Morbus Fabry

Bruno Conti Rossini

Sostituto primario

Ospedale Regionale di Locarno

Problem:

- Anesthesiologic ambulatory preanesthetic consultation for peripartal epidural anesthesia
- the call:
  - we have a pregnant patient with Fabry disease who wishes a peripertal EDA. Do you have an idea what is that?

What the hell is that

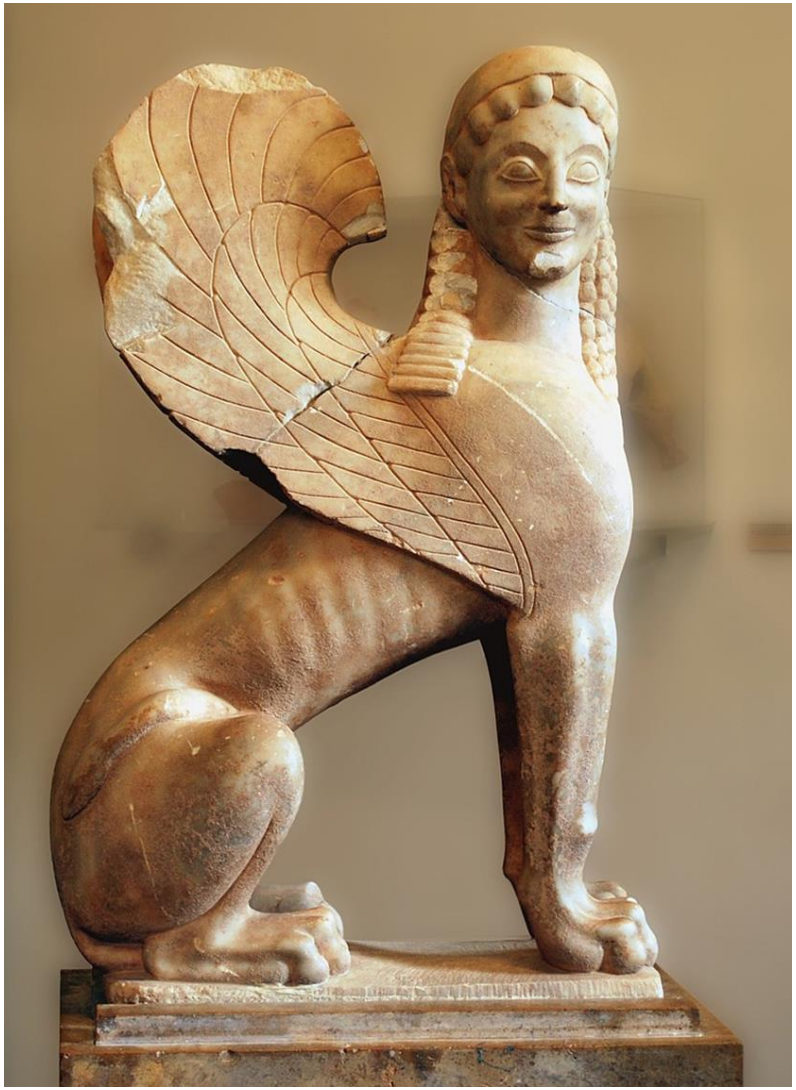
- Maybe a kind of Storage disease?
- The old pathology Book of university of Basel came to my mind.
- A vague memory of cells with big vacuolisation?
- A vague pictures of poor children with skeletal deformity, organomegalia, emerged in my mind.
- I was really troubled
- My first question :
  - How is the patient looking?
- The colleague was surprised of my question but he answered :
  - pretty good
- I thought fortunately I must be wrong

The patient

- Ptatient in good general conditions, bronchial asthma treated with seretide, BD 115/65; 87bpm, cardiopulmonary auscultation normal finding
- 5th month of pregnancy, without complications
- Asymptomatic carrier of X linked Fabry disease
- History of appendectomy in childhood
- Echocardiography: no pathologic findings

- The patient wishes a peripartal epidural anesthesia
- Sister had been refused a peripartal PDA
- Sister developed symptoms of the disease after pregnancy

The riddle



- The Sphinx is said to have guarded the entrance to the Greek city of Thebes, asking a riddle to travelers to allow them passage
- She strangled and devoured anyone who could not answer….
- What is Fabry disease?
- What should we do?

Our statement:

- We need time
  - we have no experience.
  - we have to consult Literature and ask an expert
  - at this moment we are not able to say if this is possible or not…

What have we done

- Literature (google scholar, ncbi, ovid…)
  - Anesthesia and Fabry > 4 case reports
  - Regional anesthesia and Fabry > no results
  - Peripartal epidural anesthesia > no results
- Expert opinion:
  - Never heard about that, I’m sorry I have no idea

our statement one month later:

- Female Patients with Fabry disease may suffer from cerebrovascular insults in 5% of the cases and may manifest neurologic symptoms in 77% of the cases
- We did not find literature about Fabry disease and locoregional and/or peripartal anesthesia
- We declare ourselves willing to perform a peripartal epidural anesthesia
- In absence of described cases we are unable to evaluate the risk or the procedure
- In case of CS we recommend to perform SA, because the risk is probably minor then that of GA

What happened

- 3 months later the labor began…
- after 3 hours the EDA was performed without problems
- 10 hours later the patient delivered spontaneously a healthy girl without complications
- the patient was very satisfied about the treatment and EDA

what happened next

- Three year later the patient delivered spontaneously two healthy twin males
- EDA was performed without complications.
- Since 2017 the patient is under treatment with ERT (enzyme replacement therapy) because of vestibular symptoms

What is Fabry disease

- Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism
- Characterised by deficient or absent lysosomal a-galactosidase A activity
- Deficient activity of lysosomal a-galactosidase A results in progressive accumulation of globotriaosylceramide within lysosomes of cells
- Progressive storage of these molecules leads to cellular dysfunction which might in turn trigger inflammation or fibrosis, or both

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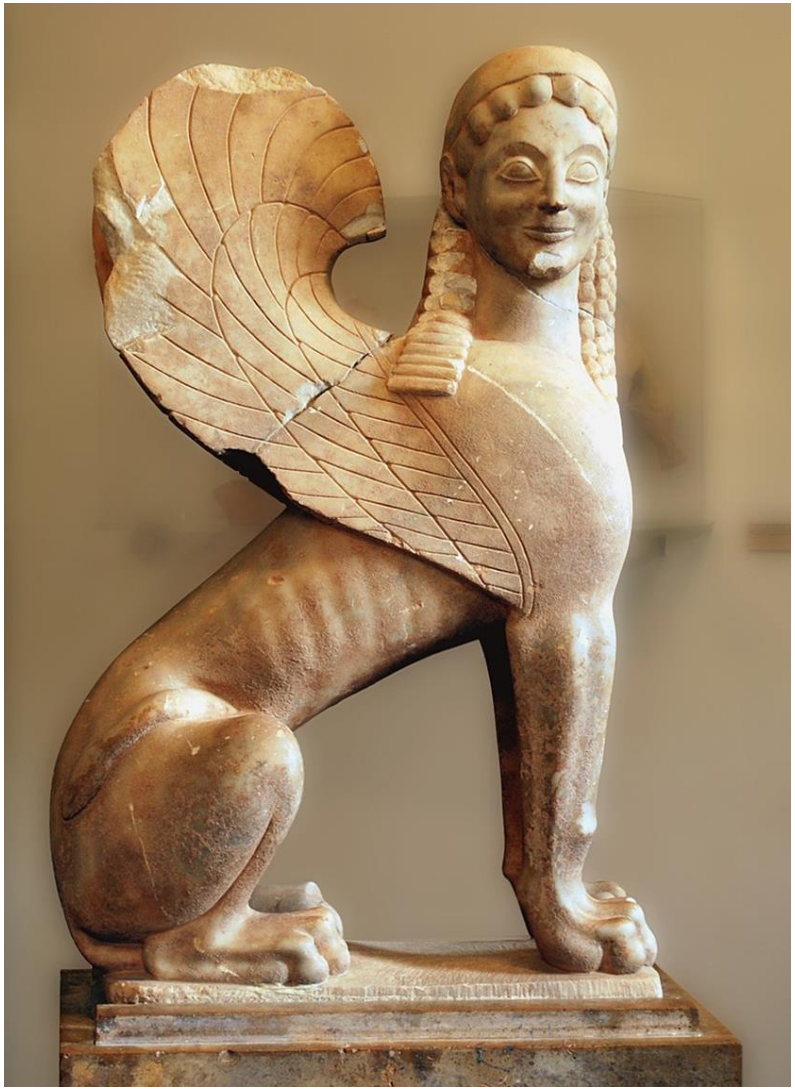
What are sphingolipids?



- Sphingolipids are a type of lipids made up of fatty acid chains that were first mentioned in 1884 in J.L.W. Thudichum's *"A Treatise on the chemical composition of the brain"*
- They were named after the Greek mythological creature, the sphinx, due to the unknown riddle of their function
- Sphingolipids are found in essentially all plants, animals, fungi and in some prokaryotes and viruses
- Specifically, they are found in membranes and as a major component of lipoproteins

Pathophysiology of Fabry disease

- Glycosphingolipids Gb3 is thought to be a major substrate burden in Fabry disease
- In many organs, such as the vascular endothelium, muscle, Heart and kidney, glycosphingolipid storage may occur either to endogenous production or through active uptake and diffusion of circulating glycolipids
- Globotriaosylceramide Gb3 accumulation also occurs in central nervous system structures, dorsal root ganglions, peripheral ganglions and peripheral nerves

Annals of Neurology Vol 23 No 5 May 1988

Fabry disease

- hemizygous males, with no residual alfa-galactosidase A activity may display all the characteristics of the disease: neurological (pain), cutaneous (angiokeratoma), renal (proteinuria, kidney failure), cardiovascular (cardiomyopathy, arrhythmia), cochleo-vestibular and cerebrovascular (transient ischemic attacks, strokes)
- heterozygous females have symptoms ranging from very mild to severe

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Fabry in females

- The phenotypic variation in females may be due in large part to random X-chromosome inactivation (Lyonization)that occur in the Morula stadium of the embryogenesis
- After Lyonization some cells will have the X chromosome with the defective gene activated and others will have the X chromosome with the functioning gene activated (mosaic)
- Thus, the severity of symptoms and organ involvement depends upon which organs or tissues have the mutated gene activated in a significant majority of the cells

Fabry disease

- Fabry Disease is pan-ethnic
- the general reported annual incidence of 1 in 100,000 may underestimate the true prevalence

Country	Period of ascertainment	Total number of cases	No per 100'000
Turkey	1997-2002	1	0,015
Netherland	1970-1996	27	0,21
UK (females only)	1980-1995	60	0,29
UK (males only)	1980-1995	98	0,27
Australia	1980-1996	36	0,85
Austria	2010	9	25
Italy	2004-2006	12	30
Taiwan	2006-2008	73	80

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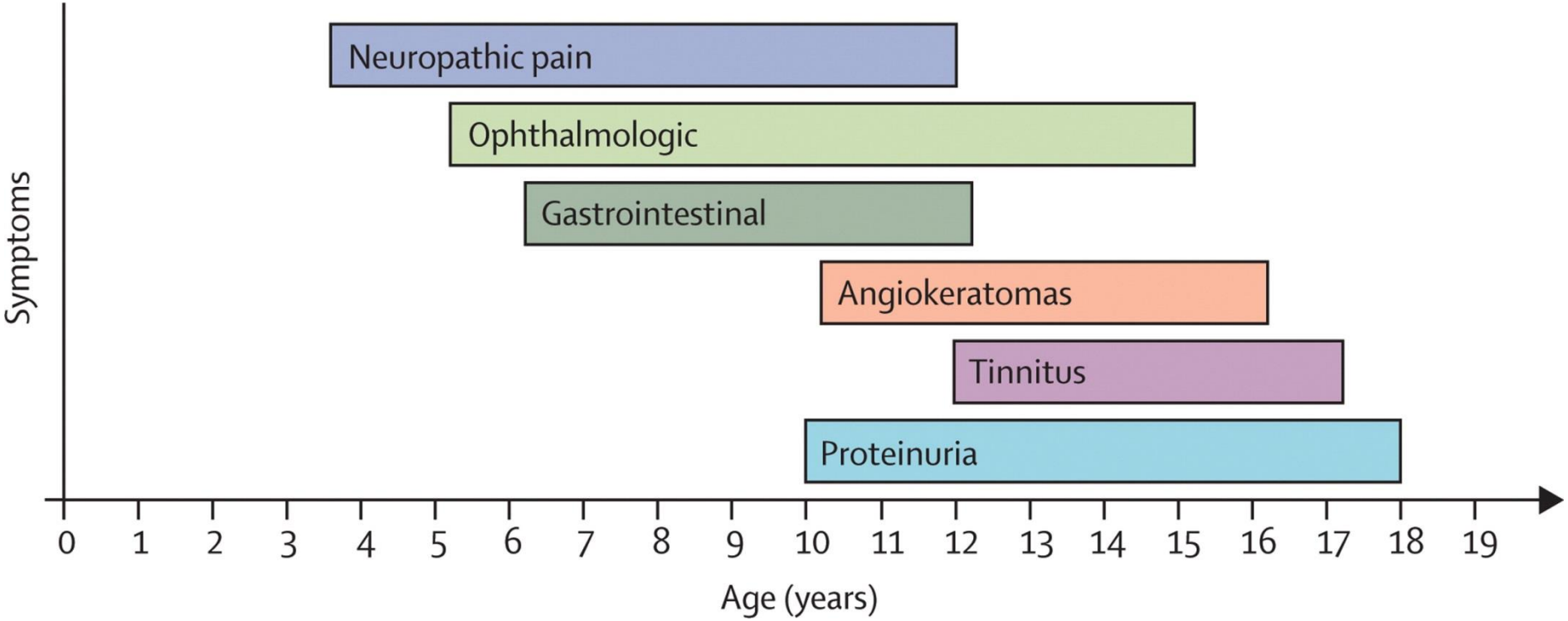
Fabry disease

- Onset of Symptoms in males



www.thelancet.com Vol 372 October 18, 2008

Presentation of the neurological phenotype in male and female patients with Fabry's disease.

caracteristic	Heterozygous females	Homozygous males
Mean survival	55-70 y	41-50 y
pain	32-90%	84-100%
Onset of neuropathic pain (mean age)	10-21 y	7-9,4 y
VAS continued	6,8	5
VAS crises	7,4	??
Audiovestibular symptoms	11-85%	57%
Fatigue	28%	24-62%
Stroke or TIA	40,3-60 y (earliest 25 y)	28,8 -34 y (earliest 12 y)
hypohidrosis	11-33%	84-100%

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Neurological symptoms

- Parenchymal: caused by accumulation of Gb3 in the cells of CNS and PNS
  - Neuropathic pain
  - Audiovestibular symptoms (dizziness, hearing loss, deafness).
  - Abdominal pain
- Vascular: caused by accumulation of Gb3 in the vascular endothelium:
  - Stroke
  - Vascular lesions of peripheral nerves

Pain

- Two forms of pain are described in patients with Fabry's disease:
  - constant burning and lancinating neuropathic pain,
  - Fabry crises in which aggravated pain is observed in attacks induced by exercise, stress and temperature changes, including fever
  - Fabry crises can last for a few minutes to several days
- Pain of Fabry is responsive to ion channel antagonists such as gabapentin and carbamazepine and other pharmacological drugs such as NMDA antagonists, tricyclic antidepressants and valproate

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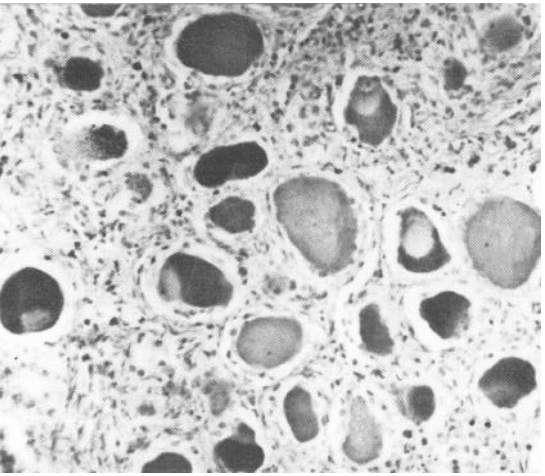
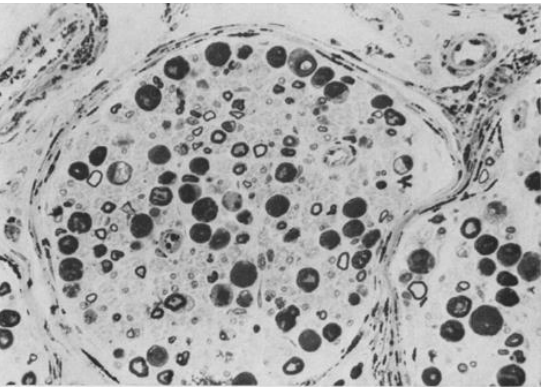
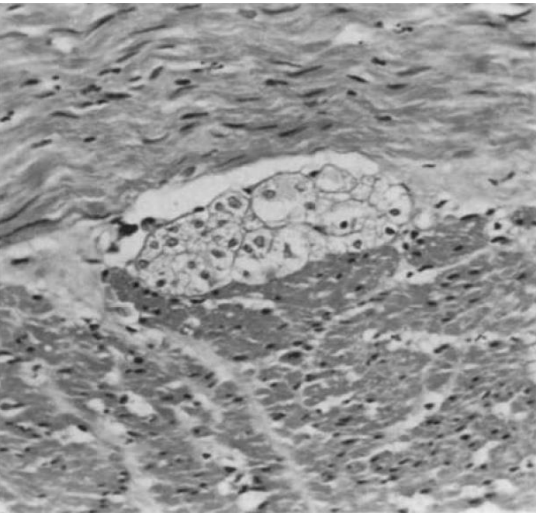






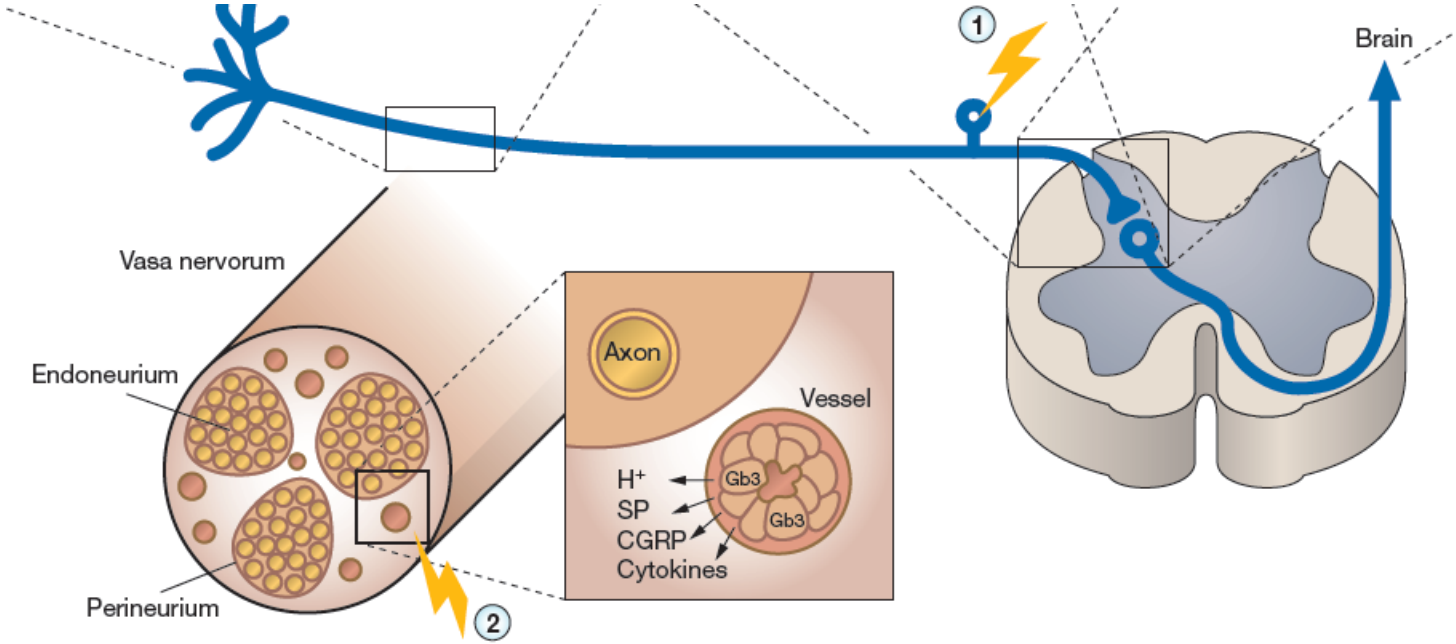
Fabry pathology of the nervous system and Pain

- Neurons of the **spinal roots** are swollen and have abnormal deposits
- Abnormal lipid deposits are observed in the perineurium and in the wall of the vessels, of the **peripheral nerves**
- Moderate reduction of myelinated nerve fiber population and degradation of myelin sheath of large nerve fibers are also observed
- Neurons **of Auerbach's, Meissner's plexuses** in the gastrointestinal tract and of the paravertebral sympathetic cell columns are foamy and swollen

Acta neuropath. (Berl.) 30, 345—354 (1974)

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

Neuropathic Pain in Fabry disease



- Gb3 accumulate in the ganglia, in peripheral nerves (**1**) and vessel endothelia (**2**)
- Decreased vessel lumen and impaired hemodynamics causes ischemia and release of protons (H+), which in turn produces an inflammatory response

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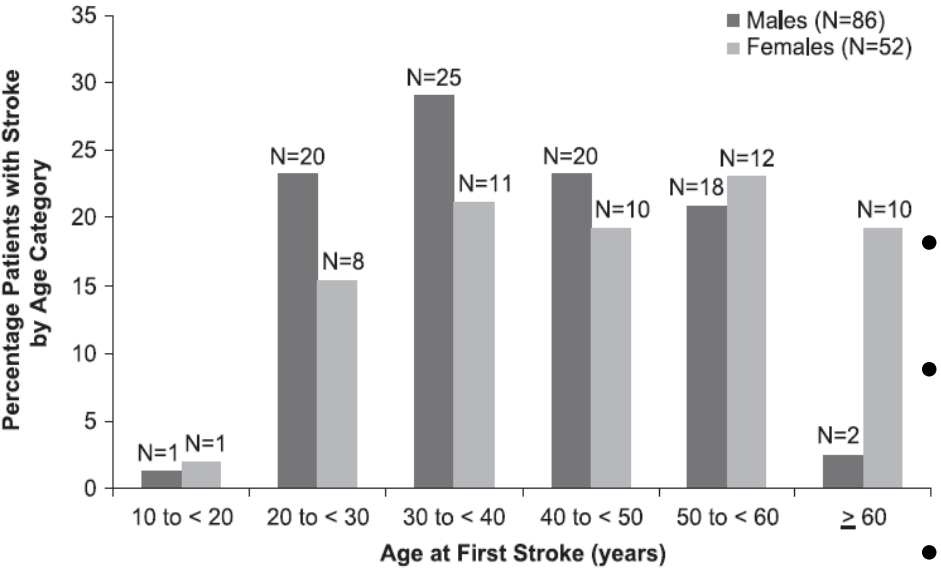
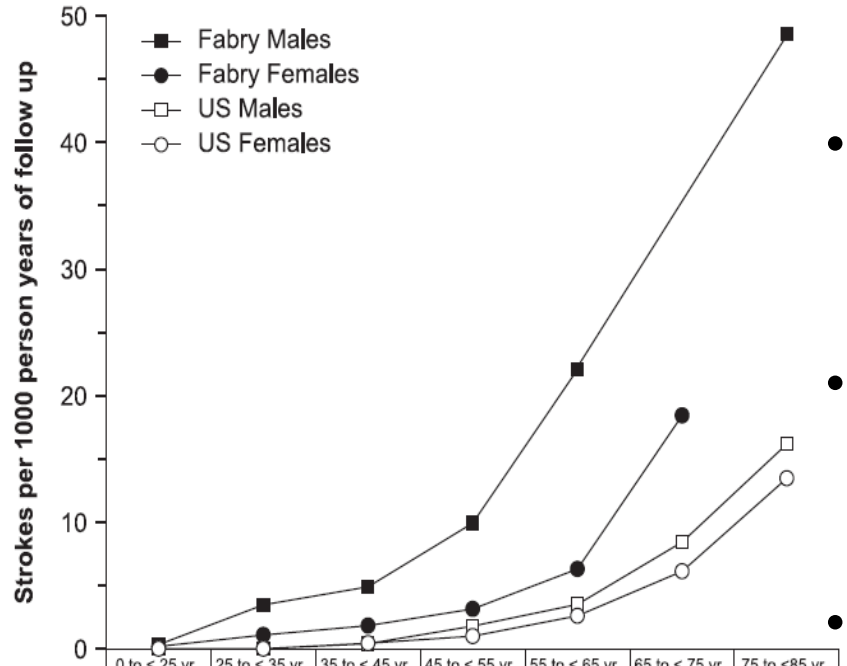
Fabry and Stroke





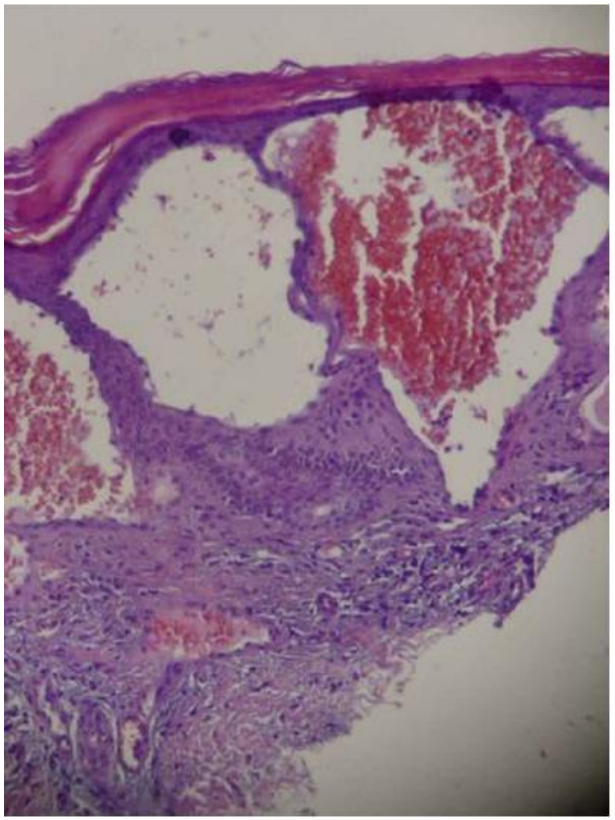
	0 to < 25 yr	25 to < 35 yr	35 to < 45 yr	45 to < 55 yr	55 to < 65 yr	65 to < 75 yr	75 to <85 yr
Fabry Males	0.32	3.47	4.89	9.92	22.05	*	48.58
Fabry Females	0.18	1.09	1.83	3.14	6.30	18.43	#
US Males	0.00	0.00	0.40	1.79	3.50	8.43	16.17
US Females	0.00	0.00	0.44	0.99	2.60	6.12	13.46

- Data from **2446 patients in the Fabry Registry** were analyzed
- **138 patients** (86 of 1243 males [6.9%] and 52 of 1203 females [4.3%]) experienced strokes.
- Median **age** at first stroke was **39.0 years in males and 45.7 years** in females
- Most patients (70.9% of males and 76.9% of females) had not experienced renal or cardiac events before their first stroke
- **50% of males and 38.3% of females experienced their first stroke before being diagnosed with Fabry disease**
- 30 patients (21 males and 9 females) had strokes at age < 30 years

Stroke. 2009;40:788-794.

Fabry skin lesions

- Angiokeratoma corporis diffusum
- Angiokeratomas when quite large are easily recognizable
- If only a few lesions exist or if they are restricted only to the genitalia or umbilical regions, they can be easily missed



Fabry related Hearth Changes

- **The classic cardiac abnormality is hypertrophic cardiomyopathy** .
- **Function:** mild diastolic dysfunction is seen in early stages and progresses to systolic and severe diastolic ventricular dysfunction in later stages of the disease.
- **Left ventricular hypertrophy (LVH):** concentric remodeling in early stages, which progresses later to concentric hypertrophy, septal and posterior wall thickness.
- **Valvular disease**: mitral insufficiency valves are thickened and distorted, with mild-to-moderate regurgitation.
- **Ischaemia**: vasospastic or stenotic coronary artery disease leads to myocardial infarction, angina, and chest pain, particularly in patients with LVH.
- **Electrocardiogram abnormalities**: voltage criteria for LVH and repolarisation changes. Short PQ interval, bundle branch block, atrioventricular conduction delay, and progressive sinus node dysfunction.
- **Arrhythmias**: bradycardia (children), Short PQ interval, supraventricular tachycardias,.atrial fibrillation, atrial flutter, and cardiac sudden death

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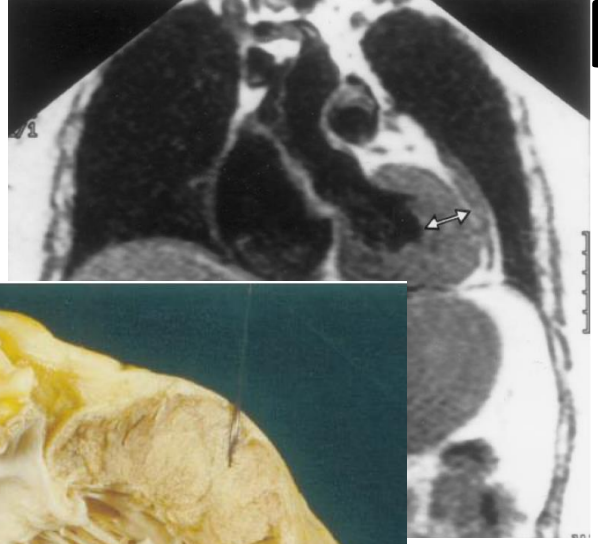
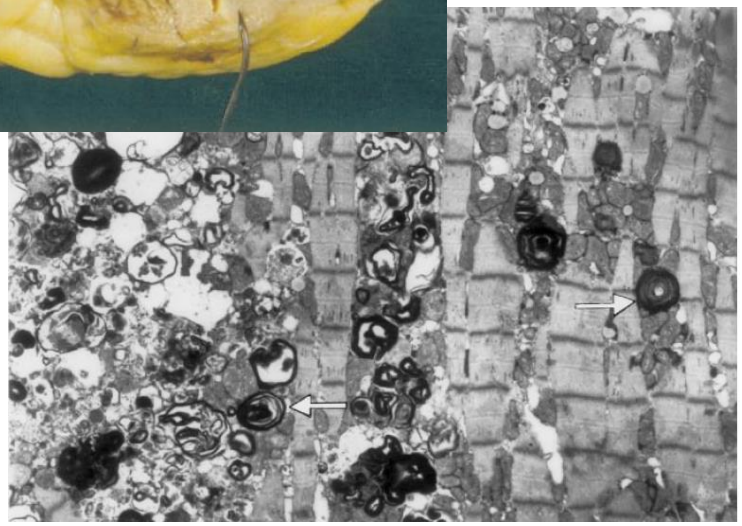
Fabry related Hearth Changes





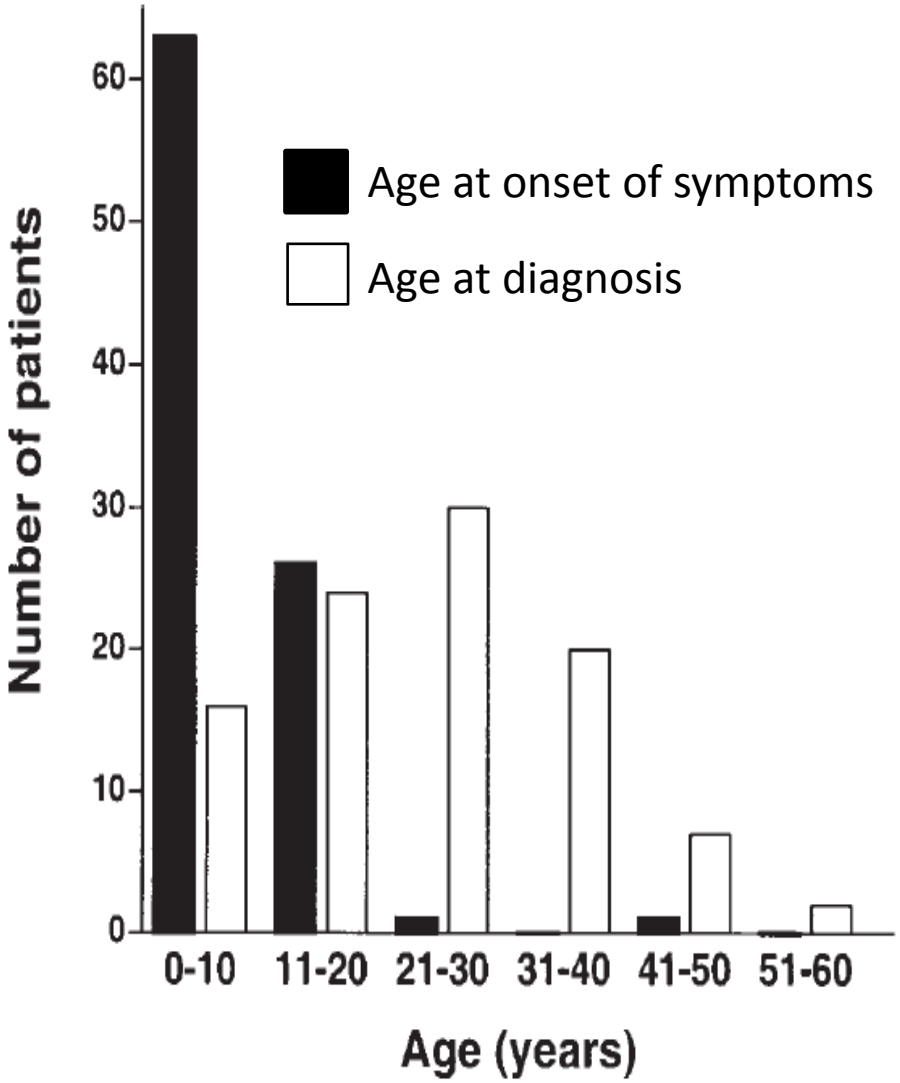
- 53-year-old woman presents progressive dyspnea
- Family history is positive for Fabry's disease
- MRI shows marked thickening of the left ventricle
- The patient is severely symptomatic despite medical therapy and is referred for cardiac transplantation
- The explanted heart shows a left ventricular concentric hypertrophy
- Electron microscopy show complex concentric lamellar bodies characteristic of Fabry's disease

Circulation 1998;98;1457-1459

Fabry and renal disease

- renal pathology increases in severity with age.
- renal lesions result from Gb3 deposition in the glomerular endothelial, mesangial, interstitial cells and podocytes
- Gb3 deposition occur also in the endothelial and smooth muscle cells of the renal arterioles
- Renal impairment often begins with microalbuminuria and proteinuria in the 2nd to 3rd decade of life
- Development of azotemia usually occur in the third to fifth decades of life

Fabry diagnosis



0025-7974/02/8102-0122/0
MEDICINE® 81: 122-38, 2002

- We investigated the clinical findings that led to the diagnosis of Fabry disease in 105 patients
- 44 patients were diagnosed because of known family history
- In these patients the age of diagnosis was 16 +/- 13 y
- 50 patients lacked a family history of Fabry disease
- For these patients the age of diagnosis was 28 +/- 12 (range, 18 mo - 55 yr, p 0.0001)
- These patients recalled experiencing clinical symptoms for 15 +/- 13 years before diagnosis (range 0–40 yr)

Fabry diagnosis

Panel 2: Gold-standard methods to diagnose Fabry's disease

Men

- α-galactosidase A activity in peripheral leucocytes or plasma if leucocyte analysis is unavailable
- α-galactosidase A gene sequencing and identification of disease-causing mutation or testing for all known familial mutations

Women

- α-galactosidase A gene sequencing and identification of disease-causing mutation or testing for a known familial mutation (α-galactosidase A activity in peripheral leucocytes is not preferred and plasma levels are unreliable)

Prenatal diagnosis

- α-galactosidase A gene sequencing assessing for a known familial mutation

conclusion

- Fabry is a rare LSD but probably underdiagnosed.
- There is only little knowledge about Fabry and anesthesia
- It may be possible to perform peripartal EDA in patients with Fabry disease
- It is important to inform the patient about the possible risks
- It is important to inform patients about the lack of data about this argument
- Don’t barricade yourself into a comfort zone but try to find the best solution and let the patient take part in the careful decision-making process