGHT	LEFT
Supraorbital N		
supratrochlear N		
Greater auricular N		
Radial N		
Median N		
Ulnar N		
Common peroneal N		
Posterior tibial N		
Supraclavicular N		
Radial cutaneous N		
Sural cutaneous N		

Description

No.of Nerves involved

Size of the nerve

Symmetry

Tenderness

Extent of enlargement

Nodular thickening / Abcess formation along the nerve

III. Examination of sensory system:

IV. Examination of motor system

V.Examination of other features:

Ear Lobe thickening

Superciliarymadarosis

B/L Gynacomastia

Pedal edema

Trophic Ulcer :

Lymph nodes:

Hepatospleenomegaly:

Diagnosis:

Slit Skin smear: No:

Report:

Skin Biopsy: No:

Report:

Treatment regimen :

Investigations:

FOLLOW –UP:

DATE	CLINICAL FEATURES	ADVICE