Treatment of reactions

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Regional Dermatology Training Centre
Moshi - Tanzania
Leprosy, “tsara’ath” 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.
Though some of the damage may be “silent”,
Most of the nerve damage occurs during
the so-called reactions

REATIONS 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
Recognise a reaction!

**Skin signs of RR**

- Increased erythema
- Swelling
- Enlargement
- New lesions
- Acro-oedema
Remind:

Inflammation:
  - Tumor
  - Rubor
  - Calor
  - Dolor
  - Functio laesae

INCREASED ERYTHEMA
ULCERATING REACTIVE TUBERCULOID

EXPANDING LESIONS
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 SWEATING

MECHANISMS
RR HISTOPATHOLOGY
granuloma formation

Reversal reaction

- LTT towards *M. leprae* antigens
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
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

IRIDOCYCLITIS
BURSITIS
ENL HISTOPATHOLOGY

ENL Immunohistopathology

immune complexes
granulocytes
CD8 but also CD4 cytotoxic cells
cytokine pattern both Th2 and Th1
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

Treatment
Since leprosy is an *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)
Since a Type-I leprosy reaction is CMI mediated: the treatment of choice is immunosuppression

When the conditions allow it is essential to do a good follow up.

VMT and even better graded Sensory Testing can be done in the field! Electrophysiology is only for research
VOLUNTARY MUSCLE TESTING

BRISTLES
SENSORY TESTING

Careful follow-up guides treatment

<table>
<thead>
<tr>
<th>Date</th>
<th>24/4</th>
<th>20/6</th>
<th>15/8</th>
<th>9/9</th>
<th>16/9</th>
<th>30/9</th>
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<tbody>
<tr>
<td>Clinical condition</td>
<td>Well</td>
<td>Well</td>
<td>No complaints</td>
<td>Severe rheumatic pain; obvious reversal reaction</td>
<td>Better</td>
<td>Well</td>
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<tr>
<td>Antireaction treatment</td>
<td>Prednisolone</td>
<td>Stop prednisolone</td>
<td>—</td>
<td>Restart prednisolone</td>
<td>Prednisolone</td>
<td>Prednisolone</td>
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<td>2</td>
<td>6</td>
<td>4</td>
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<td>4</td>
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<td>7</td>
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<td>5</td>
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<tr>
<td>ST</td>
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<td>25</td>
<td>56</td>
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<td>52</td>
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Treatment of reversal reaction

<table>
<thead>
<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>
</tr>
<tr>
<td>25-30 mg dd 1-3 weeks</td>
<td>175 mg bd 3 weeks</td>
</tr>
<tr>
<td>20-25 mg dd 1-2 months</td>
<td>150 mg bd 1-6 months</td>
</tr>
<tr>
<td>20 mg dd 1-6 months</td>
<td>125 mg bd 1-6 months</td>
</tr>
<tr>
<td>15 mg dd 1-6 months</td>
<td>100 mg bd 1-6 months</td>
</tr>
<tr>
<td>10 mg dd 2 weeks</td>
<td>50 mg bd 2 weeks</td>
</tr>
<tr>
<td>5 mg dd 2 weeks</td>
<td>25 mg bd 2 weeks</td>
</tr>
</tbody>
</table>

Higher initial steroid dose seems more effective, but after 2 month there is no difference anymore

PREDNISOLONE a panacee

- 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

CICLOSPORINE
Most important is timely diagnosis

Side effects

• In the used dosis not many. But:
  • To prevent worm infestation deworm first

• Weightgain
• Moon face
• Gastric disturbances
• Diabetes
Treatment duration
Type-I Leprosy reaction

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
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<tbody>
<tr>
<td>BT</td>
<td>3 - 6 months</td>
</tr>
<tr>
<td>BB</td>
<td>6 - 9 months</td>
</tr>
<tr>
<td>BL</td>
<td>6 –24 months</td>
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In recent years partly to the desire to simplify and shorten treatments and a misleading concept on what is evidence based, treatment were limited to 3 month.

Leading to the conclusion that steroids were of no benefit and only a risk.
TREATMENT RESULTS

WHO:

After 3 month deterioration!

Extended treatment improvement

Alternative treatments:

azathioprine
mycophenolate mofityl
tacrolimus
biologicals
Treatment of Type II leprosy reactions

SINCE ENL IS AN EPISODIC OCCURRENCE
The duration of treatment should be related to the active phase

- 25% one week,
- 50% two weeks
- Over 90% less than 1 month
  - De Souza Arauyo HC 1929
  - Inst Oswaldo Cruz, Rio de Janeiro

Remind:
- Many treatments are claimed to be effective but improvement is just the spontaneous course

Naafs 1996

**TREATMENT OF MILD ENL**

**skin only**

NSAID’s e.g. Aspirin 1.5 - 3g daily 1-2 weeks
TREATMENT OF MILD ENL with arthritis

Aspirine 1.5 - 3g daily + antimalarial e.g.
(Hydroxy) chloroquine 1 - 1.5g daily 1-2 weeks

TREATMENT OF SEVERE ENL single attack

Steroids e.g. Prednisolone

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>Duration (days)</th>
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<tbody>
<tr>
<td>120-180</td>
<td>2</td>
</tr>
<tr>
<td>100-120</td>
<td>2</td>
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<tr>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
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<td>2</td>
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<td>10</td>
<td>2</td>
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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 1-3 days
- 100-300 mg dd 1-3 days
- 100-200 mg dd 1-3 days
- 50-100 mg dd 1-3 days

**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 helpful.
Find a cause:

ENL can be provoked or maintained by:

- viral infections (flu, HIV?)
- bacterial infections (tuberculosis, ulcers)
- vaccinations (smallpox, BCG)
- worm infections
- anaemia
- pregnancy
- stress
At present the largest problem in treatment of ENL is steroid dependence!!

Try: Clofazimine  
Methotrexate  
Thalidomide

<table>
<thead>
<tr>
<th>OTHER TREATMENTS FOR ENL</th>
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<tbody>
<tr>
<td>OLD</td>
</tr>
<tr>
<td>Isoniazide</td>
</tr>
<tr>
<td>trivalentantimony</td>
</tr>
<tr>
<td>promethazine</td>
</tr>
<tr>
<td>chlorpromazine</td>
</tr>
<tr>
<td>azathioprine</td>
</tr>
<tr>
<td>colchicine</td>
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<tr>
<td>plasmaphoresis</td>
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<tr>
<td>psychotherapy</td>
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THE NERVE

RR reaction Type I R

Tuberculoid Granuloma with caseation

Nerve abscess

Courtesy dr J. Garbino
ENL inflammatory reaction in LL

Type 2 R

Non specific inflammatory reaction

Lepromatous infiltrate with oedema

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
Demyelinisation and nerve damage: a bystander effect of inflammation

- TNF-α
- proteases
- urokinase

Immunity driven

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

Spierings et al.
• 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

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
entrapment

Level of nerve damage

• cutaneous nerves
• subcutaneous nerves
• nerve trunks
MICROSCOPIC COMPRESSION

VENOSTATIC OEDEMA
Mechanical nerve damage

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

MACROSCOPIC COMPRESSION
When nerve deterioration does not stop despite adequate medical therapy a

**Nerve release**

should be done to diminish the entrapment.
Bedankt
Obrigado
Asante sana
Merci
Grazi
Danke
Thanks
Gracias
 شكرا جزيلا
Dhanyavadh