What is a rare disease?

- A disease or disorder is defined as rare in Europe when it affects less than 1 in 2000 citizens (Orphan Drug Regulation 141/2000)
- Rare diseases may affect 30 million European Union citizens.

Characteristics of rare diseases

- Rare diseases are often chronic, progressive, degenerative, and often life-threatening
- Rare diseases are disabling: the quality of life of patients is often compromised by the lack or loss of autonomy
- High level of pain and suffering for the patient and his/ her family

Characteristics of rare diseases

- There are between 6000 and 8000 rare diseases
  - 75% of rare disease affect children
  - 30% of rare disease patients died before the age of 5
  - 80% of rare diseases have identified genetic origins

- Other rare diseases are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative.

Rare disease patients face common problems

- Lack of access to correct diagnosis
- Delay in diagnosis
- Lack of quality information on the disease
- Lack of scientific knowledge of the disease
- Heavy social consequences for patient
- Lack of appropriate quality healthcare
- Inequities and difficulties in access to treatment and care

Rare Diseases

- Do I have as Internist the chance to deal with rare diseases?

YES

3rd ESIM Winter School
Saas-Fee 20 – 26 January 2013

Fabry disease: a challenge for Internists

M.Domenica Cappellini
President EFIM
University of Milan

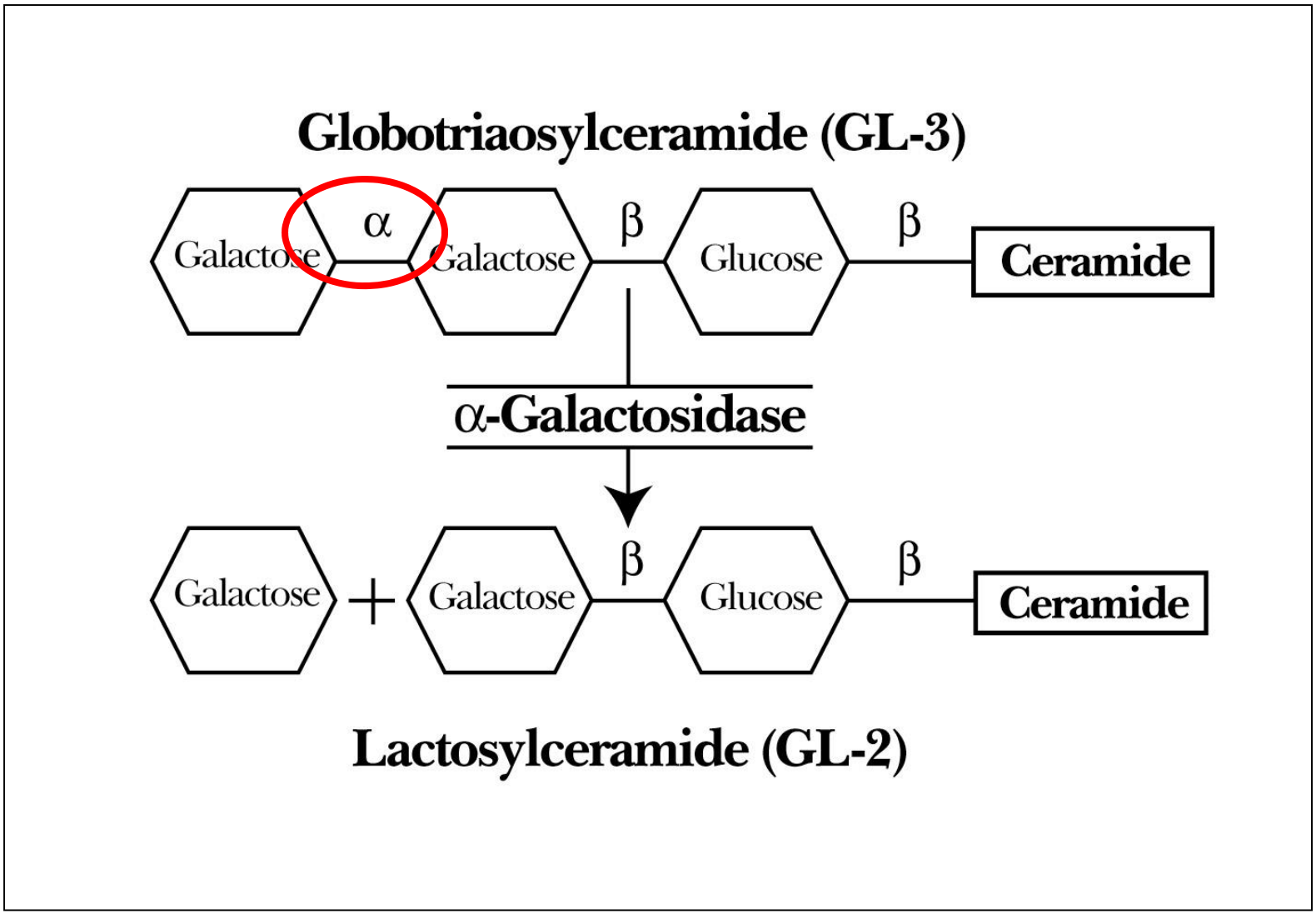
Agenda

- Disease background
- Inheritance
- Signs and symptoms
- Clinical presentation to specialists
- Diagnosis

Fabry Disease Background

- Under-recognized, genetic (X-linked) lysosomal storage disorder
- Progressive, often life-threatening
- Characterized by deficiency of the lysosomal enzyme alpha-galactosidase A (a-GAL)
- Enzyme deficiency leads to progressive cellular accumulation of glycosphingolipids (fatty substances), particularly globotriaosylceramide (GL-3), in many body tissues
- Progressive, pathologic changes result in end-organ damage in most classic Fabry cases

Metabolic Defect



α-Galactosidase Deficiency

- Defect in the gene that encodes for lysosomal enzyme α-galactosidase (α-GAL)
  - locus Xq22.1 (over 160 different mutations have been described)
- Inability to catabolize certain glycosphingolipids, primarily globotriaosylceramide (GL-3)

Fabry Disease: Inheritance

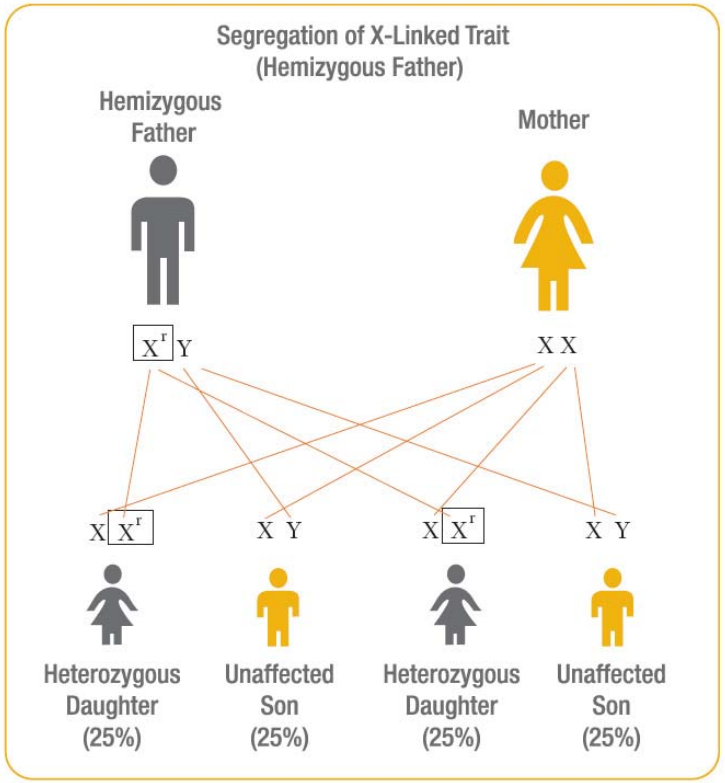
- X-linked disease but females can exhibit signs and symptoms to varying degrees
  - Due to random X-chromosomal inactivation (Lyonization)
- Disease manifestations in females more common than previously supposed[1,2]

1. Fellgiebel A, Muller MJ, Mazanek M, et al. White matter lesion severity in male and female patients with Fabry disease. Neurology 2005;65:600-602
2. Gupta S. Ries M, Kotsopoulos S, Schiffmann R. The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: A cross-sectional study of a large cohort of clinically affected heterozygous women. Medicine 2005;84:261-268.

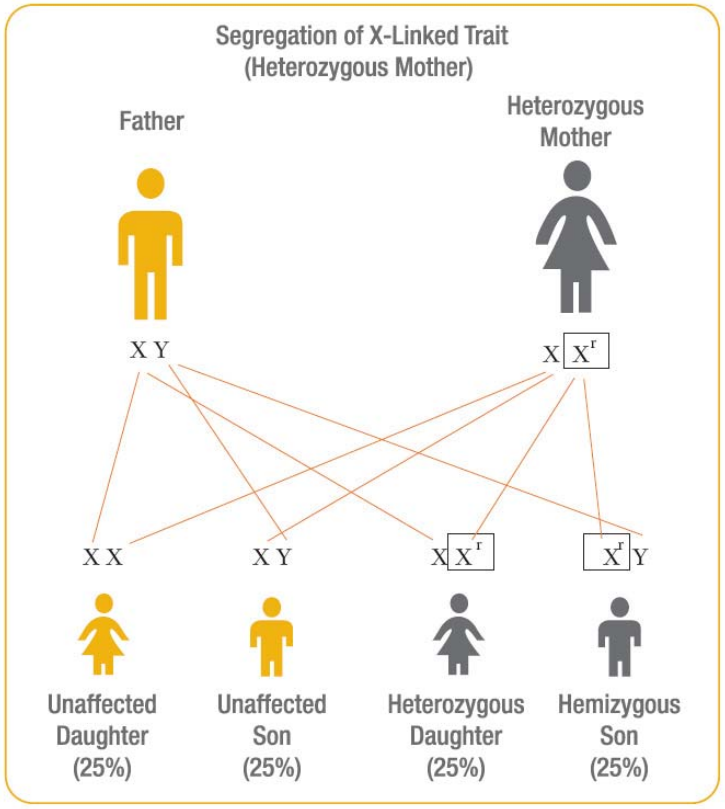
Inheritance

Hemizygous Father

- No male-to-male transmission
- Will pass defective gene to all daughters, but no sons



Inheritance



Heterozygous Mother

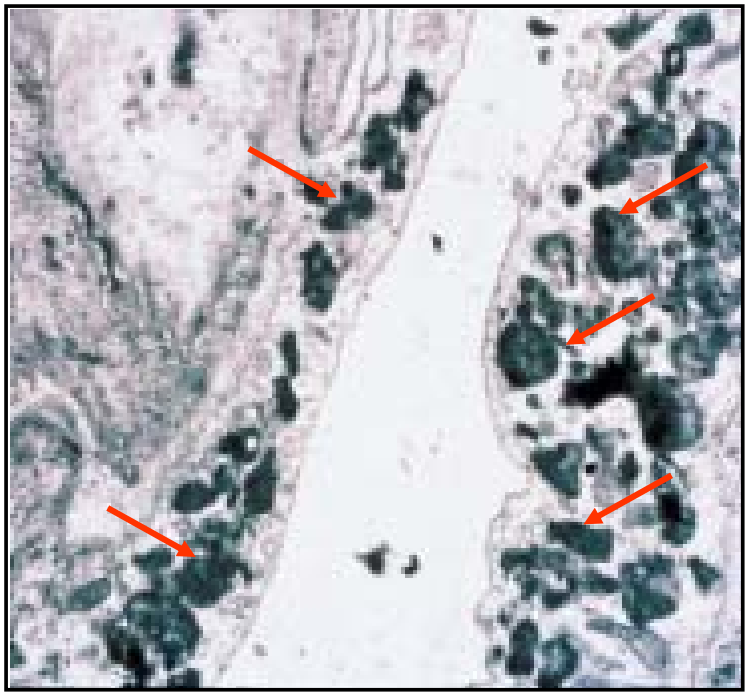
- 50% risk of passing defective gene with each pregnancy regardless of the gender of the child
- Sons who inherit gene will have Fabry disease
- Daughters may develop disease manifestations to varying degrees

Fabry Disease

- Clinical manifestations involve multiple systems:
  - Renal
  - Cardiovascular
  - Neurologic
  - Dermatologic
  - Gastroinestinal
  - Ophthalmologic
- GL-3 accumulates in tissues throughout the body
- GL-3 accumulation in renal endothelial cells may play a role in renal failure
- Average life expectancy in males is 50 years[1]

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 2001;38:750-60.

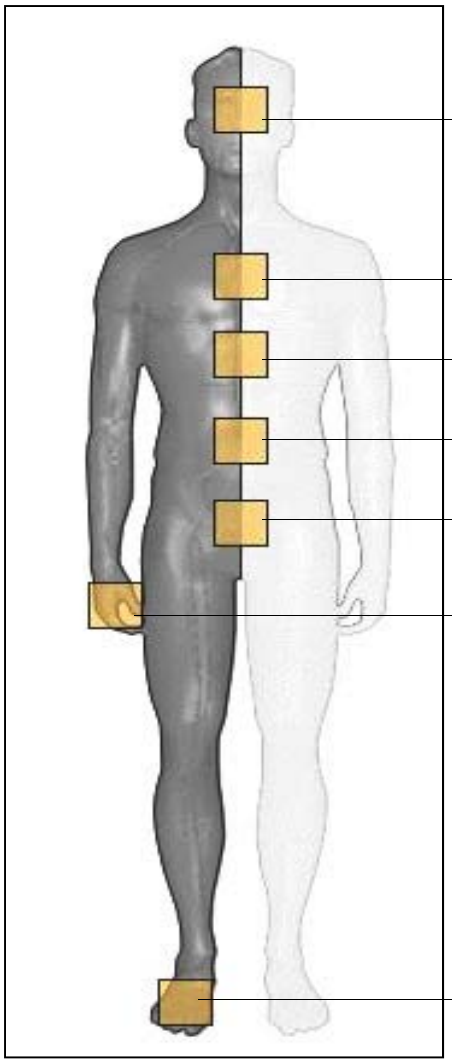
Vascular Endothelium



From R.J. Desnick, PhD, MD

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

Signs and Symptoms



Early ischemic stroke

Left ventricular hypertrophy

Hypohidrosis

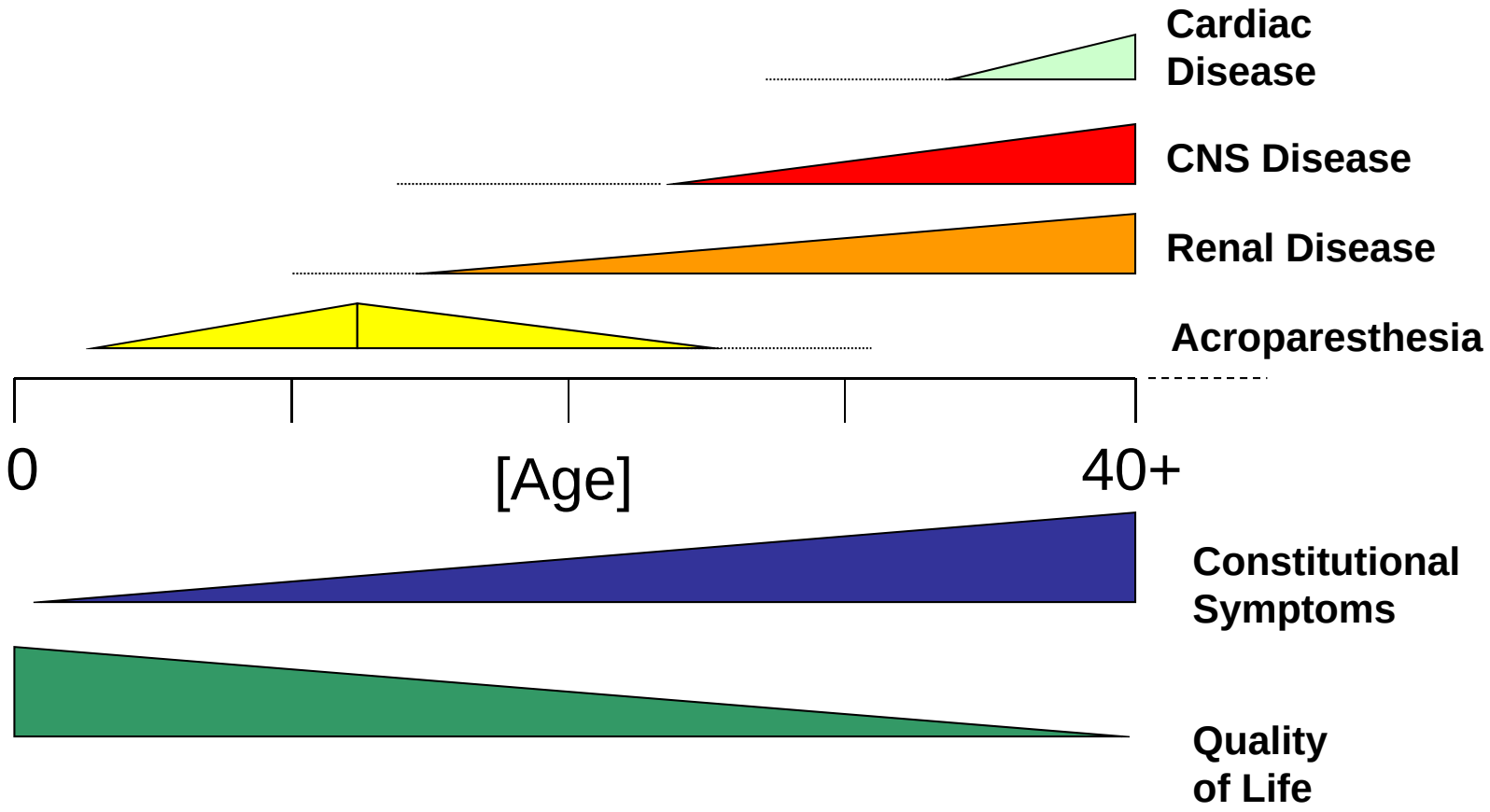
Progressive renal insufficiency

Angiokeratomas

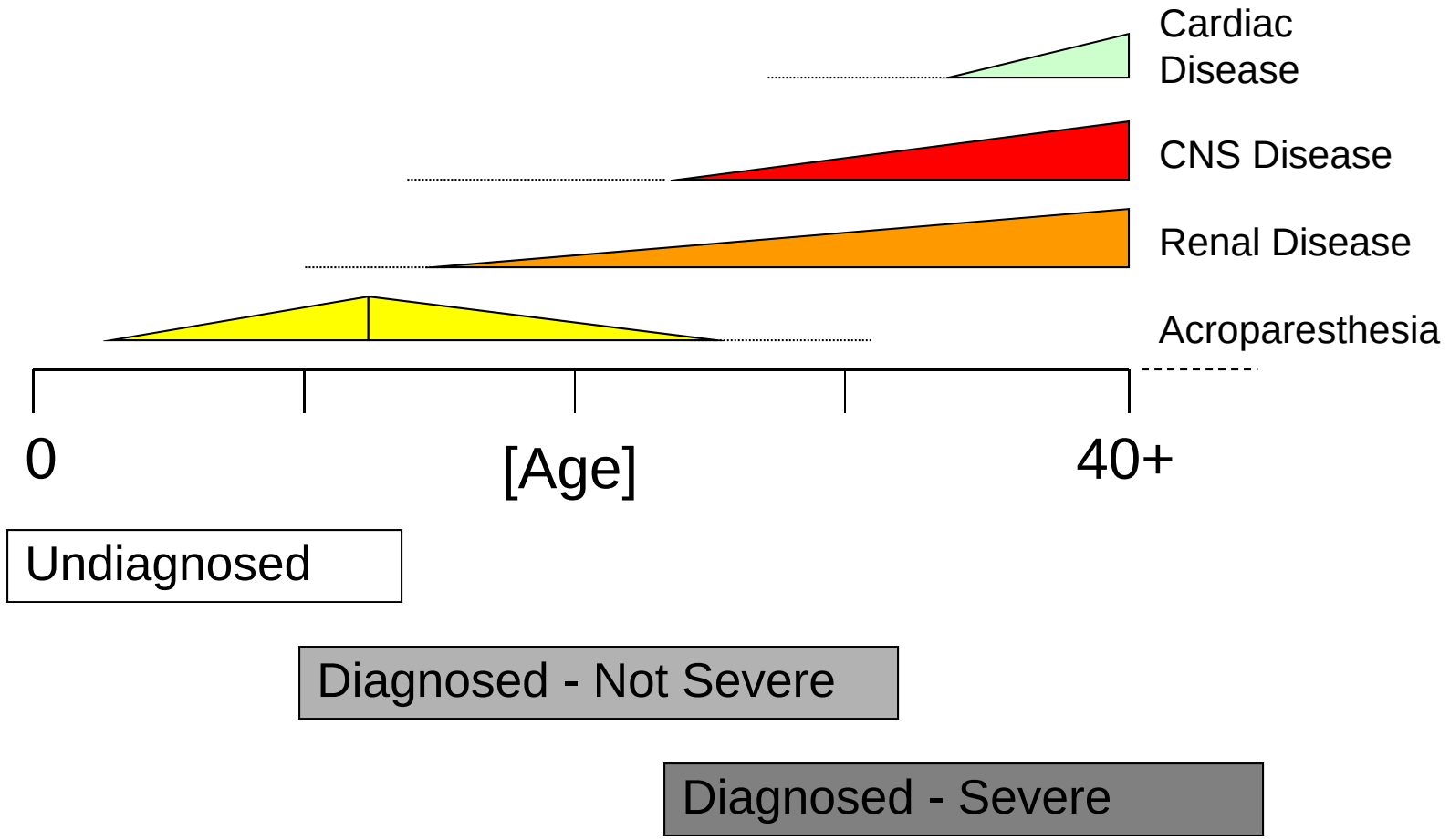
Acroparesthesia

Acroparesthesia

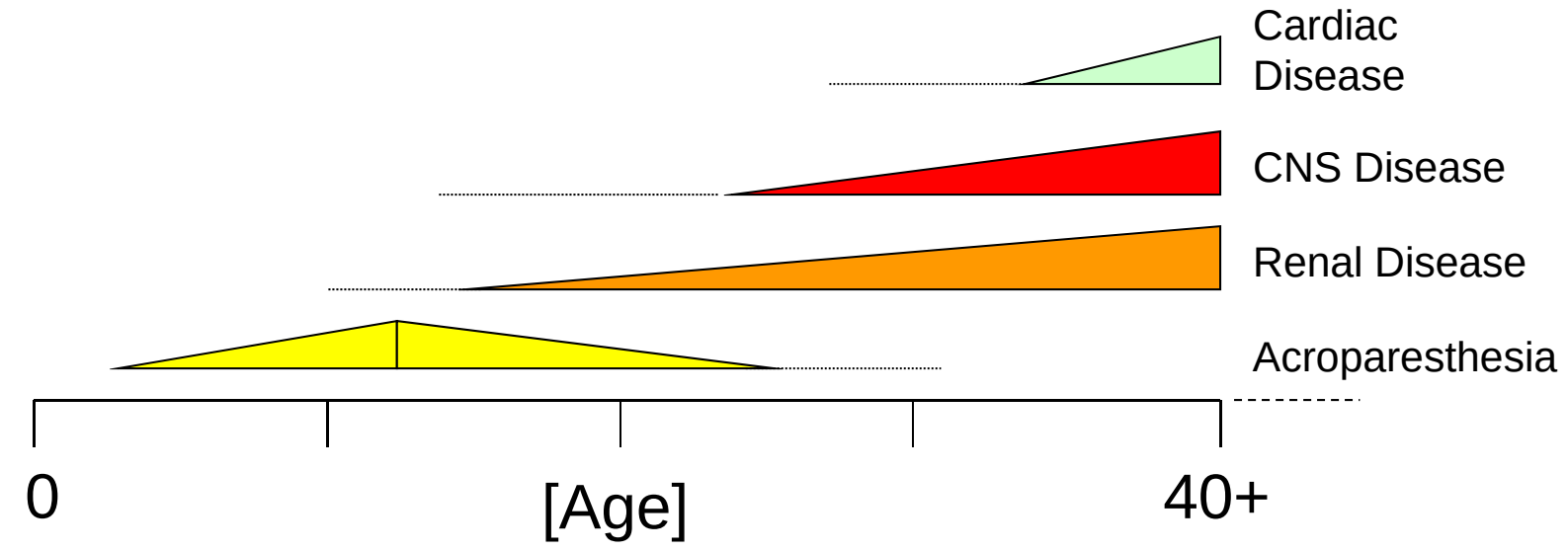
Fabry Disease Progression



Fabry Disease Progression



Fabry Disease Progression



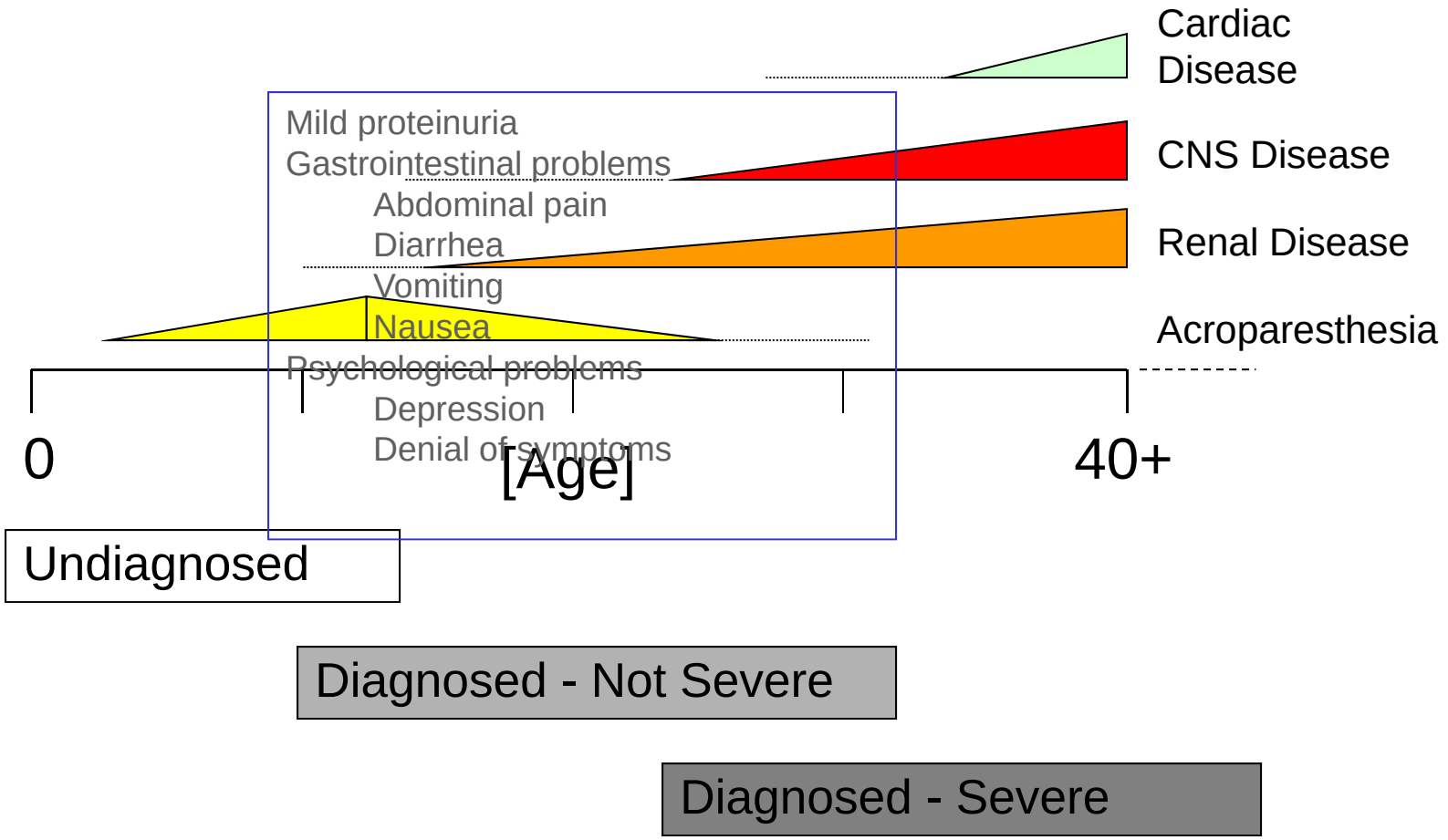
Undiagnosed

Fatigue
Growth retardation, delayed puberty
Impaired fertility
Changes in joints and bones
Chronic bronchitis
Impaired social functioning
Depression
Decreased quality of life

Diagnosed - Not Severe

Diagnosed - Severe

Fabry Disease Progression



Gastrointestinal Manifestations

- Episodic diarrhea
- Post-prandial bloating and pain
- Early satiety
- Nausea and vomiting
- Weight loss
- **Caused by GL-3 accumulation in autonomic ganglia of bowels and in intestinal vessels** (Desnick et al., 1995)

Fabry Disease: Early Manifestations

- Intermittent or constant paresthesia and acroparesthesia
  - Chronic burning, tingling pain
  - Usually in the extremities
- Episodic “Fabry crises” of agonizing, incapacitating pain
  - Can last minutes to days
  - Can disappear or worsen in adulthood
- Recurrent fever
  - Accompanying pain

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

Fabry Disease: Early Manifestations

- Angiokeratomas
- “Bathing trunk” distribution
  - Non-blanching lesions
  - Dark red to blue-black color
  - Appear in adolescence
  - Worsen in adulthood
- Hypohidrosis or anhidrosis
  - Reduced or absence of sweating
- Heat or cold intolerance
- Exercise intolerance

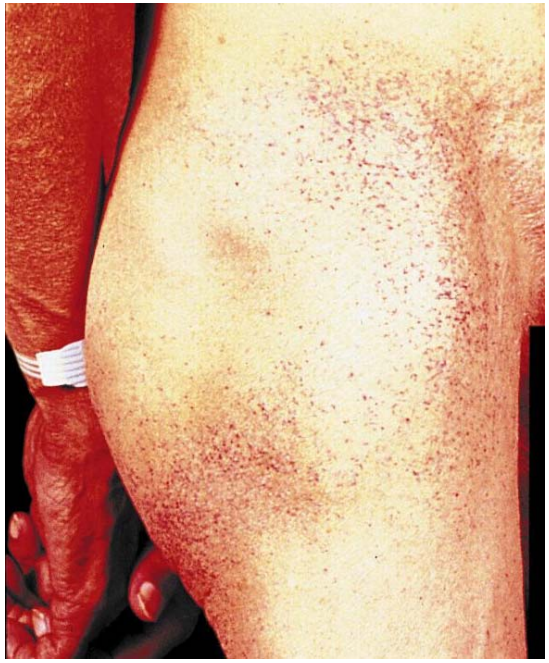
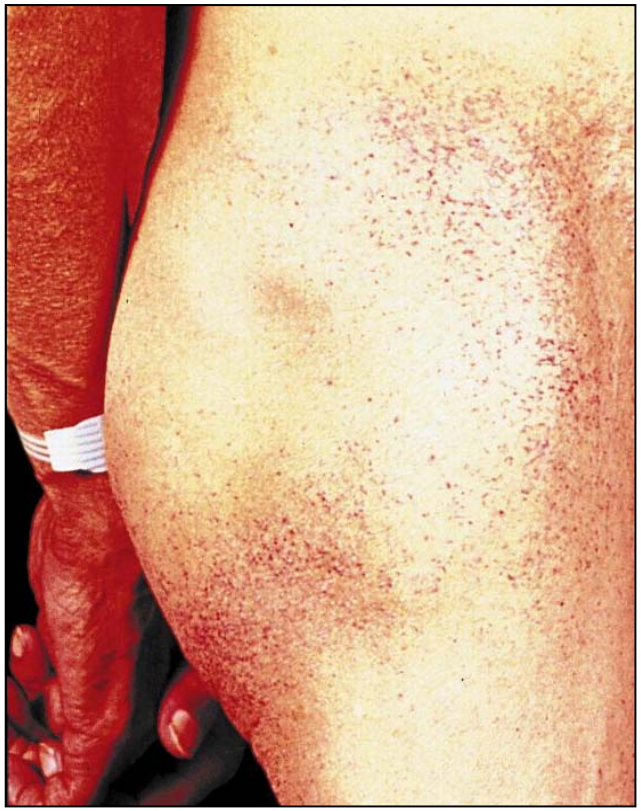
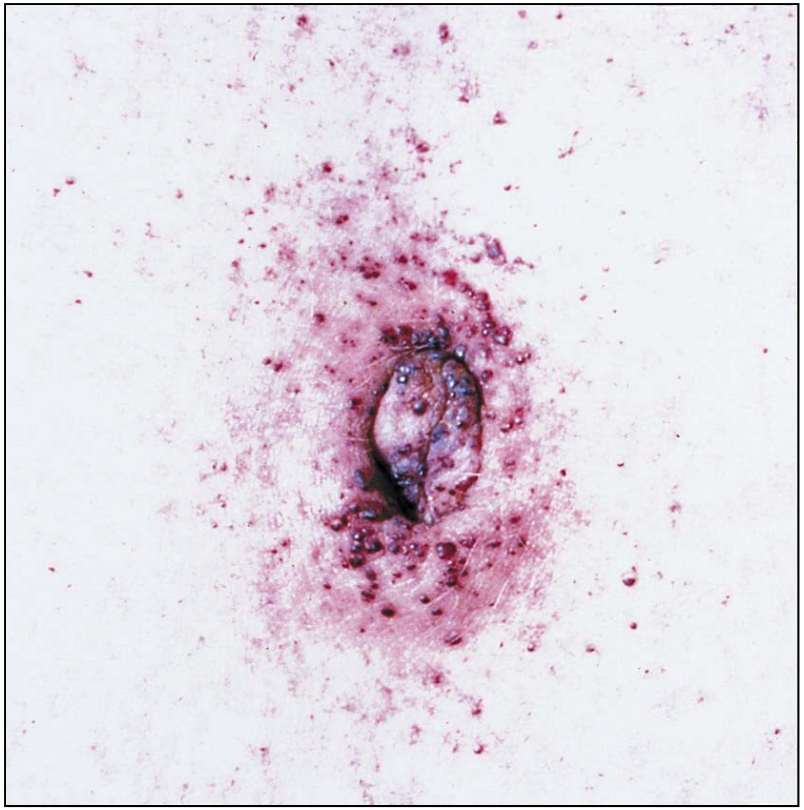


Photo from R.J. Desnick, PhD, MD

Angiokeratomas

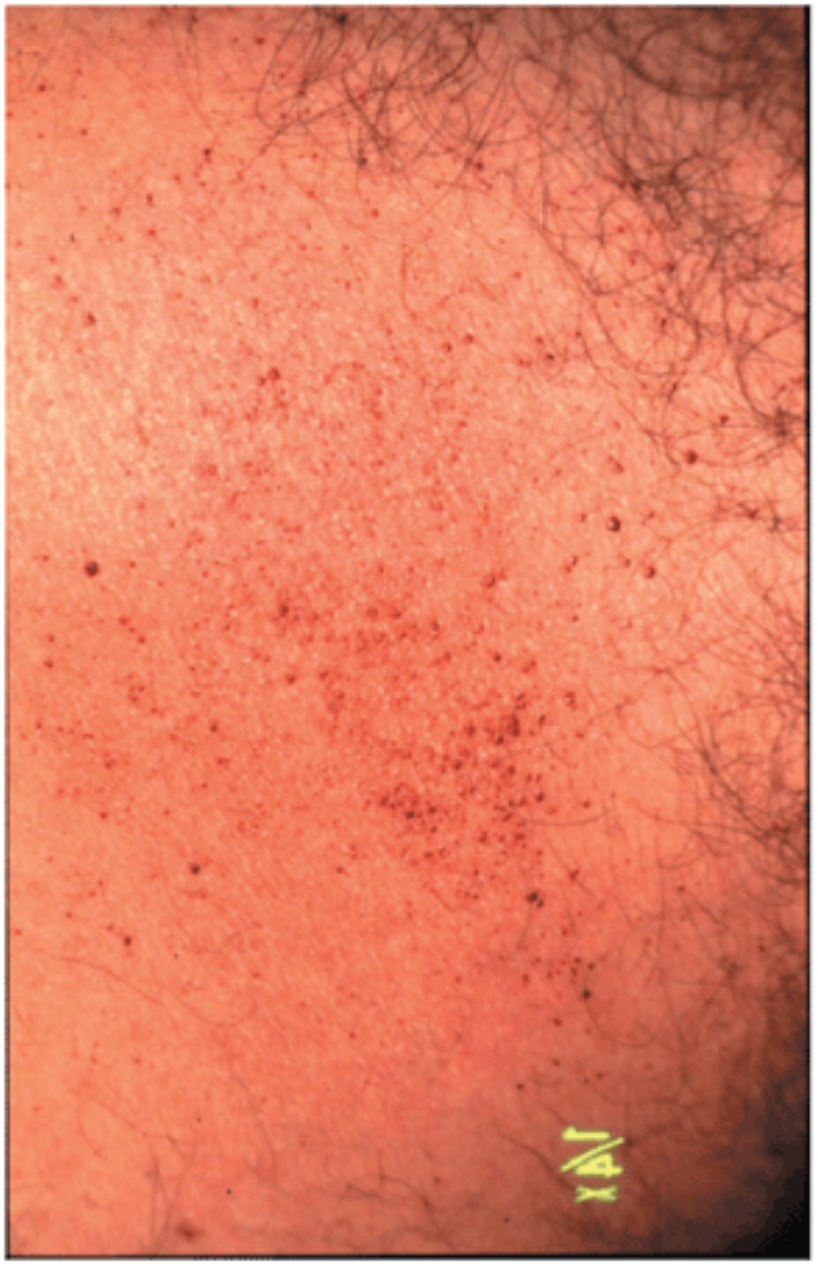




With permission, from R.J. Desnick, PhD, MD

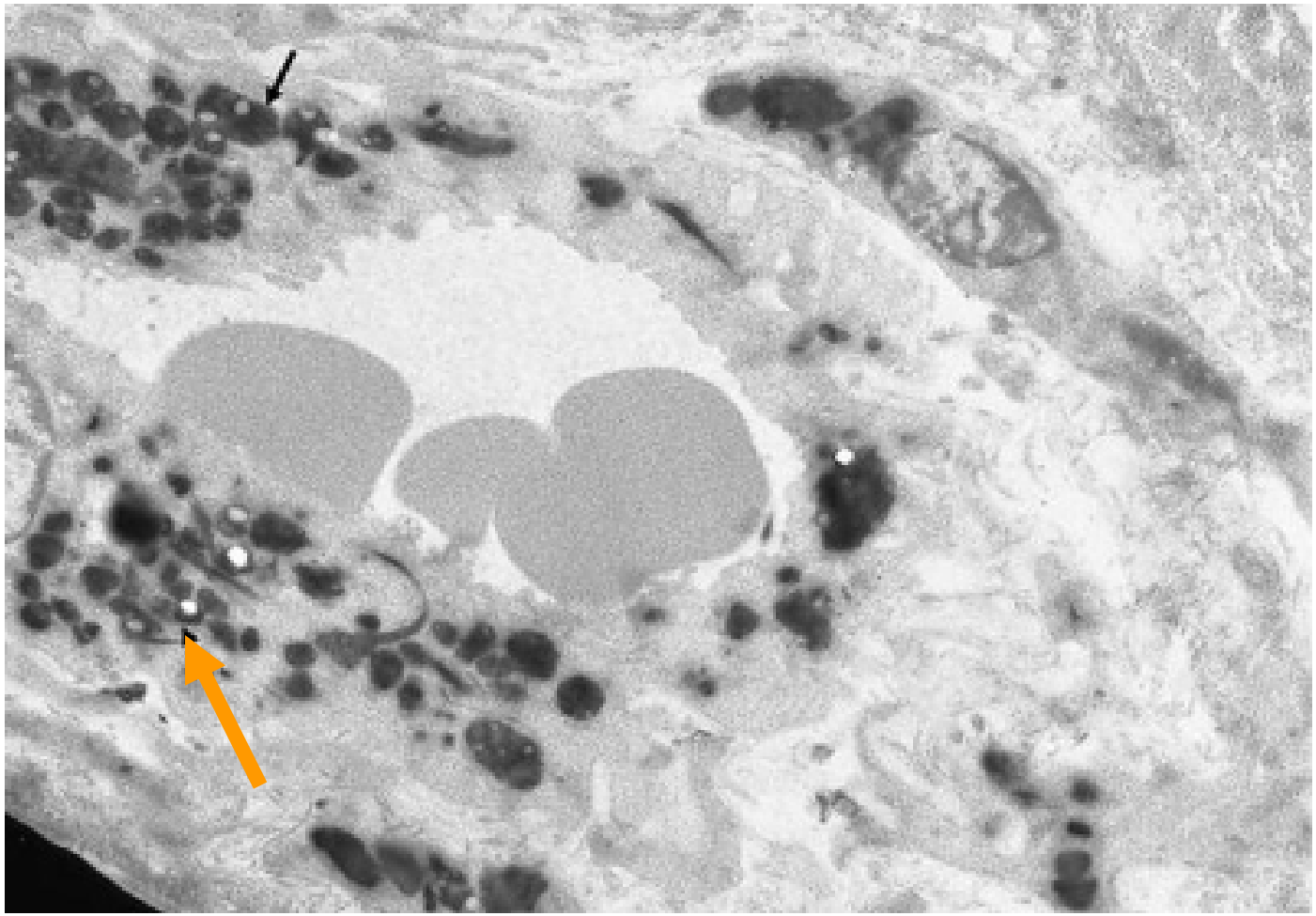
Angiokeratomas

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

Angiokeratomas



EM showing the electron dense lipid depositions in the vascular endothelium (arrows) of a skin capillary from a 29-yo male Fabry patient (x 3000).

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

Fabry Disease: Early Manifestations

Corneal and lenticular opacities

- Whorl-like corneal rays
- Visible by slit-lamp
- Typically does not affect vision
- May be a useful screening tool
- Found almost universally among males, and in approximately 70% of females with Fabry disease[1]

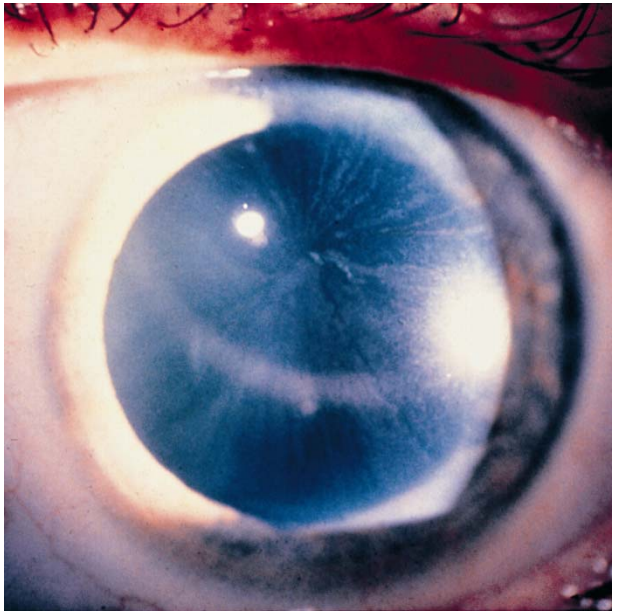


Photo from R.J. Desnick, PhD, MD

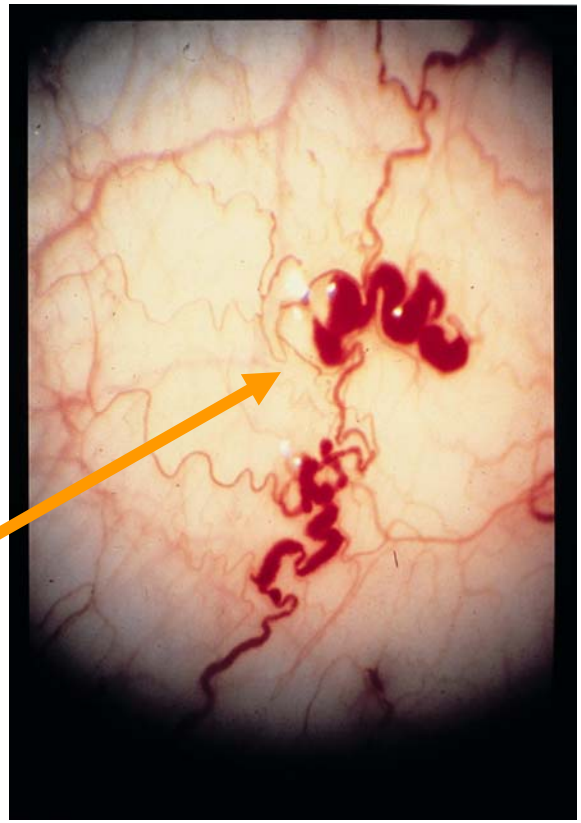
1. Sodi A, Ioannidis AS, Mehta A, et al. Ocular manifestations of Fabry's disease: data from the Fabry outcome survey. Br. J. Ophthalmol. 2007;91:210-214

Ocular Manifestations

- Corneal opacities ("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)

Ocular Manifestations

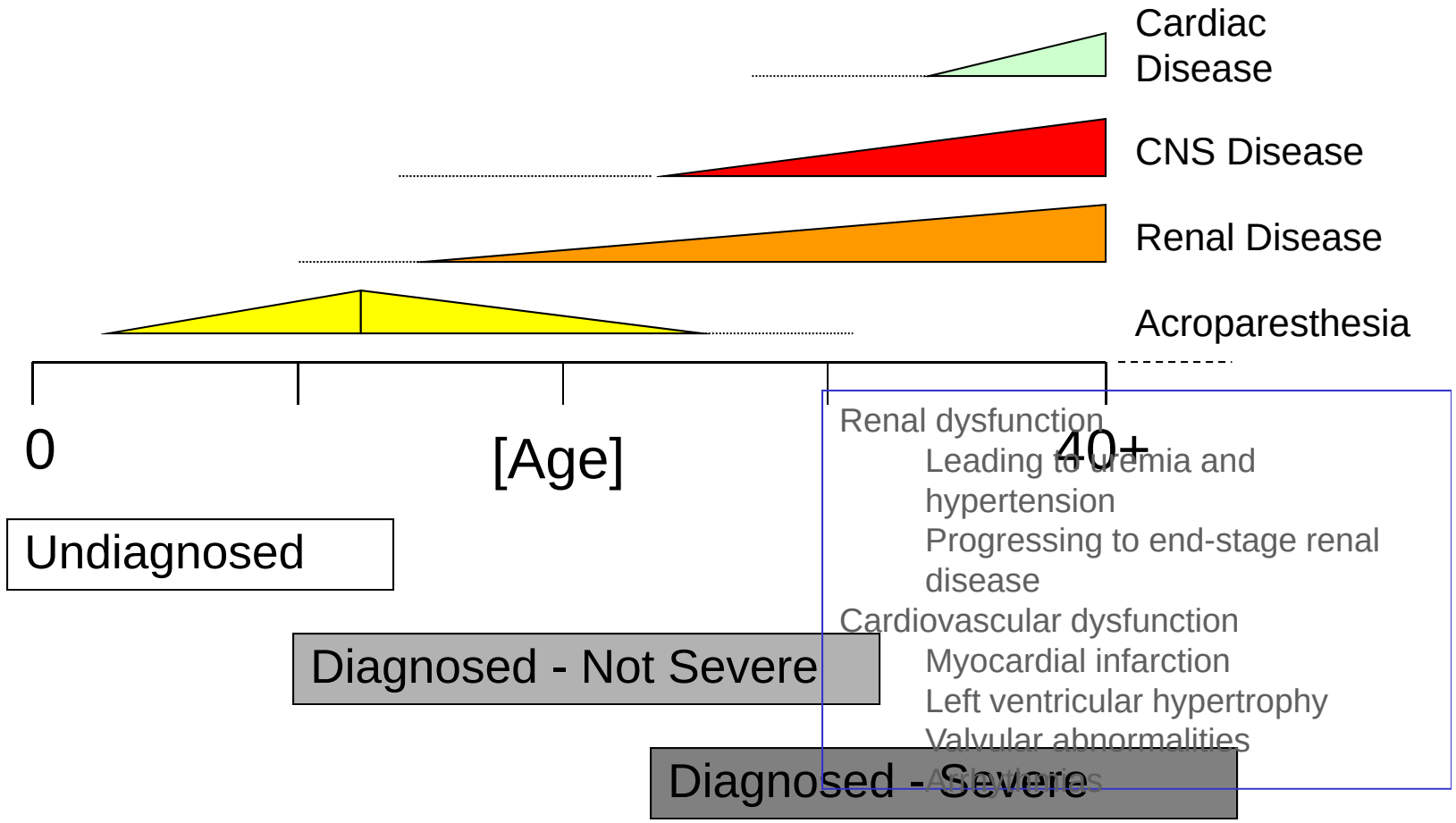
- Conjunctival and retinal vascular lesions:
  - common as a result of generalized disease process
  - do not affect vision



Note the sausage-like and markedly dilated vessels.

From R.J. Desnick, PhD, MD

Fabry Disease Progression



Fabry Disease: Later Manifestations

- Renal dysfunction
  - Leading to uremia and hypertension
  - Progressing to end-stage renal disease
- Cardiovascular dysfunction
  - Myocardial infarction
  - Left ventricular hypertrophy
  - Valvular abnormalities
  - Arrhythmias

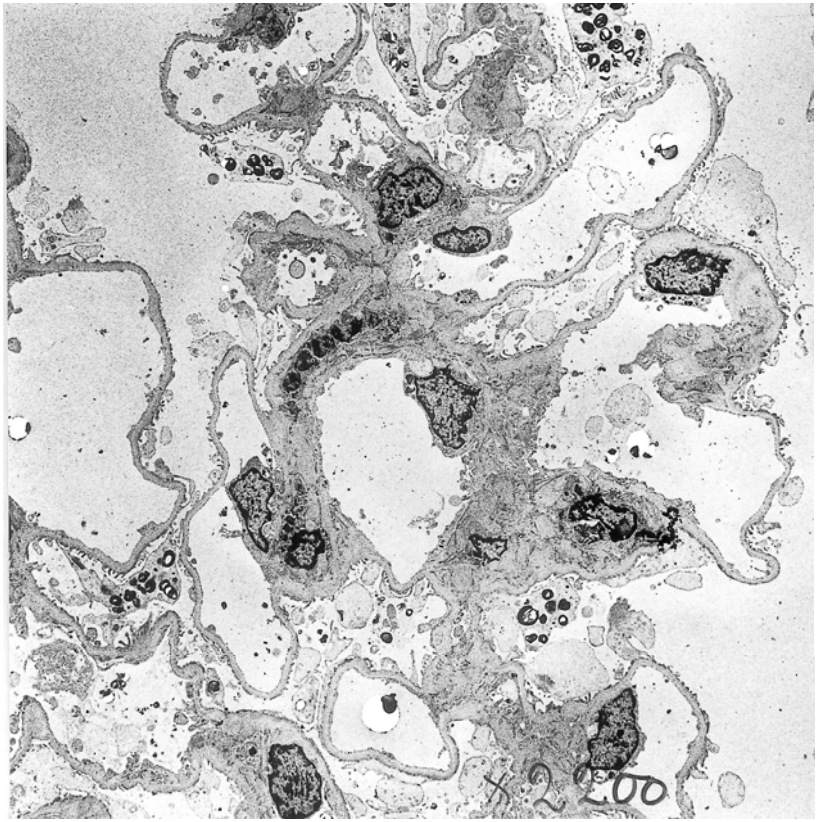
Fabry Disease: Later Manifestations

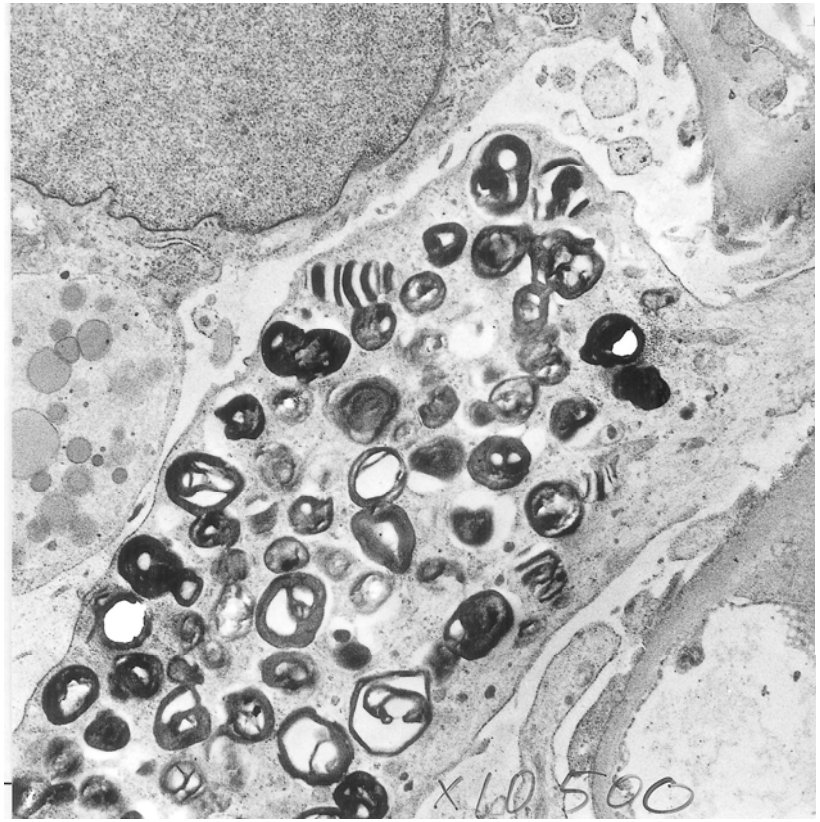
- Cerebrovascular complications
  - Risk of early stroke
  - Hemiplegia
  - Hemianesthesia
  - Transient ischemic attacks
- Neurological complications
  - Vertigo
  - Tinnitus
  - Hearing loss
  - Nystagmus
  - Diplopia

Renal Manifestations

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

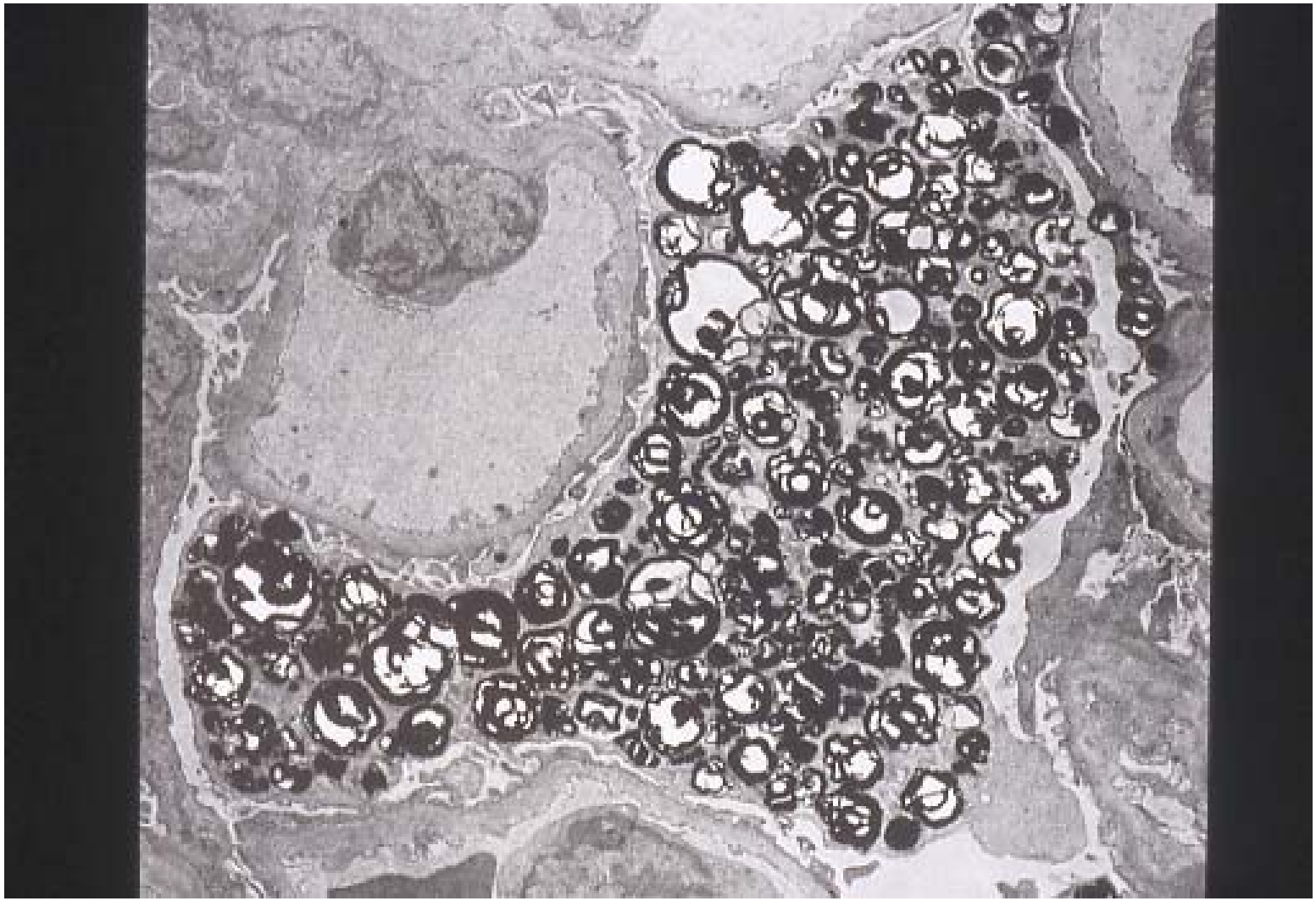
Kidney podocytes with vacuolization and multilamellar myelin bodies





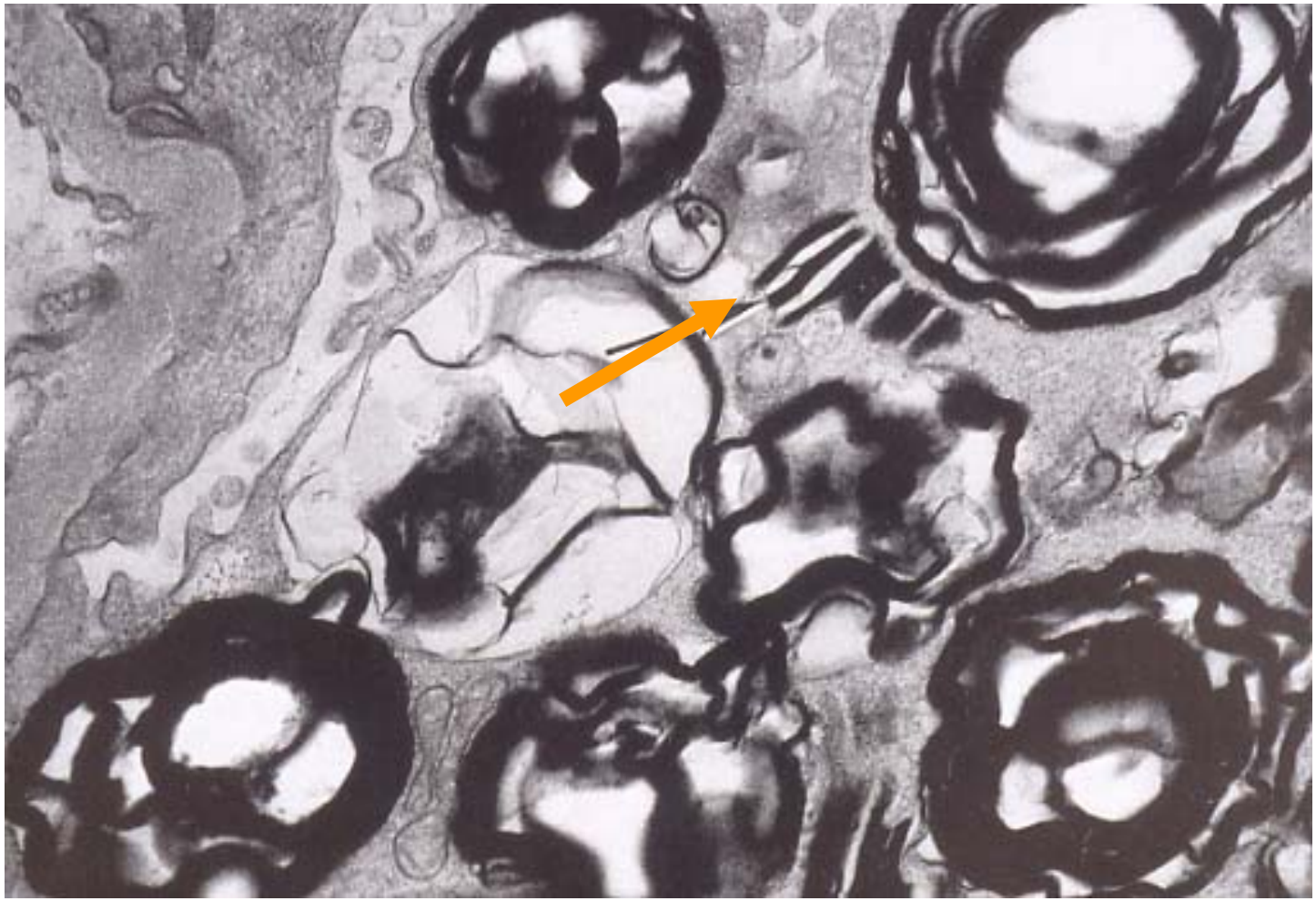
Courtesy of Dr Jarl Ahlmén, Skövde

Renal Manifestations



Electron microscopy. Renal biopsy. Lysosomal inclusons. 5000x

Renal Manifestations

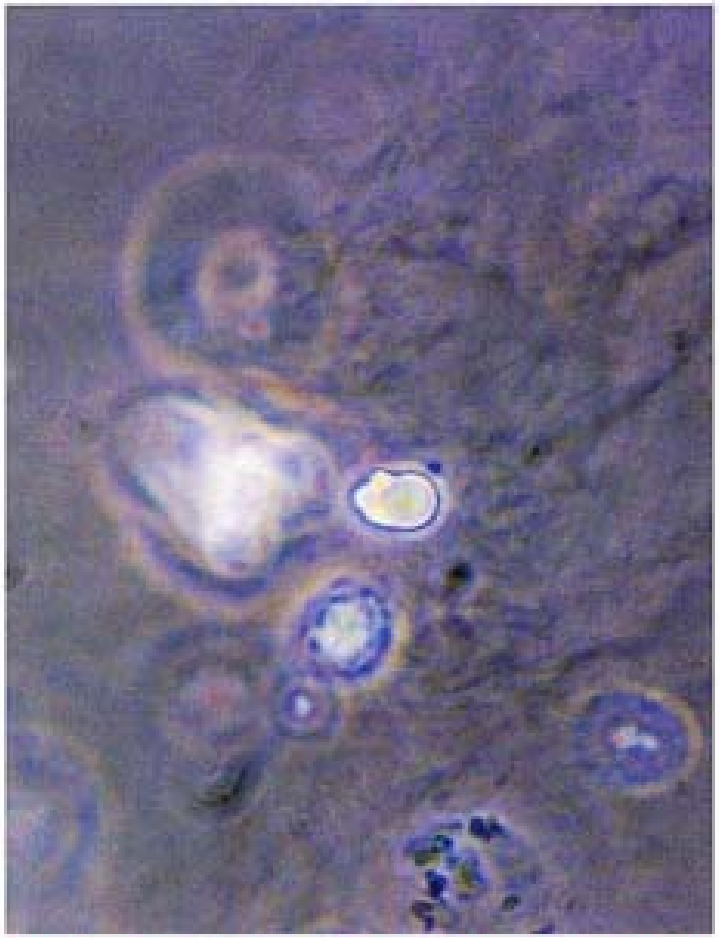


Electron microscopy. Renal biopsy. Lysosomal inclusons. 8000x

THE URINARY SEDIMENT IN FABRY DISEASE

- *By phase contrast:* cells laden with lipids and free fatty particles
- *By polarizing light:* "Maltese crosses"
- *By EM:* lysosomal inclusions appearing as round "myelin figures" made up of concentric layers of dense material separated by clear spaces

Renal Manifestations
Urinary sediment – Phase contrast



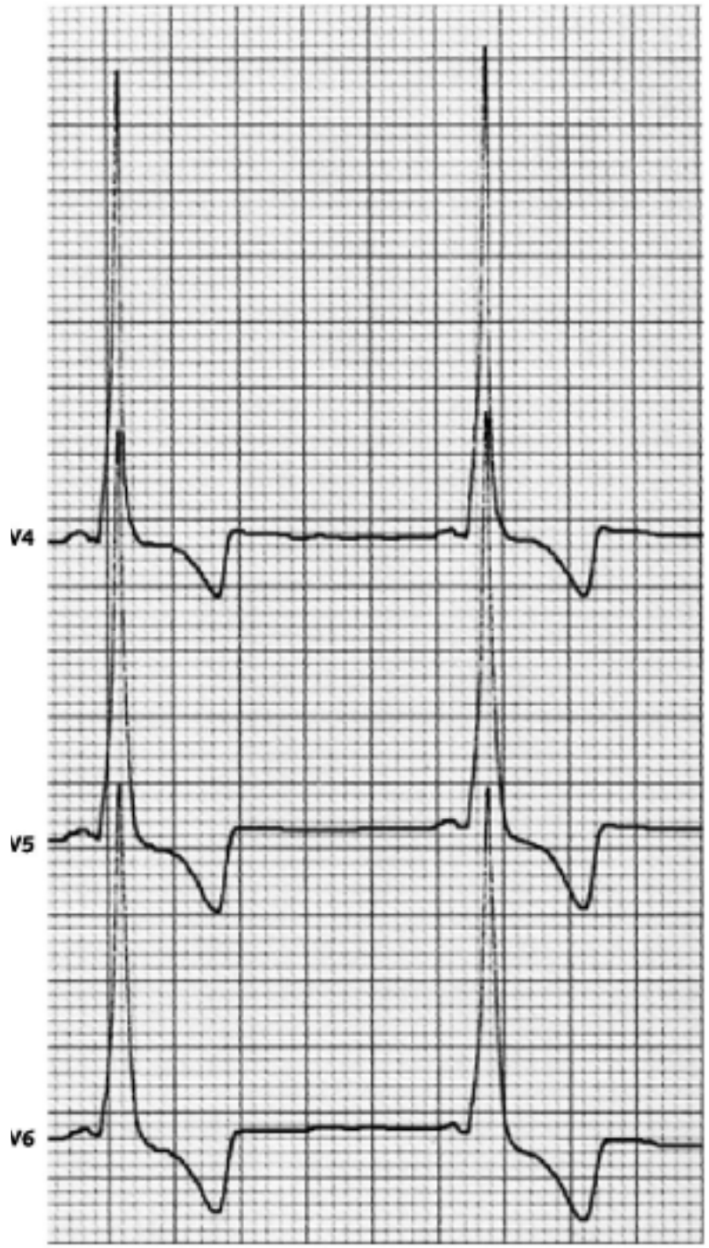
Birch DF et al. A color Atlas of Urine Microscopy, 1994

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

Mild Cardiac Variant

- Limited to cardiac manifestations (LVH, cardiomyopathy, heart failure)
- Absent or mild classical Fabry symptoms
- Glycolipid deposition, primarily in heart
- Missense mutations expressing residual activity (1-10%)
- “Experiment of nature”: rationale for enzyme replacement

Cerebrovascular/ Neurologic Manifestations

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

Clinical Presentation to a Range of Specialists

- Nephrologists
- Cardiologists
- Neurologists
- Pediatricians
- Primary Care Physicians
- Ophthalmologists
- Dermatologists

Differential Diagnosis

Shared Symptoms	Disease
Pain in the joints, elevated erythrocyte sedimentation rate	Rheumatoid or juvenile arthritis
Pain accompanied by fever and an elevated erythrocyte sedimentation rate	Rheumatic fever
Acute pain in the extremities	Erythromelalgia
Acute pain with no apparent cause	Neurosis
Pain and temperature sensitivity in the extremities	Raynaud's syndrome
Stroke-like events in brainstem structures	Multiple sclerosis
Angiokeratomas	Lupus;Petechiae
Severe abdominal pain	Acute appendicitis
Unexplained pain in extremities	"Growing Pains"

1. Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease. In: The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw Hill, 2001; 3733-74.
2. Whybra C, Wendrich K, Ries M, Gal A, Beck M. Clinical manifestation in female Fabry disease patients. Contrib Nephrol 2001;136:245-50.
3. Stryker VL, Kreps C. Fabry disease. Am J Nurs 2001;101:39-44.
4. Peters FPJ, Sommer A, Vermeulen A, Cheriex EC, Kho TL. Fabry's disease: a multidisciplinary disorder. Postgrad Med J 1997;73:710-2.
5. Kolodny EH. Fabry disease. In: Bogousslavsky J, Caplan L, eds. Stroke Syndromes. New York: Cambridge University Press 1995;453-9.
6. Morgan SH, Crawfurd MA. Anderson-Fabry disease. BMJ 1988;297:872-3.

Diagnosis

- Disease usually presents in childhood, yet often goes unrecognized until adulthood[1,2]
  - Underlying pathology is advanced
- Median age of diagnosis is 23 years for males and 32 years for females[3]
- Delayed diagnosis may be due to under-recognition of early signs and symptoms
- Symptoms of Fabry disease are similar to those of other more common disorders
- Early diagnosis is important
  - Disease is progressive

1. Shelley ED, Shelley WB, Kurczynski TW. Painful fingers, heat intolerance, and telangiectases of the ear: easily ignored childhood signs of Fabry disease. Pediatr Dermatol 1995; 12:215-9.
2. Menkes DL, O'Neil TJ, Saenz KK. Fabry's disease presenting as syncope, angiokeratomas, and spoke-like cataracts in a young man: discussion of the differential diagnosis. Mil Med 1997; 162:773-6.
3. Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis 2007;184-92.

Diagnosis

Clinical diagnosis based on:

- Family history
- Pain in the extremities
- Characteristic skin lesions (angiokeratomas)
- Characteristic “whorled” corneal opacity
- Observation of other signs and symptoms

Diagnosis

Confirmatory diagnosis

- Enzyme assay
  - Test to evaluate enzyme activity in plasma, leukocytes, tears, biopsied tissue or dried blood[1,2]
  - Males with classical Fabry disease usually have less than 1% of normal enzyme levels
  - Females can have 0-100% of normal enzyme levels
    - Normal enzyme levels in females does NOT rule of Fabry disease
- Genetic testing to identify females

1. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver C, Beaudet A, Sly W, et al., eds. Metabolic and Molecular Bases of Inherited Disease. New York: McGraw Hill 2001;3733-3774.
2. Ashton-Prolla P, Ashley GA, Giugliani R, Pires RF, Desnick RJ, Eng CM. Fabry disease: comparison of enzymatic, linkage, and mutation analysis for carrier detection in a family with a novel mutation (30delG). Am J Med Genet 1999;84:420-424

CLINICAL GUIDELINES

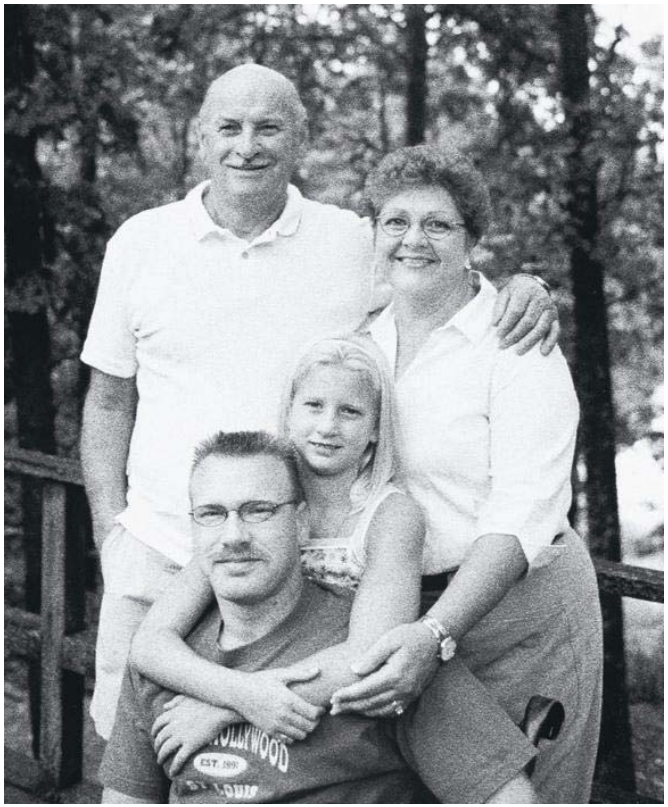
Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy

Robert J. Desnick, PhD, MD; Roscoe Brady, MD; John Barranger, MD, PhD; Allan J. Collins, MD; Dominique P. Germain, MD, PhD; Martin Goldman, MD; Gregory Grabowski, MD; Seymour Packman, MD; and William R. Wilcox, MD, PhD

Although the disease presents in childhood and culminates in cardiac, cerebrovascular, and renal disease, diagnosis is often delayed or missed.

Ann Intern Med. 2003; 138: 338-346

Genetic Counseling



- Important service to offer patients
- Can help identify other family members, including extended family
  - Potentially avoid delayed diagnoses in these family members
- Can help patients understand risk of transmitting disease to offspring

Treatment and Management

- Symptom management
- Team approach to treatment
  - Coordination among many medical specialties since disease is multisystemic

Who can diagnose Fabry disease at an early stage?

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

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

Fabry Disease Resources

- Patient Support Groups
  - Fabry Support and Information Group (FSIG)
    - www.fsig.org
  - National Fabry Disease Foundation (NFDF)
    - www.thenfdf.org
- Informational Websites
  - www.fabrydisease.com
  - www.fabrycommunity.com
  - www.fabryregistry.com