Management of Patients with Peripheral and Central Nervous System Manifestations

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Disclosure of Interests

Dr Juan Politei has been in receipt of honoraria for lectures on Fabry disease from Genzyme Corp; Shire HGT, Amicus and Protalix.

Dr Juan Politei is a member of the LATAM Advisory Board of Fabry Registry, which is sponsored by Genzyme.
Peripheral nervous system

Pathophysiology
Diagnosis
Treatment
Peripheral nervous system

What do we know about pain mechanisms in Fabry disease?

For the last 30 years:

1. Nerve ischaemia
2. DRG involvement

For the last 12 months:

1. Painful channelopathy
2. Lyso-Gl3 causes pain by direct action

Very important implications for the treatment decision...
Peripheral nervous system

Which are the most accurate methods for Fabry neuropathy diagnosis?

1. Specific questions about presence of neuropathic pain IN FABRY disease:
   - Does the patient have, or recall having, any “burning” pain in hands or feet?
   - Is there any deterioration or spreading of the pain distribution with heat or cold exposure, physical effort (sports), or fever?
   - Has the pain ever prevented the patient from participating in sports?
   - Does the patient sweat less than others during physical effort, or in a warm/hot environment?
   - Are there any family members who have had or currently have similar complaints?

2. Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ).¹
3. Self-administered version of the Fabry-associated pain questionnaire.²
4. Brief Pain Inventory

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Bedside’ sensory tests:

Thermal perception can be evaluated by:
(a) assessing the ability to discriminate the temperature of glass tubes filled with warm or cold water
(b) metal discs which mediate warm or cold temperature sensation

Perception of light-touch tests: cotton swab (skin brushing).

Vibration sensitivity can be evaluated using: a 128 Hz scaled Rydel-Seiffer vibrating tuning fork

Pain perception can be tested by: evaluating a patient’s pinprick sensation

Quantitative Sensory Test (QST)

Quantification of intra-epidermal nerve fiber density  (just when is available)
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Treatment

**Adjunctive therapy**
- Aims: pain relief
- When?
- Which?

**Enzyme replacement therapy**
- Aims: slow progression of Fabry pathology and pain control
- When?
**Peripheral nervous system**

### Adjunctive therapy: for chronic pain

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Cardiac restrictions?</th>
<th>Renal restrictions?</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>250–800 mg/day</td>
<td>May interfere with activity of other drugs, eg, warfarin</td>
<td>None</td>
<td>Filling-Katz et al. 1989</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Slowly titrated from 100 to a max of 2400 mg/day</td>
<td>None</td>
<td>Yes (with precautions in cases of renal insufficiency)</td>
<td>Ries et al. 2003b</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300 mg/day</td>
<td>None</td>
<td>None</td>
<td>Lockman et al. 1973</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75–300 mg/day</td>
<td>None</td>
<td>Yes (with precautions in cases of renal insufficiency)</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>25 to 150 mg/day</td>
<td>arrhythmias</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

“To reduce the likelihood of side-effects from polypharmacy, the dosage of each drug prescribed should be titrated to the highest tolerated dose providing significant pain control before other pain-modulating agents are added”
## Peripheral nervous system

### Adjunctive therapy: for pain crises

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Expertise in FD and Side effects</th>
<th>Cardiac restrictions?</th>
<th>Renal restrictions?</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous lidocaine</td>
<td>2–5 mg/kg</td>
<td>Good clinical response</td>
<td>arrhythmias</td>
<td>None</td>
<td>Politei JM. 2009</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100–400 mg/day</td>
<td>Caution with concomitant use of SSRIs, SNRIs, or TCAs</td>
<td>None</td>
<td>Caution in patients with renal insufficiency and epilepsy</td>
<td>O’Connor 2009</td>
</tr>
<tr>
<td>Morphine</td>
<td>Titration of 30–120 mg every 12 hs</td>
<td>Monitor for addiction Constipation</td>
<td>None</td>
<td>None</td>
<td>Gordon et al. 1995</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Titration of 20–60 mg every 12 hs</td>
<td>Monitor for addiction Constipation</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50–150 mg/day</td>
<td>[Less useful dose, reduce the risk of GI bleeding]</td>
<td>None</td>
<td>Caution in patients with renal insufficiency</td>
<td></td>
</tr>
</tbody>
</table>
Peripheral nervous system

Neuroprotective and anti-inflammatory activities of atorvastatin in a rat chronic constriction injury model.

Adjunctive therapy: Statins for neuropathic pain?

Statistical analysis regarding: statins alleviate experimental nerve injury-induced neuropathic pain.
Pain. 2015 Jul;156(7):1366


Pain: Statins--new treatment for neuropathic pain?
Nat Rev Neurol. 2011;7(5):246

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Peripheral nervous system

**Enzyme replacement therapy**

“Considering the potential link between lyso-GL3 and pain, lowering lyso-GL3 levels, using early ERT, may help decrease the pain severity.”

“chronic acroparesthesias resistant to conventional therapy”

**Table 3 Consensus criteria for initiation of ERT**

<table>
<thead>
<tr>
<th>Pain*</th>
<th>Non-classical FD, males</th>
<th>Non-classical FD, females</th>
</tr>
</thead>
<tbody>
<tr>
<td>- neuropathic pain (Class IIA)</td>
<td>- neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)</td>
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</tbody>
</table>

*As pain may be an indicator of underlying FD pathology, any type of pain related to FD is an important symptom which can indicate the need to start ERT in classical variant, regardless of patient age or gender.*
Central nervous system

Pathophysiology
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Central nervous system

What do we know about microangiopathy in Fabry disease?

Medial thickening due to glycolipid storage in the SMCs.

Hydropic swelling of multiple axons of the cerebral deep white matter.

No thrombosis in the majority of brain autopsies!

- Removal of tissue by macrophages
- Fluid filled cysts with dark grey margin (gliosis)
- Gliosis – proliferation of glia at periphery.
Central nervous system

What do we know about macroangiopathy in Fabry disease?

Vertebrobasilar Dolichoectasia in Fabry Disease: The Earliest Marker of Neurovascular Involvement?

Increased Arterial Diameters in the Posterior Cerebral Circulation in Men with Fabry Disease

Chronic state

↑ Expression MMP9

↑ Break down the ECM and SMCs

↑ damage the fibronectin mesh

↑ migration of smooth muscle cells

vicious cycle of dilatation and deformation

Central nervous system

The MRI protocol should include: T1-weighted; fluid attenuated inversion recovery/T2-weighted; T2*/susceptibility; and diffusion-weighted imaging sequences. T2*/susceptibility is sensitive for hemorrhage, and fluid attenuated inversion recovery/T2-weighted images are sensitive for the detection of CWMH burden and for identifying both lacunar and territorial stroke; T1-weighted images are sensitive to pulvinar signal changes.

MR angiography: is of value for vessel imaging, (intracranial vessel stenosis, or dolichoectasia.) Transcranial Doppler, PET, SPECT (not routine test).

“In the authors’ experience, MRI is required only approximately every 3 years for patients with stable FD, but it is indicated in the event of clinical signs of a stroke”.

Central nervous system

Treatment for cerebrovascular involvement

Primary prevention:

ERT?

Enzyme Replacement Therapy Stabilized White Matter Lesion Progression in Fabry Disease

“Although limited to a small number of patients, this analysis provides the first evidence that agalsidase beta is an effective ERT for reducing the WML burden in patients with FD aged 50 years or younger”

Antiplatelet agents: just when CVRF are present

Warfarin: when AF is present

Statins: no evidence, but…
Central nervous system

Comparative effects of more versus less aggressive treatment with statins on the long-term outcome of patients with acute ischemic stroke.

\[ \text{↑dose = better outcome} \]
Atherosclerosis. 2015;243(1):65-70

Statins in the secondary prevention of stroke: SPARCL trial, showed the benefits of statin therapy in preventing recurrent stroke. Clin Invest Arterioscler. 2015 Jul

Statin treatment reduces the risk of poststroke seizures.
Neurology. 2015;85(8):701-7

Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study. Cohort of older people with no history of vascular events, use of statins or fibrates was associated with a 30% decrease in the incidence of stroke. BMJ. 2015 May 19

Statin use in spontaneous intracerebral hemorrhage: a systematic review and meta-analysis.

\[ \text{Statin use in patients with intracerebral hemorrhage is likely associated with improved mortality and functional outcomes.} \]
Int J Stroke. 2015 Aug 26
Central nervous system

Treatment for neurocognitive involvement

ERT?

The Neurocognitive Impact of Fabry Disease on Pediatric Patients

Eight-Year Follow-Up of Neuropsychiatric Symptoms and Brain Structural Changes in Fabry Disease

<table>
<thead>
<tr>
<th>Group comparisons for the neuropsychiatric parameters between baseline and follow-up.</th>
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<tr>
<td></td>
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<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
</tr>
<tr>
<td>Education (years)</td>
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<tr>
<td>Dementia screening</td>
</tr>
<tr>
<td>Depression (%)</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Depression severity</td>
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<tr>
<td>Memory</td>
</tr>
<tr>
<td>Learning</td>
</tr>
<tr>
<td>Long term memory</td>
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<tr>
<td>Free recall</td>
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<td>Recognition</td>
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<tr>
<td>Visual memory</td>
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<tr>
<td>Visual learning</td>
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<tr>
<td>Long term visual memory</td>
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<tr>
<td>Psychomotor performance &amp; attention</td>
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<tr>
<td>Executive functions</td>
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</tbody>
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Thank you for your attention