75° CONGRESSO NAZIONALE

FIMG

Metis

Potenziare la medicina generale per migliorare l'Active Ageing

1-6 ottobre 2018

Complesso Chia Laguna - Domus de Maria (CA)

La Malattia di Fabry

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Disclosures

Member of scientific board for:

- Novartis
- Sanofi/Genzyme
- Celgene
- La Jolla
- CRISPR
- Vifor

Fabry Disease

- Deficit of α-galactosidase enzyme deficiency that causes progressive accumulation of glycosphingolipids (GL-3) in the vascular endothelium and visceral tissues
- Inherited (X-linked) lysosomal storage disorder
- Severe morbidity
  - Renal failure
  - Cardiac complications
  - Stroke
  - Early death

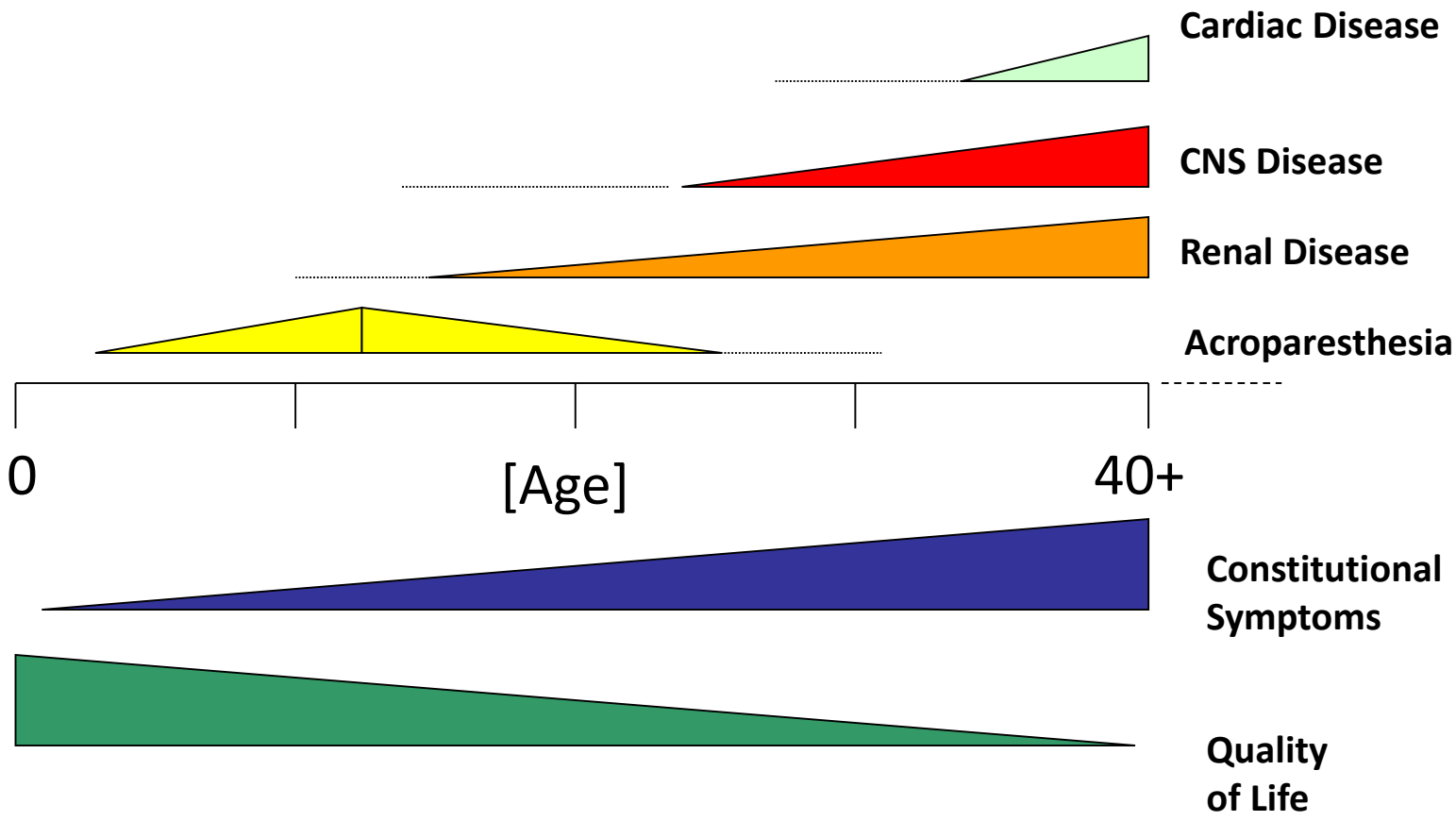
Inheritence

- X-linked
- Symptomatic females
  - carriers can experience symptoms to varying degrees
- Panethnic
- Incidence estimated to be 1:40,000 males (Desnick et al. 2001)

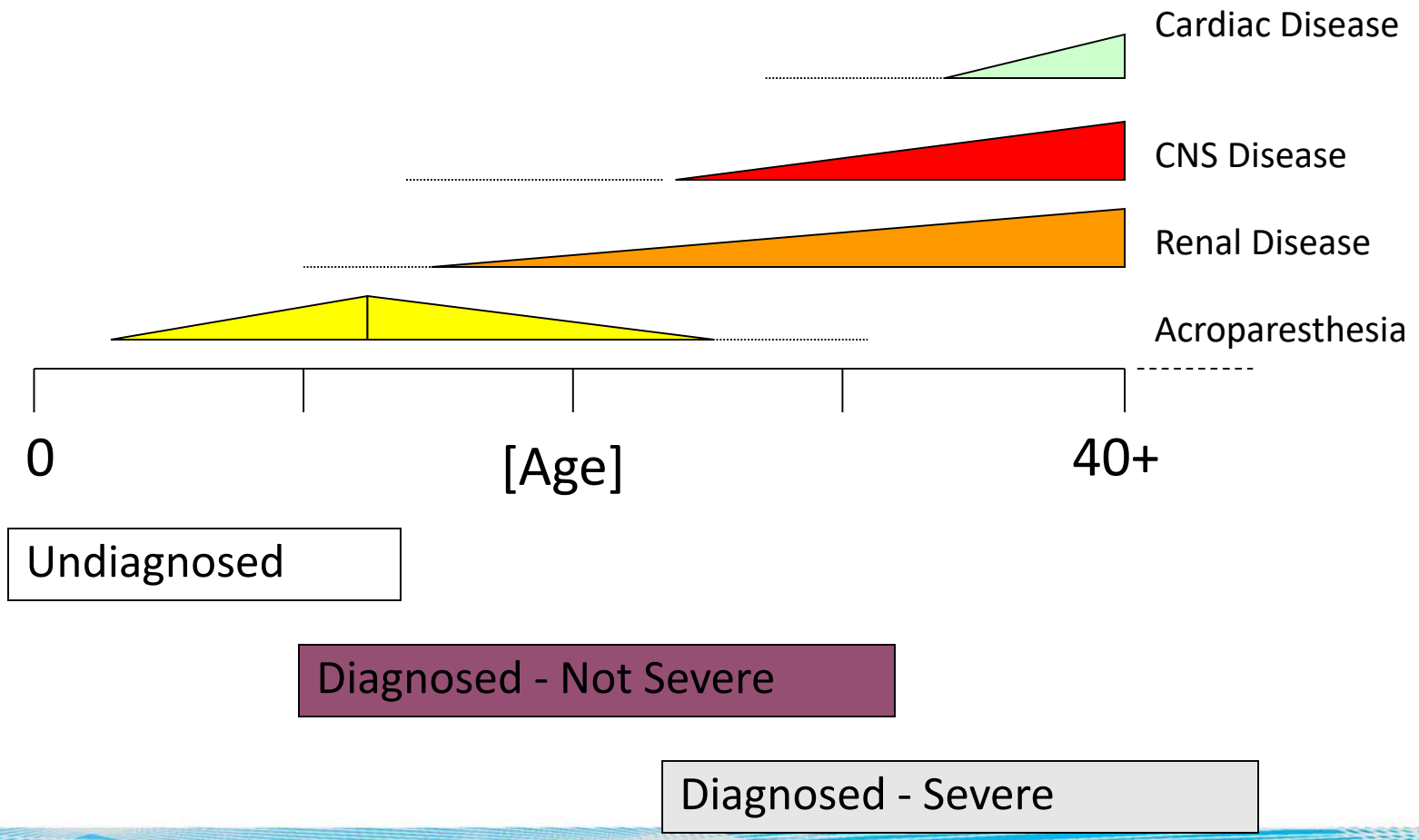
Fabry Disease

- Progressive
- Destructive
  - manifestations in multiple organ systems
- Life-threatening

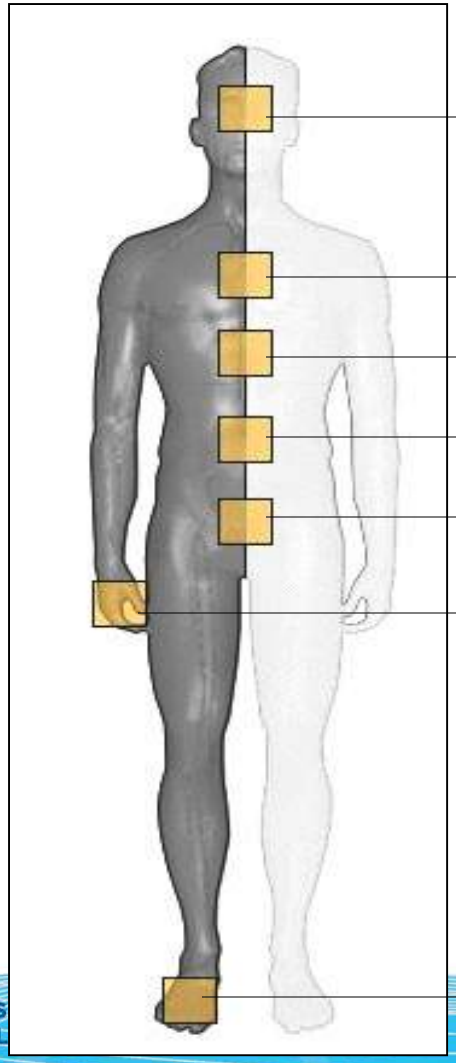
Fabry Disease Progression



Fabry Disease Progression



Signs and Symptoms



Early ischemic stroke

Left ventricular hypertrophy

Hypohidrosis

Progressive renal insufficiency

Angiokeratomas

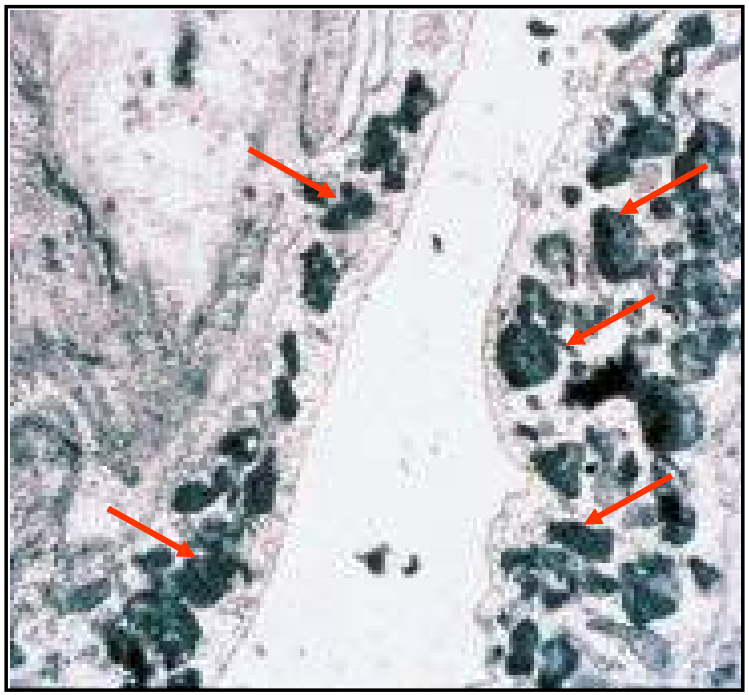
Acroparesthesia

Acroparesthesia

Pain in Fabry Disease

- Acroparesthesia
  - constant
  - affects hands and feet
  - described as burning, tingling, pain and discomfort
  - unresponsive to narcotic analgesics
  - triggered by fever, exercise, fatigue, stress, weather changes
- Caused by small-fiber neuropathy
  (Brady RO, Schiffman R., 2000)

Vascular Endothelium



From R.J. Desnick, PhD, MD

- Vascular endothelium in Fabry disease
  - Note electron-dense lysosomes containing undegraded glycosphingolipid

Pain in Fabry Disease

- "Fabry Crises"
  - episodic
  - radiates inward from hands and feet
  - described as intense, excruciating, debilitating pain
  - can last from minutes to weeks

- Caused by GL-3 deposits in the endothelial cells of the microvasculature and in cells surrounding peripheral nervous system

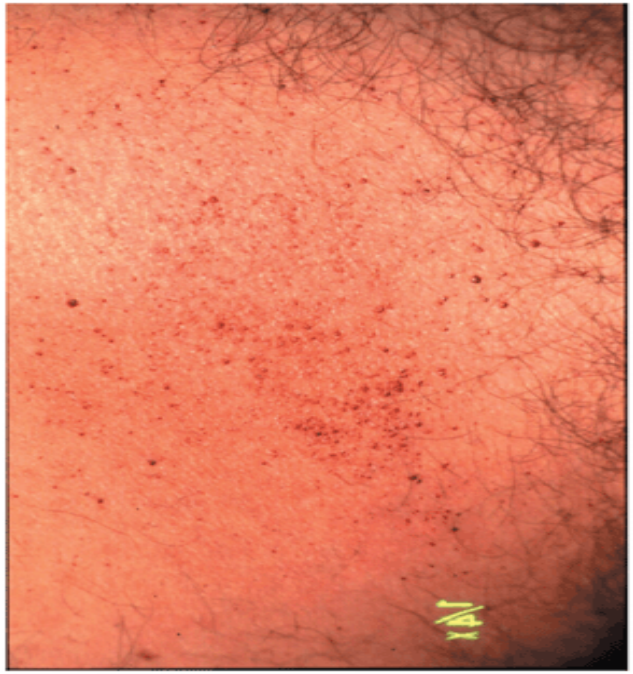
Dermatologic Manifestations

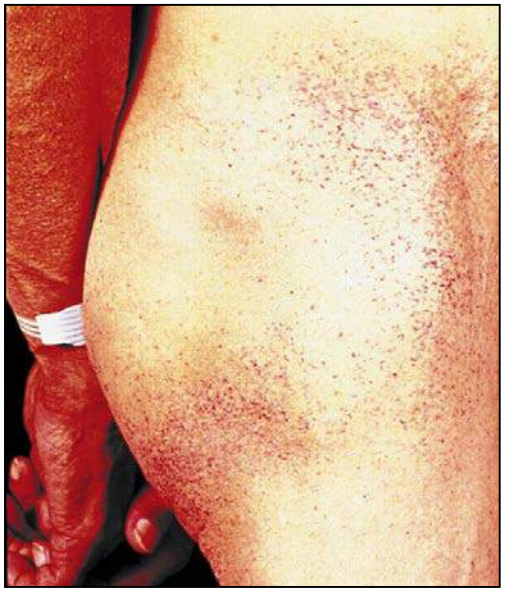
- Hypohidrosis or anhidrosis
- Heat and cold intolerance
- Angiokeratomas
  - reddish, purplish skin lesions
  - non-blanching
  - range in size from pinpoint to several millimeters
  - found in area from umbilicus to thigh
- Caused by endothelial cells filled with GL-3

(Meroni et al., 1997)

Angiokeratomas

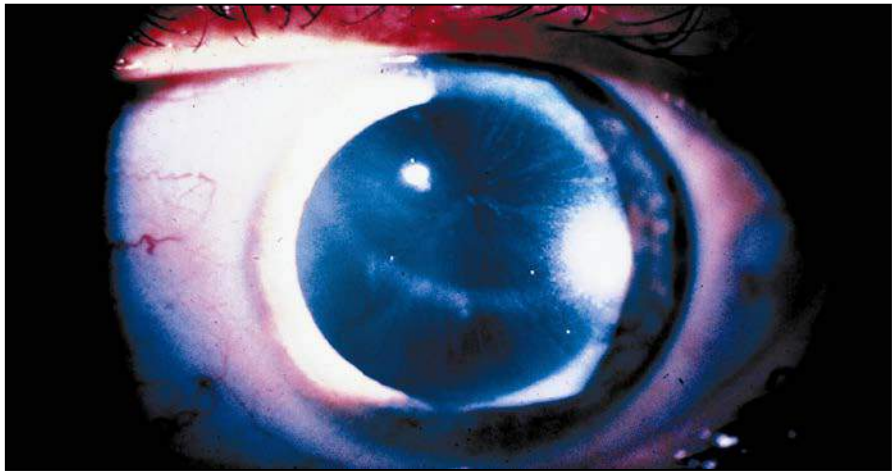
Characteristic dark-red to blue-dark angiectases, typically found between the umbilicus and thigh. The lesions range in size from pinpoint to several millimeters.





Breunig et al. KI 2003; 63 (suppl 84): S181-5

Corneal Opacity



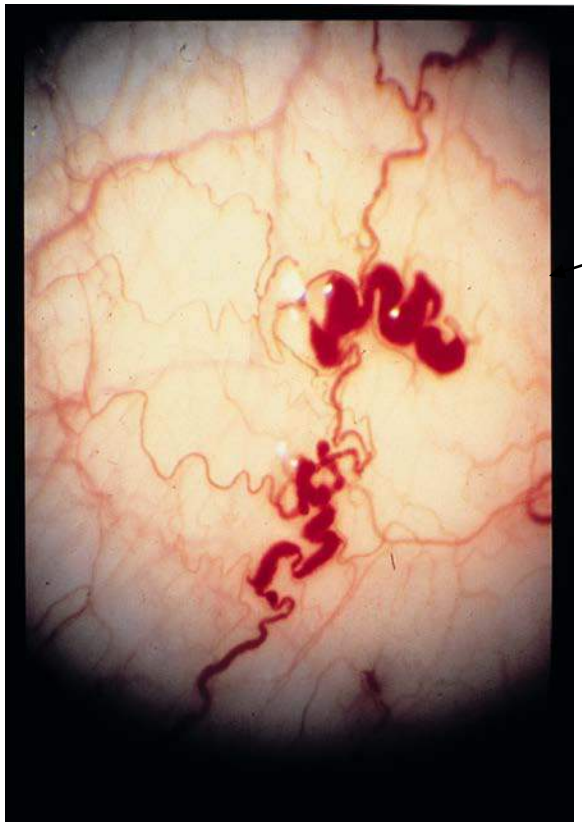
“cornea verticillata”

“whorled” or “spoke-like” pattern on cornea
does not affect vision
present in both males and females
caused by GL-3 deposits in corneal epithelium
(Desnick et al., 1995)

Note “spoke-like” pattern on cornea, visible through slit-lamp ophthalmoscopy

With permission, from R.J. Desnick, PhD, MD

Conjunctival Involvement



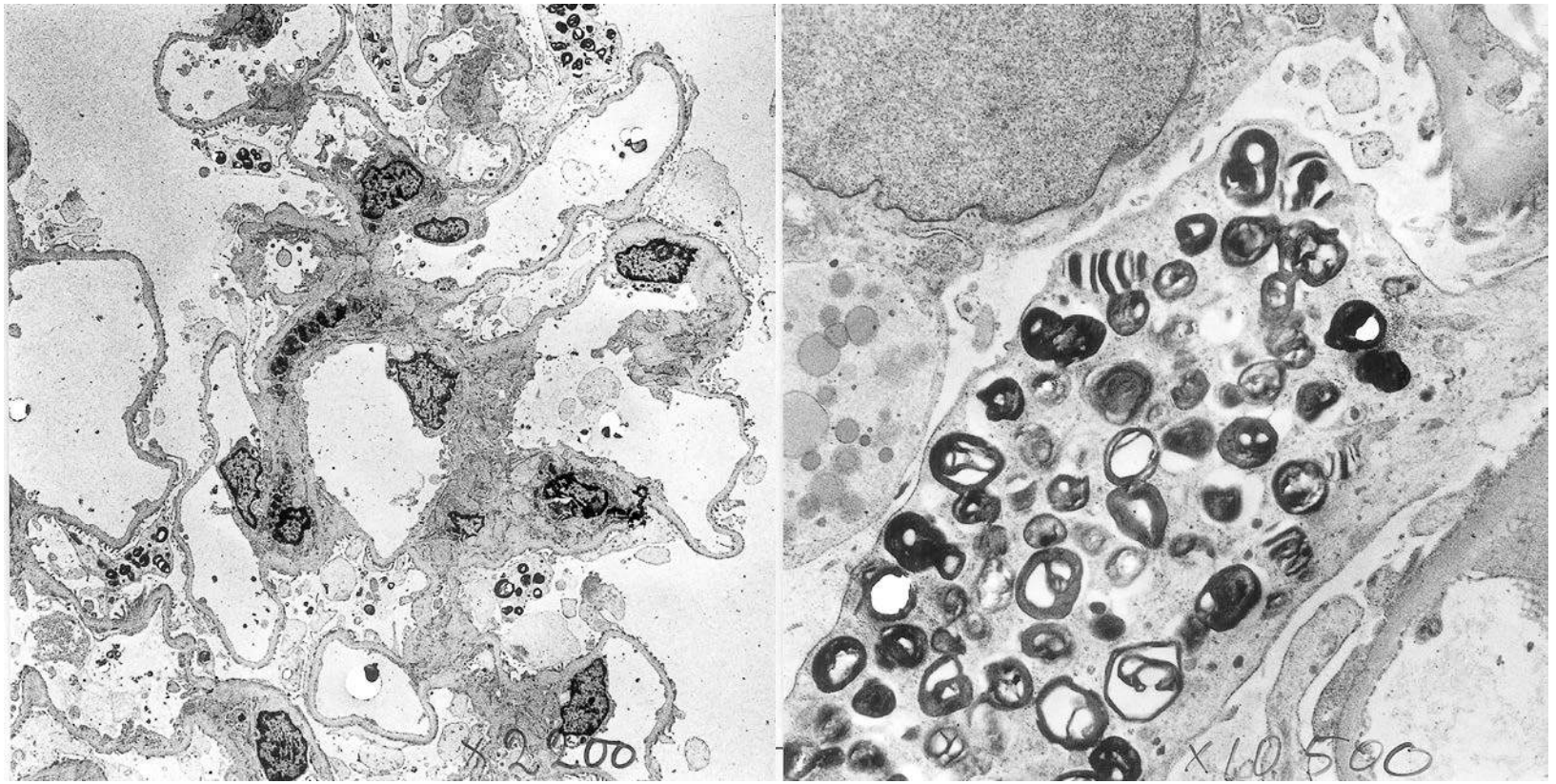
- Note the sausage-like and markedly dilated vessels.

From R.J. Desnick, PhD, MD

Renal Manifestations

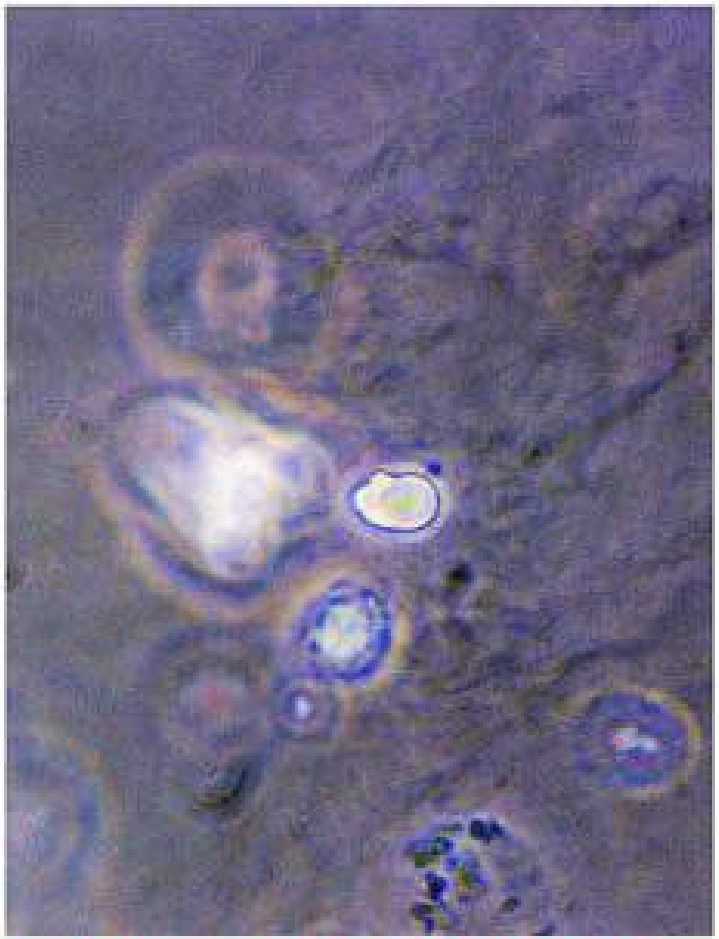
- Progressive renal insufficiency
  - proteinuria, isosthenuria, azotemia
  - elevated serum creatinine levels
- End-stage renal disease
- Most frequent cause of death among males

Kidney podocytes with vacuolization and multilamellar myelin bodies



Courtesy of Dr Jarl Ahlmén, Skövde

Renal Manifestations
Urinary sediment – Phase contrast



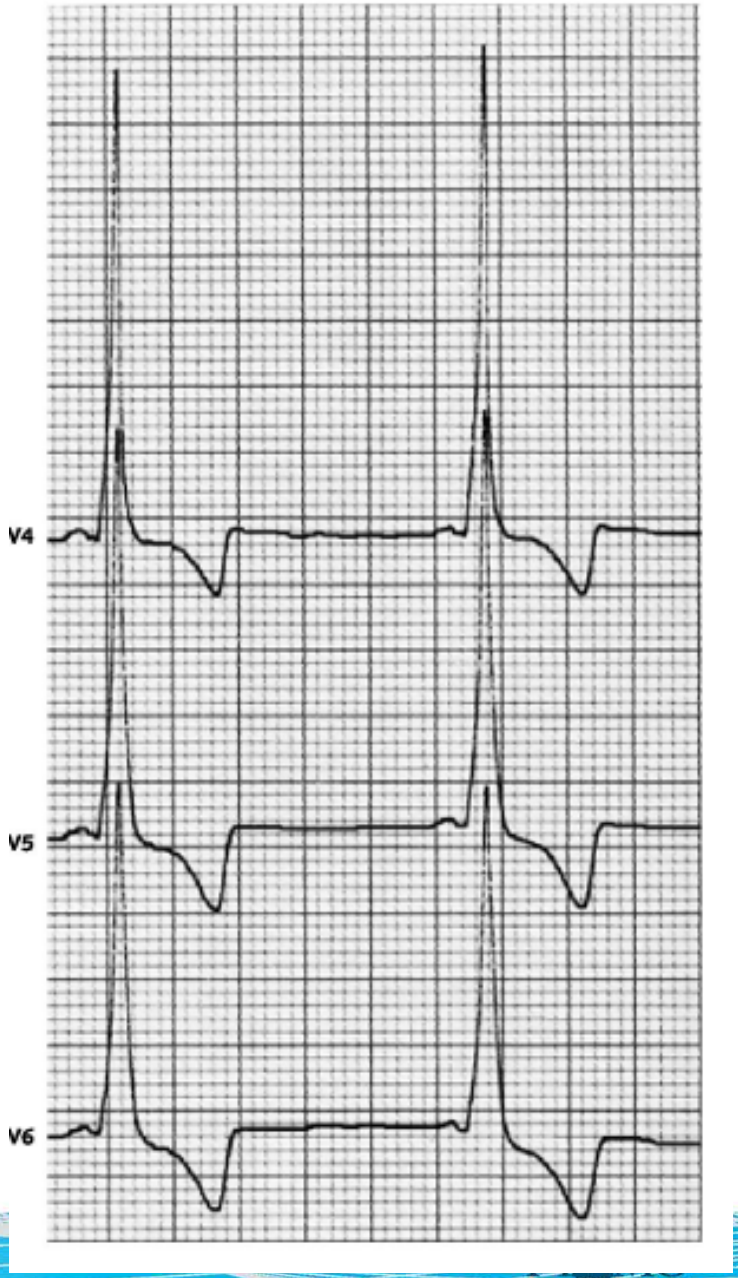
Birch DF et al. A color Atlas of Urine Microscopy, 1994

Cardiac Manifestations

- Left ventricular hypertrophy
- Coronary artery disease
  - myocardial infarction
- Valvular disease
  - mitral insufficiency
- Conduction abnormalities
- Arrhythmias
- Congestive heart failure

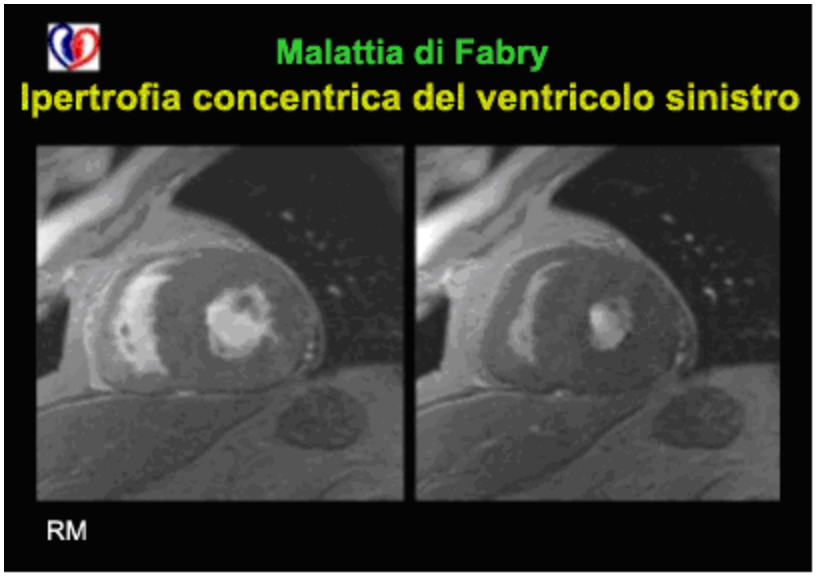
ECG abnormalities in Fabry Disease

Electrocardiogram of a 41-year-old man with classic Fabry disease showing sinus bradycardia with short PR interval (88 msec) and left ventricular hypertrophy with QRS widening and a repolarization abnormality.



Desnick et al - Ann Int Med 2003

Manifestazioni Cardiache



La cardiomiopatia ipertrofica determina spesso l'ostruzione della via di efflusso, ed è correlata all'ipertrofia settale che si estende al muscolo papillare del foglietto mitralico anteriore[20]

Cerebrovascular/ Neurologic Manifestations

- early stroke
- hemiparesis
- diplopia
- dysarthria
- nystagmus
- nausea/vomiting
- vertigo/dizziness
- head pain
- hemiataxia
- ataxia of gait

Who can diagnose Fabry disease at an early stage?

With the advent of enzyme replacement therapy, it is important that **general practitioners, pediatricians, and physicians in a range of specialties** recognize the signs and symptoms of Fabry disease so that effective treatment can be given.

Mehta et al. *Eur J Clin Invest.* 2004; 34: 236-42

CONCLUSION

- Fabry disease is a very rare but deadly X-linked genetic disease, primarily affecting males but also females
- Now that a treatment has been developed, it is of great importance to unveil the presence of disease in families: diagnosing a patient provides benefit to several people
- Initiating treatment in advanced stages can slow progression of the disease, but rarely reverses pre-existing damages, in particular in the kidneys. Early diagnosis is key to a successful management

Grazie per l'attenzione