NERVE DAMAGE and repair

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Leprosy, “tsara’ath” is a disabling disease due to nerve damage

Leprosy is a disabling disease due to nerve damage

The leprosy stigmata, lagophtalmos, claw hands, dropfeet, absorption of fingers and toes, ulceration and blindness are foremost associated with and caused by nerve damage

SOCIO-ECONOMIC DISABILITY
Though some of the damage may be “silent”, Most of the nerve damage occurs during the so-called reactions

**REACTIONS OCCUR:**
- before treatment
- during treatment
- after treatment

**Two types of nerve damaging reactions:**
- Type I = Reversal Reaction (RR)
- Type II = Erythema Nodosum Leprosum (ENL)

**In order to manage a reaction this must be recognized first**
In order to understand, diagnose and treat an involved nerve it is good to look at the skin, the phenomena may be the same.

**Skin signs of RR**
- Increased erythema
- Swelling
- Enlargement
- New lesions
- Acro-oedema

**Remind:**
- Inflammation:
  - Tumor
  - Rubor
  - Calor
  - Dolor
  - Functio laesae
INCREASED ERYTHEMA

SWELLING

ULCERATING REACTIVE TUBERCULOID
NERVE SIGNS

- Enlarged nerves
- Tender nerves
- Loss of sensation
- Loss of muscle strength
- Loss of sweating

ENLARGED AND TENDER NERVES

LOSS OF SENSATION

LOSS OF MUSCLE STRENGTH
LOSS OF MUSCLE STRENGTH

LOSS OF SWEATING

MECHANISM

RR HISTOPATHOLOGY
granuloma formation
Reversal reaction

- LLT towards *M. leprae* antigens ↑

? WHICH ANTIGENS? there seems to be HETEROGENEITY

Each person has an individual CMI response

During a reactional episode the maximum LTT response may switch from one antigen to another.
One would expect that since we know the genome of *M. leprae* we should by now know the antigens or antigenic determinants responsible. But we do not!

It is not unlikely however that those are not *M. Leprae* specific.

Therefore one should look at cross reacting determinants.

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Pictures from research done in the Early 1980th immunofluorescence, Polyclonal antibody And Late 1980th monoclonal antibodies (received from Arend Kolk)
It is clear that *M. leprae* and skin have antigenic determinants in common.
NORMAL ??

NERVE IN SKIN RECOGNIZED BY ANTI-M. LEPRAE AND ANTI-NEUROFILAMENT

BAL (broncheal lavage) AND ANTI-M. LEPRAE

Heatshock proteins
stress proteins
bacterial versus human
Activated macrophages stain with a great number of monoclonal antibodies directed against \textit{M. leprae}.
Antigenic similarity (mimicry)
The “parasite” may induce or “unlatch” an auto-immune reaction

COULD IT BE THAT THE REVERSAL REACTION IN PAUCIBACILLARY LEPROSY IS AN AUTO-IMMUNE PHENOMENON?

ANTIGENIC SIMILARITY

During RR

- Increase CD4+ T cell infiltration
- Increase mRNA for IL-1β, IL-2, TNF-α, IFN-γ
- Decrease mRNA for IL-4, IL-5, IL-10
- (Yamamura et al.)
Analyses of the cytokine pattern in vivo and of skin derived lymphocyte clones in vitro indicate that the RR is a Th1 type of CMI reaction.

Claudia Verhagen et al.

REVERSAL REACTION

In the tissues a shift towards Th1 activity.

Different patients have a variable recognition pattern and per se a variable eliciting response via different cytokine profile. Depending on hosts genetics and immunological/environmental history.

Hypothesis: Naafs 2001

The elicited cytokines act in concert which leads to a response: “reaction”
Leprosy is an immunological disease induced and/or maintained by *M. leprae*.

**WHAT ABOUT ERYTHEMA NODOSUM LEPROSUM?**

Severe damage may occur during Erythema Nodosum Leprosum (ENL). Type II leprosy reaction.

It is not common during a single attack, but occurs frequently in chronic recurrent ENL.
ENL-Type II leprosy reaction

ULCERATING ENL

ENL IS AN EPISODIC OCCURRENCE

EM-like: courtesy José Augusto da Costa Nery
Duration of ENL untreated

- 25% one week,
- 50% two weeks
- Over 90% less than 1 month
  - De Souza Arauyo HC 1929
  - Inst Oswaldo Cruz, Rio de Janeiro
- Many treatments are claimed to be effective but improvement is just the spontaneous course
  Naafs 1996

ENL- the patient feels unwell

may run a fever
has leucocytosis
may have proteinuria

PATIENT IS ILL

ENL – a generalized disease

- Skin
- Nerves
- Lymph nodes
- Eyes
- Joints
- Testis/epididymis
- Peritoneum
- Liver
- Spleen
- Periost
- Tendon sheaths
- Muscles
ARTHRITIS

IRIDO CYCLITIS

BURSITIS
**ENL HISTOPATHOLOGY**

**ENL Immunohistopathology**

- Immune complexes
- Granulocytes
- CD8 but also CD4 cytotoxic cells
- cytokine pattern both Th2 and Th1

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**ENL Immunopathology**

- Non-specific stimulus → influx of CD4 Th 2 cells into the tissues
  - IL 4 and others → CD4 and CD8 cytotoxic cells
  - B cells → plasma cells → antibody production
  - Antigens in the tissues → immune complexes
  - Complement activation
  - Granulocyte chemotaxis
  - Tissue destruction
THE NERVE

Histopathological patterns

- Tuberculoid pattern
- Borderline pattern
- Multibacillary leprosy
- Multibacillary leprosy and endoneural hyalinization/fibrosis
- Non specific oedema
- Non specific inflammatory infiltrate endo and perineural (mycobacterial antigenic determinants present)
- Non specific inflammatory infiltrate and demyelination (mycobacterial antigenic determinants present)
- Demyelination
- Complete demyelination, endo and perineural hyalinization/fibrosis
- No changes

Jardim et al, Lep Rev, 2004; Garbino et al, Hansen Int, 2004

ENL inflammatory reaction in LL
Type 2 R

Non specific inflammatory reaction
Lepromatous infiltrate with oedema

RR reaction Type I R

Granuloma Tuberculoid, with caseation
Nerve abscess

Courtesy dr J. Garbino

Courtesy dr J. Garbino
evolution in leprosy neuropathy

- **Bacillisation**: ML on SC = chronic demyelination
- **Reactions**: neuritis Type 1 or type 2 = acute oedema, demyelination and axonal loss
- **Intraneural fibrosis**: chronic interstitial neuropathy

Often the bacilli are not seen in the endoneurium though there is it where the nerve fibre supporting Schwann cells are.

It is very difficult for them to enter since within the endoneurium there are no lymph vessels.

Most likely they enter via activated endothelial cells that express adhesion molecules, either for the bacillus itself or for the carrying cell.

David Scottard

Different explanations for the initial demyelination

Segmental demyelination is a hallmark of leprosy

Demyelinisation and nerve damage: a bystander effect of inflammation

- TNF-α
- proteases
- urokinase
A number of adhesion molecules that might be involved have been incriminated. But the mechanism is still under discussion.

Hypophosphorylation

It has been shown that down regulation of the phosphorylation of the NF leads to cytoskeletal abnormalities and atrophy of the axon with demyelination.

Immunity driven

M. leprae specific HLA class II restricted killing of human Schwann cells by CD4+ T helper-1 cells

Spierings et al.
Multiple mononeuropathy pattern in the skin

“Micro - multiple mononeuropathy”

Garbino JA. Hansen Int. 1998

Frequency of nerve involvement

Motor nerve conduction studies
(stimulation and recording technique with surface electrodes)

José A Garbino et al

Parameters: CMAP, (compound motor action potential), Distal latency (DL), Conduction velocity (CV), Temporal dispersion (TD) and F wave

- CMAP amplitude: wrist, elbow and above elbow
- DL in the wrist, CV over the forearm and across the elbow
- CMAP TD: at the elbow and above
- F wave: all the nerve length


Demyelinating features - different patterns

CMAP TD in T1R: subacute/chronic demyelination (months)
CMAP CB in T2R: acute oedema (weeks-months)

a) before treatment  b) after treatment
RESULTS

- Temporal Dispersion is related to the reaction of the Schwann cells to a subacute inflammation during T1 R
- The Conduction Block is related to focal and more acute intraneural edema (acute entrapment) during T2 R
- In both reactions if the inflammation is uncontrolled, demyelination will lead to axonal degeneration

Level of nerve damage

- cutaneous nerves
- subcutaneous nerves
- nerve trunks

MICROSCOPIC COMPRESSION
VENOSTATIC OEDEMA

Elbow tunnel: cubital, retro-epicondylian and at the septum muscularis entrapment sites


MACROSCOPIC COMPRESSION
Late nerve impairment

- Reversal reaction (T1 R) very chronic (subacute) immune mediated process years after MDT (motor nerve conduction – Temp dispersion) due to remnant antigen or auto-antigens? It may flare up when the patients get HAART when HIV infected.
- Interstitial neuropathy – silent neuropathy during late stage of LN
- post-leprosy syndrome = Kind of post-polio syndrome: earlier physiologic remodelling of motor units in the aging due to the previous motor axon lesion

Since leprosy is a *M. leprae* antigen driven disease, the antigens should be diminished. The treatment of choice to do this is WHO-MDT. Important is to know that one of the constituents dapsone (DDS) also acts against the Type-I leprosy reaction. (Prevention) There are indications that anti-mycobacterial treatment stops the demyelination. (Naafs 1977) But it is not yet proven.
Since a Type-I leprosy reaction is CMI mediated: the treatment of choice is immunosuppression.

**Treatment of reversal reaction**

<table>
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<tr>
<th>Prednisolone</th>
<th>Ciclosporine</th>
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<tbody>
<tr>
<td>30-40 mg dd 1 week</td>
<td>200 mg bd 1 week</td>
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<td>25-30 mg dd 1-3 weeks</td>
<td>175 mg bd 3 weeks</td>
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<td>20-25 mg dd 1-2 months</td>
<td>150 mg bd 1-6 months</td>
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<td>20 mg dd 1-6 months</td>
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<td>15 mg dd 1-6 months</td>
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<td>10 mg dd 2 weeks</td>
<td>50 mg bd 2 weeks</td>
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<td>5 mg dd 2 weeks</td>
<td>25 mg bd 2 weeks</td>
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**PREDNISOLONE vs CICLOSPORINE**
- Inhibition of transcription of: IL-2, IL-3, IFN-γ, TNF-α
- Inhibition of expression of IL-2 receptors
- Inhibition of CD4 Th1 helper cells

**Treatment duration**

- **Type-I Leprosy reaction**
  - BT patients: 3 - 6 months
  - BB patients: 6 - 9 months
  - BL patients: 6 - 24 months
TREATMENT RESULTS

WHO:
After 3 month deterioration!

Alternative treatment:
azathioprine
mycophenolate mofityl
tacrolimus
biologicals

TREATMENT OF MILD ENL
skin only

NSAID's e.g. Aspirin 1.5 - 3g daily 1-2 weeks

TREATMENT OF MILD ENL
with arthritis

Asperin 1.5 - 3g daily + antimalarial e.g.
(Hydroxy) chloroquine 1 - 1.5g daily 1-2 weeks
**TREATMENT OF SEVERE ENL**

**single attack**

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<th>Steroids e.g. Prednisolone</th>
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When an exacerbation occurs, increase dosage 2 fold or go back to the initial dose or use or add Thalidomide.

**Treatment of severe ENL**

**single attack**

- 200-400 mg dd days 1-3
- 100-300 mg dd days 1-3
- 100-200 mg dd days 1-3
- 50-100 mg dd days 1-3

**Thalidomide**

**TREATMENT OF CHRONIC AND RECURRENT ENL**

- Each single attack as described before.
- When needed maintenance treatment with thalidomide.
- Try to avoid maintenance with steroids.
- High dose clofazimine 100-300mg can be helpfull.

**OTHER TREATMENTS FOR ENL**

**OLD**
- Isoniazide
- Trivalentantimony
- Promethazine
- Chlorpromazine
- Azathioprine
- Colchicine
- Plasmaphoresis
- Psychotherapy

**NEWER**
- Cyclosporine
- Pentoxiphylline
- IV-immunoglobulin
- Vaccination

**NEW AND FUTURE**
- New immunomodulators: tacrolimus, mycophenolate mofetyl, cytokine network modulation, anti TNF-α-antibodies (inflixamab) and others receptor blockers etc.
- Methotrexate
When nerve deterioration does not stop despite adequate medical therapy a nerve release should be done to diminish the entrapment.

Bridging the gap

When the nerve seems to be damaged over a small area, e.g. Median nerve at the wrist, N. Tibialis posteror at the ankle. A graft may be considered taking in account the fact that the proximal part of the nerve fibre is still alive and has a potency to sprout and follow small “pipelike” structures to grow out.
Miko et al (1993 Lancet and Lepr. Rev.) showed that sprouting is extensive but also that in long standing disease there are hardly subcutaneous and cutaneous structures left to guide the sprouting axon.

On the other hand regularly some sensory recovery is seen even after 20 years or more. Deep sensation and deep pain seem to reappear first.

The first to do so was John Hargrave in Australia at the end of the 70th. He grafted the median nerve and failed

Batista not much later suggested end to side the superficial branch of the median to the ulnar.

Marcos Virmond suggested recently in his PhD thesis a bovine tubular pericardial graft

Pereira et al in this congress reported success from a muscle graft in the N.Tibialis posterior

Gigi Conforti who should have given this lecture had success a.o. in diabetes with venous grafts filled with a muscle. The sprouts follow than the lining of the muscle fibre skeleton

However more research is needed

I thank all my teachers and collaborators
From the past:

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Jan van Droogenbroeck
Gunnar Bjune
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Roël Chin a Lien
Raoul Fleury

But most of all: Pranab K Das who keeps me earth bound, and my past student now my teacher Jose Garbino