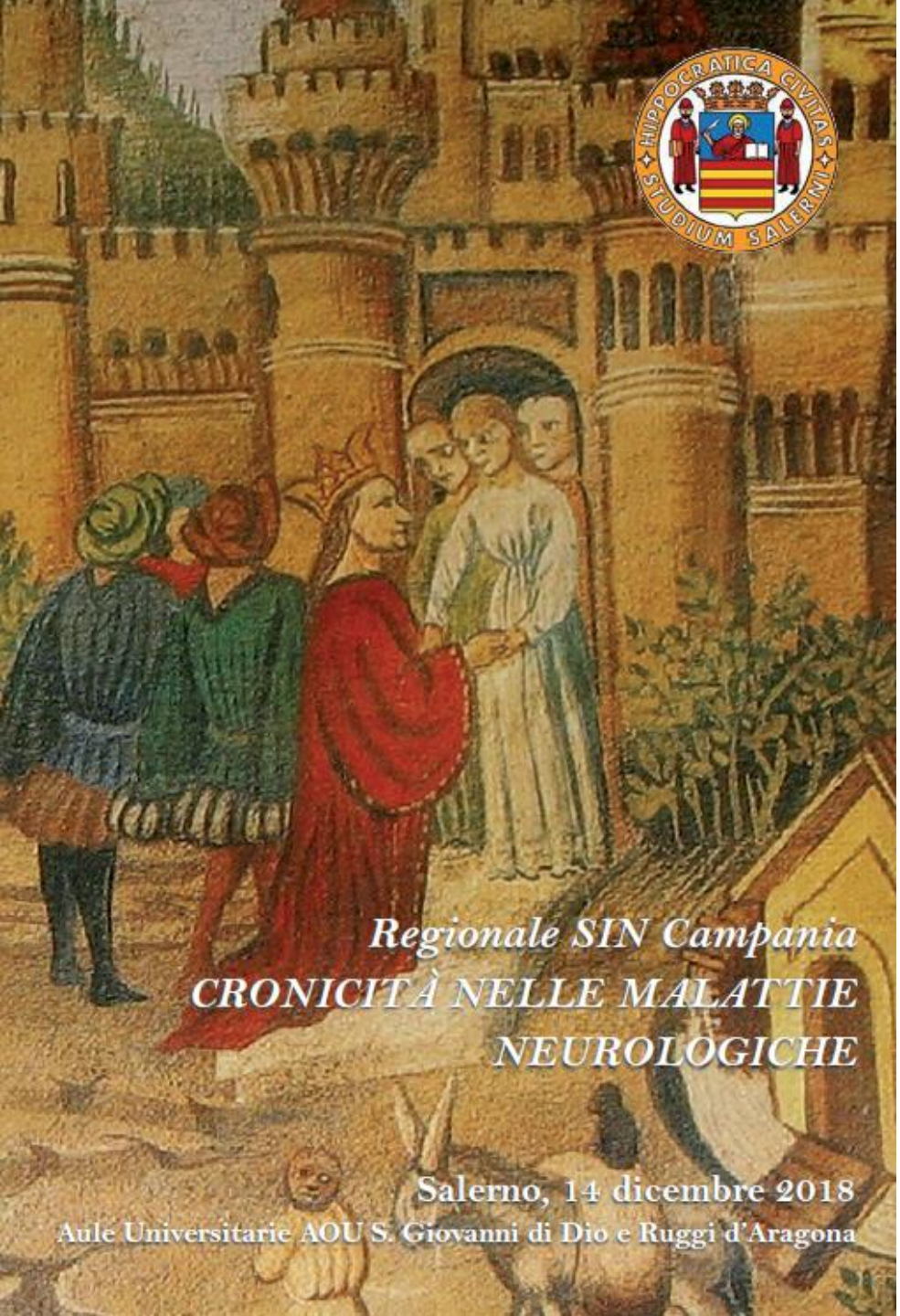


Complicanze neurologiche nella Malattia di Fabry

Vincenzo Andreone

UOS di Urgenze Cerebrovascolari

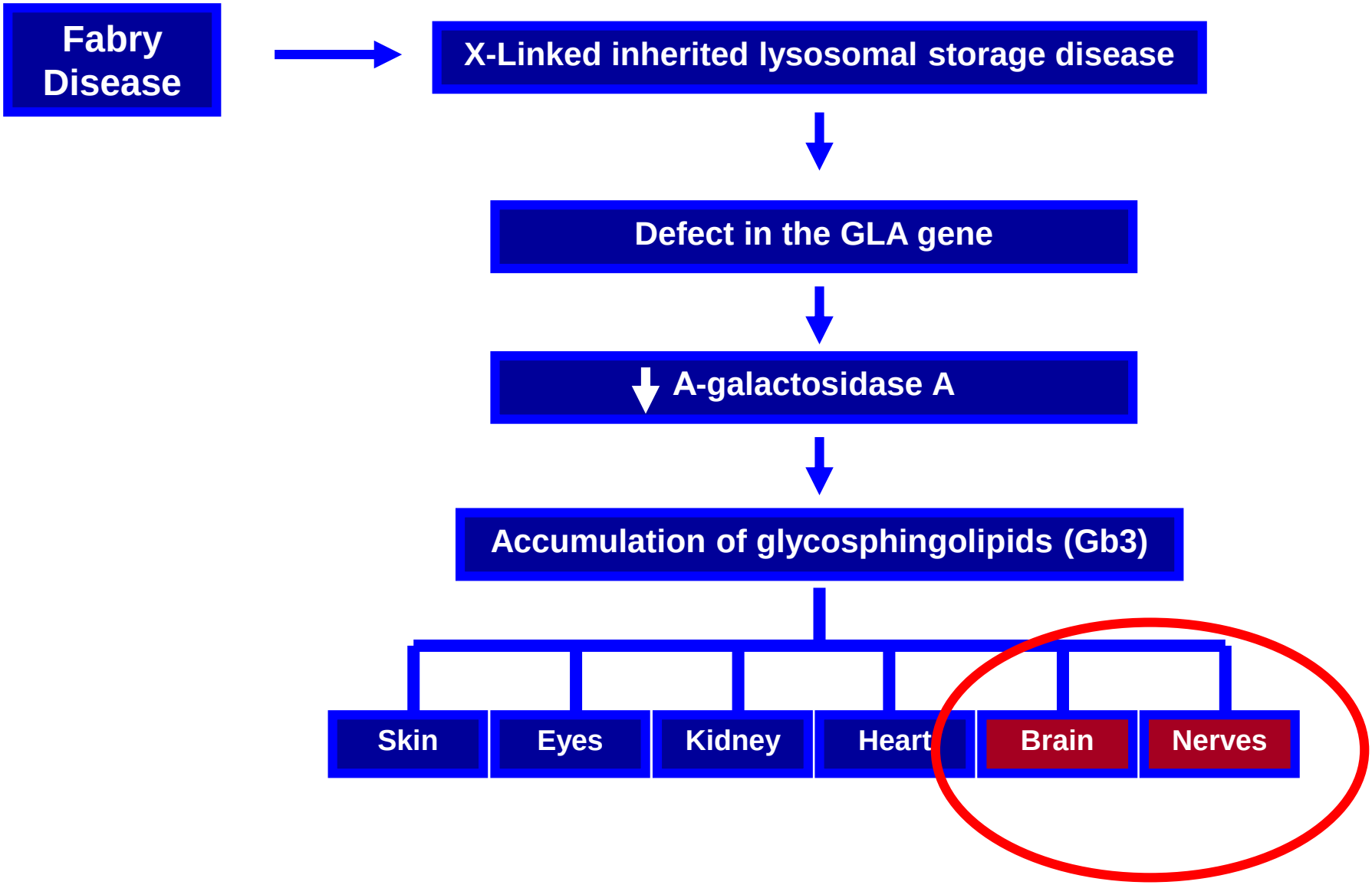
Divisione di Neurologia & Stroke Unit

Direttore: C. Florio

Antonio Cardarelli
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

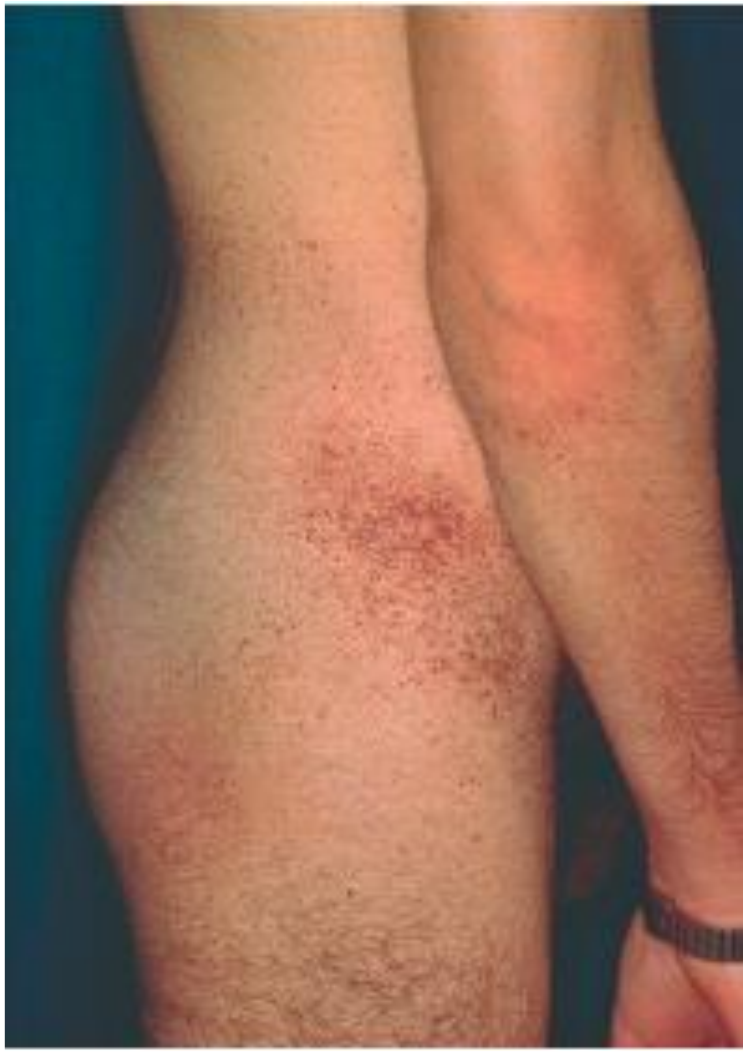
Fabry Disease

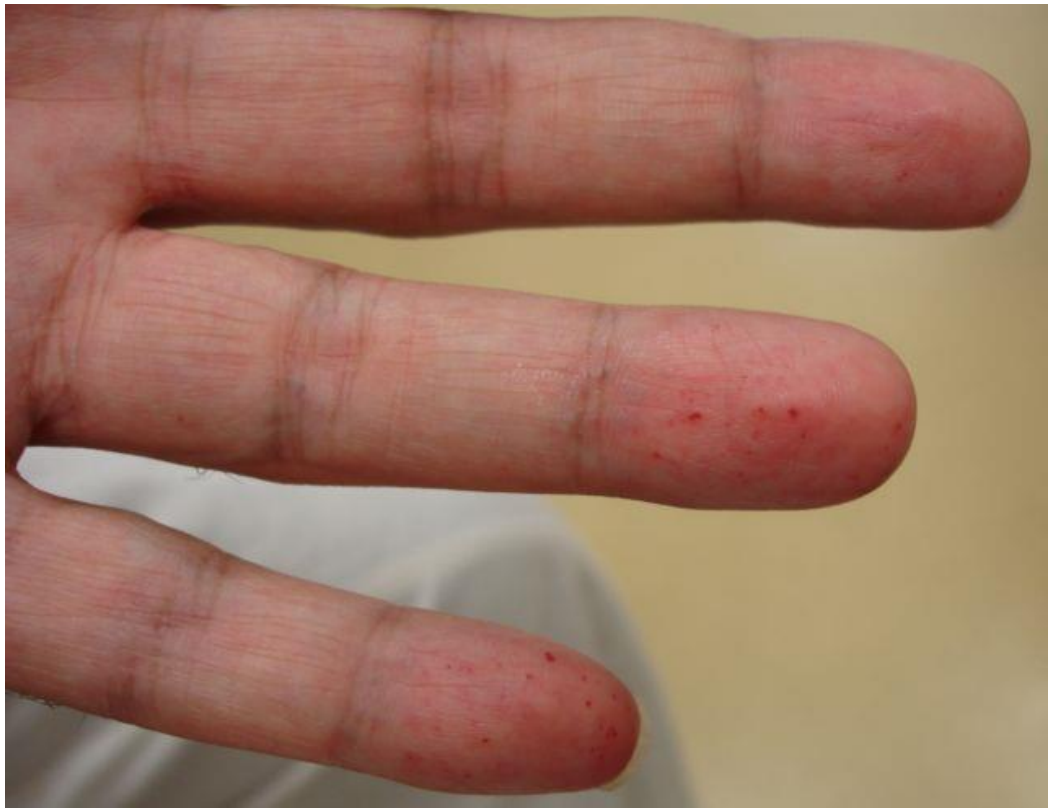
1. X-linked disorder
2. multisystemic disorder
3. affects males and females
4. in females: broader clinical heterogeneity, onset of symptoms about 10 years later

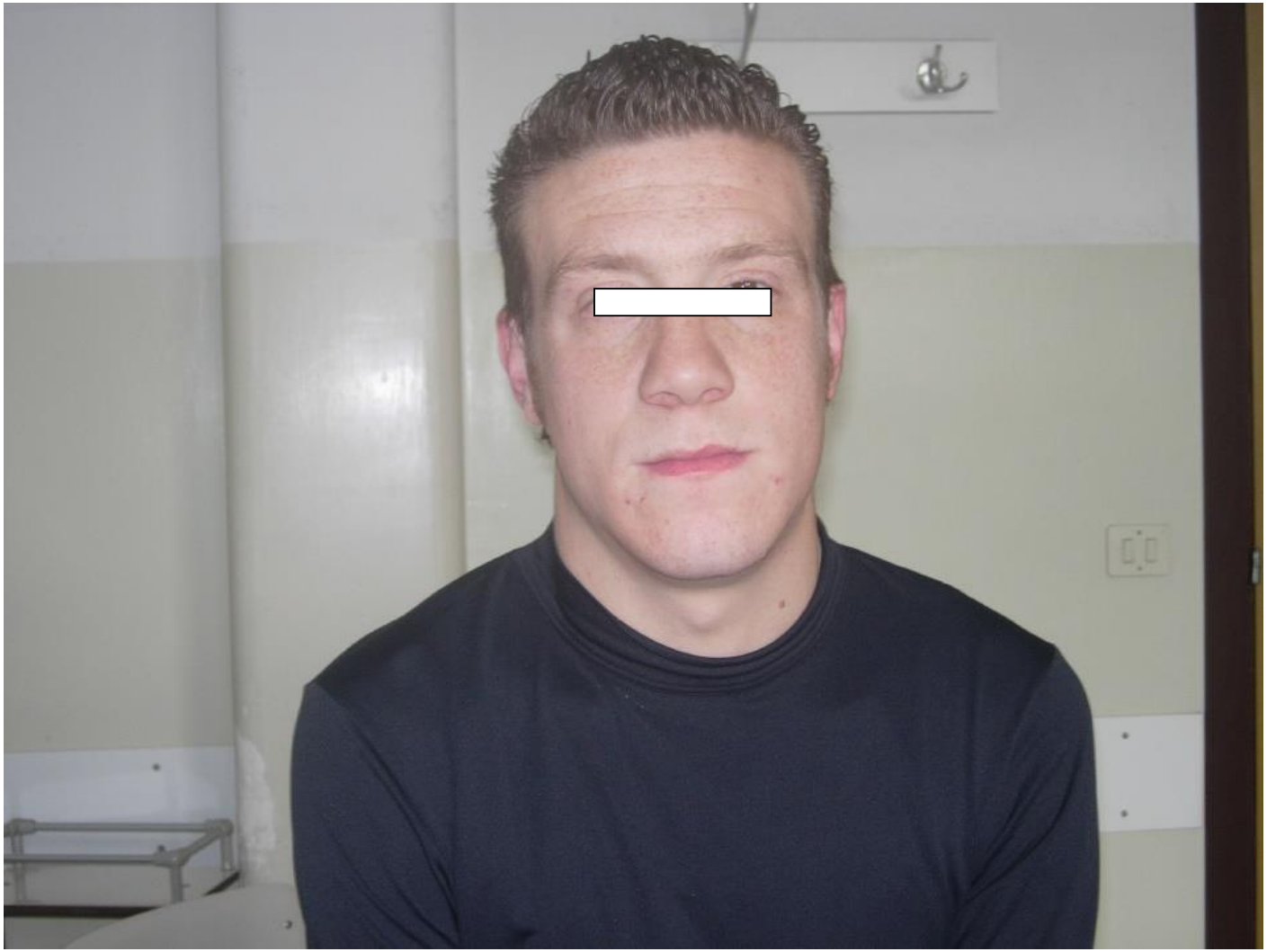

Fabry Disease
X-Linked inherited lysosomal storage disease
Defect in the GLA gene
A-galactosidase A
Accumulation of glycosphingolipids (Gb3)
Skin
Eyes
Kidney
Heart
Brain
Nerves

Vascular glycolipid deposition	Classical Hemizygotes	Atypical Hemizygotes
SKIN	Angiokeratoma	
EYES	Cornea verticillata	
PERIPHERAL NERVES	Acroparesthesias	
HEART	Cardiomyopathy/ Infarctions	Cardiomyopathy/ Infarctions
BRAIN	TIA, Strokes	TIA, Strokes
KIDNEY	Renal Failure	

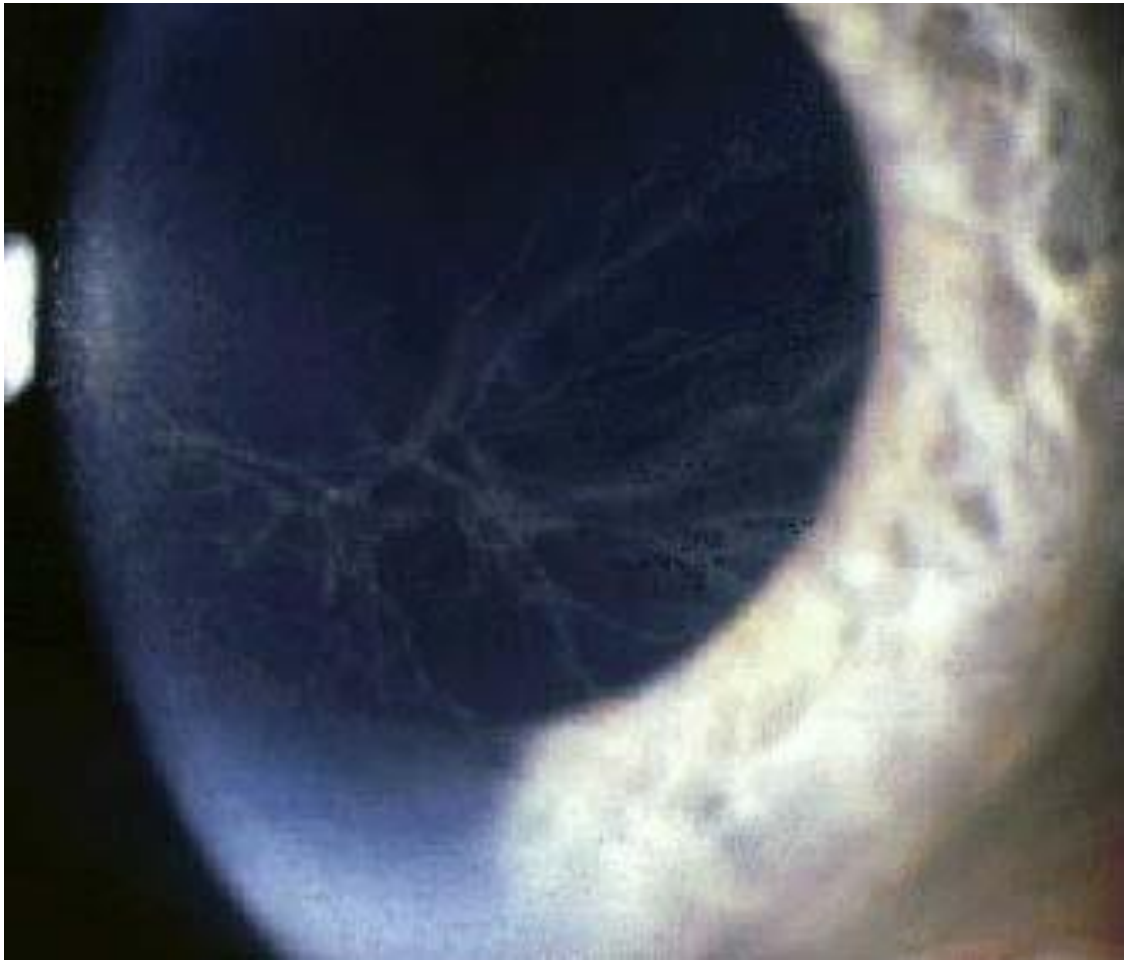
Angiokeratoma







Cornea verticillata



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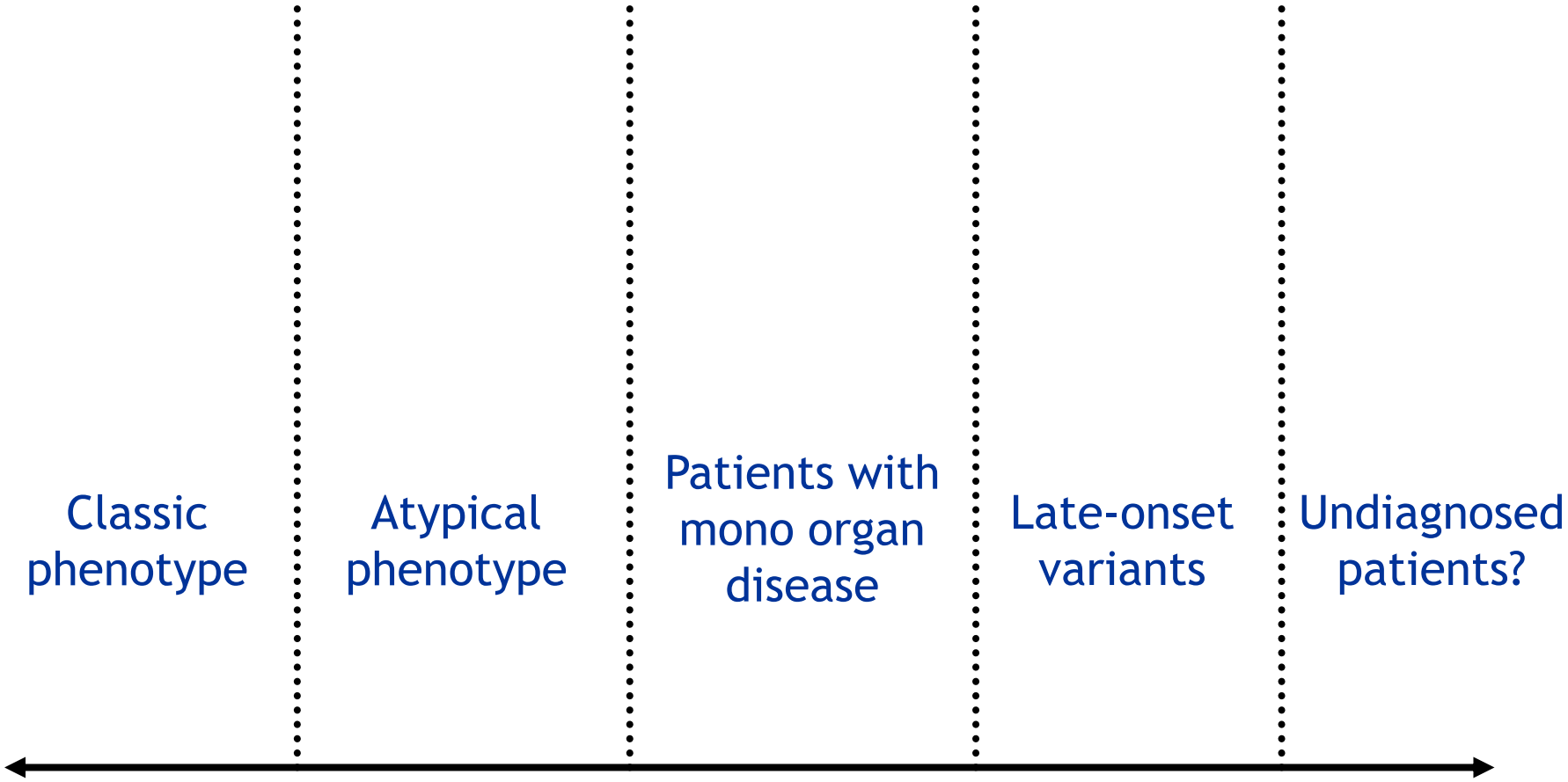


Fabry's disease spectrum

Fabry's Disease: what is the real incidence?

Incidence:

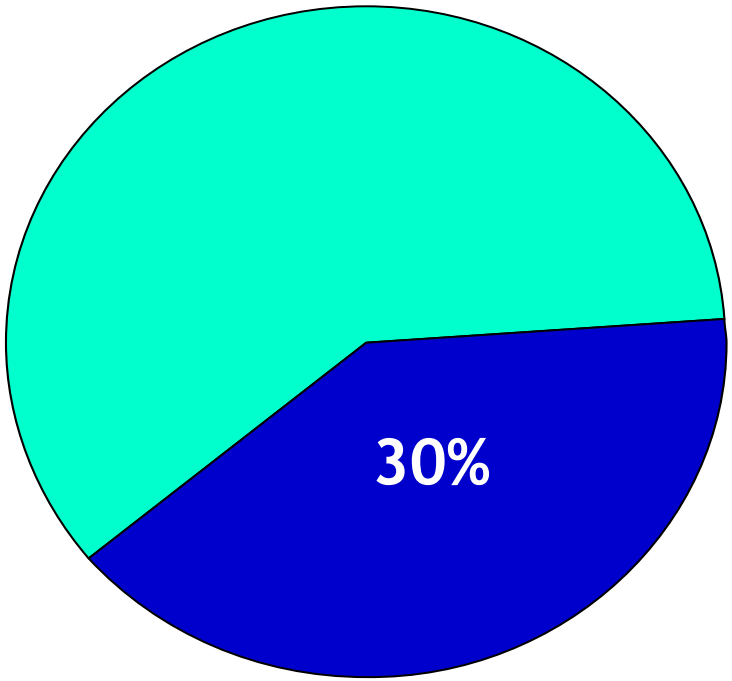
1:40.000 (Desnick et al, 1995)

1:117.000 (Melkle et al, 1999)

1: 4.600 newborns (Spada et al, 2006)

1: 1.500 newborns (Hwu WL et al, 2009)

3–5% of "idiopathic" hypertrophic cardiomyopathy cases



Stroke of undetermined cause

Fabry's Disease: **4.9 % of cryptogenic stroke patients ?**
1.2 % of young stroke patients ?

(Rolfs et al, Lancet 2005)

Neurological features of Fabry's disease

Peripheral nervous system

- Burning pain in the hands and feet
- Paraesthesia
- Fabry crises
- Hypohidrosis
- Gastrointestinal symptoms
- Small-fyber dysfunction > large-fiber

Neurological features of Fabry's disease

Peripheral nervous system

Burning pain in the hands and feet

Paraesthesia

Fabry crises

Hypohidrosis

Gastrointestinal symptoms

Small-fyber dysfunction > large-fiber

Central nervous system

Cerebrovascular events
- ischaemic stroke
- TIA

Psychiatric disorders (especially depression)

Cognitive impairment

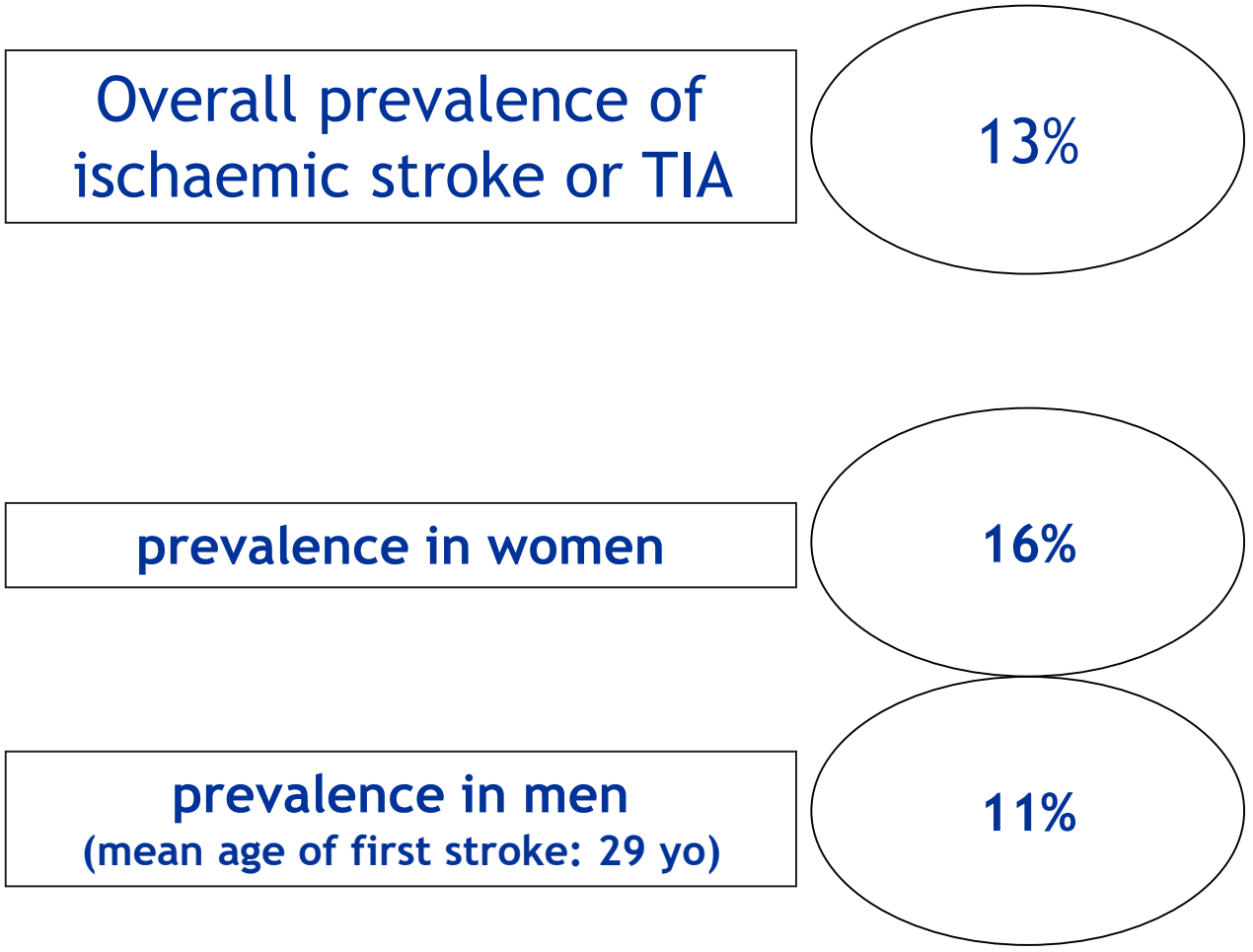
Audiovestibular symptoms
- Tinnitus
- Hearing impairment
- Vertigo

Presentation of the neurological phenotype in male and female FD

Characteristic	Heterozygous females	Hemizygous males
Mean survival	55 -70 years	41 -50 years
Burning pain	32 – 90%	84 – 100%
Audiovestibular symptoms	11 – 85%	57%
Stroke or TIA	5 – 18%	12 – 31%
• mean age of onset	40.3 – 50 years	28.8 – 34 years

Stroke in Fabry's Disease

Fabry Outcome Survey (FOS)



Mehta A, Ginsberg L. Natural history of the cerebrovascular complications of Fabry disease. *Acta Paediatr Suppl 2005; **94: 24-27**.*

Stroke in Fabry's Disease

Natural History Data from the Fabry Registry

Prevalence of stroke in women
(mean age of first stroke: 47 yo)

4.3%

Prevalence of stroke in men
(mean age of first stroke: 39 yo)

6.9%

Stroke. 2009;40:788-794

Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events

Natural History Data From the Fabry Registry

Stroke in Fabry's Disease

Natural History Data From the Fabry Registry

How many experienced their first stroke before being diagnosed with Fabry disease ?

50% of men and 38.3% of women

How many had not experienced renal or cardiac events before their first stroke ?

71% of men and 77% of women

Stroke. 2009;40:788-794

Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events

Natural History Data From the Fabry Registry

Stroke in Fabry's Disease

Natural History Data From the Fabry Registry

On follow up after their first stroke:

- 60% of males and 25.5% of females exhibited stage 3 to 5 chronic kidney disease
- 66.1% of males and 59.5% of females had left ventricular hypertrophy

Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events

Natural History Data From the Fabry Registry

Stroke. 2009;40:788-794

Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events

Natural History Data From the Fabry Registry

Stroke in Fabry's Disease

Frequency of unrecognized Fabry's disease among patients with cryptogenic strokes

1	Rolfs A et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. *Lancet*. 2005;366:1794-1796.	4.9 % of cryptogenic stroke patients 1.2 % of young stroke patients
2	Brouns R et al.; BeFaS Investigators. Belgian Fabry study: prevalence of Fabry disease in a cohort of 1000 young patients with cerebrovascular disease. *Stroke*. 2010;41:863-868.	alfa-GAL A deficiency may play a role in up to 1% of young patients presenting with cerebrovascular disease
3	Baptista MV.et al.; PORTuguese Young STROKE Investigators. Mutations of the GLA gene in young patients with stroke: the PORTYSTROKE study- screening genetic conditions in Portuguese young stroke patients. *Stroke*. 2010:41-431-436.	estimated prevalence of Fabry disease among young adult patients with stroke in Portugal by a-galactosidase A genotyping was 2.4%

Stroke in Fabry's Disease

Frequency of unrecognized Fabry's disease among patients with cryptogenic strokes

4

Wozniak MA et al. Frequency of unrecognized Fabry disease among young European- American and African-American men with first ischemic stroke. *Stroke*. 2010:41:78-81.

Alterations in the A-Gal A gene in 2/558 patients

SIFAP 2013 (stroke in Fabry patients)

5

Rolfs A et al.; sifap Investigators. Acute Cerebrovascular Disease in the Young. The Stroke in Young Fabry Patients Study. *Stroke*.2013;44:340-349.

Definite Fabry disease occurs in 0.5% and probable Fabry disease in further 0.4% of young stroke patients

6

Canadian Fabry Stroke Screening Initiative Study Group 2017

Lanthier et al. Prevalence of Fabry Disease and Outcomes in Young Canadian Patients With Cryptogenic Ischemic Cerebrovascular Events. *Stroke*. 2017;48:1766-1772

In this Canadian cohort of patients with cryptogenic IS or TIA, the prevalence of Fabry was 0.3%

Cerebrovascular Complications of Fabry's Disease

Panayiotis Mitsias, MD, and Steven R. Levine, MD

Fabry's disease (FD) is a rare, sex-linked disorder resulting from α-galactosidase deficiency. Cerebrovascular complications have been reported in the literature but have not been systematically analyzed. We report 2 patients and review 51 previously reported cases (descriptive meta-analysis) to clarify the clinical, radiologic, and pathologic features. The average age at onset of cerebrovascular symptoms was 33.8 years for hemizygous individuals (n = 43) and 40.3 years of heterozygotes (n = 10). The most frequent symptoms and signs were as follows (in descending order of frequency): hemiparesis, vertigo/dizziness, diplopia, dysarthria, nystagmus, nausea/vomiting, head pain, hemiataxia, and ataxia of gait, in the hemizygote group; and memory loss, dizziness, ataxia, hemiparesis, loss of consciousness and hemisensory symptoms, in the heterozygote group. The vertebrobasilar circulation was symptomatic in 67% of the hemizygotes and 60% of the heterozygotes. Intracerebral hemorrhage was found in 4 patients (3 hemizygotes and 1 heterozygote). Elongated, ectatic, tortuous vertebral and basilar arteries were the most common angiographic and pathologic features. For the hemizygotes, the recurrence rate for cerebrovascular disease was 76% and the death rate was 55%; 86% of the heterozygotes had recurrent cerebrovascular event(s) and 40% died. The cerebrovascular manifestations of FD, in both hemizygotes and heterozygotes, are predominantly due to dilative arteriopathy of the vertebrobasilar circulation, frequently recur, and portend a poor prognosis.

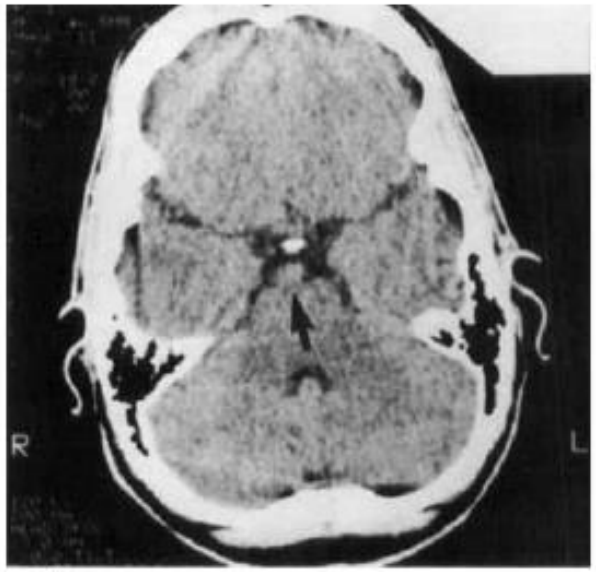
Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease. Ann Neurol 1996;40:8–17

Cerebrovascular complications in Fabry's disease

- Predilection for involvement of posterior circulation
- Medium and small-sized arteries markedly thickened and lumina narrowed
- Haemorragic strokes
- Vascular abnormalities (eg: basilar dolichoectasia)

	Average age at onset	Recurrence rate
Hemizygote	33,8 yrs	76%
Heterozygote	40,3 yrs	86%

Mitsias and Levine, Ann Neurol 40:8-17, 1996



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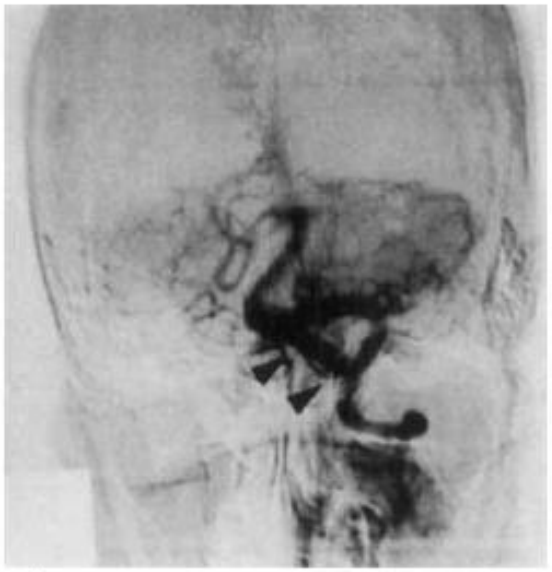

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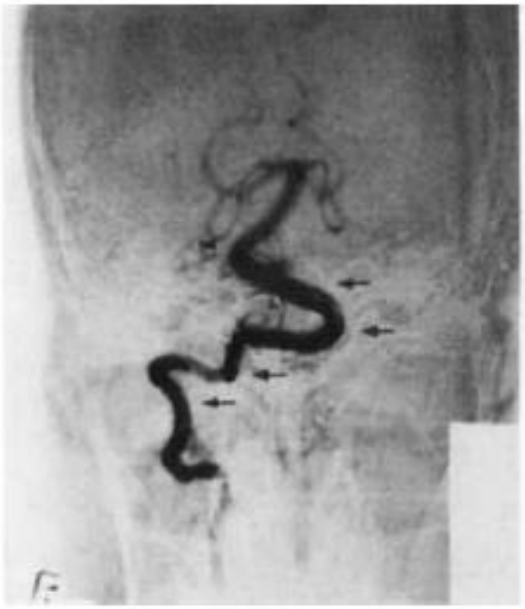

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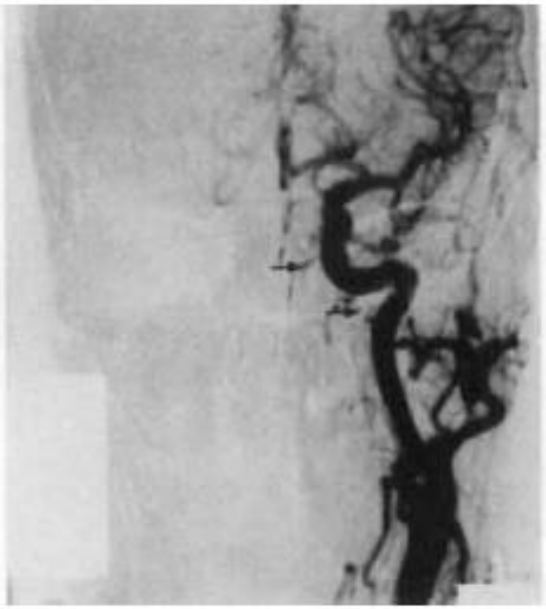

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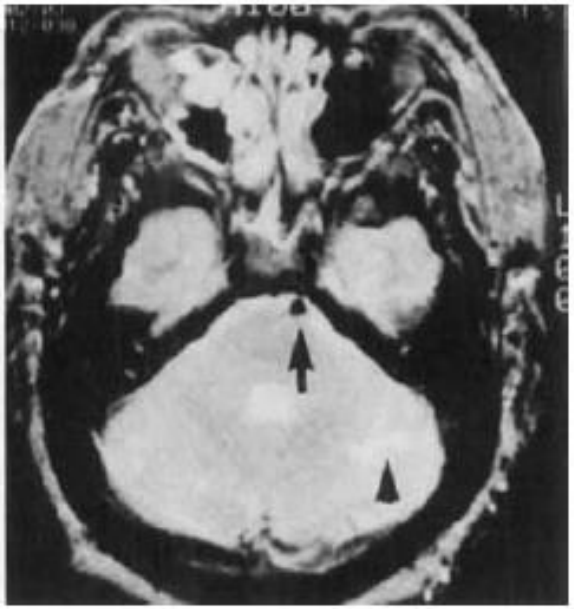


C

Mitsias and Levine, Ann Neurol 40:8-17, 1996

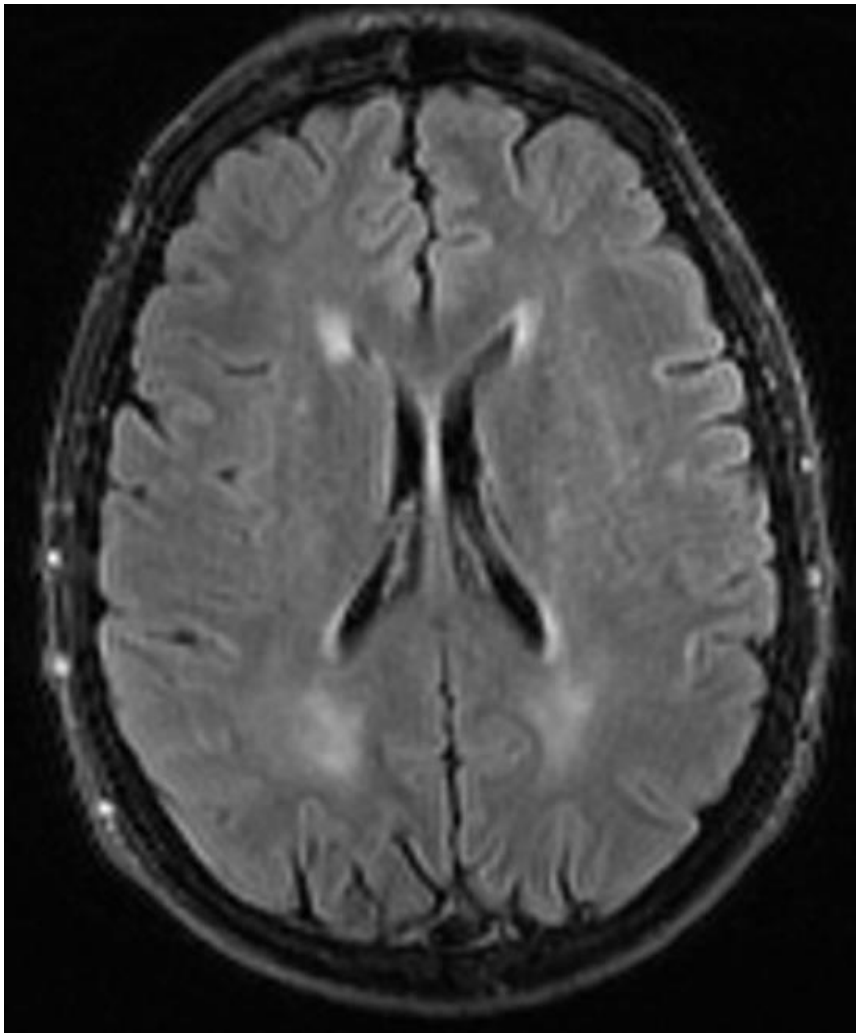
Types of cerebrovascular events in Fabry's disease

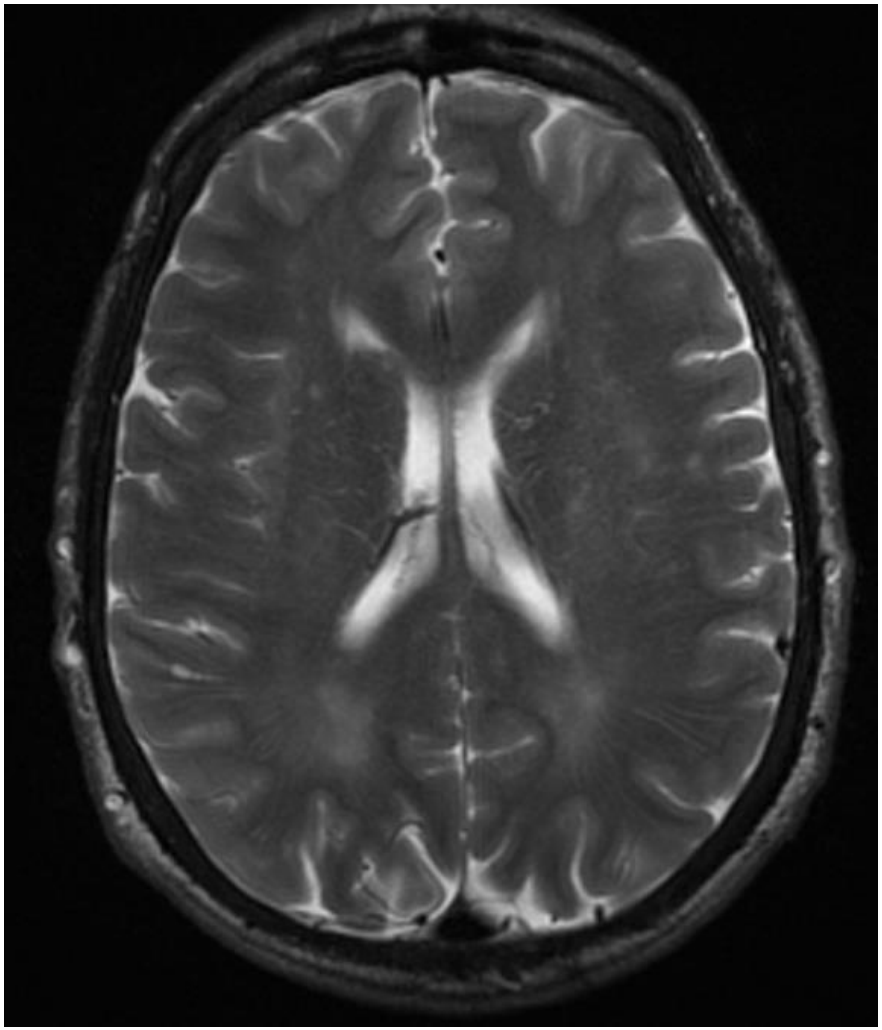
- Territorial strokes
- Watershed strokes
- Lacunar strokes
- Haemorragic strokes
- Vascular abnormalities (eg: basilar dolichoectasia)
- White matter lesions (WMLs)
- Dorsal thalamus abnormality (Pulvinar T1 hyperintensity)?

Stroke Pathogenesis in Fabry's disease

- Cardiogenic embolism
  - Arrhythmias
  - Cardiomyopathy
  - Valvular heart disease
  - Ischaemic heart disease
- Hypertension secondary to renal failure
- Vascular disease in situ
  - Glycosphingolypid accumulation in small and large vessels
- Changes in the local patterns of blood flow.
- Changes in blood constituents
  - Leucocyte adhesion molecules
  - Homocysteine concentrations.

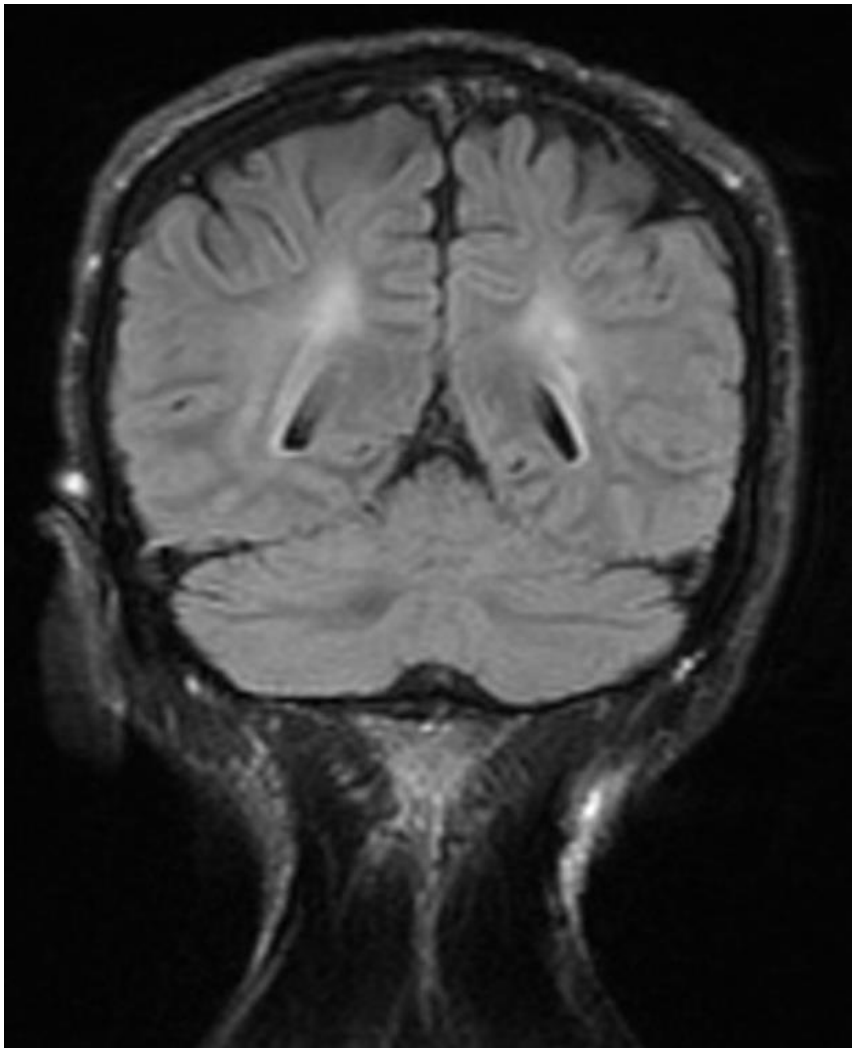
WMLs in Fabry's disease

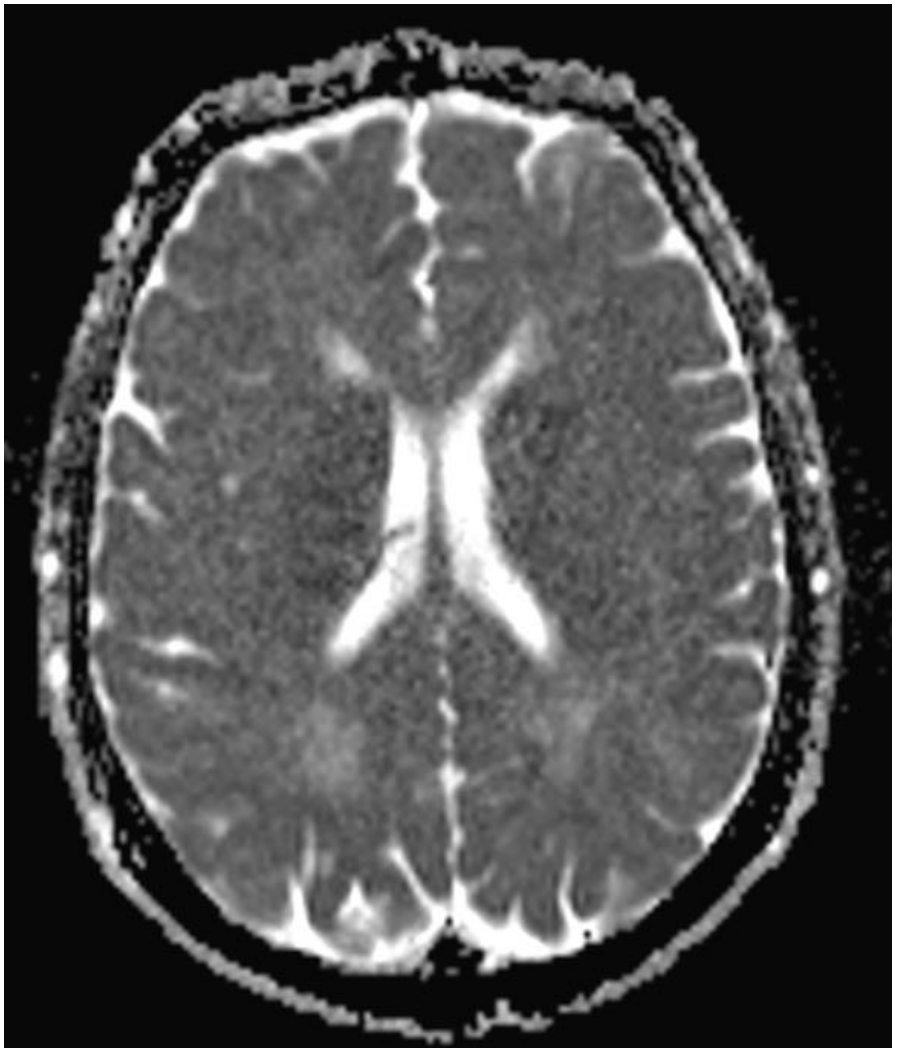




Male, 52 yrs old

WMLs in Fabry's disease





Male, 52 yrs old

WMLs in Fabry's disease

1. White matter lesions (WMLs) are frequently found even in young FD patients.
2. In a longitudinal MRI study of 50 men with FD (mean age, 33 years), 52% had WMLs. The lesions were present in all patients aged >55 years. (*Neurology*. 1998)
3. MRI abnormalities could even be found in young children with FD. (*J Pediatr*. 2005)
4. Men and women with FD who were equally affected clinically showed a comparable severity of WML load. (*Neurology*. 2005)

WMLs in Fabry's disease

GL3 deposition or GL3-induced cellular dysfunction

↓

increased cerebral blood flow and
altered vascular reactivity

↓

increased interstitial pressure in
the deep white matter + WM metabolic vulnerability

↓

gliosis, demyelination, and increased
interstitial water content

↓

WMLs

Moore DF, Altarescu G, Barker WC, Patronas NJ, Herscovitch P, Schiff mann R. White matter lesions in Fabry disease occur in ‚prior' selectively hypometabolic and hyperperfused brain regions. *Brain Res Bull* 2003; **62:** 231–40.

WMLs in Fabry's disease / Multiple Sclerosis

- FD has been proposed as a possible differential diagnosis for MS, due to the heterogeneity and the overlap of the clinical presentation of both disorders

- Misdiagnosis of MS could lead to a delayed start or even a wrong treatment option;

Neuroradiology (2017) 59:563–570
DOI 10.1007/s00234-017-1829-8

DIAGNOSTIC NEURORADIOLOGY

Corpus callosum involvement: a useful clue for differentiating Fabry Disease from Multiple Sclerosis

Sirio Cocozza[1] · Gaia Olivo[1] · Eleonora Riccio[2] · Camilla Russo[1] · Giuseppe Pontillo[1] · Lorenzo Ugga[1] · Silvia Migliaccio[2] · Dario de Rosa[1] · Sandro Feriozzi[3] · Massimiliano Veroux[4] · Yuri Battaglia[5] · Daniela Concolino[6] · Federico Pieruzzi[7] · Antonino Tuttolomondo[8] · Aurelio Caronia[9] · Cinzia Valeria Russo[10] · Roberta Lanzillo[10] · Vincenzo Brescia Morra[10] · Massimo Imbriaco[1] · Arturo Brunetti[1] · Enrico Tedeschi[1] · Antonio Pisani[2]

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Parkinson's disease prevalence in Fabry disease: A survey study

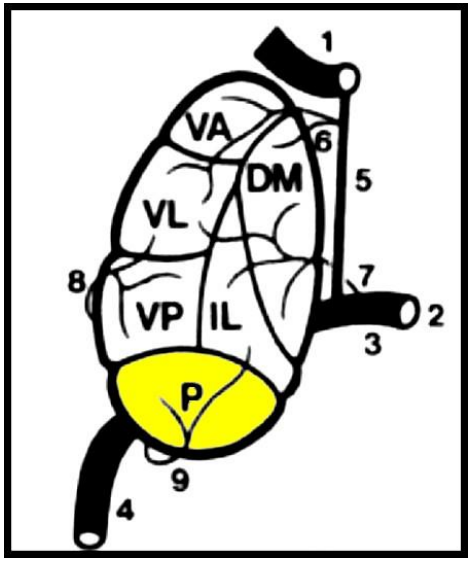
Adina H. Wise[a], Amy Yang[b], Hetanshi Naik[b], Chanan Stauffer[b], Natasha Zeid[b], Christopher Liong[a], Manisha Balwani[b], Robert J. Desnick[b], Roy N. Alcalay[a,*]

[a] Department of Neurology, Columbia University Medical Center, 710 W. 168th St., New York, NY 10032, United States
[b] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai Hospital, 1428 Madison Ave, Atran Building, 1st Floor, New York, NY 10029, United States

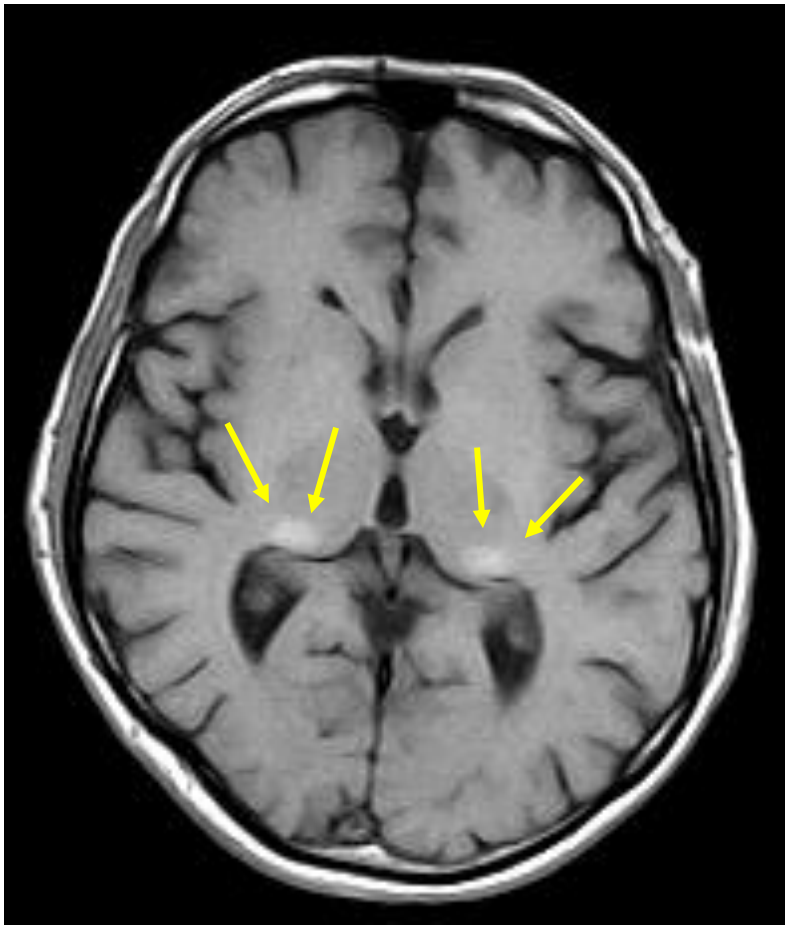
A potential role of lysosomal dysfunction in the pathogenesis of PD

A total of 90 Fabry patients (77 from the online survey and 13 from the Icahn School of Medicine at Mount Sinai (ISMMS)) were included in the analysis. Two of the Fabry disease patients who completed the online survey were diagnosed with PD (2/90, 2.2%).

Pulvinar Sign in Fabry's disease



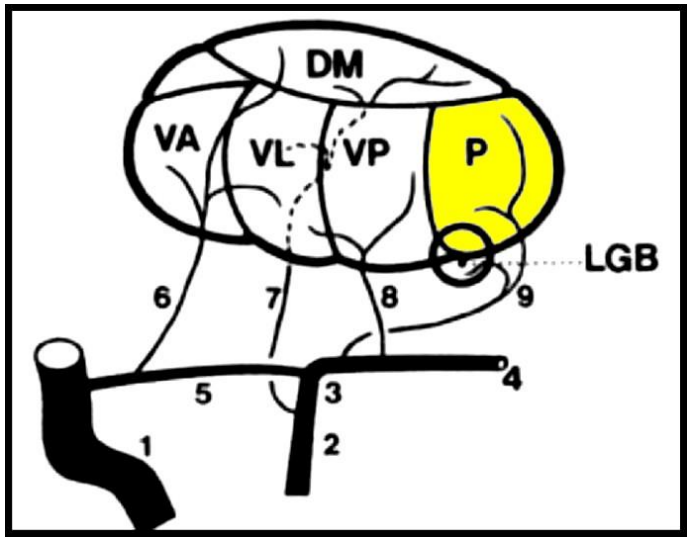
(modified from de Freitas and Bogousslavsky, 2002)



Axial T1

Burlina et al. The pulvinar sign: frequency and clinical correlations in Fabry disease. J Neurol (2008) 255:738-744

Pulvinar Sign in Fabry's disease



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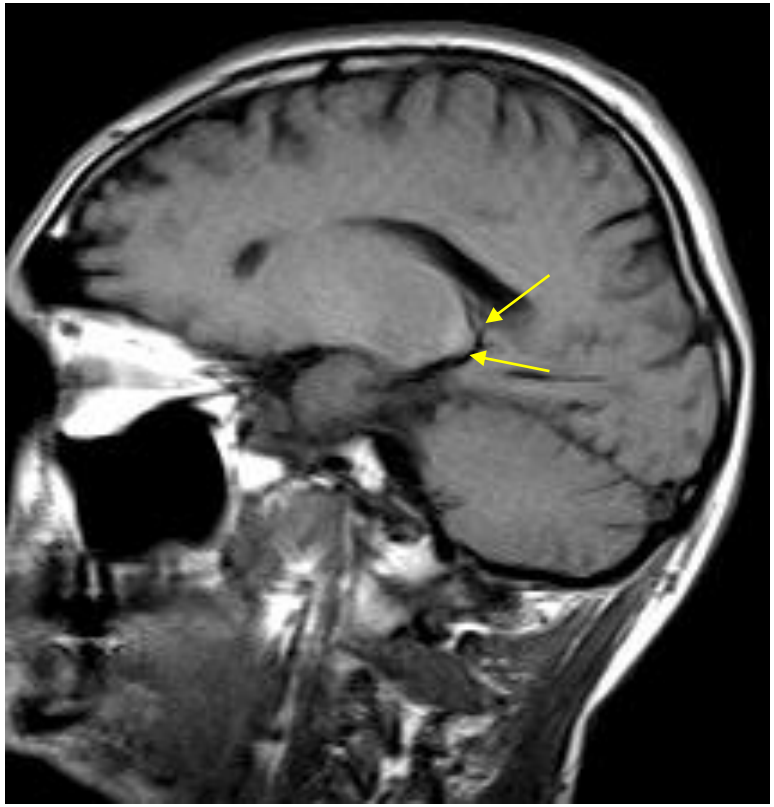


Sagittal T1

Burlina et al. The pulvinar sign: frequency and clinical correlations in Fabry disease. J Neurol (2008) 255:738-744

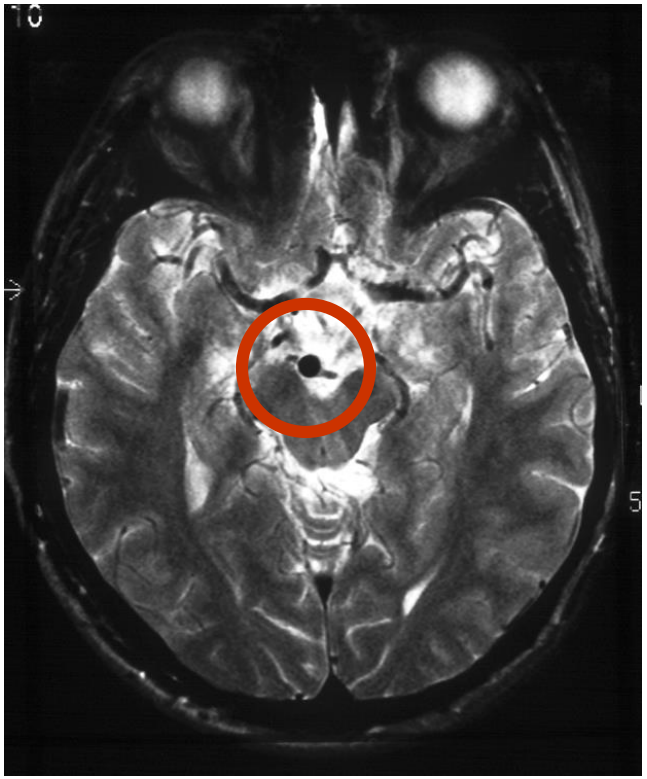
Pulvinar Sign in Fabry's disease

Table 2 The presence of the *pulvinar sign* in brain MRI of Fabry patients: this study and data from the literature, as reported in the text (refs. 13–16). Statistical analysis according to the Fisher exact test ($p = 0.00003$)

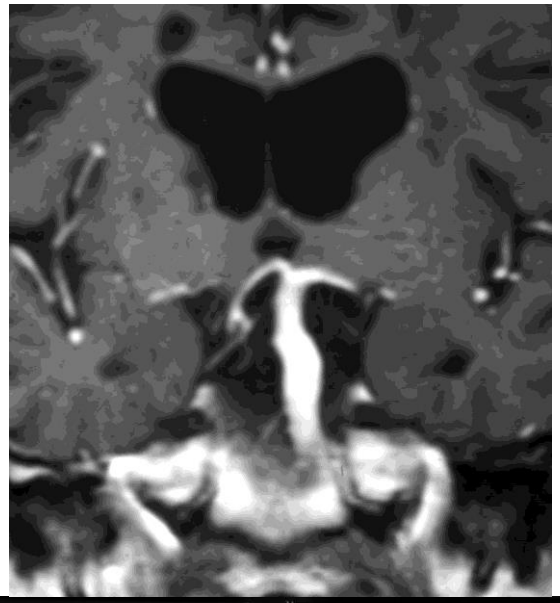
Pulvinar sign	Males, N (%)	Females, N (%)
Present	35 (25 %)	0 (0 %)
Absent	105 (75 %)	43 (100 %)

Burlina et al. The pulvinar sign: frequency and clinical correlations in Fabry disease. J Neurol (2008) 255:738-744

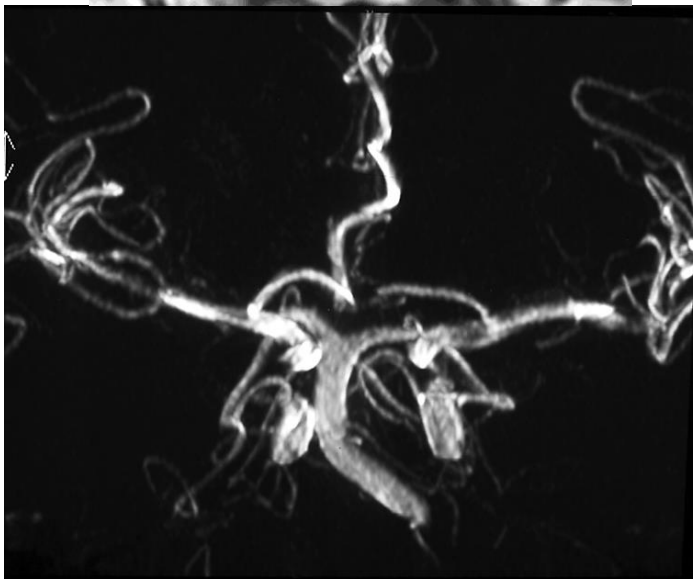
Vascular abnormalities



Signal void in T2

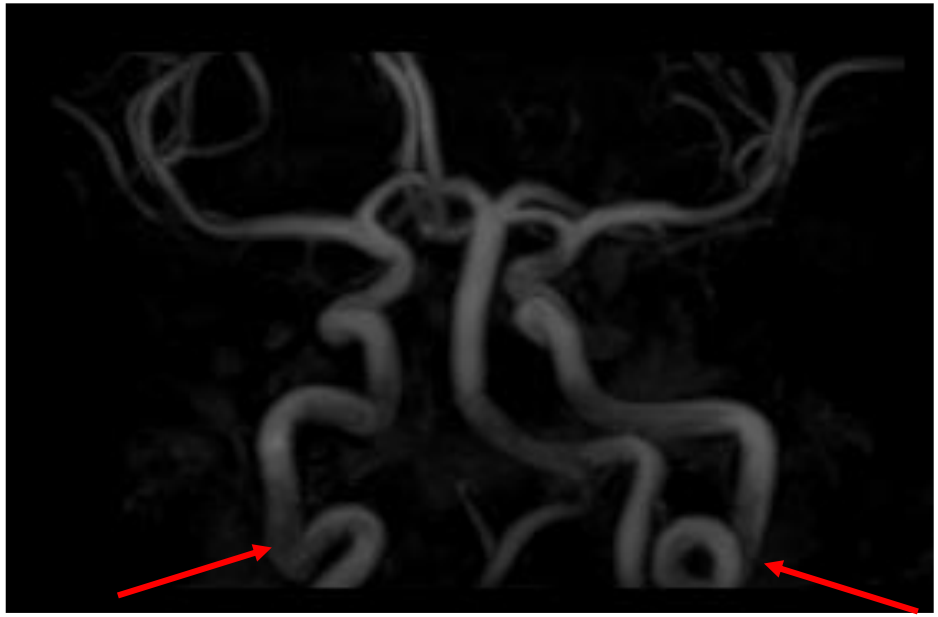


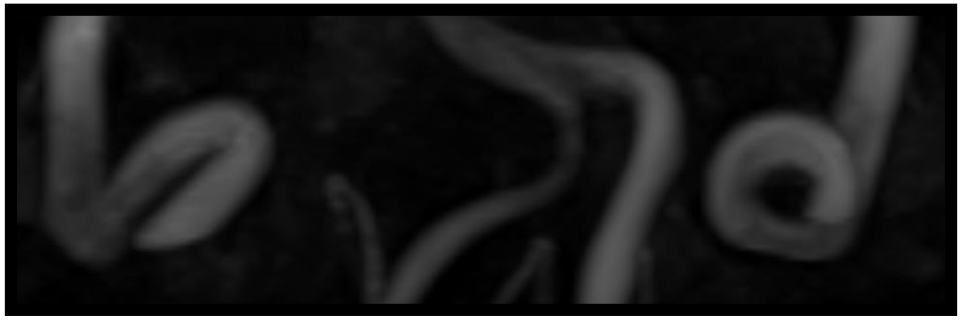
T1 Gd+



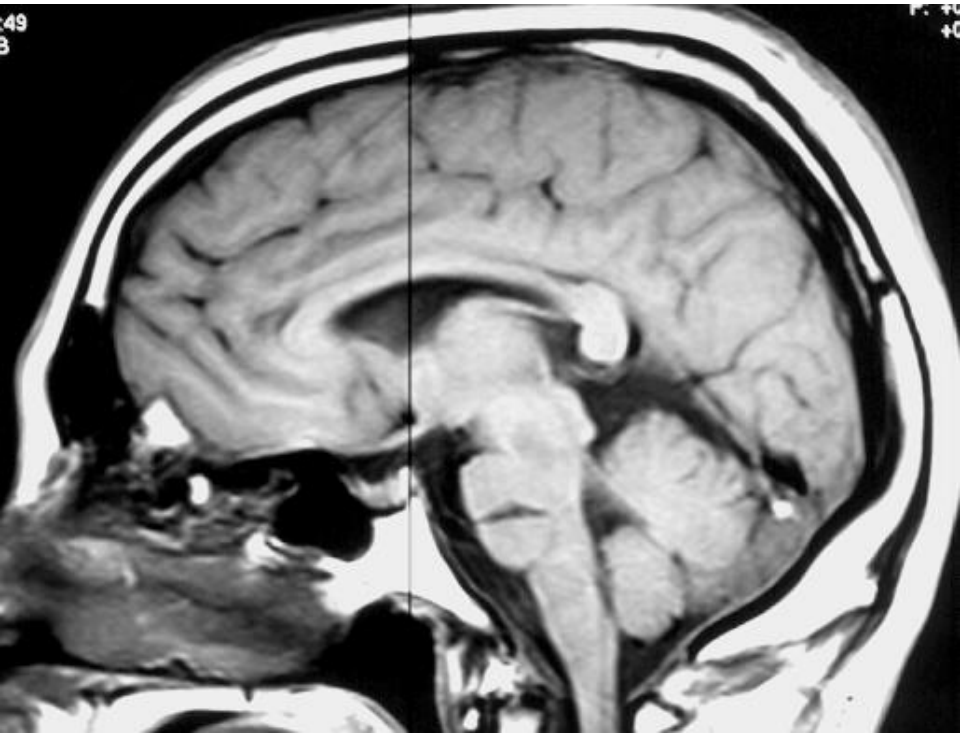
ToF MRA

Vascular abnormalities

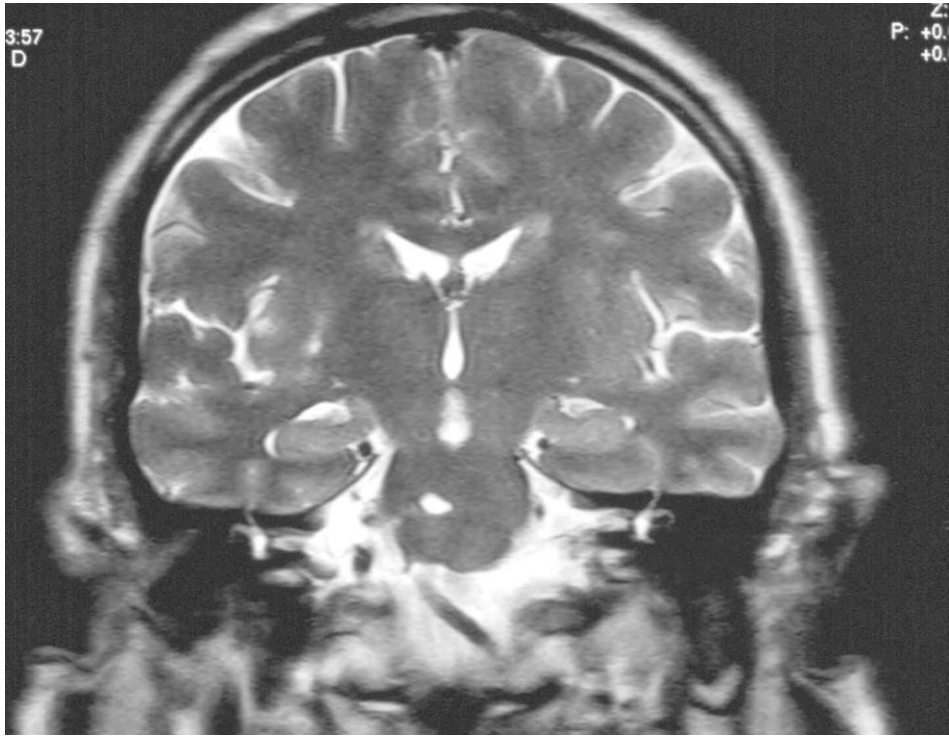




Lacunar infarcts



T1



T2

Courtesy: dott. Borsini

Enzyme replacement therapy **ERT**

Algaldasi-βf (Fabrazyme,Genzyme)

Fabrazyme 35mg — Genzyme

Algaldasi -αf (Replagal, SHIRE)

Replagal 0.2mg — (((SHIRE

Chaperon: Migalastat (GalafoldTM; Amicus Therapeutics)

Enzyme replacement therapy **ERT**

- ERT significantly reduces microvascular endothelial deposits of Glycosphingolipids
- beneficial effects on cardiac and renal parameters have been reported
- the influence of ERT on WMH progression or stroke risk is unclear. In particular, it has been suggested that ERT might be unable to influence progression of cerebrovascular disease in FD because of the relative impermeability of the blood-brain barrier to its passage.

ERT and peripheral manifestations

some positive effects on:

- reduction of neuropathic pain
- improvement of detection threshold for thermal sensation
- sweat function

Lack of recovery in some patients with severe dysfunction of thermal perception suggested that early ERT, prior to irreversible nerve fiber loss, was necessary.

ERT and CNS manifestations

1. A reduction of pathologically elevated cerebral blood flow could be measured under enzyme replacement therapy

2. Five of 17 men and two of six women receiving agalsidase beta demonstrated neurological deterioration, especially those who had presented with cerebrovascular disease already before starting ERT (Buechner et al, 2008)

3. Beneficial effects of ERT on clinical central nervous system manifestations (eg, reduction of strokes) or brain structural alterations in FD have not been proven.

A Comprehensive Strategy for Therapy in Fabry Disease next to ERT

1. Anti platelet therapy (aspirin, clopidogrel)
2. ACEI or ARB
3. Supplement with folic acid, vit B6 & B12 to reduce homocysteine
4. Dietary protein/salt restriction
5. Tight glycemic control in diabetes
6. Reduce elevated Ca-P product
7. Statins
8. Consider correction of anemia
9. Smoking cessation
10. Weight control
11. Avoid nephrotoxic drugs

Conclusion

- Male patients with Fabry's disease present from childhood with burning, lancinating pain (sometimes accompanied by acroparesthesia) and hypohidrosis
- Female patients with Fabry's disease are phenotypically more heterogeneous than are male patients, but can also present with severe symptoms
- A "cerebrovascular variant" is suggested.

Conclusion

- Stroke appears in early life, with male patients presenting at a lower age than female patients, although the frequency is higher among females
- Misdiagnosis and delays in diagnosis are major problems; it is important for neurologists to consider a diagnosis of Fabry's disease in patients presenting with neuropathic pain and premature idiopathic stroke

Conclusion

- Early initiation of enzyme replacement therapy (ERT) before irreversible organ failure is the most important.

- Evidence of a favorable impact of ERT on central nervous system signs and symptoms has not been established.