# Management of Patients with Peripheral and Central Nervous System Manifestations

KDIGO

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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.

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# Peripheral nervous system

Pathophysiology

Diagnosis

Treatment

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# Peripheral nervous system

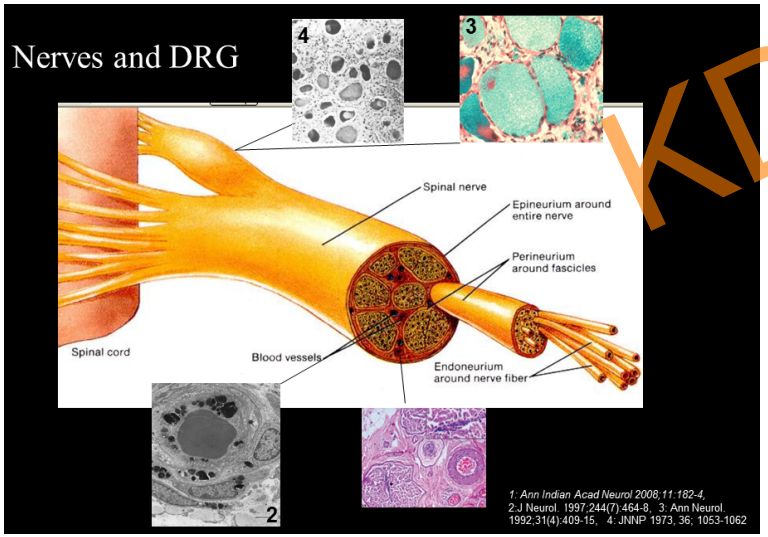
What do we know about pain mechanisms in Fabry disease?

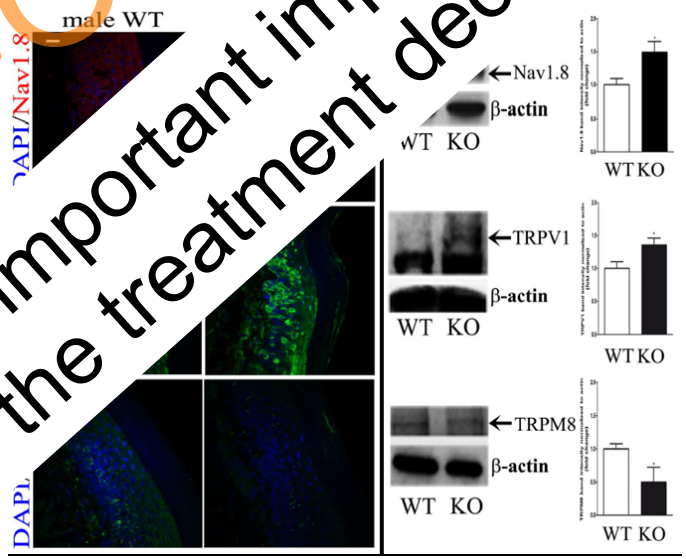
For the last 30 years:

1. Nerve ischaemia
2. DRG involvement

For the last 12 month

1. Painful char
2. Lyso-Gl3 causes

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Very important implications for the treatment decision…



PLoS One.2014.22;9(10)
Neurosci Lett. 2015 May 6;594:163-8

# 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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1: Health Qual Life Outcomes 2012;10:116. 2:Orphanet J Rare Dis. 2015;10(1):113.

# Peripheral nervous system

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

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*Quantitative Sensory Test (QST)*

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

# Peripheral nervous system

## Treatment

***Adjunctive therapy***

Aims: pain relief

When?
Which?

***Enzyme replacement therapy***

Aims: slow progression of Fabry pathology and pain control

When?

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# Peripheral nervous system

## *Adjunctive therapy: for chronic pain*

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

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"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*

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

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# Peripheral nervous system

**Neuroprotective and anti-inflammatory activities of atorvastatin in a rat chronic constriction injury model**.
Int J Immunopathol Pharmacol. 2012;25(1):219-30.

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

***Adjunctive therapy: Statins for neuropathic pain?***

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**Atorvastatin as novel treatment for neuropathic pain.** Clin J Pain. 2013;29(12):e46-8

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

# 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."

Current guidelines for instituting enzyme replacement therapy in Fabry disease patients

| | |
|---|---|
| Fa | |
| Adu | |
| Ped | |
| | if asymptomatic, consider at 10–15 yr |
| Females (all ages) | Monitor; institute if significant symptoms[a] or evidence of progression of organ involvement |

**"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."**

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"chronic acroparesthesias resistant to conventional therapy"

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

| | Pain* |
|---|---|
| | activities) with pain medication (Class IIB) |
| **Non-classical FD, males** | - neuropathic pain (Class IIA) |
| **Non-classical FD, females** | - neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB) |



Genet Med. 2006;8(9):539-48. Orphanet J Rare Dis. 2015 Mar 27;10:36

# Central nervous system

Pathophysiology

Diagnosis

Treatment

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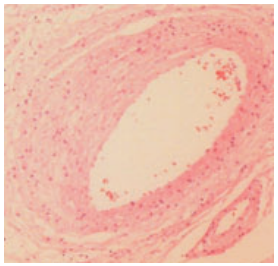
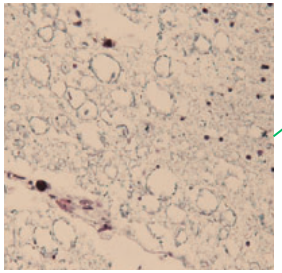
# Central nervous system

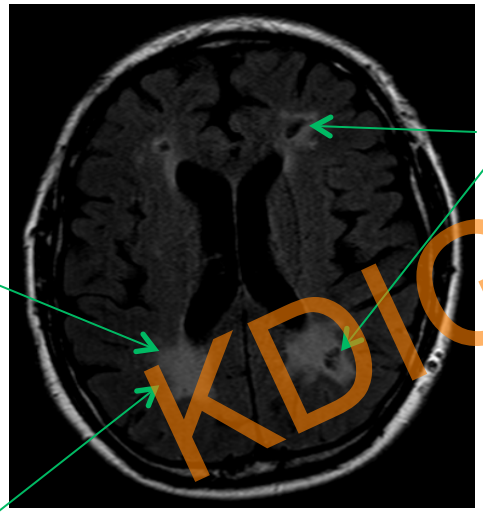
## What do we know about microangiopathy in Fabry disease?



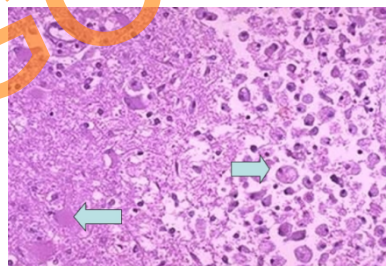
Medial thickening due to glycolipid storage in the SMCs.

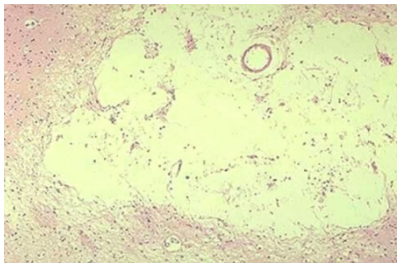


Hydropic swelling of multiple axons of the cerebral deep white matter.

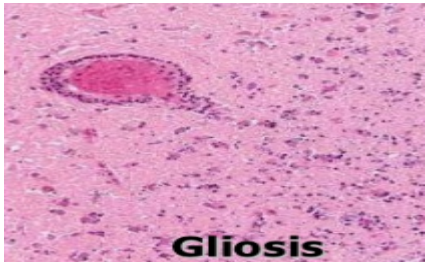


– Removal of tissue by macrophages
– Fluid filled cysts with dark grey margin (gliosis)
– Gliosis – proliferation of glia at periphery.





**No thrombosis in the majority of brain autopsies!**

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Cerebrovascular Involvement in Fabry Disease. Current Status of Knowledge. Stroke. 2015;46(1):302-13.

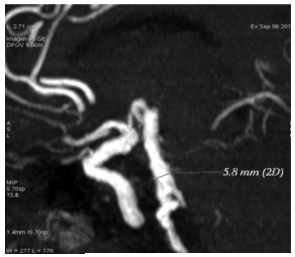
# Central nervous system

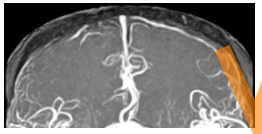
## What do we know about macroangiopathy in Fabry disease?

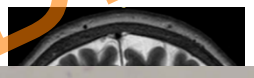
**Vertebrobasilar Dolichoectasia in Fabry Disease: The Earliest Marker of Neurovascular Involvement?**

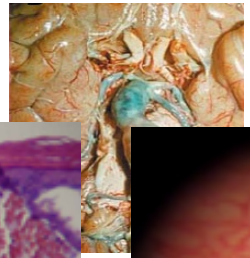
**Basilar Artery Diameter Is a Potential Screening Tool for Fabry Disease in Young Stroke Patients**

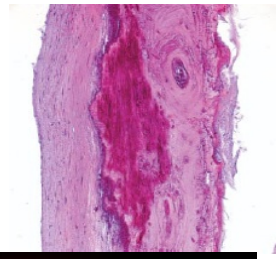
**Increased Arterial Diameters in the Posterior Cerebral Circulation in Men with Fabry Disease**

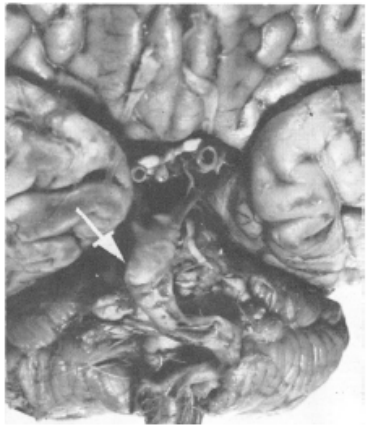


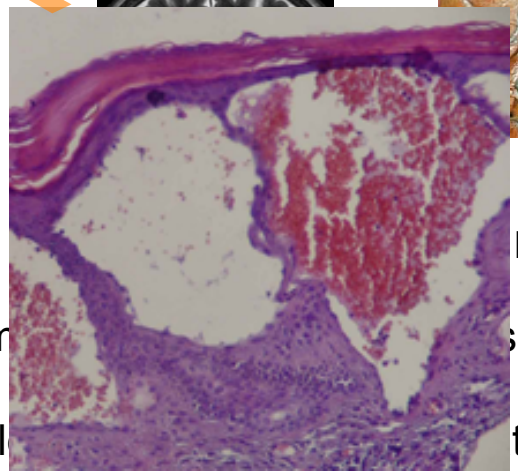


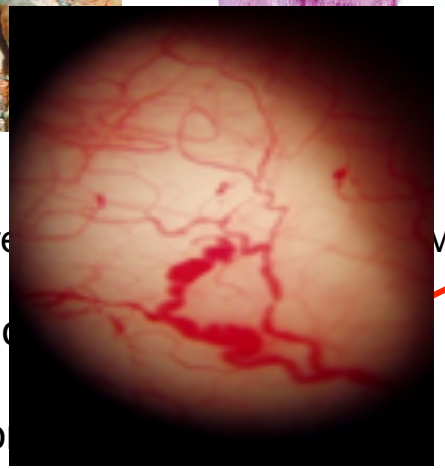






Journal of Neurology, Neurosurgery, and Psychiatry, 1973, 36, 1053–1062





Chron… Bre… MCs

m… sm…

…cl… tio…

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*Politei et al. Journal of Inborn Errors of Metabolism & Screening 2014 2:1-6. Fellgiebel et al. Cerebrovasc Dis 2011;31:294–299.* Uçeyler et al. PLoS One. 2014 27;9(1).

# 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).

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***"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".***



Cerebrovascular Involvement in Fabry Disease. Current Status of Knowledge. Stroke. 2015;46(1):302-13.

# Central nervous system

## Treatment for cerebrovascular involvement

Primary prevention:

ERT?

**Enzyme Replacement Therapy Stabilized White Matter Lesion Progression in Fabry Disease** Cerebrovasc Dis 2014;38:448–456

"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…*

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# Central nervous system

**Comparative effects of more versus less aggressive treatment with statins on the long-term outcome of patients with acute ischemic stroke.**
***↕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 Investig Arterioscler. 2015 Jul

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

Statins and Brain

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**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.**
***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

Am J Med Genet B Neuropsychiatr Genet. 2015;168(3):204-10

TABLE IV. Comparison of Neurocognitive Functioning for ERT+ and ERT- groups

| | ERT− vs. ERT+ | |
|---|---|---|
| **Domain** | **t** | ***P*-value** |
| Cognitive Functioning (PedsQL™ CFS–Total Score - Parent Report) (*ERT+* n = *7*; *ERT−* n = *13*) | −2.153 | 0.045 |

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

PLoS One. 2015 Sep 4;10(9):e0137603

Group comparisons for the neuropsychiatric parameters between baseline and follow-up.

| | Baseline | Follow-up |
|---|---|---|
| N | . | 14 (4M) |
| **Age at baseline (years)** | 39 (19–55) | 47 (27–64) |
| **Education (years)** | 12.5(8–20) | . |
| **Dementia screening** | 30 (27–30) | 29.5 (24–30) |
| **Depression (#)** | 7 (50%) | 3 (21.4%) |
| Mild | 6 | 2 |
| Moderate | 1 | 1 |
| **Depression severity** | 7.5 (0–27) | 3 (0–21) |
| **Memory** | | |
| Learning | 62 (29–67) | 58 (33–73) |
| Long term memory | | |
| - Free recall | 13.5 (3–15) | 13.5 (6–15) |
| - Recognition | 15 (12–15) | 15 (13–15) |
| **Visual memory** | | |
| Visual learning | 37 (33–41) | 36 (18–41) |
| Long term visual memory | 35 (36–41) | 31.5 (16–40) |
| **Psychomotor performance & attention** | 19.7 (13.6–54) | 22.5 (12–37) |
| **Executive functions** | 46.4 (34–89) | 56 (34–99) |

Thank you for your attention

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