Malattia di Fabry: diagnosi e aspetti radiologici differenziali

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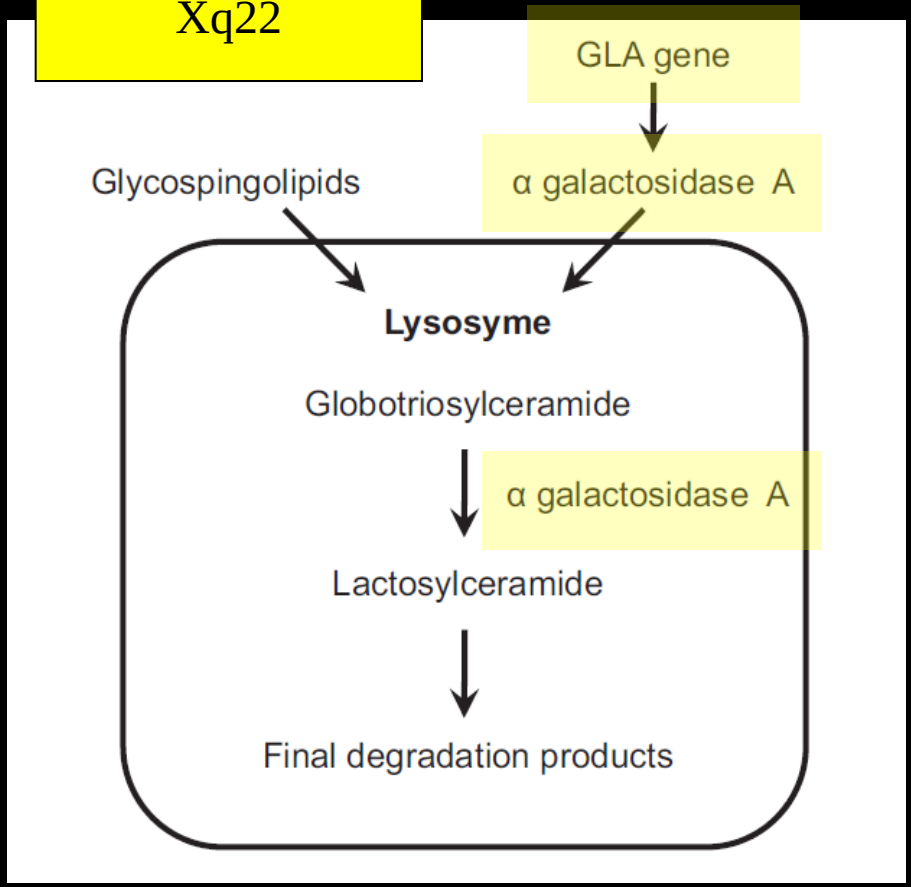
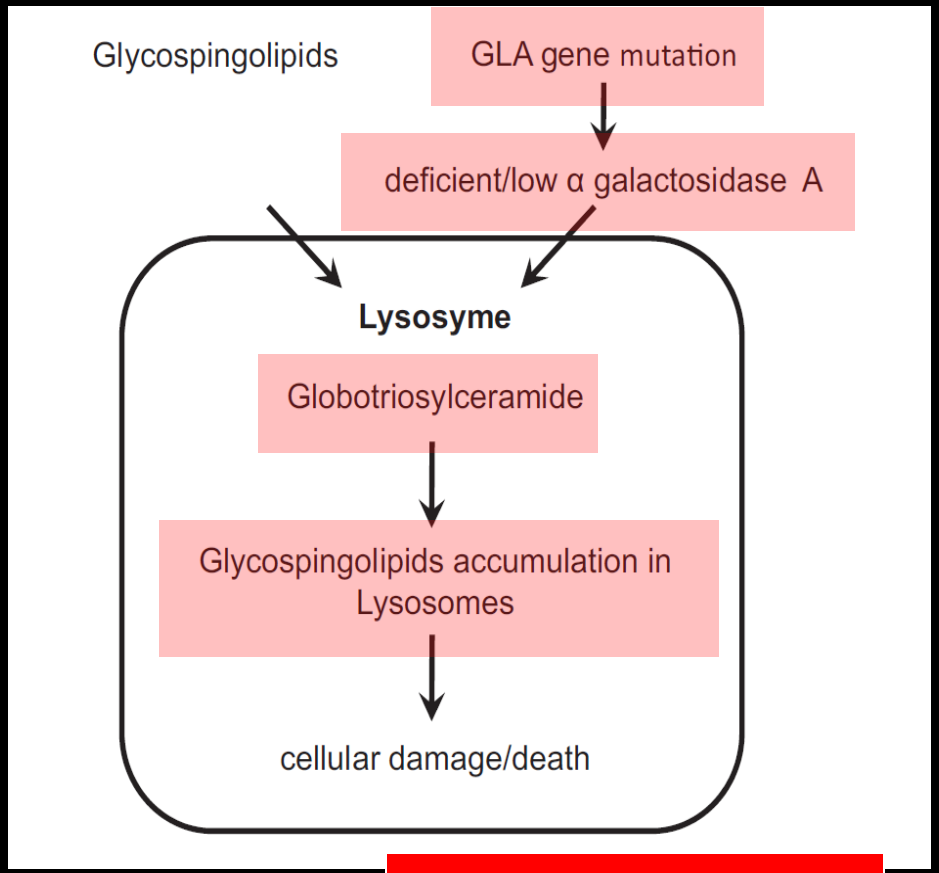
Outline

- Neurological features of FD:
  - Peripheral Nervous System
  - Central Nervous System
- Pathophysiology
- (Clinical) conclusion:
  - "…are there pathognomonic/specific (neurological) features…?"
  - "…when to search for FD?"
- (Lab) conclusion:
  - "…is it Fabry disease?"

chromosome
Xq22

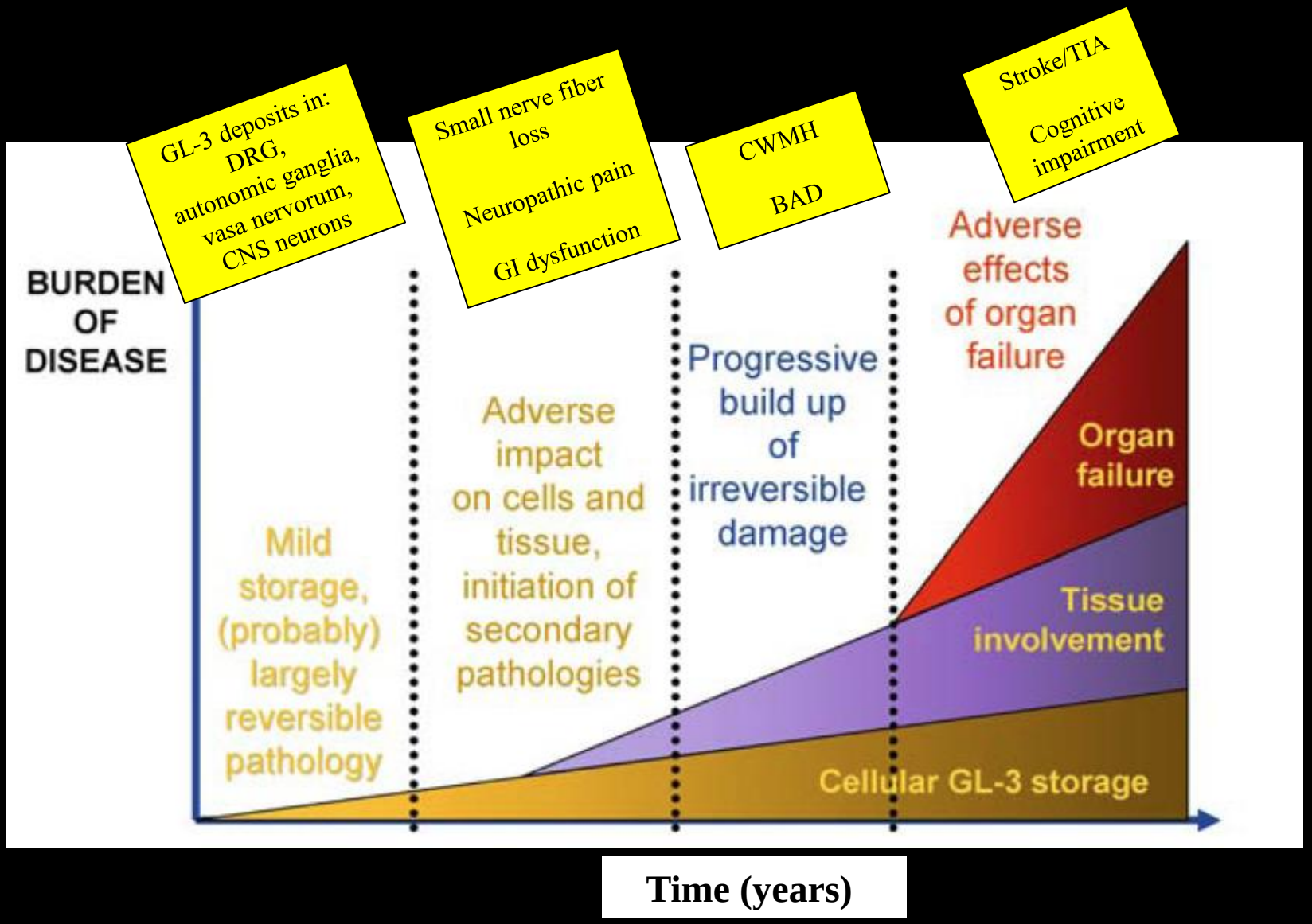




Prevalence:
1/40,000 – 1/117,000

El Abassi R et al. *J Neurol Sci* 2014;344:5-19

Pathophysiology: accumulation, tissue injury, compromised function



Politei J, Burlina A. *Fabry disease*.
In: Burlina A, ed. Neurometabolic Hereditary Diseases: Diagnosis and Treatment
Springer 2016

Peripheral nervous system

Peripheral neuropathy (especially small fibre), autonomic dysfunction

Neuropathic pain

- Episodic pain crises (triggered, for example, by warming)
- Acroparaesthesiae

Impaired temperature sensation

Hypohidrosis

Intestinal dysmotility (including abdominal pain and diarrhoea)

Peripheral vasomotor dysregulation

Central nervous system

Cerebrovascular events

- ischaemic stroke
- Transient ischaemic attack

Tinnitus

Hearing impairment

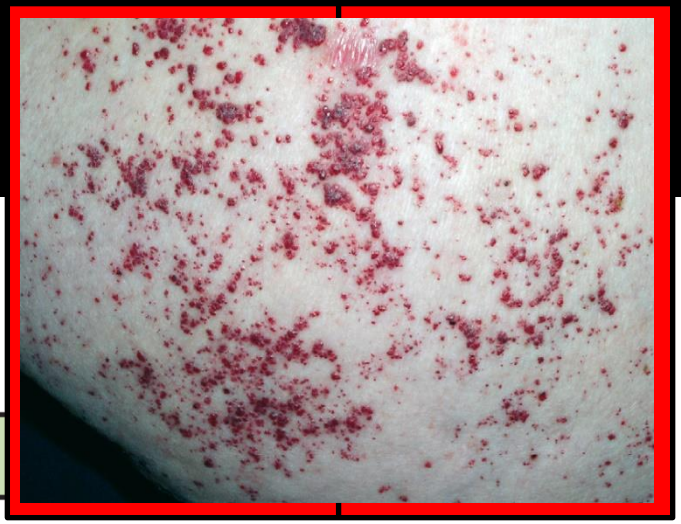
Vertigo

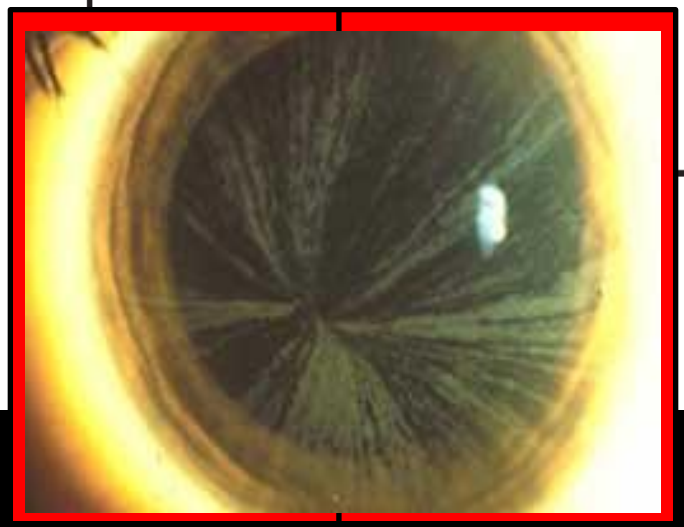
Psychiatric disorders (especially depression)

Cognitive impairment

Fellgiebel A et al. *Lancet Neurol* 2007;5:791-5

Early symptoms…





Symptoms

Neuropathic pain

Ophthalmologic

Gastrointestinal

Angiokeratomas

Tinnitus

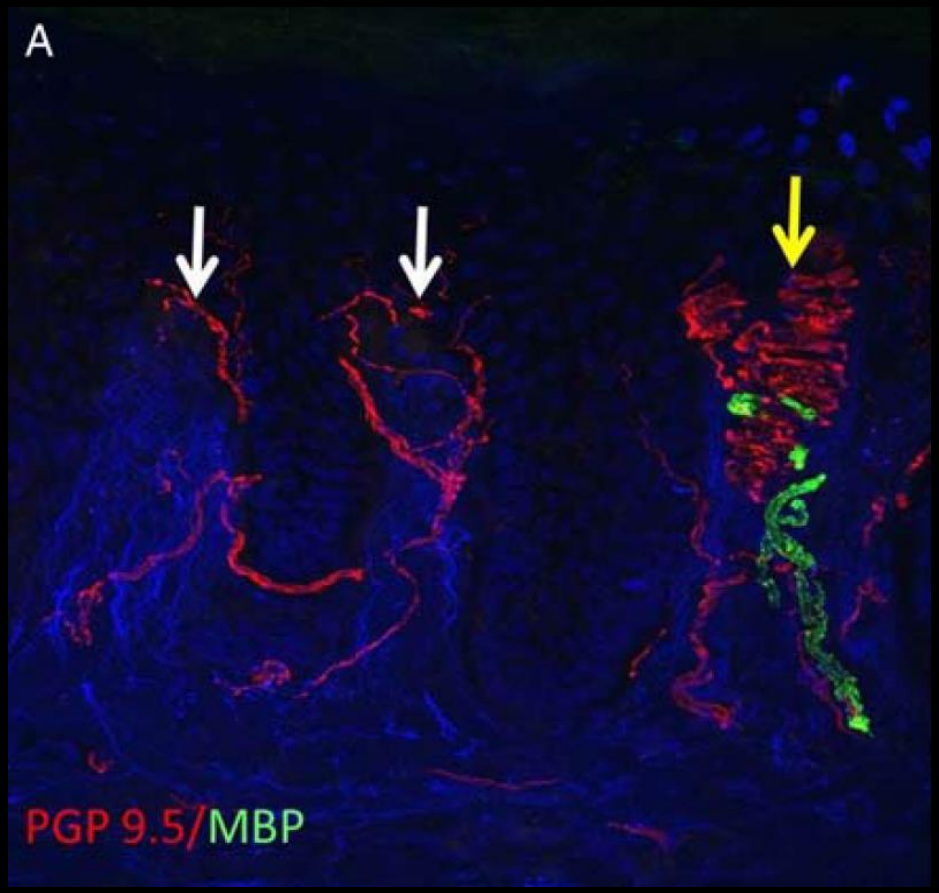
Proteinuria

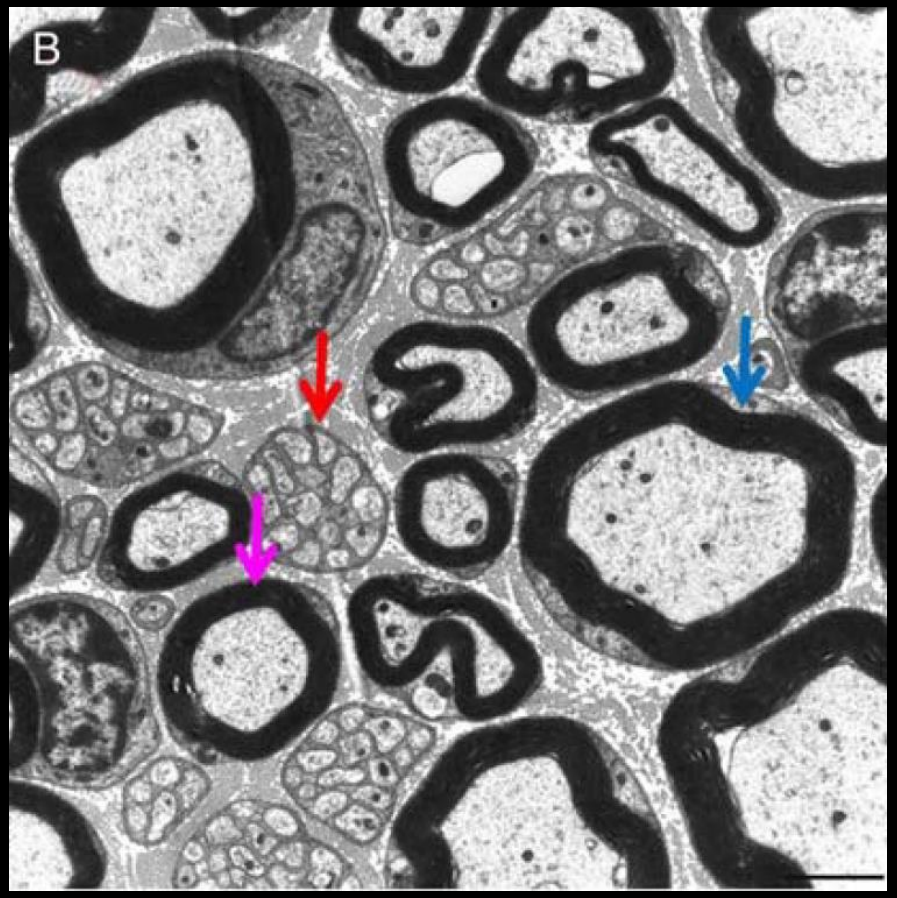
8 9 10 11 12 13 14 15 16 17 18 19

Age (years)

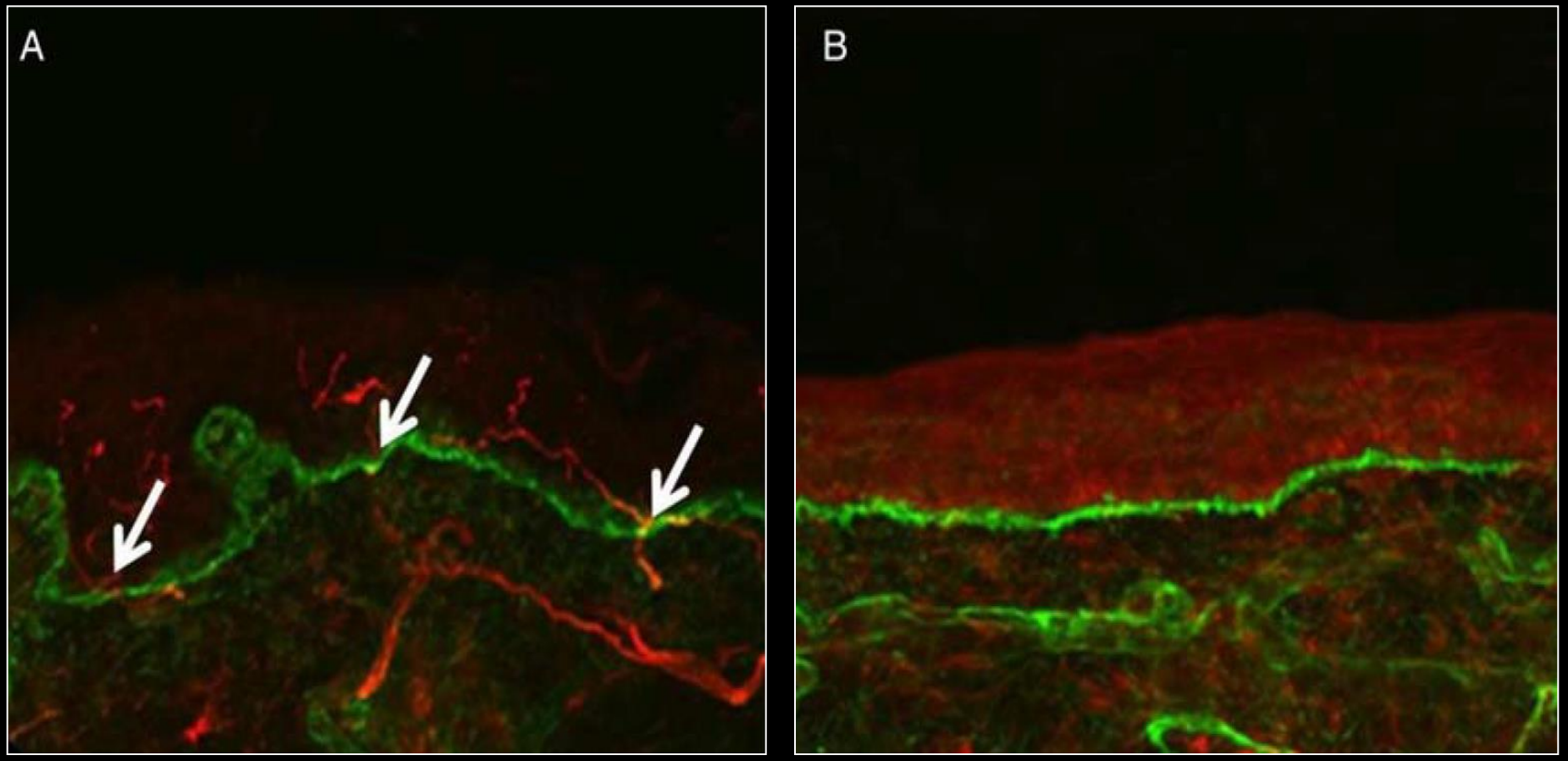
Zarate YA and Hopkin RJ. *Lancet* 2008;372:1427-35

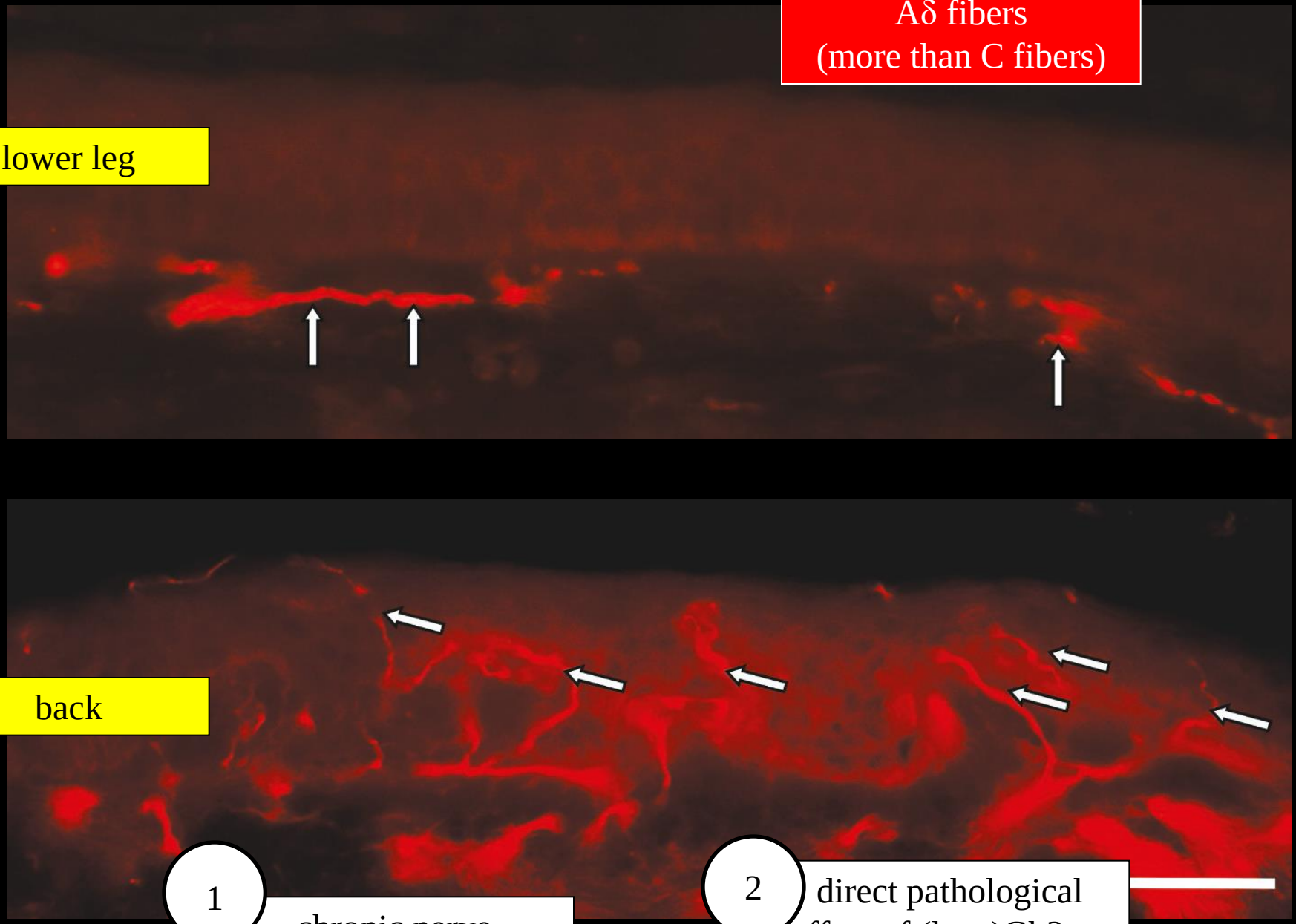
Small Fiber Neuropathy (SFN) in FD

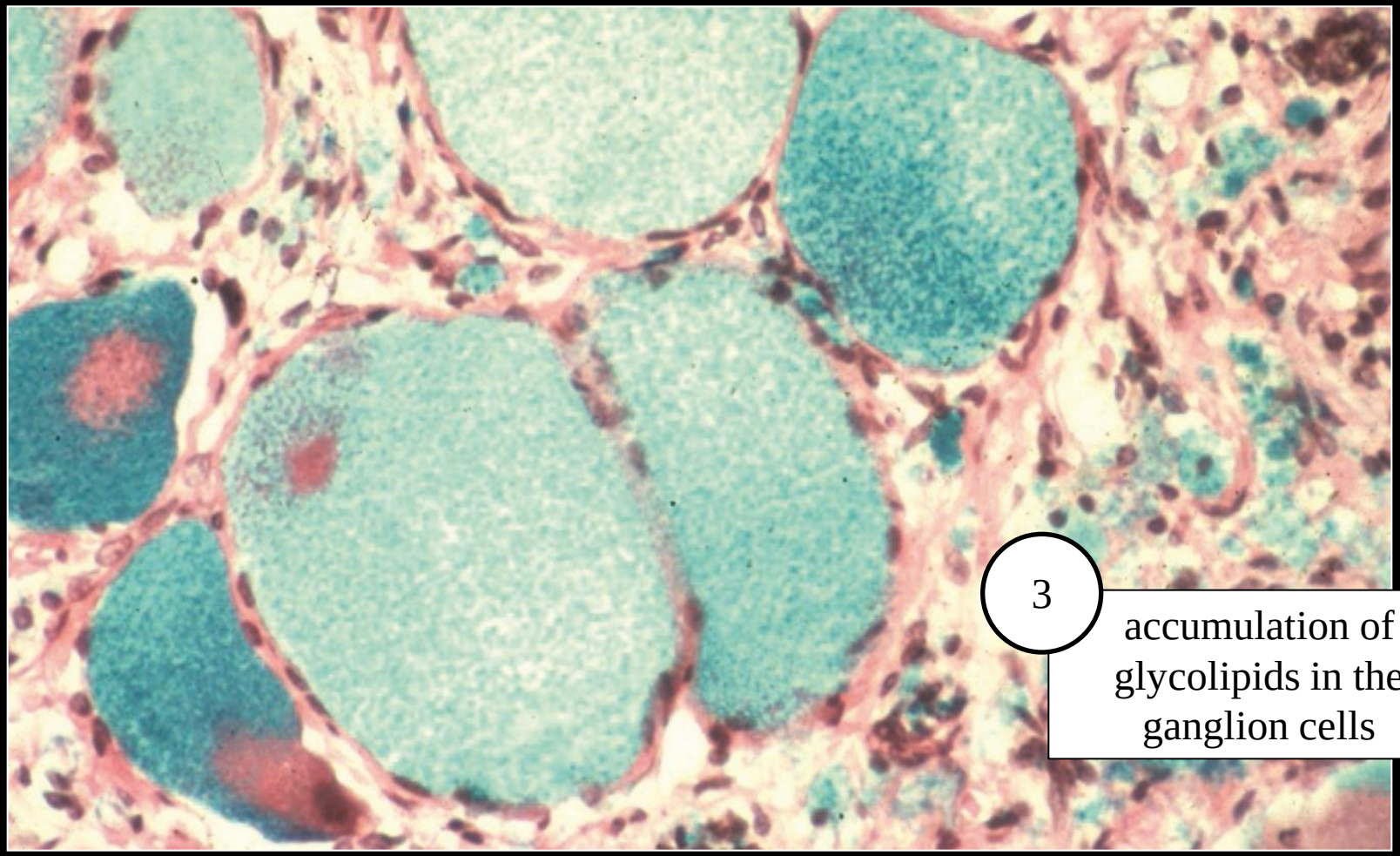




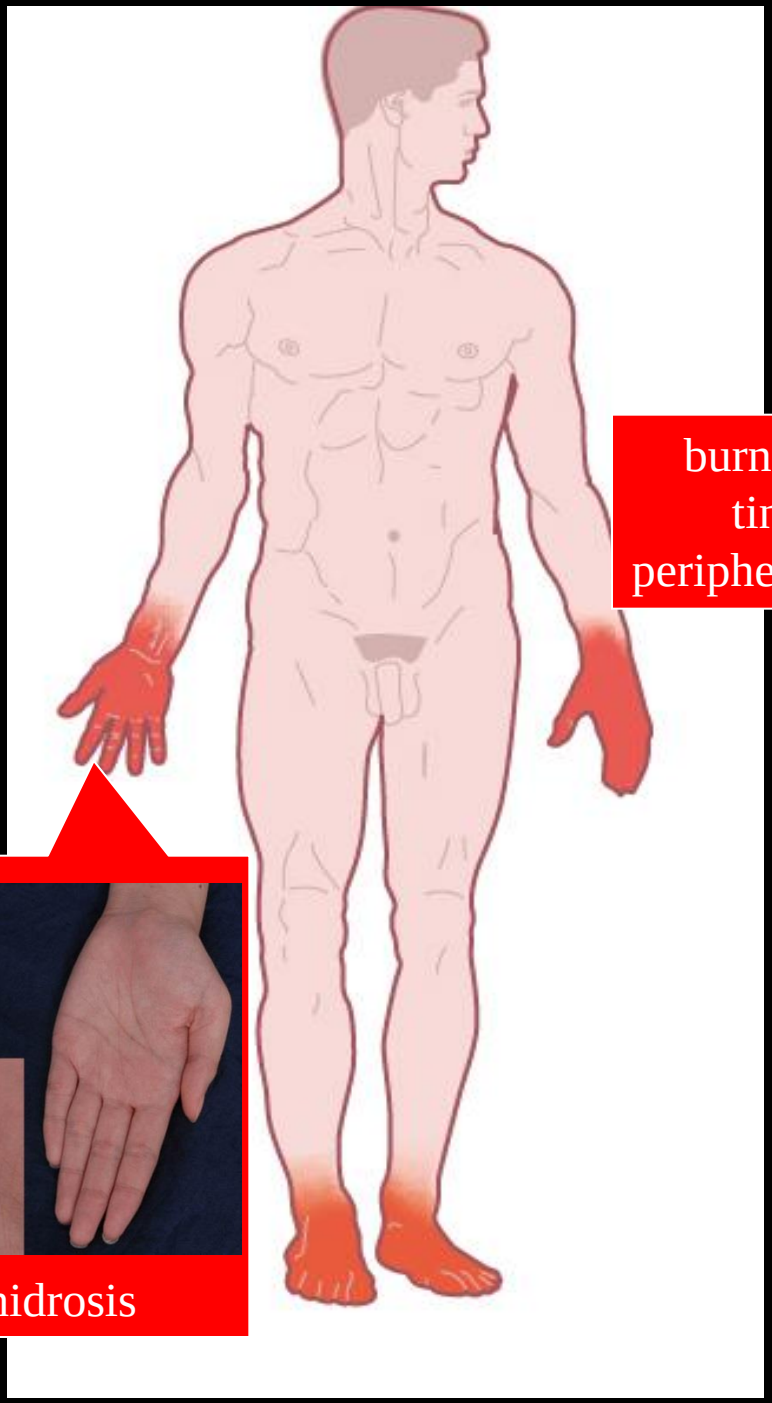
Themistocleus AC et al. *Pract Neurol* 2014;14:368-379


A
B


Aδ fibers
(more than C fibers)
lower leg
back
1
chronic nerve ischemia
2
direct pathological effect of (lyso)Gb3 on the ganglia or axons



Burlina et al. *BMC Neurol* 2011;11:61



Hypohidrosis

boys, 60 – 80% (9 yrs)
girls, 40 – 60% (16 yrs)

burning, nagging, tingling pain peripheral dysesthesias

«pain crises»

(excruciating, agonizing, lightning, stabbing)

Trigger:
rapidly changing body temperature

(i.e, fever, stress, physical activity,…)

diminishing over time

impairment of quality of life, depression

Misdiagnosis of neuropathic pain in FD

Symptom (number of patients)	Diagnosis (number of patients)	Treatment (number of patients)
Acroparesthesias (34)	Rheumatic fever (12)	Analgesics (10)
	Cryptogenic (10)	None (8)
	Viral disorders (5)	Penicillin (7)
	Psychogenic (3)	Insoles (4)
	Rheumatism (3)	Antibiotics (3)
	Gout (3)	Rest (2)
	Flat feet (2)	Allopurinol + colchicine (1)
	Growing pains (2)	
	"Bone problems" (2)	
	Circulatory problems (1)	
	Arthritis (1)	
	Brucellosis (1)	
	Raynaud's phenomenon (1)	

Marchesoni CL et al. *J Pediatr* 2010;156:828-831

Primary	Secondary
Idiopathic	Metabolic
▶ Idiopathic small fibre neuropathy	▶ Impaired glucose tolerance
▶ Burning mouth syndrome	▶ Diabetes mellitus
	▶ Rapid glycaemic control
	▶ Vitamin B12 deficiency
	▶ Dyslipidaemia
	▶ Hypothyroidism
	▶ Chronic kidney disease
Hereditary/genetic	Infections
▶ $Na_v1.7$ mutations	▶ HIV
▶ $Na_v1.8$ mutations	▶ Hepatitis C
▶ Familial amyloid polyneuropathy	▶ Influenza
▶ Fabry's disease	Toxins and drugs
▶ Tangier's disease	▶ Anti-retrovirals
	▶ Antibiotics—metronidazole, nitrofurantoin, linezolid
	▶ Chemotherapy—bortezomib
	▶ Flecainide
	▶ Statin
	▶ Systemic lupus erythematosus
	▶ Vasculitis
	▶ Inflammatory bowel disease
	▶ Paraneoplastic
	▶ Monoclonal gammopathy/amyloid

Causes of small fiber neuropathy

…routine screening for FD is not warranted in patients with isolated SFN

De Greef BT et al. *PLoS One*. 2016;11(2):e0148316

Themistocleus AC et al. *Pract Neurol* 2014;14:368-379

FabryScan

Please cross the answer most applicable to you:
Absolutely correct O, Fairly true O, Not really true O, Most definitely not O

1. **In the past have you suffered from a feverish infection at the same time as from pain in your hands or feet?**
2. Do you regularly notice a reddening of the skin over the painful part of the body?
3. **Compared with others in the same situation, do you sweat less or even not at all?**
4. Are your pains particularly distinctive for a burning sensation?
5. **Is the maximum of pain localised in your hands and/or your feet?**
6. **Have you ever noticed small spots of reddening on the skin around the pelvis?**
7. **Is there any swelling of the joints in conjunction with your symptoms of pain?**
8. **Is your physical capacity clearly much more restricted in the summer months as compared to other people?**
9. **Were sports at school only restrictedly possible owing to the pain?**
10. **Do the symptoms of pain occur with high outdoor temperatures?**
11. Does the skin in the painful area feel warmer to the touch as compared to the areas that are not pain-ridden?
12. Do you spend more time than others on the toilet?
13. Does hot water (for example when bathing or rinsing) trigger an unpleasant feeling in your hands or feet?
14. **When you wake up in the morning, do you frequently suffer from a "stiffness" of the painful joints that lasts for longer than 30 min?**
15. **Are you frequently conscious of tingling sensations in your hands and/or feet that are not painful?**

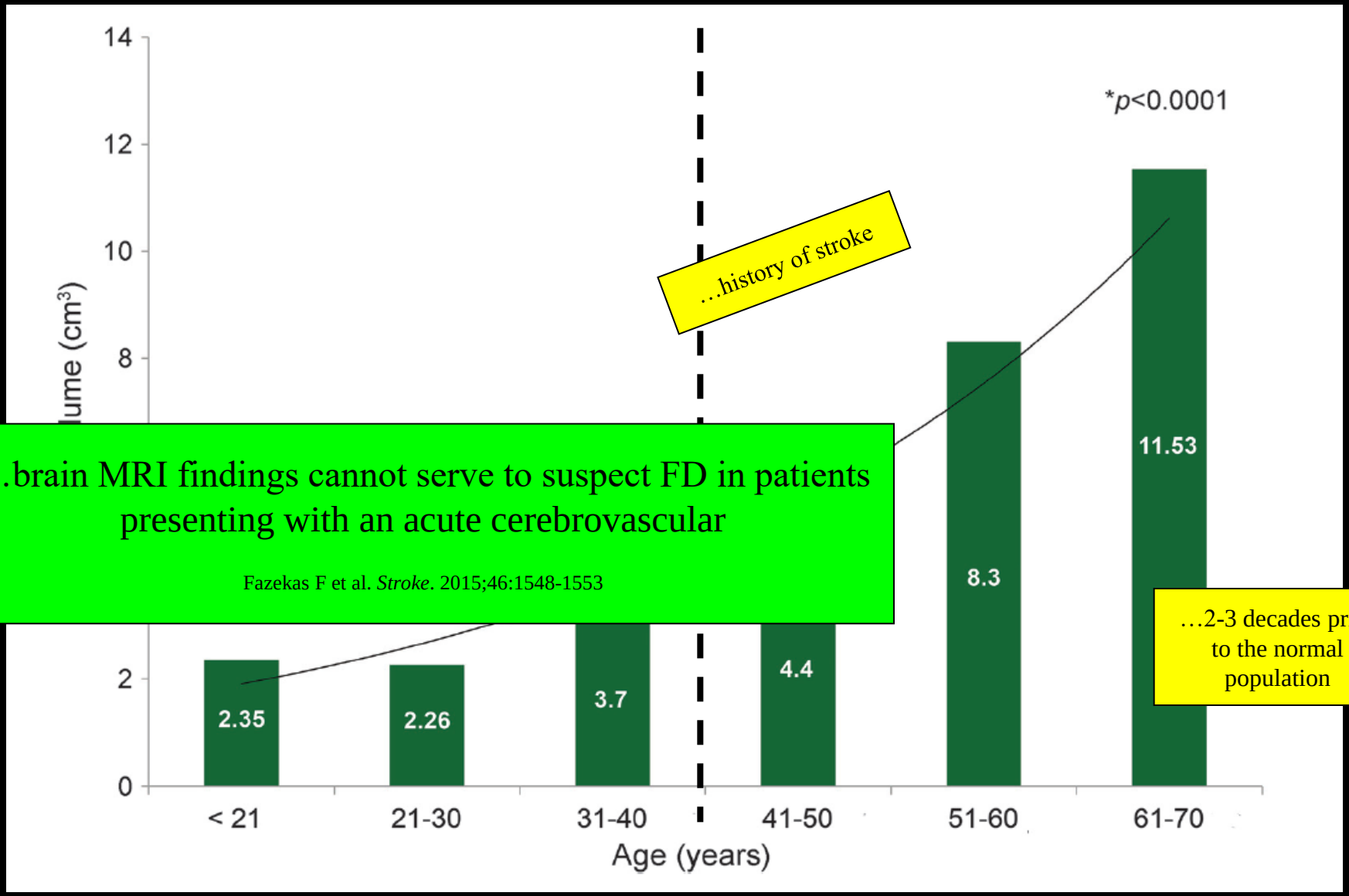
Arning K et al. *J Neurol* 2012;259;2393-2400

White Matter Hyperintensities (WMH)

11/187 (5.9%)
1M, 10F

- asymmetric, confluent white matter lesions on MRI without or with very mild corpus callosum T2-hyperintensities and/or
- lack of gadolinium enhancement and/or normal spinal MR imaging and/or
- ectatic vertebrobasilar arteries and/or
- lacking evidence of intrathecally derived immunoglobulin synthesis (diagnostic standard: oligoclonal bands)

Bottcher T et al. *PlosOne* 2013;8:e71894



…brain MRI findings cannot serve to suspect FD in patients presenting with an acute cerebrovascular

Fazekas F et al. *Stroke*. 2015;46:1548-1553

…2-3 decades prior to the normal population

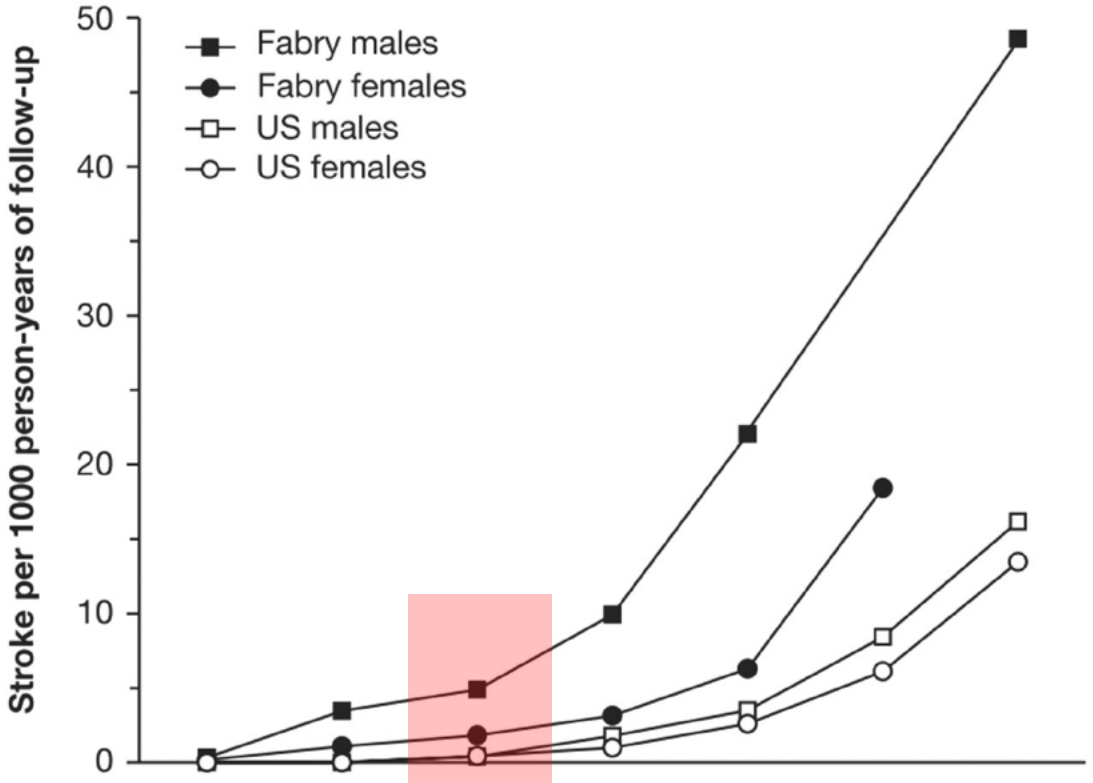
Rost N et al. *Neurology* 2016;86:1880-1886

Stroke in FD

Prevalence:
men, 6.9%
women, 4.3%

Age:
28 – 50 yrs
men, 39.0 yrs
women, 46.0 yrs
(22% under 30 yrs)

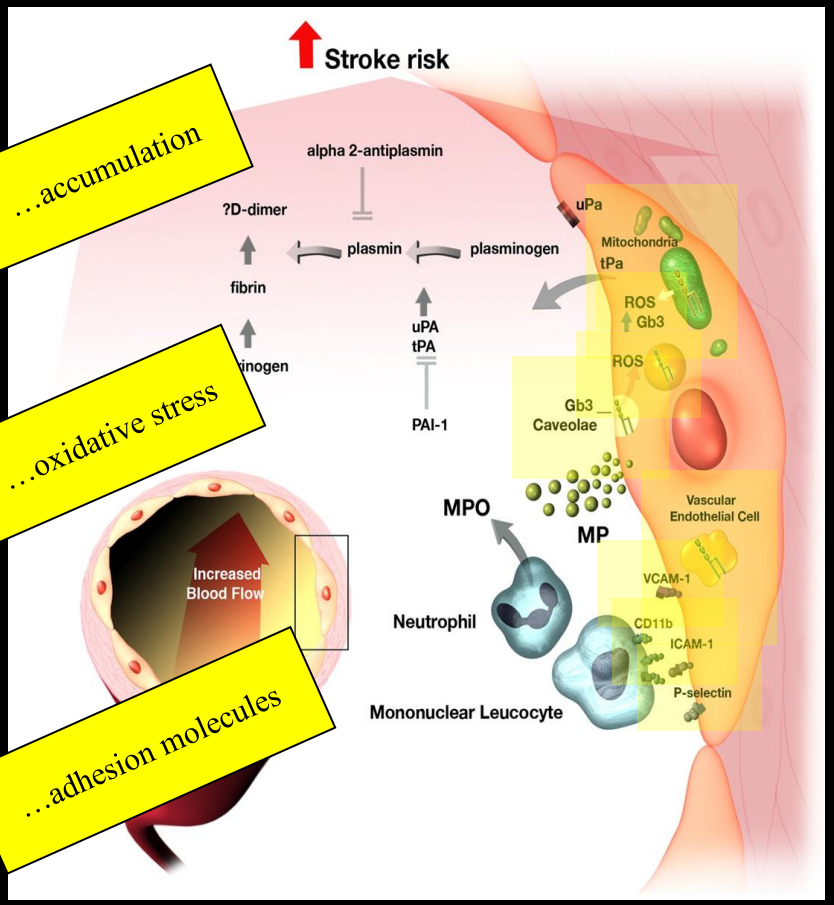
50% men
38% women
not yet diagnosed



Age groups	0 to <25 years	25 to <35 years	35 to <45 years	45 to <55 years	55 to <65 years	65 to <75 years	75 to <85 years
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

Kolodny E et al. *Stroke* 2015;46:302-313

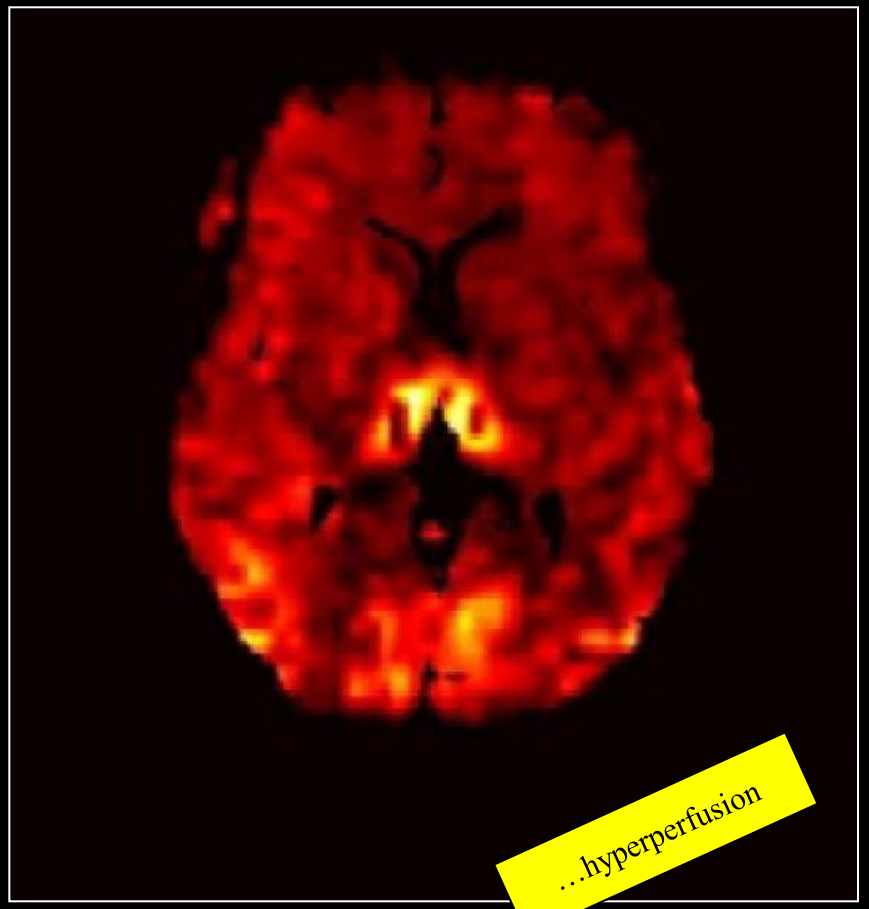
Mechanisms of cerebral vasculopathy in FD



…accumulation

…oxidative stress

…adhesion molecules



…hyperperfusion

Schiffmann R. *Pharmacol Therap* 2009;122:65-77

Moore DF et al. *J Neurol Sci* 2007;257:258-263

Prevalence of Fabry disease among younger patients with stroke

…mutations identified?

Trial	Patients Screened, n	Patients With Fabry Disease, n (%)		Age Range, Y	Mean Age at First Stroke, Y
		Men	Women		
Rolfs et al[32]	721	21 (4.9)	7 (2.4)	18–55	38.4 (men); 40.3 (women)
Brouns et al[33]	103	0	0	16–60	51.3
Wozniak et al[34]	154	1* (0.6)	...		t stated
Brouns et al[15]	1000 (573 ischemic stroke)	2 (0.4)	3 (0.[illegible]		3.2
Rolfs et al[38]	5023 (3396 ischemic stroke)	11 (0.4			ot stated
Baptista et al[14]	493 (364 ischemic stroke)				45.4
Marquardt et al[35]	1046			103	...
Sarikaya et al[36]	150 (135			18–55	43
Dubuc et al[37]			0	16–55	40.5

*All patie

…routine screening for FD is not warranted in young patients with stroke

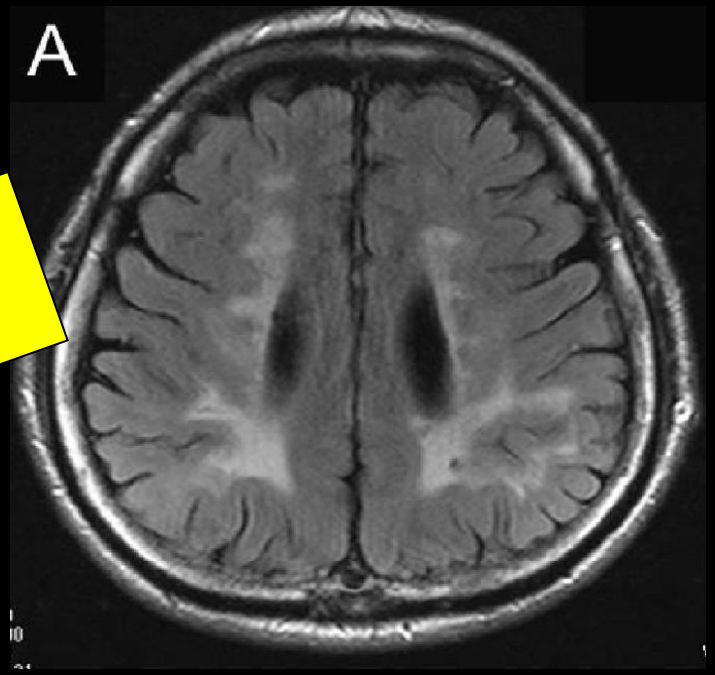
Kolodny E et al. *Stroke* 2015;46:302-313

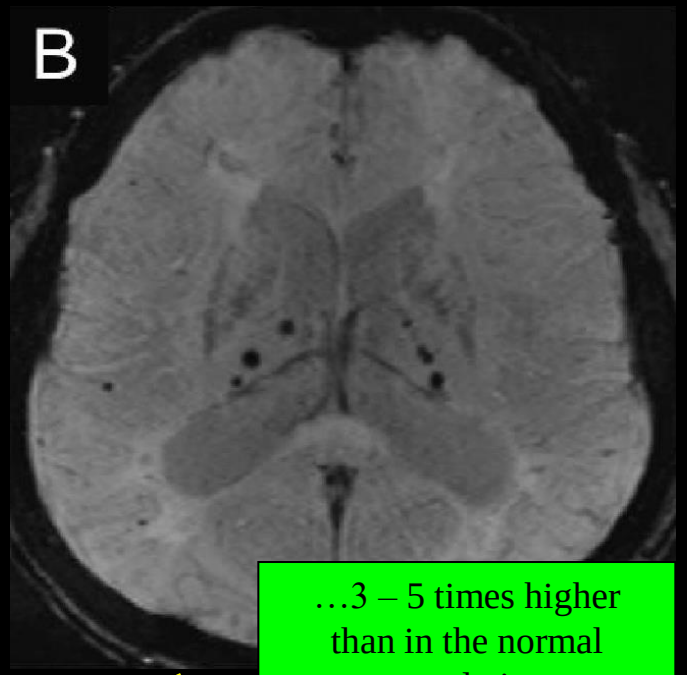
Kolodny E et al.

Kilarsky et al	[illegible]ar stroke	0 (0.0)	0 (0.0)	<70	
Fancellu et al	[illegible] any stroke (plus)	1 (0.5)	1 (0.5)	18-55	48
Romani et al	108 ischemic stroke/TIA	1 (0.9)	2 (1.8)	18-60	48.
Song et al	357 ischemic stroke/TIA	0 (0.0)	0 (0.0)	18-55	
Poli et al	353 ischemic stroke (IPSYS)	0 (0.0)	0 (0.0)	18-45	37

(D313Y)
S126G
A143T
stroke-only phenotype?

Cerebral Microbleeds (CMBs)

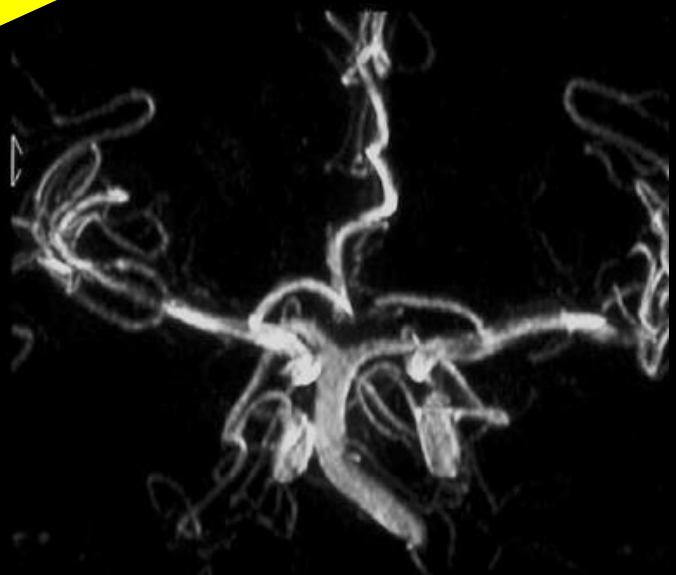




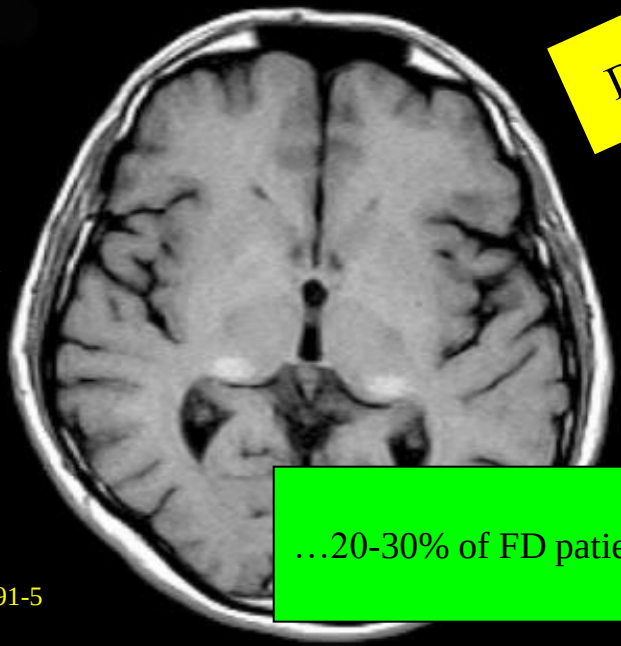
…3 – 5 times higher than in the normal population

Kono Y et al. *J Stroke Cerebrovasc Dis* 2016;25:1320-1325

Dolichoectasia

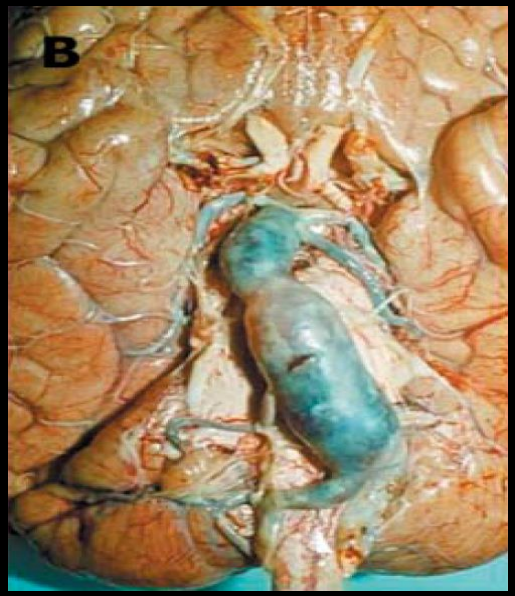


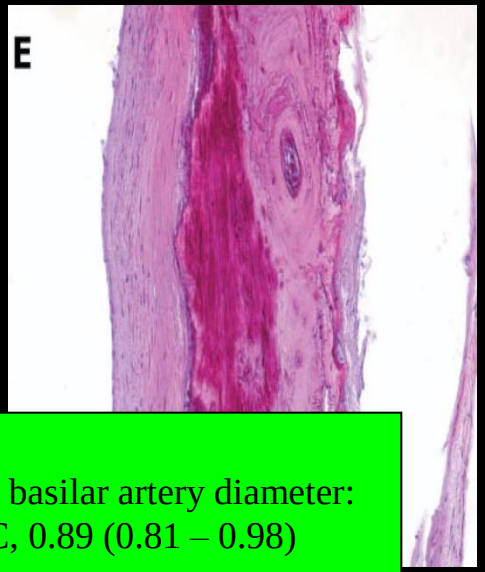
"Pulvinar Sign"

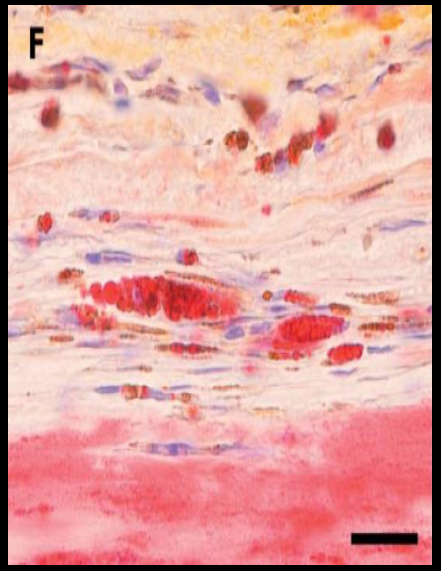


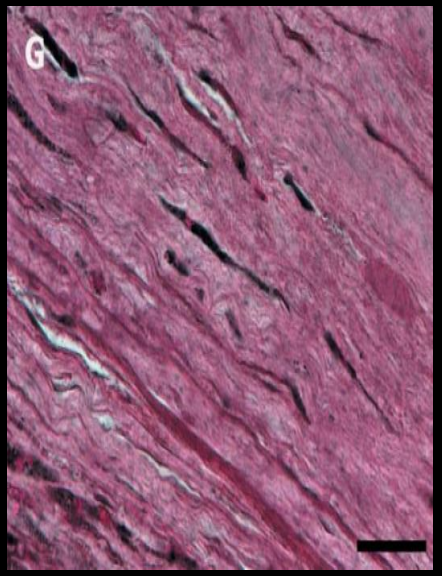
…20-30% of FD patients

Fellgiebel A et al. *Lancet Neurol* 2007;5:791-5









enlarged basilar artery diameter:
AUC, 0.89 (0.81 – 0.98)

Fellgiebel A et al. *Cerebrovasc Dis* 2011;31:294-299

Garzuly F et al. *Brain* 2005;128:2078-83

(Clinical) conclusion

- PNS:
  - Length-dependent SFN → "Fabry's crises"

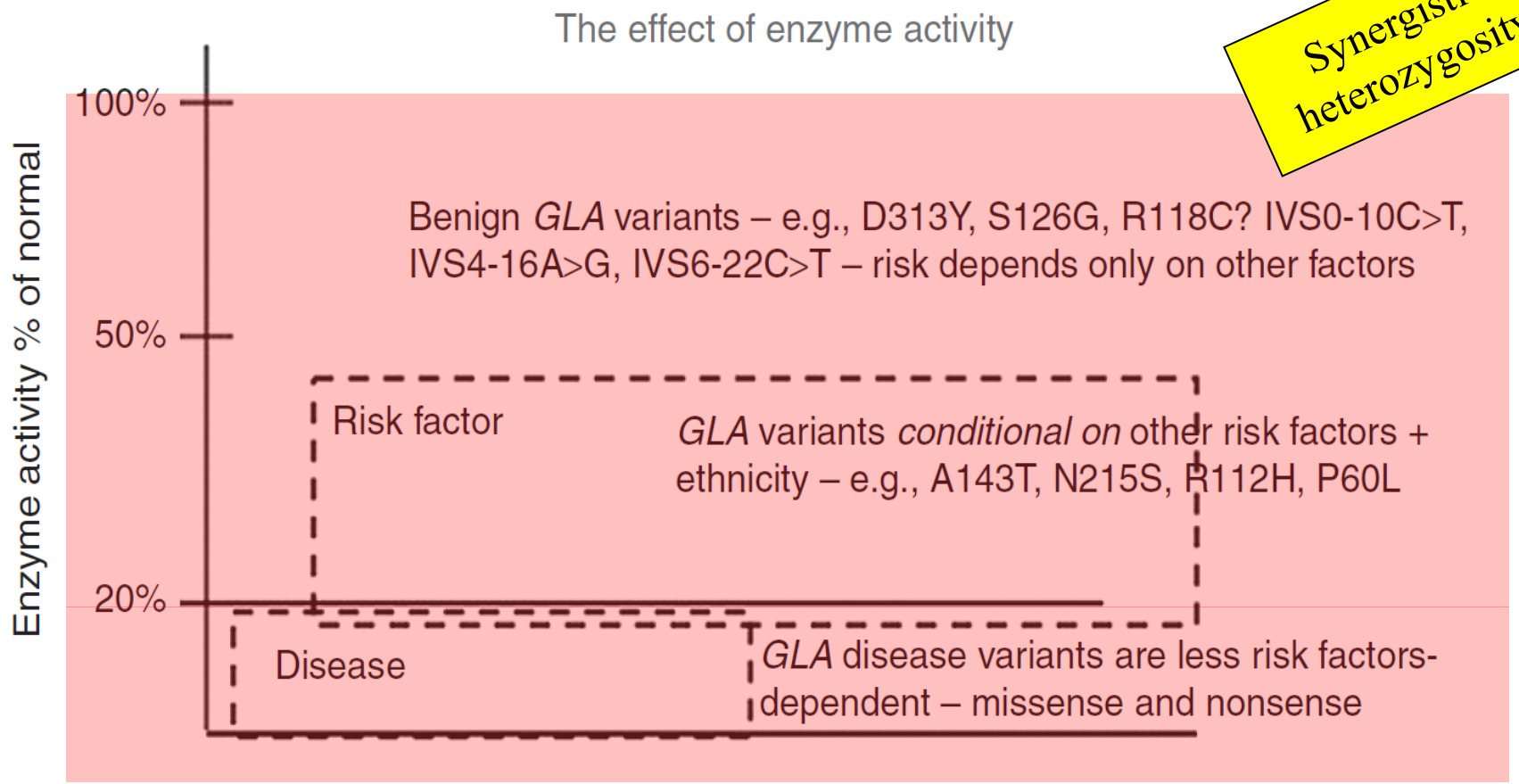
  } non-specific

- CNS:
  - Stroke (IS, ICH) → posterior circulation
  - Pulvinar sign
  - Increased diameter of the basilar artery
  - Extensive CWMHs (CMBs)

  } non-specific

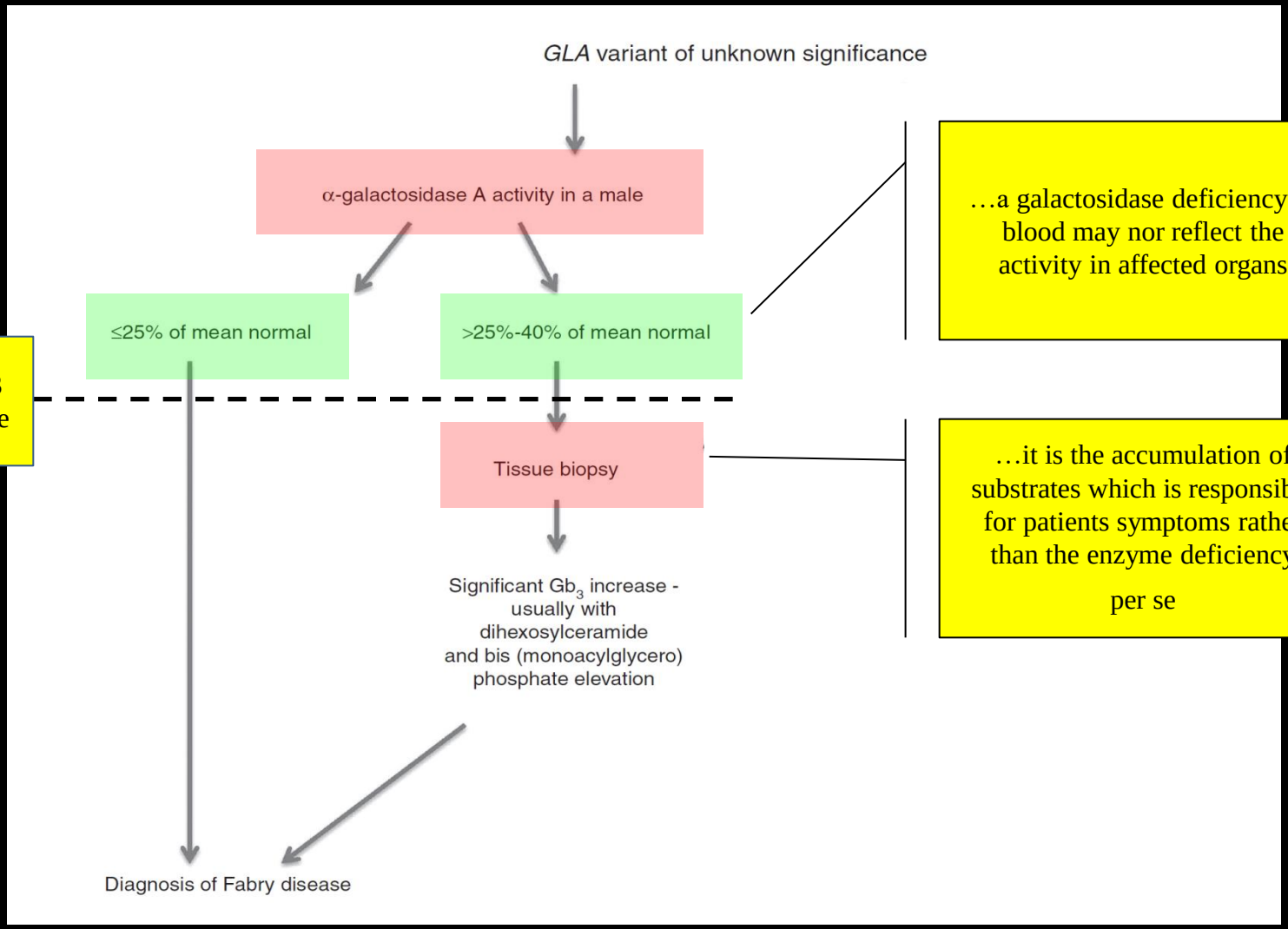
…clinicians should increase their awareness of the wide spectrum of (neurological) manifestations of FD

(Lab) conclusion



Schiffmann R et al. *Genet Med* 2016;8:906-101

Algorithm for evaluating *GLA* variants of unknown significance

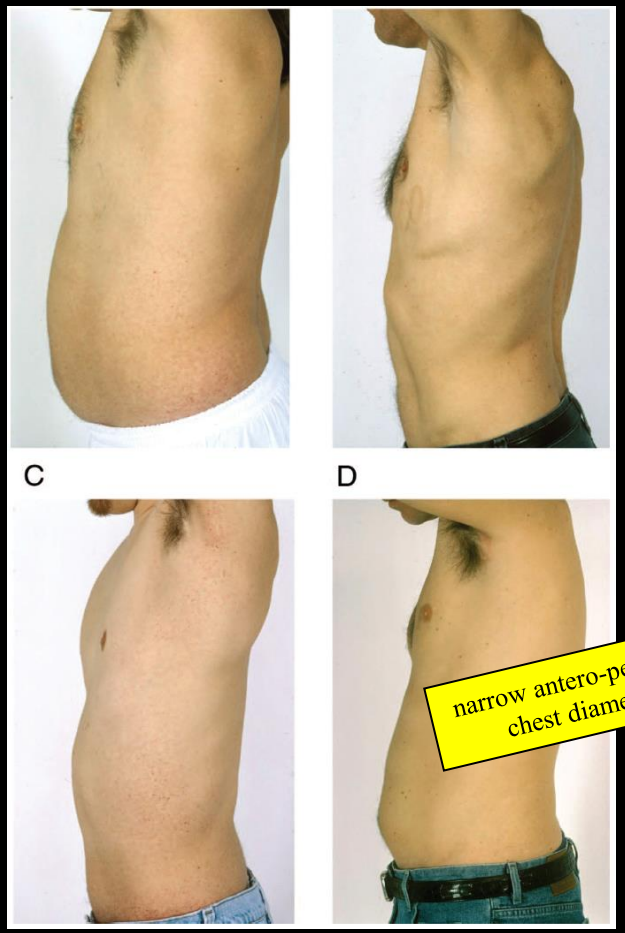


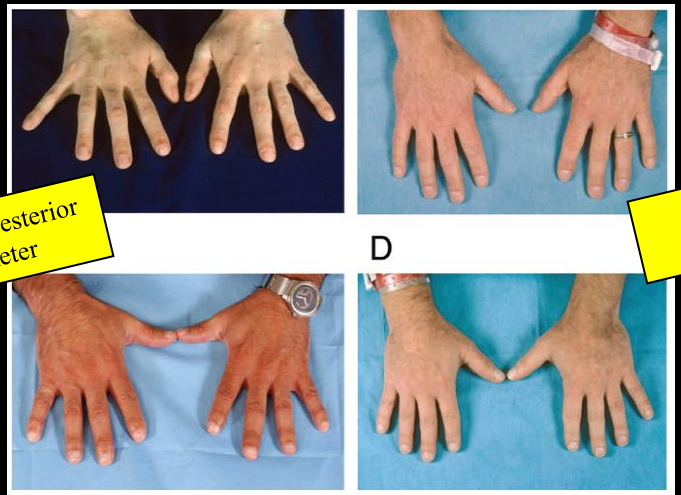
Gb3 or lyso-Gb3 in plasma or urine

…a galactosidase deficiency in blood may nor reflect the activity in affected organs

…it is the accumulation of substrates which is responsible for patients symptoms rather than the enzyme deficiency per se

Schiffmann R et al. *Genet Med* 2016;8:906-101





Ries M et al. *Genet Med* 2006;8:906-101


…thanks for your attention!