SNO CIENZE EUROLOGICHE SPEDALIERE

LA MALATTIA DI FABRY

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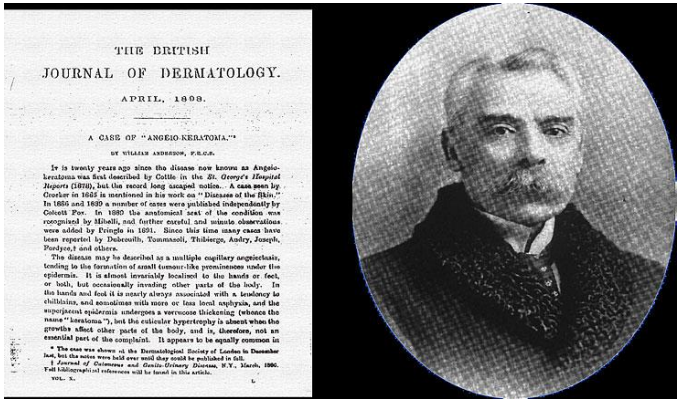
Malattia di Fabry

INSUFFICIENZA LISOSOMIALE GENETICAMENTE DETERMINATA

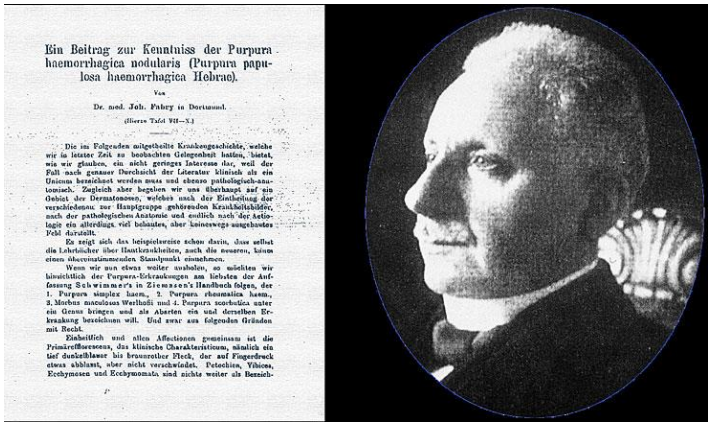
I Lisosomi sono organuli citoplasmatici, delimitati da membrana, contenenti una serie di enzimi in grado di degradare tutti i tipi di polimeri biologici:

- PROTEINE
- ACIDI NUCLEICI
- LIPIDI
- POLISACCARIDI

Svolgono la funzione di “sistema digestivo” della cellula, degradando sia materiale trasportato dall’esterno della cellula, che componenti cellulari non più utili


THE BRITISH
JOURNAL OF DERMATOLOGY.
APRIL, 1898.

A CASE OF "ANGEIO-KERATOMA."

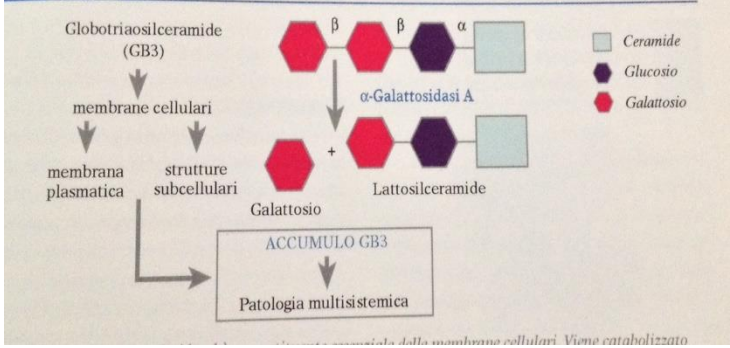

Ein Beitrag zur Kenntniss der Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae).

Von

Dr. med. Joh. Fabry in Dortmund.

Descritta per la prima volta nel 1898 da due medici, Anderson in Inghilterra e Fabry in Germania

MALATTIA DI FABRY



- Incidenza pari a 1 su 40.000 maschi.
- L'enzima deficitario è l' a-galattosidasi A
- Il deficit provoca accumulo di glicosfingolipidi soprattutto globotriaosilceramide Gb3 nei tessuti viscerali e nell'endotelio vascolare di tutto l'organismo con conseguente coinvolgimento vascolare essenzialmente a livello renale, cardiaco e del sistema nervoso centrale

IL GENE….

- α- GALATTOSIDASI A (GLA)
- Mappa sul braccio lungo del cromosoma X
- Ad oggi sono state identificate circa 585 mutazioni sul gene con alcuni "hot spot" dove si localizzano le mutazioni più frequenti
- Circa il 75% sono mutazioni puntiformi nonsense o missense
- Il restante 25% sono riarrangiamenti, inserzioni,delezioni, difetti di splicing e del codone di stop

….L'ENZIMA….

A-GALA determina il distacco del galattosio da sfingolipidi complessi quali Gb3 garantendo il riutilizzo di questi prodotti da parte della cellula…

FABRY Newborn Screening TUSCANY-UMBRIA RESULTS

Screened newborns 66625

November 2014 – December 2017

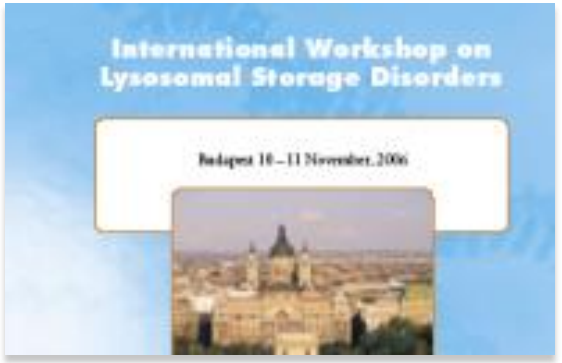
	NBS Positive	Positive at recall	Confirmed by mutation analysis	Prevalence
			Affected	
Fabry (GLA)	**21**	**15**	**15**	**1 : 4441**

IN PASSATO

Forma Classica

Variante Renale

Variante Cardiaca



NOW….

Forma asintomatica

Forme intermedie

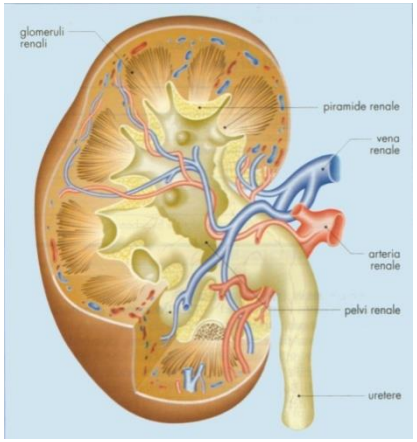
Forma Classica SEVERA

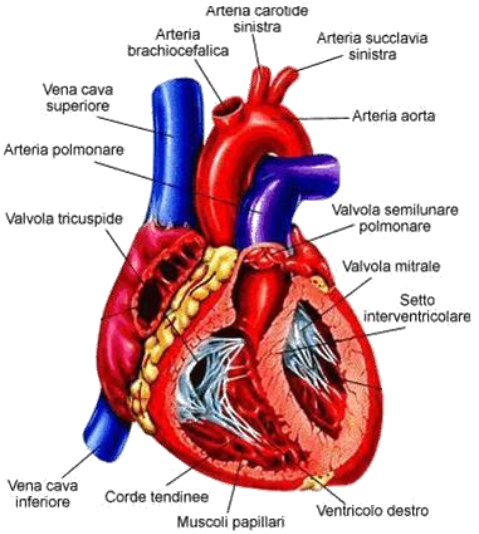
FOS data suggests women "carriers" can exhibit progressive Fabry disease

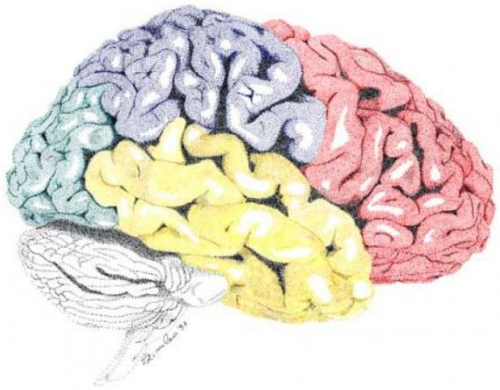
- Fabry is an X-linked genetic disease
- Women were historically considered to be "carriers" and not symptomatic1,2,3
- Data suggest women can experience the full range of Fabry symptoms experienced by men1,2,3

1. Mehta A *et al. Eur J Clin Invest.* 2004; 34: 236-242
2. Deegan PB *et al. J Med Genet.* 2006; 43: 347-352
3. Hughes DA *et al. Mol Genet Metab.* 2011; 103: 207-14

PATOLOGIA MULTISISTEMICA







CNS manifestations of Fabry's disease

Andreas Fellgiebel, Matthias J Müller, Lionel Ginsberg

Background Fabry's disease is a rare hereditary lysosomal storage disease with multiorgan involvement. Deficiency of α-galactosidase A activity leads to accumulation of neutral glycosphingolipids, especially in vascular endothelial and smooth-muscle cells. Along with progressive renal and cardiac dysfunction, stroke is a major and often life-threatening burden of the disease. Cerebral vasculopathy, confirmed by neuropathological, neuroradiological, and functional studies, occurs commonly and leads to ischaemic cerebrovascular events at an early age.

Lancet Neurol 2006; 5: 791–95

Department of Psychiatry, University of Mainz, Mainz, Germany (A Fellgiebel MD, M J Müller MD); and Department of Neurology, Royal Free Hospital, London,

Panel: Neurological features of Fabry's disease

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

MALATTIA DI FABRY: diagnosi clinica

Ricercare:

- ☐ lesioni ischemiche a carico del circolo posteriore,
- ☐ dolicoectasia dell'asse vertebrobasilare,
- ☐ dist. gastrointestinali
- ☐ cardiomiopatia ipertrofica,
- ☐ cornea verticillata,
- ☐ angiocheratomi,
- ☐ ipoacusia n-s,
- ☐ polineuropatia,
- ☐ proteinuria.

Zarate 2008

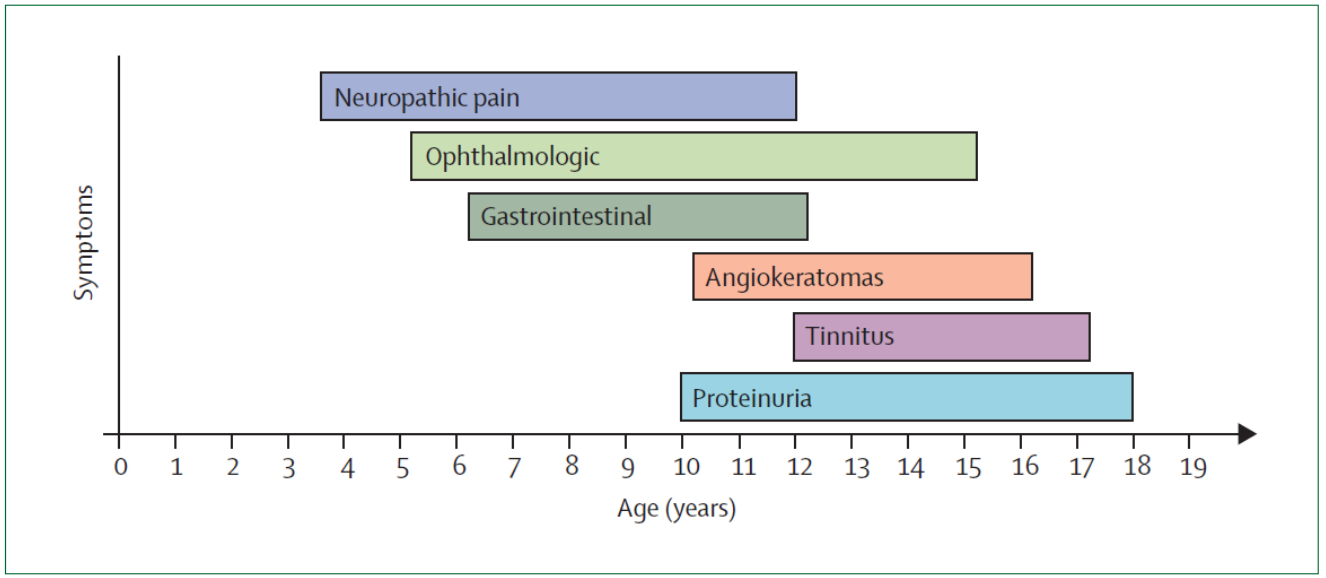


Figure 3: Ranges of age at onset of different clinical manifestations in men with Fabry's disease

Acta Paediatr Suppl. 2005 Mar;94(447):24-7; discussion 9-10.

Natural history of the cerebrovascular complications of Fabry disease.

Mehta A[1], Ginsberg L; FOS Investigators.

Author information

Abstract

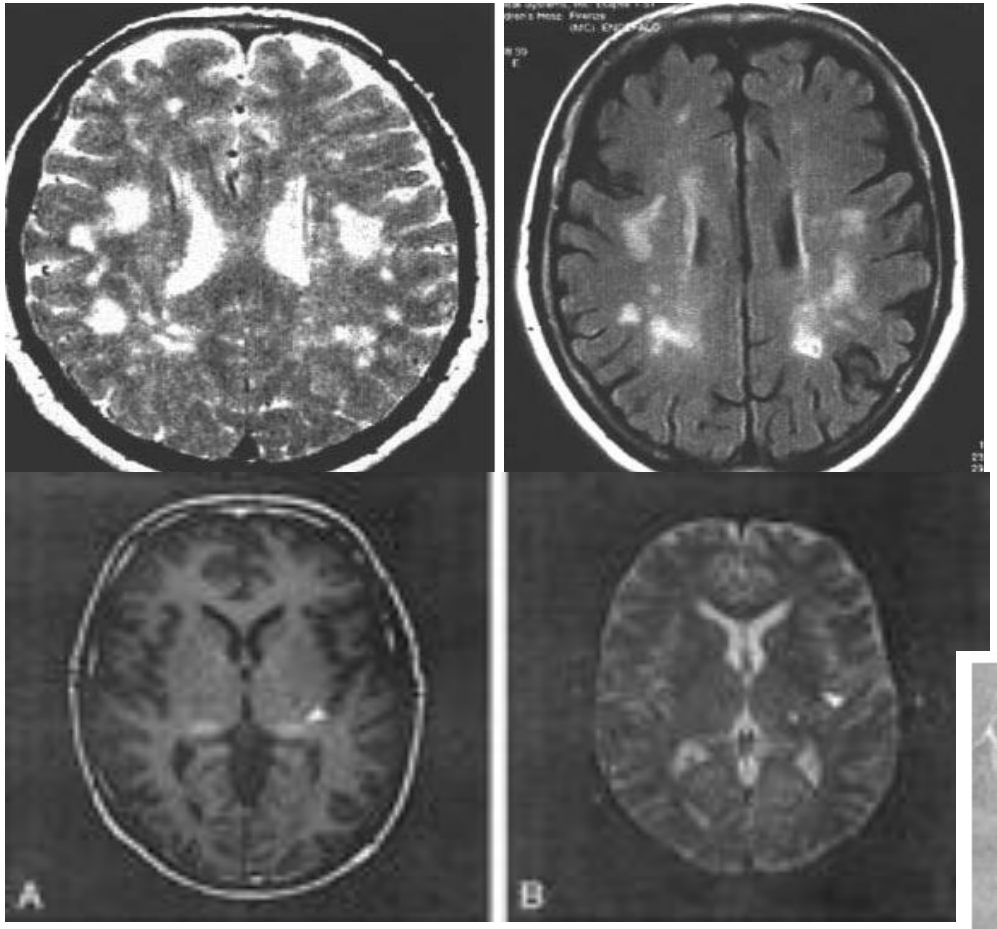
Fabry disease is a rare, X-linked lysosomal storage disease caused by an inborn deficiency of alpha-galactosidase A, which results in progressive accumulation of globotriaosylceramide in a range of cells and tissues. Neurological symptoms of Fabry disease, including peripheral neuropathy and cerebrovascular events, are among the most significant clinical aspects. In this paper we present the natural history and mechanisms involved in the cerebrovascular complications of Fabry disease using data reported in FOS-- the Fabry Outcome Survey--and other registries and clinical studies. We discuss ways in which these manifestations can be modified by intervention, including both general measures for cerebrovascular disease and enzyme replacement therapy.

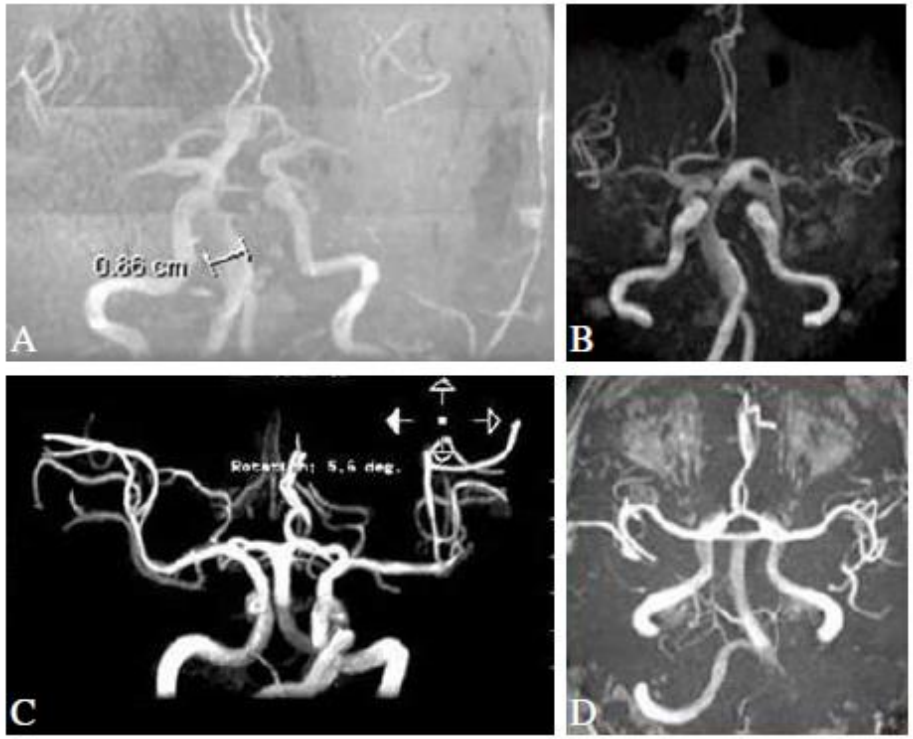
CONCLUSION: Data from FOS have provided important insights into the natural history of the cerebrovascular complications of Fabry disease. Furthermore, the database has demonstrated that significant renal or cardiac disease often co-exists with cerebrovascular disease, and may predispose patients with Fabry disease to neurological disability and stroke.

La prevalenza degli eventi cerebrovascolari nei p. FOS→13% (III-IV decade negli uomini con rischio di eventi cerebrovascolari 12 volte più elevato rispetto a soggetto sani dello stesso sesso e della stessa età)

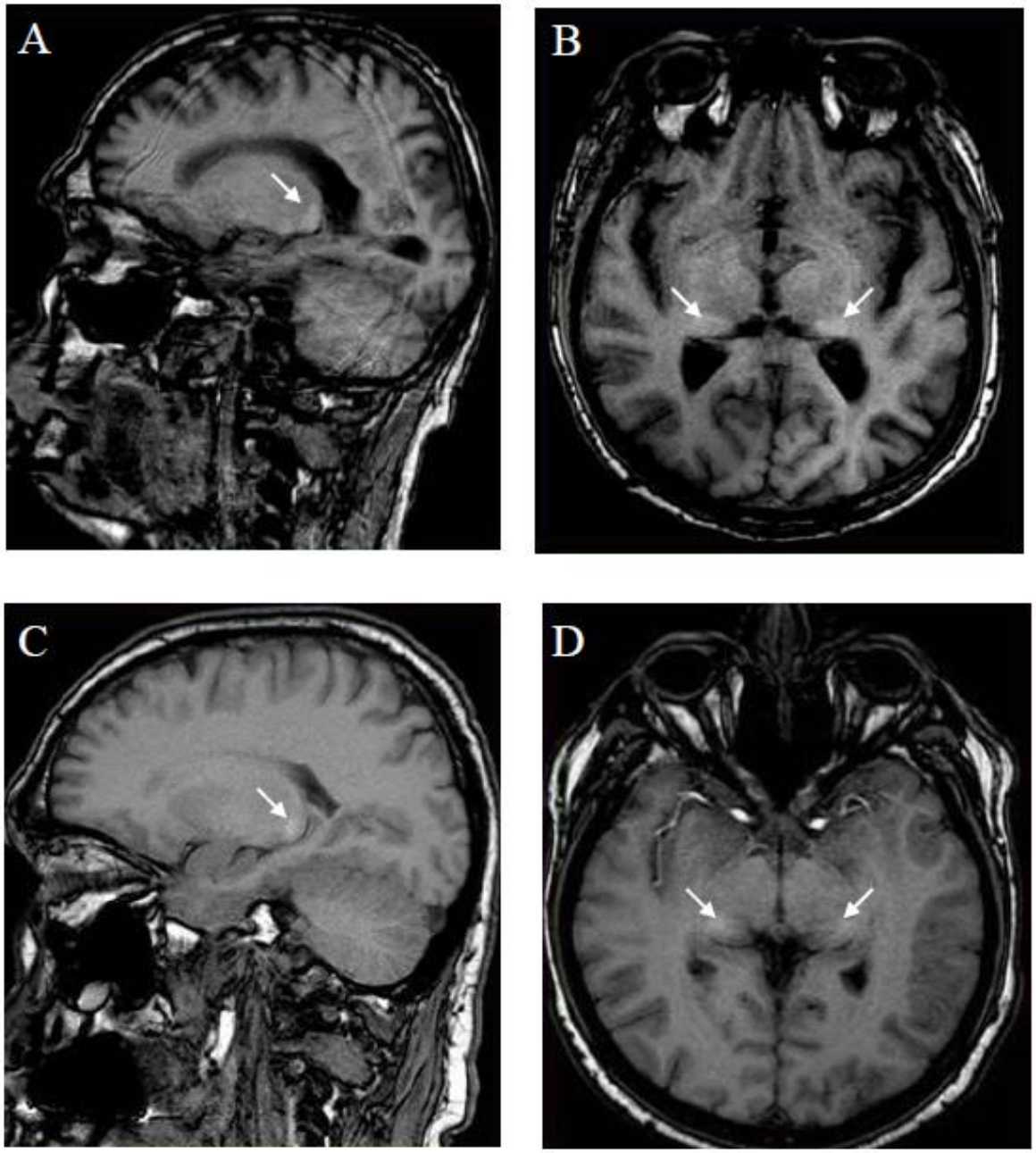
Prevalenza 16% donne, 11% uomini

Maggior prevalenza di eventi cerebrovascolari in p. FOS con coinvolgimento cardiaco e renale





Dolicoectasia vertebro-basilare



Pulvinar signs: hyperintensity in the pulvinar on T1-weighted images is a common finding in FD, likely reflecting the presence of calcification. Recent findings suggest that the pulvinar sign is a highly specific sign, distinctively characteristic of FD

ORIGINAL ARTICLE

Fabry Disease: prevalence of affected males and heterozygotes with pathogenic *GLA* mutations identified by screening renal, cardiac and stroke clinics, 1995–2017

Dana Doheny, Ram Srinivasan, Silvere Pagant, Brenden Chen, Makiko Yasuda, Robert J Desnick

J Stroke Cerebrovasc Dis. 2018 Mar;27(3):575-582. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.045. Epub 2017 Nov 11.

Prevalence of Fabry Disease in Young Patients with Stroke in Argentina.

Reisin RC[1], Mazziotti J[2], Cejas LL[2], Zinnerman A[3], Bonardo P[2], Pardal MF[2], Martínez A[3], Riccio P[4], Ameriso S[5], Bendersky E[6], Nofal P[7], Cairola P[8], Jure L[9], Sotelo A[10], Rozenfeld P[11], Ceci R[11], Casas-Parera I[12], Sánchez-Luceros A[13]; AISYF Investigators.

Prevalence of Fabry Disease and Outcomes in Young Canadian Patients With Cryptogenic Ischemic Cerebrovascular Events

Sylvain Lanthier, MD, OD, CSPQ*; Gustavo Saposnik, MD, MSc*; Gerald Lebovic, PhD; Karen Pope, MSc; Daniel Selchen, MD, FRCPC; David F. Moore, MD, PhD; on behalf of the Canadian Fabry Stroke Screening Initiative Study Group†

Clinical Sciences

Clinical Pregenetic Screening for Stroke Monogenic Diseases

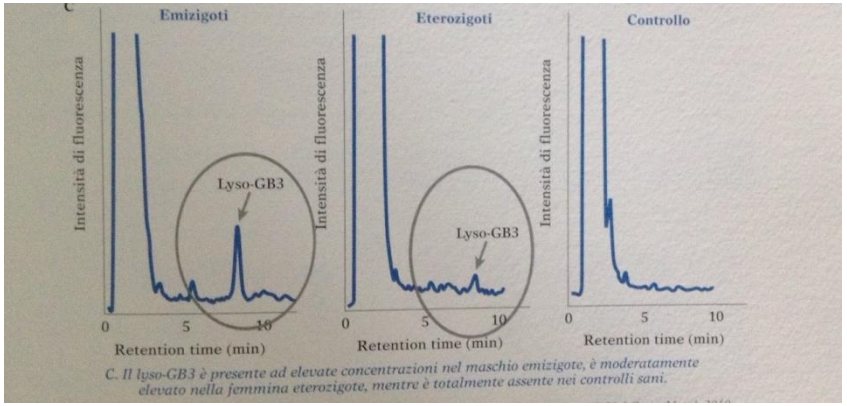
Results From Lombardia GENS Registry

Anna Bersano, MD, PhD; Hugh Stephen Markus, MD, PhD; Silvana Quaglini, PhD; Eloisa Arbustini, MD, PhD; Silvia Lanfranconi, MD; Giuseppe Micieli, MD; Giorgio B. Boncoraglio, MD; Franco Taroni, MD; Cinzia Gellera, MD; Silvia Baratta, PhD; Silvana Penco, PhD; Lorena Mosca, PhD; Maurizia Grasso, MD; Paola Carrera, BSc; Maurizio Ferrari, MD; Cristina Cereda, MD; Gaetano Grieco, PhD; Stefania Corti, MD, PhD; Dario Ronchi, PhD; Maria Teresa Bassi, PhD; Laura Obici, MD; Eugenio A. Parati, MD; Alessando Pezzini, MD, PhD; Maria Luisa De Lodovici, MD; Elena P. Verrengia, MD; Giorgio Bono, MD, PhD; Francesca Mazucchelli, MD; Davide Zarcone, MD; Maria Vittoria Calloni, MD; Patrizia Perrone, MD; Bianca Maria Bordo, MD; Antonio Colombo, MD; Alessandro Padovani, MD, PhD; Anna Cavallini, MD; Simone Beretta, MD; Carlo Ferrarese, MD, PhD; Cristina Motto, MD; Elio Agostoni, MD; Graziella Molini, MD; Francesco Sasanelli, MD; Manuel Corato, MD; Simona Marcheselli, MD; Maria Sessa, MD; Giancarlo Comi, MD, PhD; Nicoletta Checcarelli, MD; Mario Guidotti, MD; Davide Uccellini, MD; Erminio Capitani; Lucia Tancredi, MD; Marco Arnaboldi, MD; Barbara Incorvaia, MD; Carlo Sebastiano Tadeo, MD; Laura Fusi, MD; Giampiero Grampa, MD; Giampaolo Merlini, MD, PhD; Nadia Trobia, PhD; Giacomo Pietro Comi, MD, PhD; Massimiliano Braga, MD; Paolo Vitali, MD; Pierluigi Baron, MD†; Caspar Grond-Ginsbach, PhD; Livia Candelise, MD, PhD; on behalf of Lombardia GENS Group*

Prevalenza di MF in p. con stroke giovanile: 0.3%

DIAGNOSI

- Clinica
- Dosaggio dell'attività enzimatica mediante Dried Blood Spot (DBS)
- Ricerca mutazione nel gene GLA
- Dosaggio Gb3 sierico ed urinario (spettrometria Tandem-massa)
- LysoGb3



C. Il lyso-GB3 è presente ad elevate concentrazioni nel maschio emizigote, è moderatamente elevato nella femmina eterozigote, mentre è totalmente assente nei controlli sani.

DIAGNOSI DIFFERENZIALE
Monogenic diseases and ischemic stroke

BBA Clinical 3 (2015) 96–106

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Table 1
Common mutations in monogenic diseases for details see the text.

Monogenic diseases	Involved genes	Genes functions	References
MELAS	*tRNA (Leu) A3243G*	Mitochondrial tRNA	[21,22]
	tRNA (Leu) T3271C	Mitochondrial tRNA	[23]
	tRNA (Lys) A8344G	Mitochondrial tRNA	[24]
Familial hemiplegic migraine	*CACNA1A*	Encoding the alpha1A sub-unit of the voltage-gated calcium channels in neurons	[39]
CADASIL	*NOTCH3*	Unknown	[40]
CARASIL	*HTRA1*	Protease	[40]
FABRY	*α-GAL A*	Encoding α-galactosidase A enzyme	
Small vessel disease	*COL4A1*	Encoding the α1[IV]-chain of type IV collagen	[40]
HERNS	*TREX1*	Encoding three-prime repair exonuclease 1	[40]
Stroke and vasculopathy with ADA2 mutations	*CECR1*	Encoding the ADA2 protein (important for endothelial and leukocyte development and differentiation)	[63]
Homocystinuria	*Multiple genes encoding different enzymes*	Deficiencies of this enzymes can cause very high plasma concentrations of homocysteine and homocystinuria	[12]
Sickle cell disease	*Haemoglobin beta chain gene*	Encoding for beta chain of normal haemoglobin (mutation of this gene causes polymerization or aggregation of abnormal hemoglobin -, HbS - within red blood cells)	[39]
Vascular Ehlers-Danlos syndrome	*COL3A1*	Encoding collagen type III	[12]
Marfan syndrome	*FBN1*	Encoding fibrillin 1	[65]
Pseudoxanthoma elasticum	*ABCC6*	ATP-binding cassette C6	[66]

MALATTIA DI FABRY terapia

La terapia enzimatica sostitutiva riduce le complicanze renali e cardiache, ma mancano dati sulla riduzione delle complicanze cerebrovascolari.

Migalastat monoterapia o in associazione a ERT. Prima terapia chaperonica orale

Terapia Sintomatica

Work in Progress → Terapia Genica

PROGETTI PISA

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Mitochondrial DNA haplogroups may influence Fabry disease phenotype

C. Simoncini[a], L. Chico[a], D. Concolino[b], S. Sestito[b], L. Fancellu[c], W. Boadu[c], G.P. Sechi[c], C. Feliciani[d], M. Gnarra[d], A. Zampetti[e], A. Salviati[f], M. Scarpelli[g], D. Orsucci[a], U. Bonuccelli[a], G. Siciliano[a], M. Mancuso[a,*]

Table 1
Frequency of mtDNA haplogroups among patients and controls. Haplogroup I and H were more frequent in the patient group than in controls ($P < 0.001$ [significance levels after Bonferroni's correction = 0,005]).

Haplogroups	Controls (n)	%	Patients (n)	%	P
H	73	40,4	49	63,6	0,0007
I	3	1,7	10	13,0	0,0004
J	13	7,2	7	9,1	n.s.
K	14	7,7	0	0	n.s.
T	14	7,7	3	3,9	n.s.
U	24	13,3	4	5,2	n.s.
V	5	2,8	1	1,3	n.s.
W	4	2,2	0	0	n.s.
X	6	3,3	0	0	n.s.
OTHERS	25	13,8	3	3,9	n.s.
TOTAL	181		77		

Table 2
Frequency of mtDNA haplogroup clusters among patients and controls. Haplogroup cluster HV was more frequent in the patient group than in controls ($P < 0.005$ [significance levels after Bonferroni's correction = 0,01]).

Haplogroup clusters	Controls (n)	%	Patients (n)	%	P
HV	78	43,1	50	64,9	0,0017
WIX	13	7,2	10	13,0	n.s.
JT	27	14,9	10	13,0	n.s.
UK	38	21,0	4	5,2	n.s.
OTHERS	25	13,8	3	3,9	n.s.
Total	181		77		

ONGOING:
call for collaboration

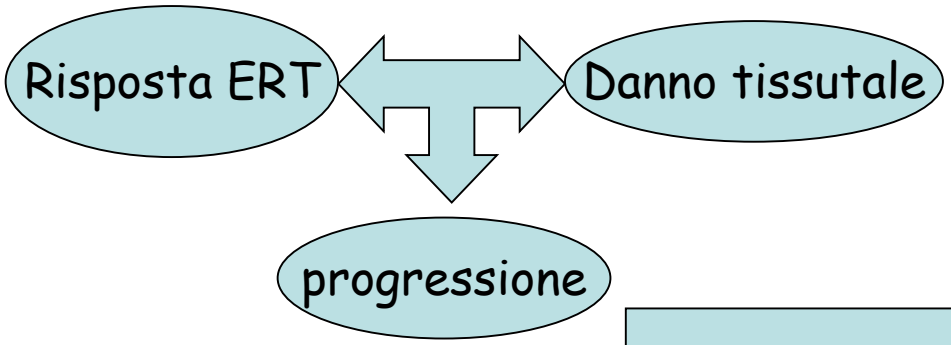
Multicenter longitudinal collaborative study: Oxidative stress parametres and mitochondrial DNA background as possible early and disease-status biomarkers of Fabry disease

- individuare un possibile biomarcatore per la malattia di Fabry, facilmente dosabile, utile sia come marcatore precoce di danno tissutale che come predittore di progressione di malattia che come possibile surrogato biochimico di risposta al trattamento

- Lyso-Gb3 biomarcatore affadibile. Tuttavia, questo marcatore non è facilmente accessibile nella maggior parte dei laboratori ed il suo ruolo negli stadi molto precoci di malattia come predittore dello sviluppo delle manifestazioni cliniche e\o di danno d'organo e\o come marcatore che possa condizionare il medico ad iniziare la terapia non è completamente chiaro

Progetti Pisa: call for collaboration

Obiettivi: individuare un possibile biomarcatore per la malattia di Fabry



APLOGRUPPI MITOCONDRIALI

LYSO-GB3

STRESS-OSSIDATIVO

Ongoing (march 26° 2018)

Pisa + Five groups

Fabry DNA: 88

Oxidative stress data: 30 patients

Goal: 100 patients, and at least 5 cases at T0 to monitor biochemically

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