

Leprosy

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Introduction

Leprosy

- Oldest disease known to man
- Origin ?? Egypt, India, (600 B.C)
- Crusade, middle east to Europe highest prevalence (*1096 onwards*)
- Remained an alarming diseases for decades
- Patients suffer from stigma and segregation

Leprosy care in Ethiopia

- The first infectious disease that Ethiopia launched a National Control Program supported by the UNICEF (*1948, Emperor Haileselassie I*)
- Country wide vertical Leprosy Control Program (1970 -1994)
- Integrated with the general health care system from 1995 onwards
- Orthodox church (*Gabre-kiristos*) the first shelter

In 1930 leprosaria was built by the help of the Sudan Interior Mission which was named after the Princess Zenebework



The Princess Zenebework; modified with new buildings and renamed All African Leprosy Rehabilitation and Training center (ALERT) in 1965.



Armour Hansen Research Institute (AHRI) ; was built in 1966, to enlarge knowledge of leprosy through basic research



Leprosy...

Prevalence

- Globally, dramatic decrease within the past 10-15 years; from millions to few hundred thousands (*because of MDT*)
- In Ethiopia 0.6/10,000
- New case detection 4-5000/year

Leprosy...

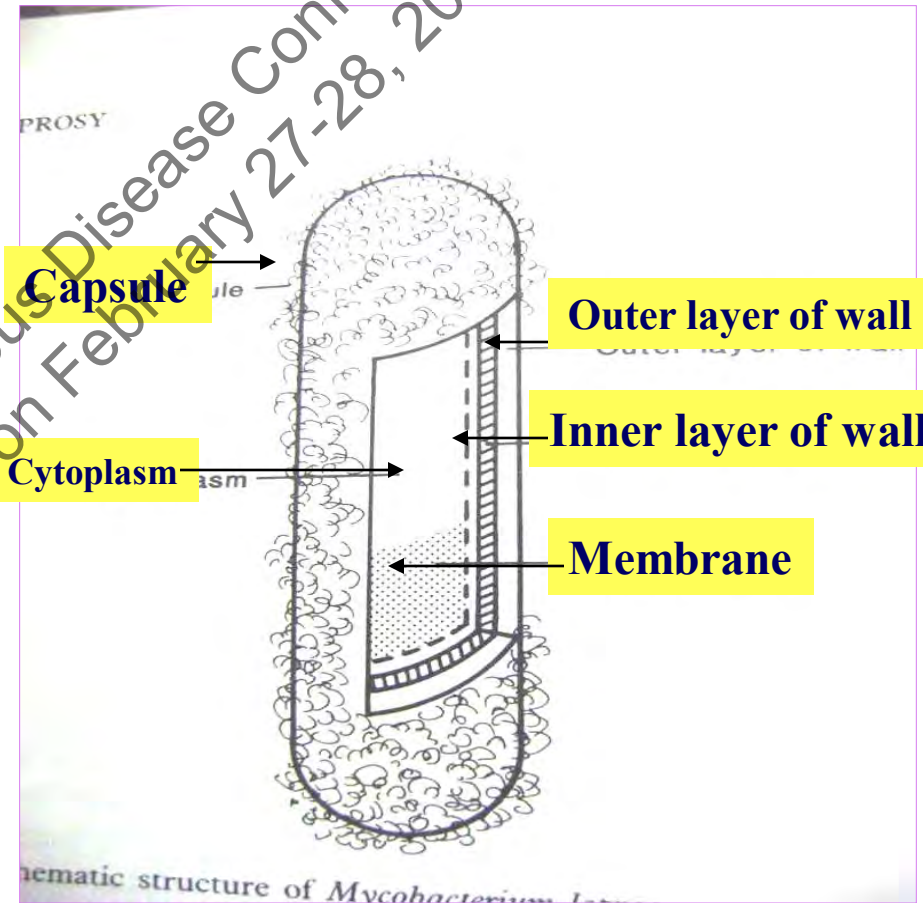


Etiology

- Gerhard Henrik Armauer Hansen discovered the etiologic agent *Mycobacterium Leprae* in 1873

Mycobacterium Leprae

- Gram positive, Acid fast bacilli
- Divides by binary fission (12-14 days)
- Obligate intracellular organism
- Cannot be cultured in vitro, mice foot pad inoculations
- Mildly infectious
- Preference for cooler parts of the body $<37^{\circ}\text{C}$
- Invades skin and peripheral nerves



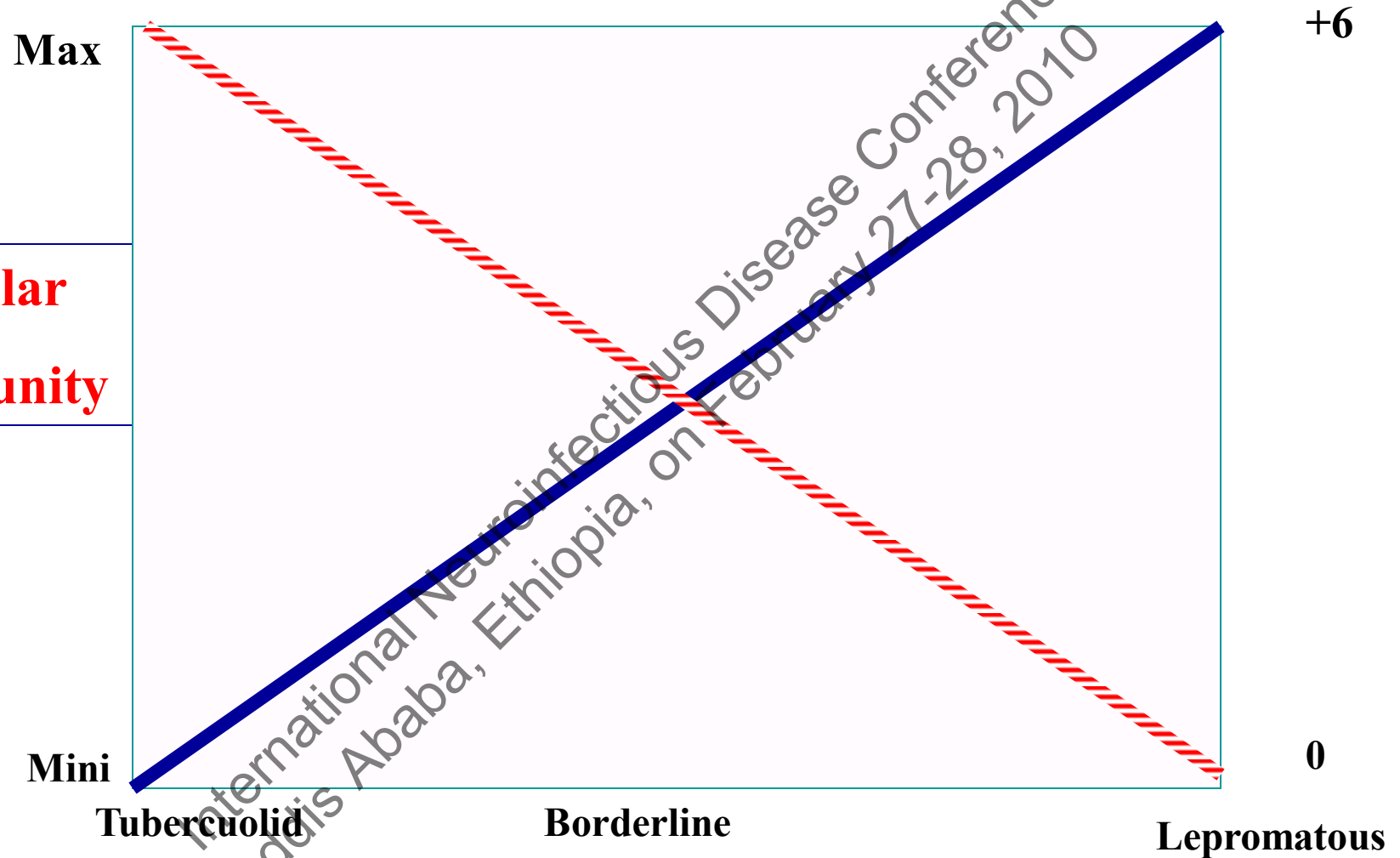
Phenolic glycolipid I; antigenic specificity to M.leprae

Leprosy...

Pathogenesis

- Leprosy develops in minority of infected persons
- ?? Genetic susceptibility
- Spectrum of disease manifestations depending on the interaction between the hosts immune response and bacterium
- Type 1 helper T (Th1) response (PB)
- Type 2 helper T (Th2) response (MB)

Immunity / disease progression in leprosy



Leprosy...

Diagnosis

85-90% cases diagnosed clinically

1. Skin lesion with loss of sensation
2. Nerve enlargement and/or loss of nerve function
3. Positive slit skin smear

At least one of the signs must be present

10- 15% doubtful cases are diagnosed by histopathology

Leprosy...

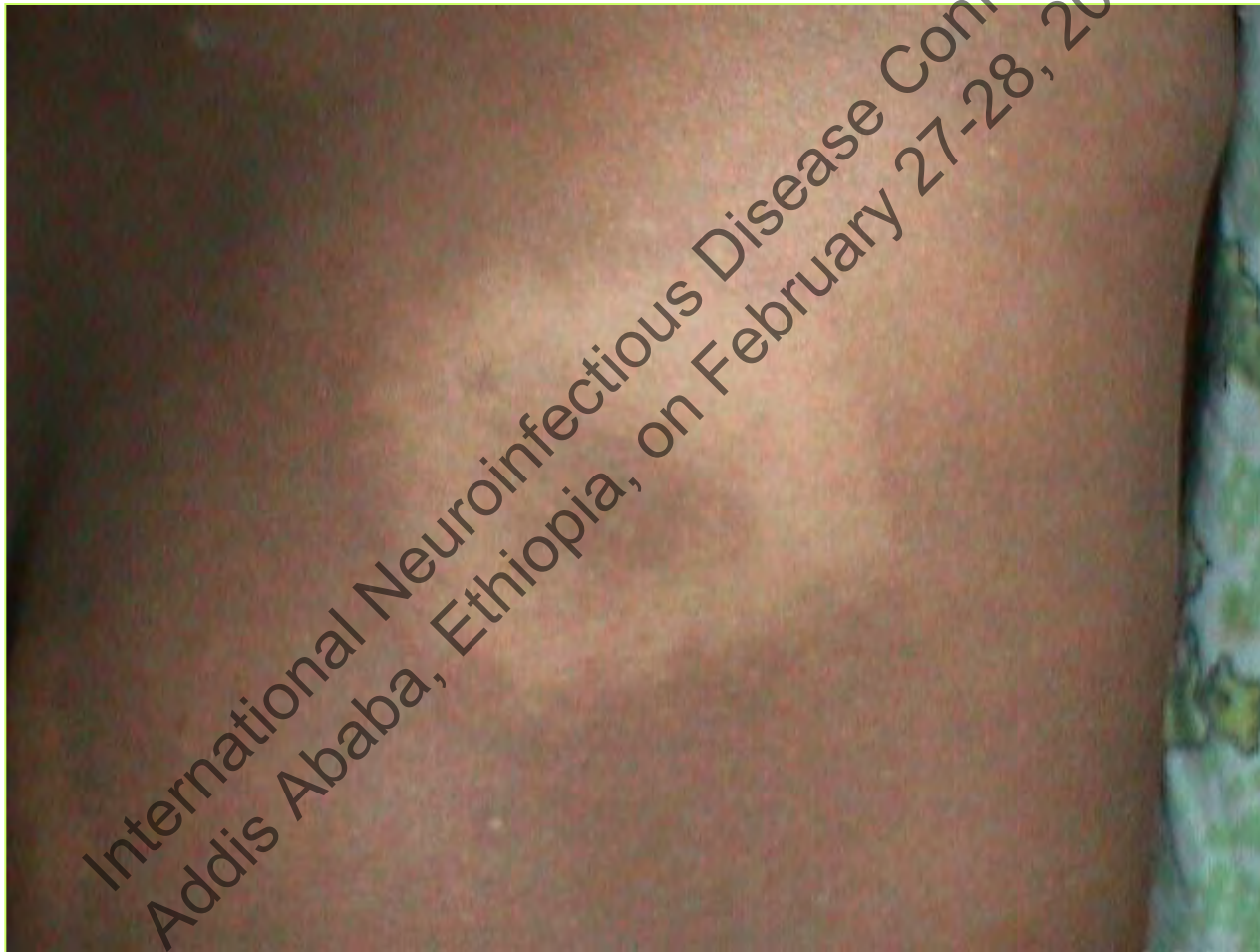
Classification

- **Redley and Jopling (1962, 1966)**
 - Clinical, bacteriological, histological, immunological and criteria's
 - TT, BT, BB, BL, LL
- **Redley & Waters *(1969) Jopling **(1971)**
 - TT, **TI, BT, BB, BL, *LI, LL
- **WHO classification (1982, 1984, 1995)**

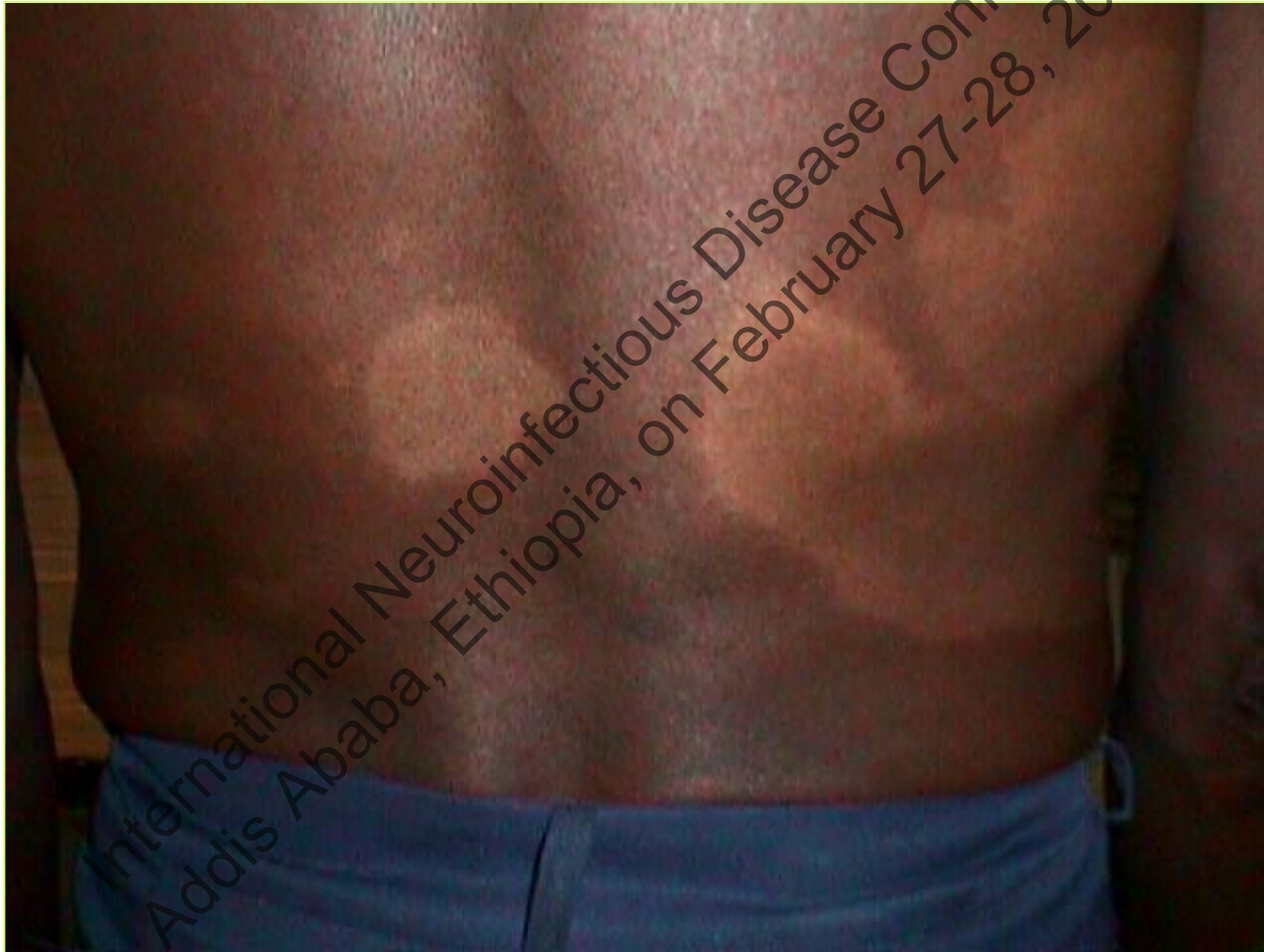
Number of lesions and bacillary Index

 - Pauci bacillary (PB): $< \text{ or } = 5$ lesions, BI=0
 - Multi bacillary (MB): > 5 lesions

Tuberculoid (TT)



Borderline tuberculoid (BT)



Mid borderline (BB)



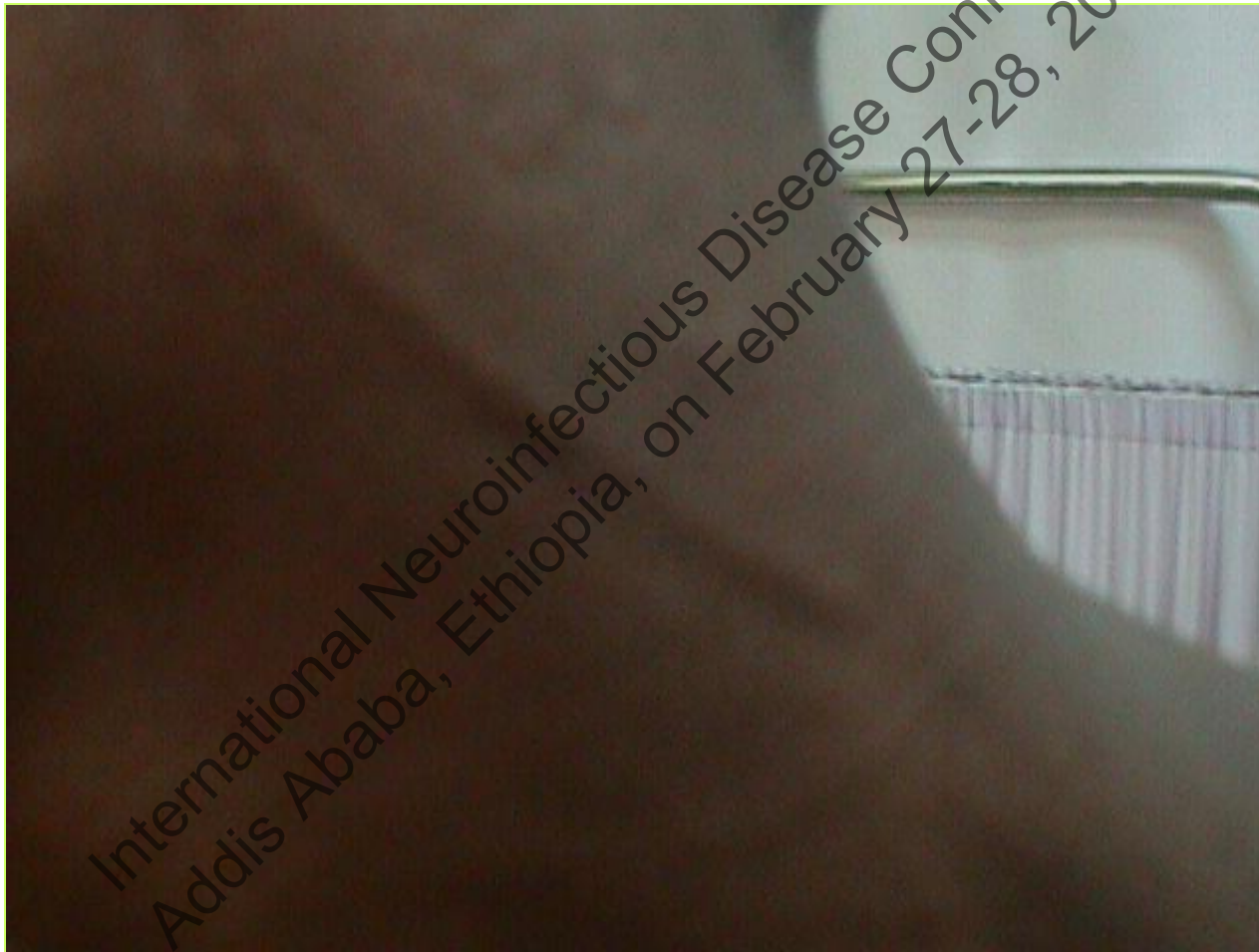
Borderline lepromatous (BL)



Lepromatous (LL)



Pure neural leprosy



Indeterminate leprosy



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Leprosy neuropathy I

- Invasion of peripheral nerves with *M. leprae* induces inflammatory reaction depending on the immunity of the host
 - Polar Tuberculoid
 - Borderline Tuberculoid
 - Lepromatous

Leprosy neuropathy I...

Polar tuberculoid

- Heavy lymphocytic infiltrate
- Replacement of the endoneurium by epithelioid granuloma
- Caseation and abscess formation
- Gross destruction of the nerve anatomy
- Fibrosis of the epineurium
- Often limited to a single peripheral nerve

Leprosy neuropathy I...

Borderline leprosy

- Infiltration with mixture of macrophage epithelioid cells and lymphocytes, schwann cell contain bacilli
- Combined features of lepromatous bacillary invasion and tuberculoid inflammation
- Granulomata are formed with intervening strands normal looking but heavily bacillated schwann cells
- Epithelioid granuloma and edema compress the remaining schwann cells
- Reversal reactions occur frequently with acute neuritis

Leprosy neuropathy I...

Lepromatous type BB,BL,

- Heavy bacillary invasion of schwann cells with minimal inflammatory response
- Reactive proliferation of perineural cells
- Intra-neural infiltration with macrophages
- Foamy degeneration demyelization, destruction of nerve parenchyma
- Endo neural fibrosis
- Damage and destruction of axis cylinder (Wallerian degeneration)
- Glove and stocking anesthesia

Leprosy neuropathy II

Immunologically mediated inflammatory response to *M. leprae* antigens (Leprosy Reactions)

- **Type I:** *Reversal Reaction (RR)*

Borderline leprosy (*BT, BB, BL*), *(*TI*)

- **Type II:** *Erythema Nodosum Leprosum (ENL)*

Lepromatous leprosy (*BL, LL*)

Leprosy neuropathy II...

Prevalence of reaction

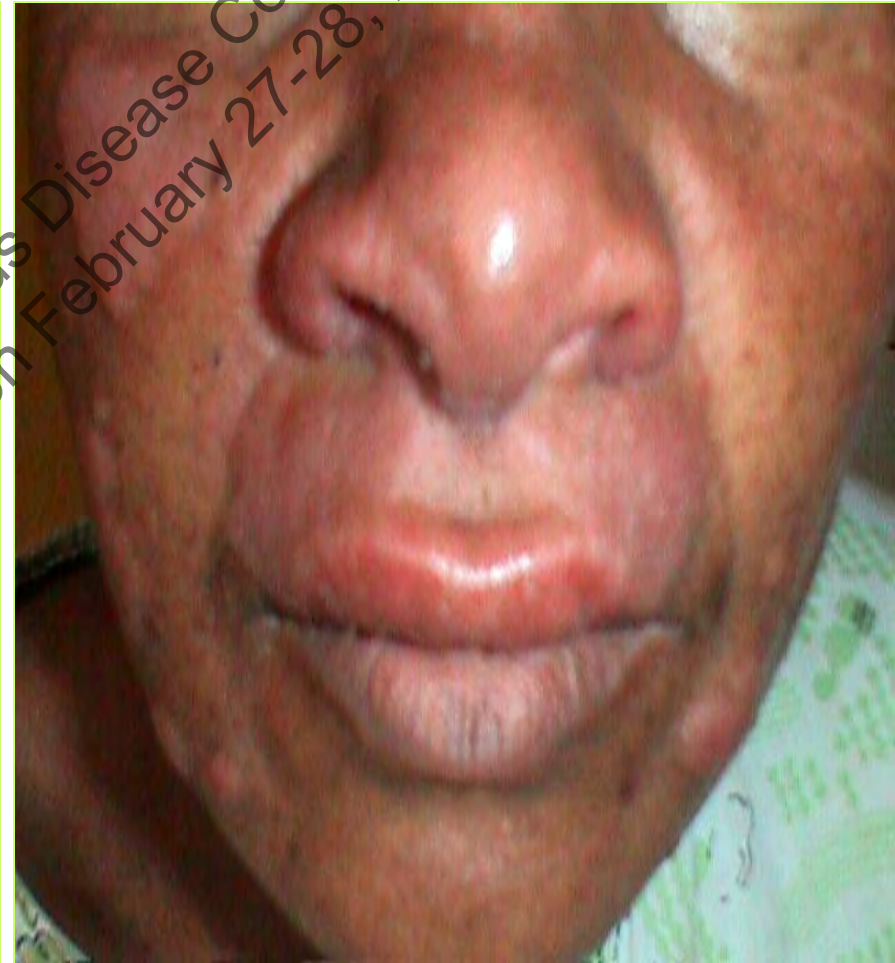
- Reaction occur at any time in leprosy
- 25% of borderline cases within the first 6 months of MDT
- 65% of MB cases

Type I reversal reactions (RR)

Cellular immune response

- Delayed cellular hypersensitivity to *M. leprae* antigens (*Gell and coombs type 4*)
- Increased T cell activity (*CD4+ Lymphocytes*)
- Tuberculoid type inflammations with epitheloid granuloma, caseation and abscess formation, replacement of the endoneurium by granuloma
- Gross destruction of the nerve anatomy, involving multiple nerves
- Inflammation limited to skin and peripheral nerves

Type I reversal reaction (RR)



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Type I reversal reaction (RR)...



Type II erythema nodosum leprosum (ENL)

- Immune complex deposition (*Type III Gell and Coombs*)
- Dense polymorph infiltrations and increased TNF α
- Vasculitis, edema, cellular disintegrations
- Nerve structure may be preserved; showing nodular inflammations containing dense polymorph infiltrations and bacillary depositions
- Systemic inflammatory response (skin, nerve, eye, liver, spleen, mucous membranes, lymph nodes testicles muscle, joint and bones)

Type II; Erythema Nodosum Lerpsum (ENL)



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Type II; Erythema Nodosum Lerpsum (ENL)



Neuritis



- Inflammation of nerves without skin reaction
- Common cause of nerve damage and disability
- 55% of new MB cases have nerve involvement
- 10-15% of new cases have grade 2 (NTBL program 2008)

Clinical types of neuritis

Acute	Sub-acute	Chronic
<ul style="list-style-type: none">• Sever tenderness• Rapid NFI• Follow type I or II reaction• Less than two months	<ul style="list-style-type: none">• Moderate tenderness• Progressive but slow NFI• More than 3 months	<ul style="list-style-type: none">• Mild or no tenderness• Gradual deterioration of NFI• More than 6 months

Monitoring of nerve function impairment (NFI) in neuritis

- Voluntary Muscle function Test (VMT)
- Sensory Testing (ST), graded monofilament testing (STG) (0.02-300gm)
- Cold and hot test
- Two point discriminations
- Triple thermal thresh hold test
- Test track

Management of leprosy

- Early diagnosis and treatment with Multi-Drug Therapy (MDT)



MB



PB

Management leprosy reactions

Type I (RR)

Steroid treatment (prednisolone)

- Adequate dose and duration of treatment
- Regular monitoring of NFI

Other drugs

- Azathiopurine, Cyclosporine

Type II (ENL)

- Prednisolone
- Clofazmine, Thalidomide, NSAID (*non steroidal anti-inflammatory drugs*)

Management of neuritis

- **Acute**

Standard dose of steroid

- **Sub-acute**

Individualized dose of steroid

- **Chronic/Recurrent**

Individualized dose steroid / surgical release

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Surgical management of leprosy neuropathy

- Drainage of nerve abscess in acute neuritis
- Nerve decompression/ release of nerve entrapment/transposition of nerves in chronic and recurrent neuritis
- Reconstructive surgery in permanent nerve damages, management of secondary complications like ulcers, osteomyelitis and other orthopedic related problems

Patients at risk for Reaction and Neuritis

- MB classification
- Skin patches overlying peripheral nerves
- Multiple nerve enlargement
- Pregnant and lactating women
- Children at around puberty
- Concomitant infection (HIV, Tb etc)



Leprosy and HIV co-infection

In Leprosy endemic countries and HIV epidemics

The speculations were that HIV may influence

1. **Prevalence** (*increased number of new cases & transmission among HIV cases*)
2. **Diagnosis** (*confusion with other mycobacteriosis, augmenting HIV serology, spread of HIV with SSS*)
3. **Classification** (*shift towards lepromatous spectrum*)
4. **Treatment** (*difficult to treat with MDT*)
5. **Reactions** (*increased incidence of type I & *II reaction & neuritis, treatment failure to steroids, pathological abnormalities*) in leprosy
6. HIV neuropathy may confuse with leprosy neuritis
7. HIV on immunity may affect leprosy as observed in M. tuberculosis and M. Avium

Leprosy and HIV co-infection

Existing evidences suggest

- HIV has insignificant effect on the prevalence of leprosy (*Long incubation period and low incidence of leprosy make it impossible for prospective cohort study*)
 - *Ethiopia 22/581 (3.8%) 2000; India, 1996; Mali 11/740 (1.5%) ,1995;
** Tanzania 83/679 (12.2%) , **Uganda 26/191(13.6%),1994;
- Diagnosis and treatment of leprosy
 - Efficiency of MDT unaffected, relapses are rare ***case control studies*
- No significant difference in the number of MB and PB cases among HIV negative and positive group (*except India 9 years cohort only 4 MB cases*)

Leprosy and HIV co-infection..

- Increased incidence of reactions (type I) and neuritis reported in HIV infected leprosy patients compared to non HIV controls (*12/26 (46.1%) vs. 28/165 (17%), Uganda*)
- HIV infection and leprosy enhance each other to give more fulminant neuritis (*HIV associated necrotizing vasculitis cause additional nerve damage***) case reports
- Immunological/pathological studies of nerves during reactions and neuritis show inconsistent effect of HIV on leprosy as compared to tuberculosis (*slow inflammation and cell turn over in leprosy*)
 - The cell mediated response to *M. leprae* remains intact even in advanced stage of HIV/AIDS
 - No difference noted with cellular infiltration, cytokine response and granuloma formation on histology of lesions

Leprosy and HIV co-infection...

- The response to steroid treatment in acute reaction and neuritis showed no difference between cases and controls
- False positive serological assays for leprosy (increased PGL1 positive) were detected among HIV cases.
- Several case reports of leprosy presenting as Immune Reconstitution Inflammatory Syndrome, when HIV patients start (HAART) *(9 cases reported in the past 12 yrs most with type I reaction)*



***Leprosy and HIV experience at ALERT
presented at 17th ILC Hyderabad, India
Feb, 2008***

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Leprosy and HIV •••

- ART program launched in 2005
- 7816 cases were registered till, 2008 ; 3155 males & females 4661
- A Retrospective cross sectional analysis of medical records revealed 43 leprosy cases with HIV
- 21 male , 22 females, with age range 29-55 years
- The duration of leprosy ranged 1 to 20 years
- 6 leprosy patients were diagnosed while on ART*

Leprosy and HIV •••

- 30 (70%) had recurrent reaction and neuritis within the past 3 years (2005-2008)
- Type I reaction 7 (23%)
- Type II reaction 4 (13%)
- Neuritis occurred in 19 (63%)
- All were treated with systemic steroid

Leprosy and HIV

- Out come of steroid treatment
 - 9 (30%) improved
 - 7 (23%) remained the same
 - 14 (47%) deteriorated
- 23 (77%) had WHO disability grade 1 and 2



Improvement = 2 or more point increase on VMT and /or 2 point recovery ST

Leprosy and HIV ...

Results

- Increased incidence of reaction and neuritis (30/43, 70%)
 - Severe and multiple nerve damage and disability (28, 93%) **
 - Poor response to steroid treatment (9, 30% improvement)
 - Increased disability (23, 77%; disability grade 1+2)
- Six new leprosy cases with Type I reactions ??
immune reconstitution disease*

Leprosy and HIV...

- Leprosy patients with HIV
 - Require close follow up and monitoring of reaction
 - Search for alternative drugs for treatment of reactions
- Screening of new HIV cases for leprosy (clinical or serological tests)

Leprosy and HIV...

Conclusion

The interaction between leprosy and HIV have been studied insufficiently, therefore further large scale research on clinical, pathological, immunological and management aspects of co-infected patients is needed.

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Case reports of leprosy as IRD
Presented at 17th ILC Hyderabad,
India Feb, 2008

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Case 1

- 64 yrs old male
- Divorced, with 4 children
- Government employee
- One month after HAART
- Developed numbness & rheumatic pain

P/E

- Erythema edema of face and hands
- Grossly enlarged peripheral nerves with tenderness +



Case 1...

- VMT:- ulnar, median common peronial weakness (1-2)
- ST:- complete loss both feet and partial R hand
- BI= 0
- CD4 count 270- 503

Diagnosis: MB leprosy with RR

- Treated with MDT/MB and steroid
- Edema resolved
- VMT recovered by 3 points in all nerves and ST loss by 2/3 in both feet

Case 2

- 39 yrs old, female
- Married with 3 children
- House wife
- Developed swelling of face and skin lesions
- 5 months after HARRT

P/E

- Edema of face hands, feet
- Multiple erythematous edematous plaque lesions
- Enlarged and tender nerves ++



Case 2

- VMT = normal
- ST = complete loss R foot BI=0
- CD4 count 175-503

Diagnosis; MB leprosy with Type I (RR)

- Treated with MDT/MB and predinidolone
- Skin lesions resolved
- Sensation recovered by 1/3

HIV cases with Leprosy...

Results

- Leprosy reactions occurred < 5 months after HAART when the CD4 count increased (immune reconstitution phenomenon)
- The sever type I (reversal reactions) indicate increased cellular immunity to *M.leprae*
- The response to steroid treatment was satisfactory (*early diagnosis, acute phase*)

HIV co-infection ...

- Leprosy often presents as immune reconstitution disease with severe Type I reaction
 - HAART “trigger” CMI (HIV suppress the host immunity ? to *M. leprae*)
 - Sudden unexplained switching on of Th 1 response to *M. leprae* antigens “unmask” previous sub clinical infections
- The risk of leprosy as IRD remains high in endemic countries (*Brazil, India ↑ Leprosy and HIV*)
- Further detailed prospective clinical, immunological study is needed to explain the underlying phenomenon of leprosy as IRD



Thank you

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