Malattia di Fabry: esperienze a confronto

Sabato 25 Novembre 2017

LE MANIFESTAZIONI IN ETÀ PEDIATRICA: L'UTILITÀ DELLO SCREENING NEONATALE

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Società Medico Chirurgica di Ferrara

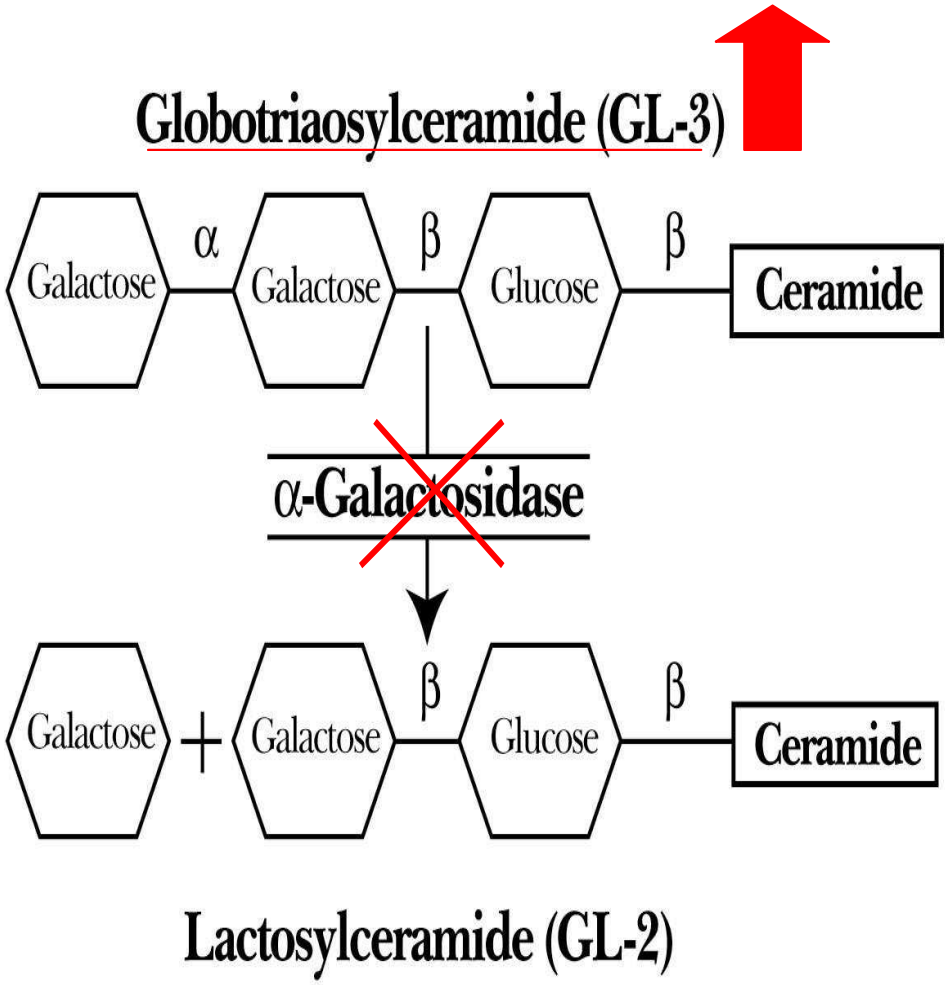
dal 1846

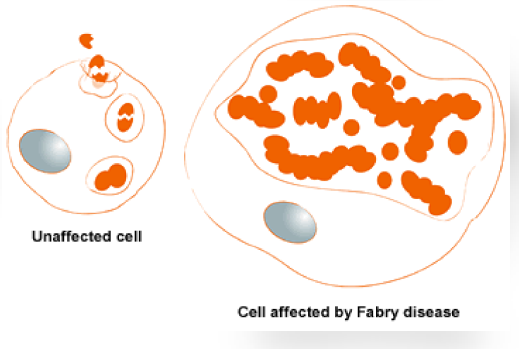
MALATTIA DI ANDERSON-FABRY

E' UNA MALATTIA

- Rara
- Da accumulo lisosomiale
- Ereditaria
- Sistemica, multiorgano
- Dercorso lentamente progressivo
- Gravata da alta Morbidità e Mortalità

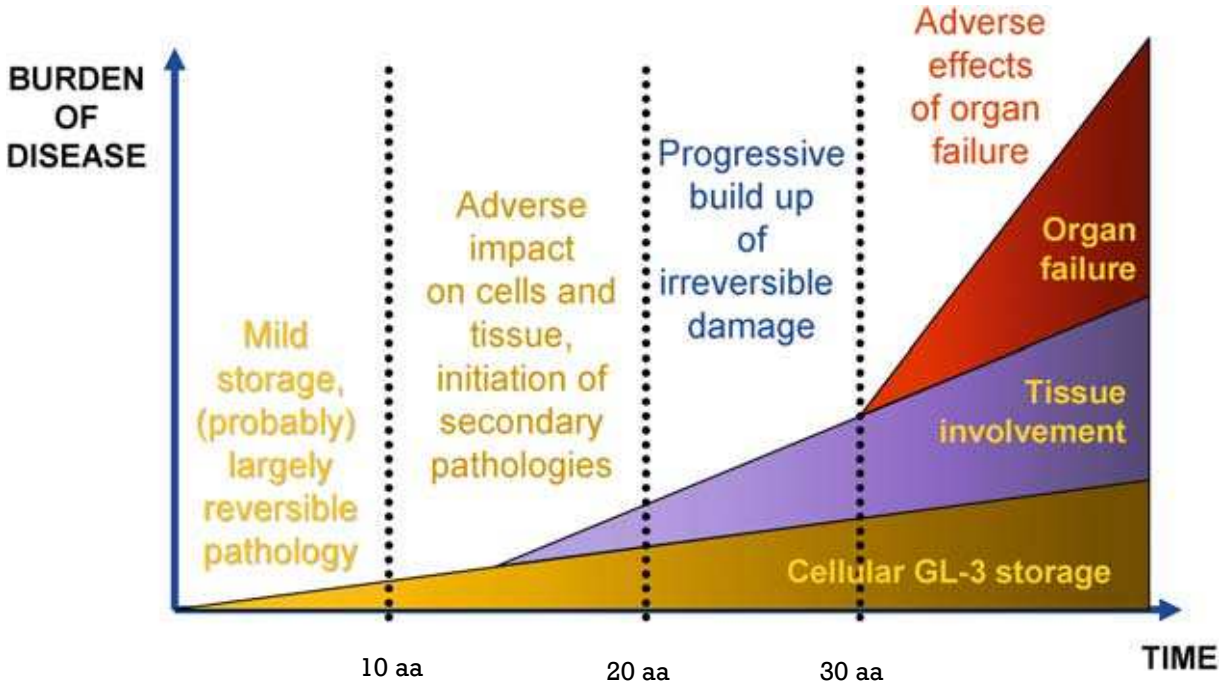
- Terapia enzimatica sostitutiva (disponibile dal 2001)





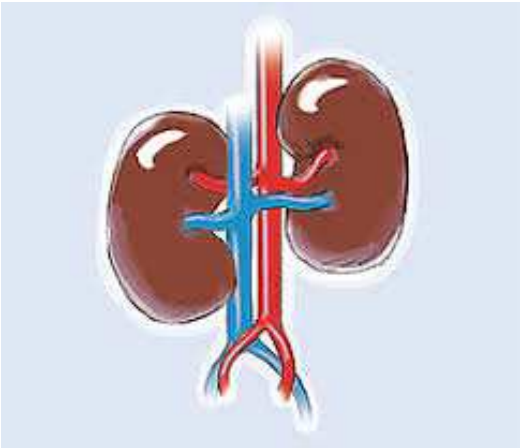
Cellule endoteliali, renali, cardiache e dei neuroni gangliari delle radici dorsali…

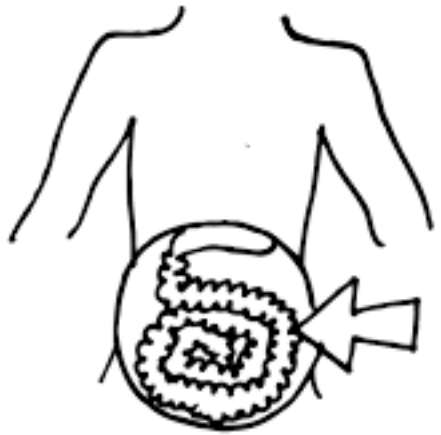
MODELLO DI PROGRESSIONE..



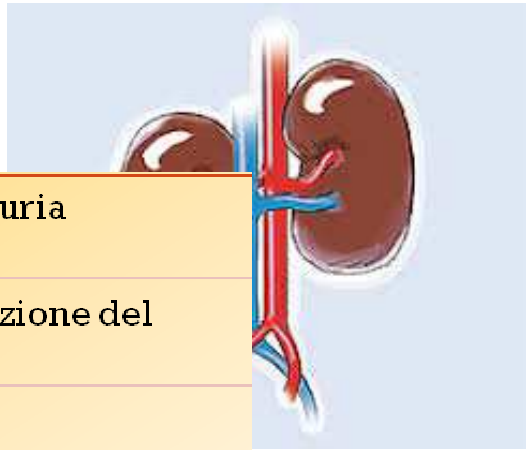
J Inherit Metab Dis (2007) 30:184–192

MALATTIA DI ANDERSON-FABRY: MALATTIA SISTEMICA, MULTIORGANO





MALATTIA DI ANDERSON-FABRY: MALATTIA SISTEMICA

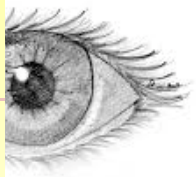


RENE	Proteinuria
	Diminuzione del filtrato
	IRT

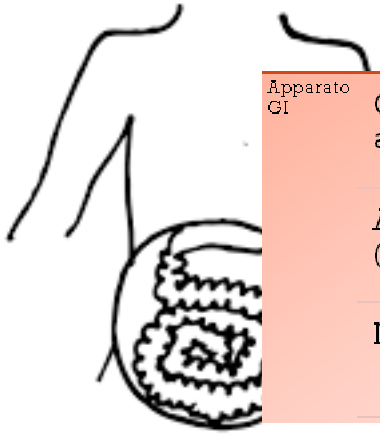
CUORE	Cardiopatia ipertrofica
	disturbi della conduzione
	Insufficienza valvolare

SN	TIA
	Ictus
	Alterazioni labirintiche
	Dolore neuropatico

Occhio	Cornea verticillata
	Cataratta della capsula posteriore
	Lesioni vascolari della congiuntiva e della retina



Cute	Angiocheratomi
	Ipo-anidrosi/intolleranza al caldo
	Iperidrosi



Apparato GI	Crisi dolorose addominali localizzat
	Alterazioni dell'alvo (diarrea o stipsi)
	Nausea/vomito

PRESENTAZIONE CLINICA

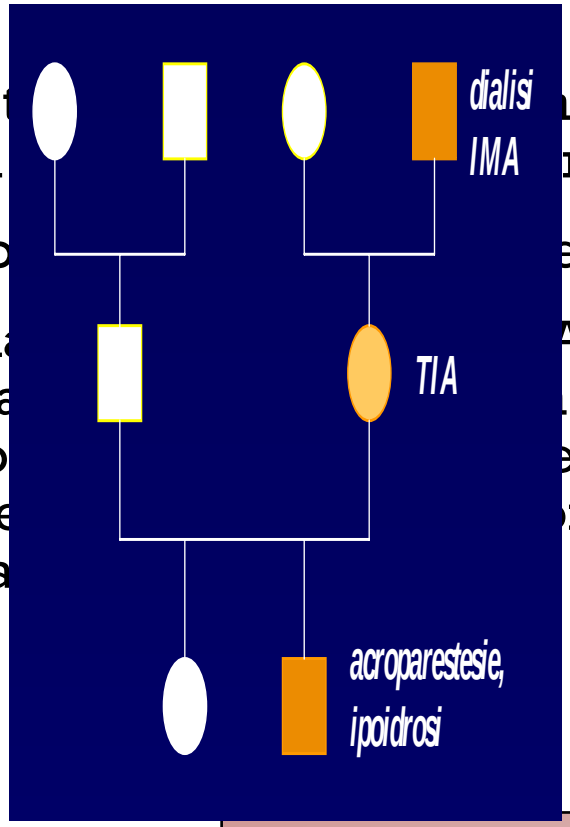
Dipende :

- dal coinvolgimento d'organo
- dal fenotipo clinico
- dallo stato di avanzamento della malattia

- Ma quando compaioni queste manifestazioni?

- Sono già presenti in età pediatrica?

LA STORIA DI ANTONIO..



- All'et… …bulatorio di gastroenterologia per storia da circa 6 mesi … …ricorrente associata ad alvo alterno.
- Anto… …eso BMI 24 (>97°P)
- La ma… …Antonio è un bambino introverso, pigro che non ama gioca… … facilmente. Quando corre diventa tutto rosso ma suda poco… …e, l'attività fisica, gli scatena crisi di dolore alle mani e ai pie… …no interpretate come una scusa per non fare attività fisica…

c. 352C>T (p. Arg 118 Cys)
Attività enzimatica residua 29%

DOLORE.. ACROPARESTESIE..
Ipoidrosi

Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry

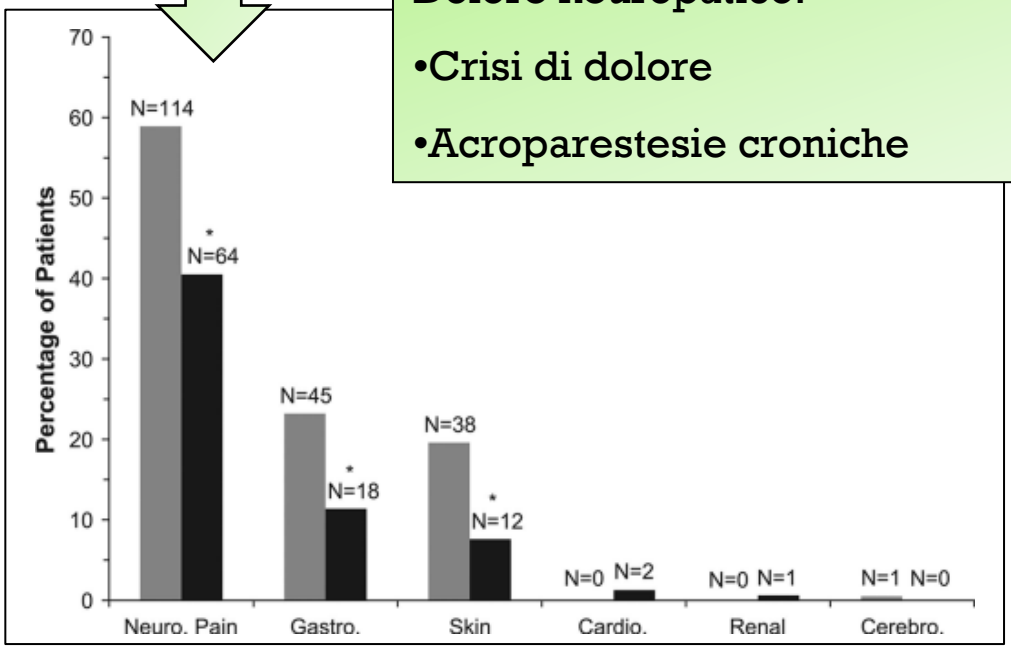
ROBERT J. HOPKIN, JOHN BISSLER, MARYAM BANIKAZEMI, LORNE CLARKE, CHRISTINE M. ENG, DOMINIQUE P. GERMAIN, ROBERTA LEMAY, ANNA TYLKI-SZYMANSKA, AND WILLIAM R. WILCOX

Parameter	Male pediatric patients	Female pediatric patients
Total number of pediatric patients in the Fabry Registry, (age <18 at enrollment)		
n	194	158
Age in yrs at registry enrollment		
Mean (SD)	11.4 (4.52)	11.1 (4.43)
Median (range)	12 (<1*, 17)	12 (<1*, 17)
Ethnicity, n (%)		
Caucasian	124 (63.9)	109 (69.0)
Black	8 (4.1)	2 (1.3)
Hispanic	18 (9.3)	17 (10.8)
Asian	14 (7.2)	0
Other	11 (5.7)	5 (3.2)
Not stated	19 (9.8)	25 (15.9)
Family members diagnosed with Fabry, n (%)		
Yes	156 (80.4)	131 (82.9)
No	12 (6.2)	1 (0.6)
Not stated	26 (13.4)	26 (16.5)
Age in yrs at first Fabry symptoms		
N	132	65
Mean (SD)	6.6 (3.27)	8.4 (3.94)
Median (range)	6 (<1*, 14)	9 (<1*, 16)
Age category, n (%)		
0–<5 yrs	37 (19.1)	12 (7.6)
≥5–<8 yrs	41 (21.1)	12 (7.6)
≥8–<12 yrs	41 (21.1)	28 (17.7)
≥12–<15 yrs	13 (6.7)	8 (5.1)
≥15–<18 yrs	0	5 (3.2)
Not stated	62 (32.0)	93 (58.9)
Age in yrs at Fabry diagnosis		
n	178	153
Mean (SD)	8.6 (4.75)	8.3 (4.88)
Median (range)	9 (<1*, 17)	9 (<1*, 17)

M 59%
vs
F 41%

Dolore neuropatico:

- Crisi di dolore
- Acroparestesie croniche



Sintomi/segni di presentazione

Pediatr Res 64: 550–555, 2008

Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry

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Talvolta il dolore può essere così
ntollerabile da indurre idee
uicide

Table 3. *BPI scores among pediatric patients ≥12 yrs of age in the Fabry Registry*

Parameter	Males	Females	All patients
Total number of patients ≥12 to <18 yrs of age with BPI data†	19	26	45
First recorded BPI score for worst pain in the past 24 hrs‡			
Mean (SD)	4.4 (3.51)	1.5 (2.45)*	2.7 (3.23)
Median (range)	5 (0, 10)	0 (0, 9)	1 (0, 10)
0–3 (mild)	9 (47.4%)	22 (84.6%)	31 (68.9%)
4–7 (moderate)	4 (21.1%)	3 (11.5%)	7 (15.6%)
8–10 (severe)	6 (31.6%)	1 (3.8%)	7 (15.6%)
First recorded BPI score for average pain§			
Mean (SD)	3.8 (2.54)	2.3 (2.47)¶	3.0 (2.59)
Median (range)	3 (0, 10)	1.5 (0, 8)	3 (0, 10)
0–3 (mild)	10 (52.6%)	18 (69.2%)	28 (62.2%)
4–7 (moderate)	7 (36.8%)	7 (26.9%)	14 (31.1%)
8–10 (severe)	2 (10.5%)	1 (3.8%)	3 (6.7%)

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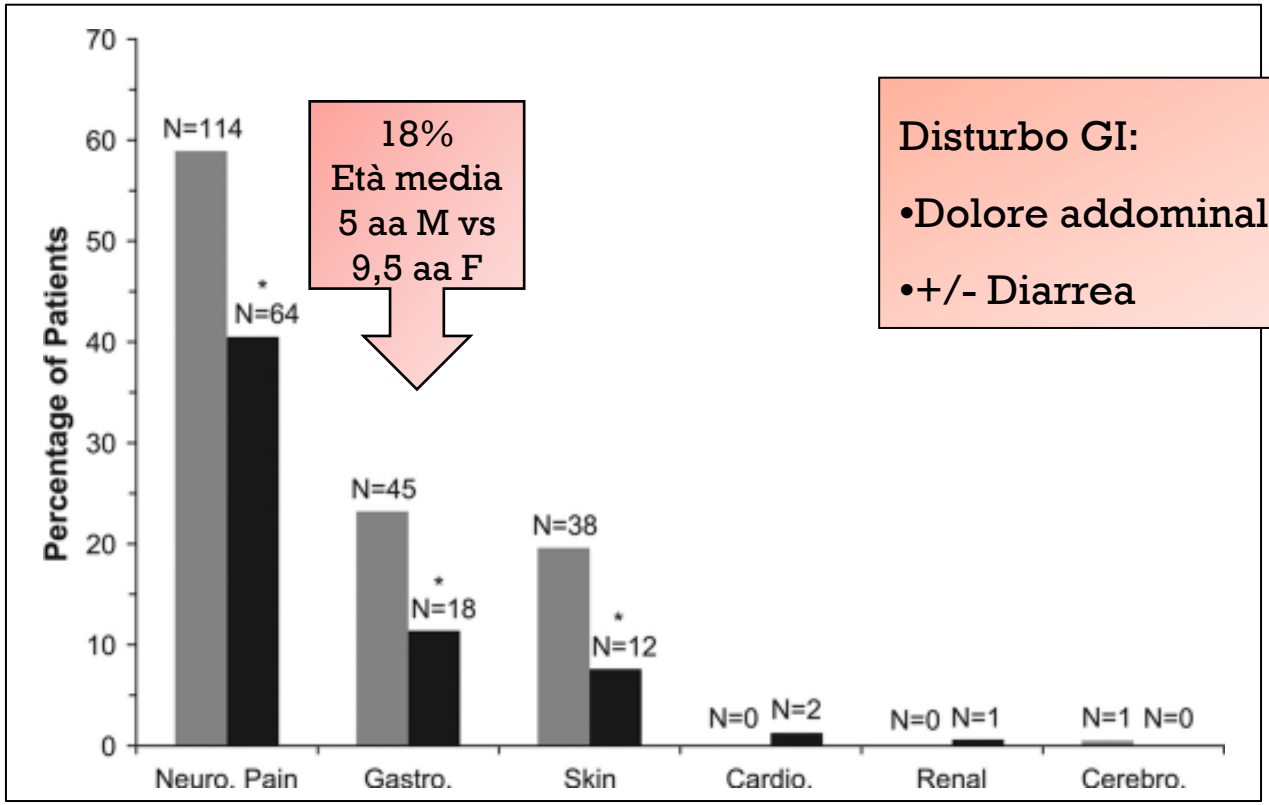

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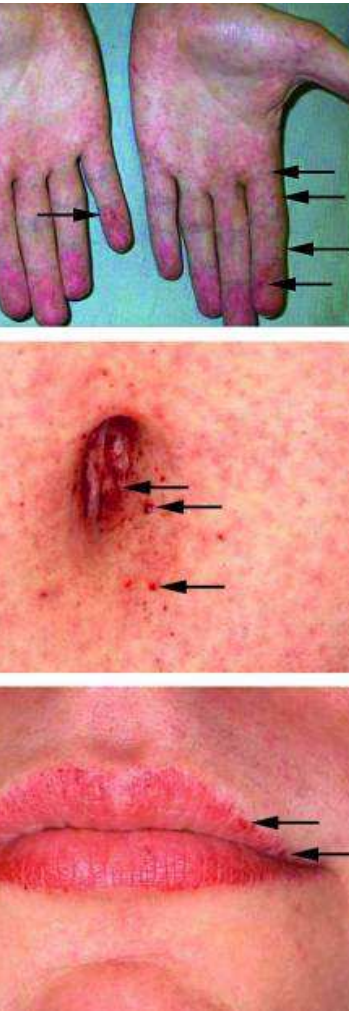
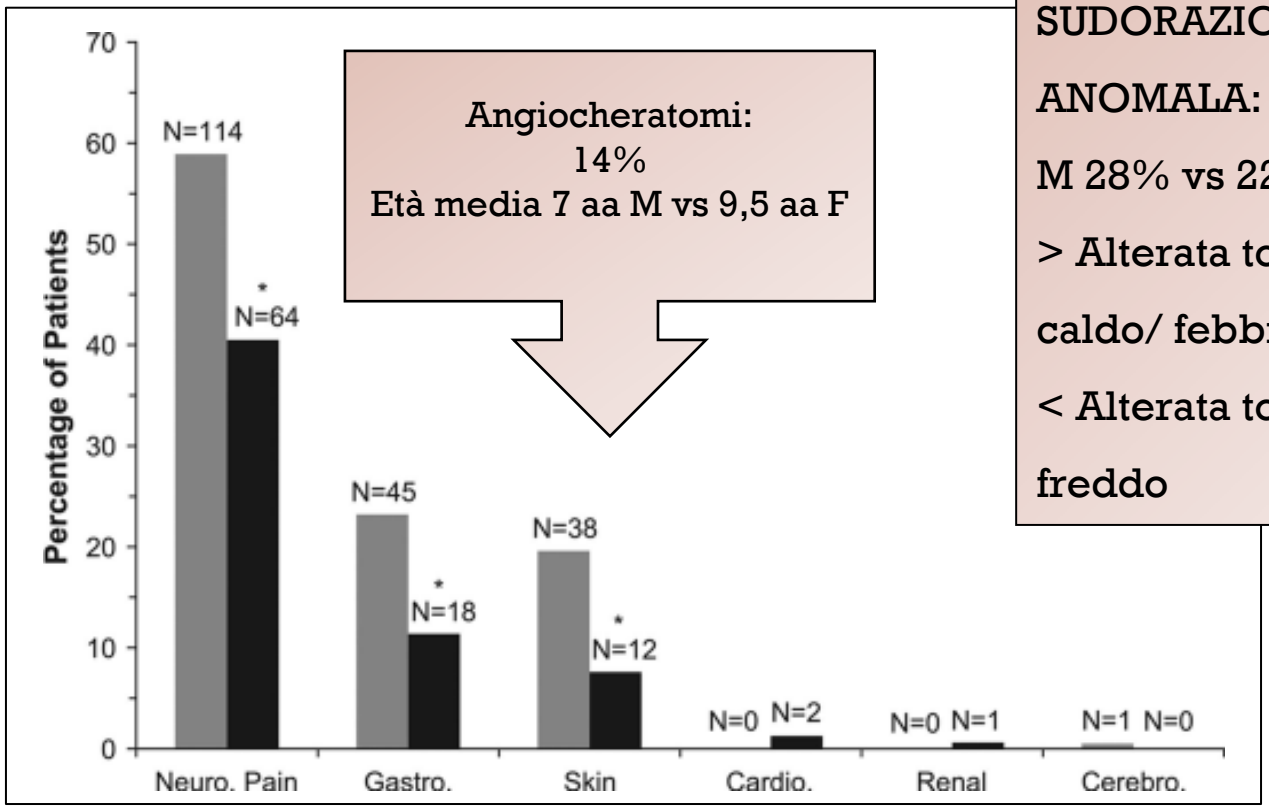




Angiocheratomi:
14%
Età media 7 aa M vs 9,5 aa F

SUDORAZIONE ANOMALA:

M 28% vs 22% F

> Alterata tolleranza al caldo/ febbre

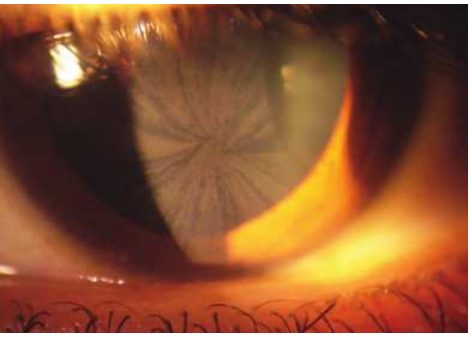
< Alterata tolleranza al freddo

Sintomi/segni di presentazione

Pediatr Res 64: 550–555, 2008

Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry

C. M. Eng · J. Fletcher · W. R. Wilcox · S. Waldek · C. R. Scott · D. O. Sillence · F. Breunig · J. Charrow · D. P. Germain · K. Nicholls · M. Banikazemi



Organ system	Males ($N = 713$)		Females ($N = 430$)	
	Median age at onset (years)[a]	Percentage of males with symptom	Median age at onset (years)[b]	Percentage of females with symptom
Overall	9		13	
Neurological	9	67	10	47
Neurological: pain	9	62	10	41
Neurological: other	8	12	12	12
Skin	9	31	17	12
Ophthalmological	9	11	16	12
Gastroenterological	8	19	14	13
Respiratory	11	3	30	2
Renal	20	17	28	11
Cardiovascular	12	13	32	10
Cerebrovascular	10	5	26	4

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Table 5 Age at first clinical event

Clinical event		Fabry Registry patients[a]	
		Males ($N = 910$)	Females ($N = 775$)
Renal event[b]	% of patients	13	2
	Age (SD)	38.5 (11)	37.3 (10)
	Median (range)	38 (14–79)	38 (17–59)
Cardiovascular event[c]	% of patients	19	14
	Age (SD)	39.0 (12)	47.6 (13)
	Median (Range)	41 (5–76)	47 (14–78)
Cerebrovascular event[d]	% of patients	7	5
	Age (SD)	38.6 (12)	43.2 (14)
	Median (range)	38 (18–80)	43 (19–67)

[a]Only patients with known enzyme replacement therapy status
[b]Dialysis or transplantation
[c]Arrhythmia, myocardial infarction, angina pectoris, congestive heart failure, significant cardiac procedure
[d]Stroke

Fabry disease in infancy and early childhood: a systematic literature review

120 papers
41 pazienti <5 aa

Dawn A. Laney, MS[1], Dawn S. Peck, MS[2], Andrea M. Atherton, MS[3], Linda P. Manwaring, MS[4], Katherine M. Christensen, MS[5], Suma P. Shankar, MD, PhD[1], Dorothy K. Grange, MD[4], William R. Wilcox, MD, PhD[1] and Robert J. Hopkin, MD[6]

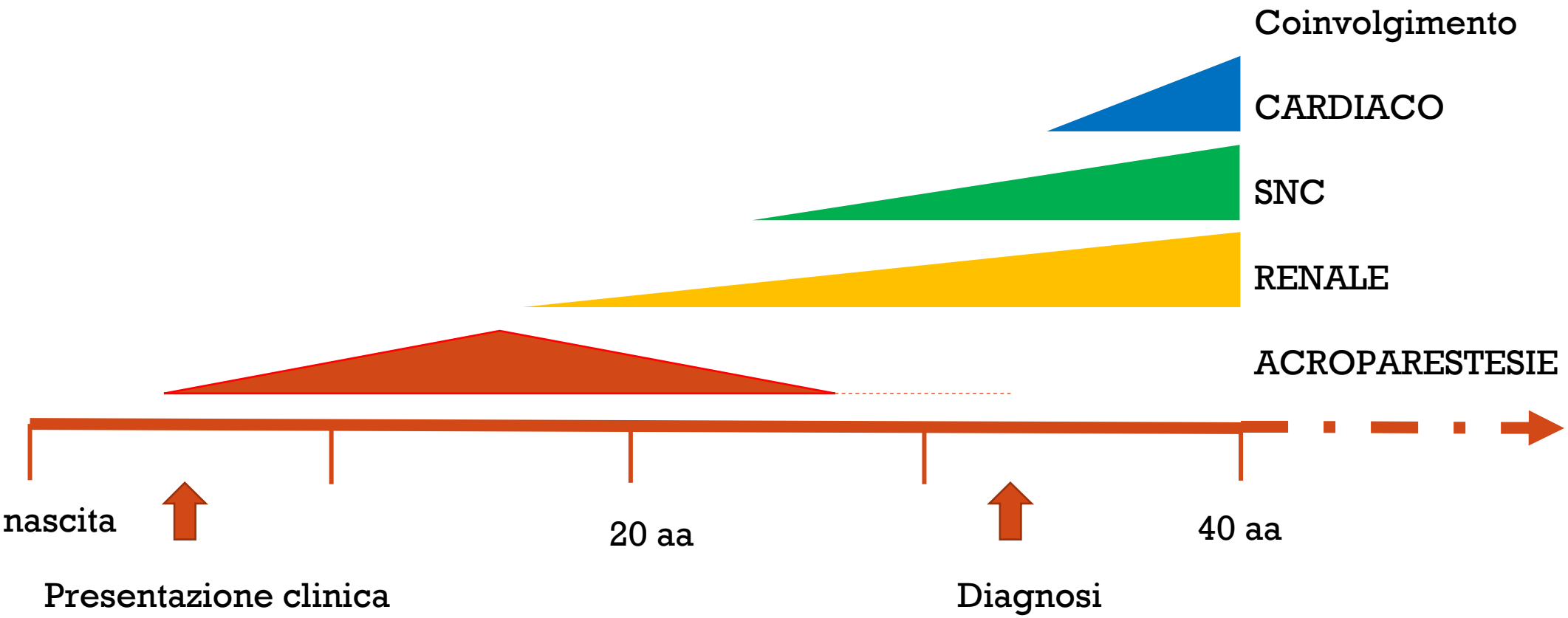
Table 2 Summary of reported clinical manifestations in Fabry patients (newborn–4 years)[2,13,16,27–32,36,40,41,51]

Fabry-related signs and symptoms	Earliest report of symptom
Storage of globotriaosylceramide found in organs on biopsy	Prenatal
Corneal whorls/verticillata	Prenatal/ newborn
Gastrointestinal problems, including nausea, vomiting, diarrhea, constipation, and abdominal pain	1.0 year
Slow growth in boys (mean height/weight <50th percentile)	2.0 years
Intermittent acroparesthesia/neuropathic pain triggered by stress, heat, fatigue, or exercise	2.0 years
Hypohidrosis or anhidrosis	2.5 years
Fabry crises of agonizing neuropathic pain typically begin in the hands and feet and may radiate proximally	2.5 years
Heat, cold, and/or exercise intolerance	3.5 years
Retinal vascular tortuosity	4.0 years
Tinnitus/vertigo	4.0 years
Low glomerular filtration rate	4.0 years
T-wave inversion on electrocardiogram	4.0 years
Trivial cardiac valve disease	4.0 years
Angiokeratoma	4.4 years

6 bambini
1-4 aa

9 bambini
2-4 aa

PROGRESSIONE CLINICA



SINTOMI D'ALLARME IN ETA' PEDIATRICA

Acroparestesie

- Episodi frequenti di dolore addominale

Febbre ricorrente

- Ipo/anidrosi

Intolleranza al calore

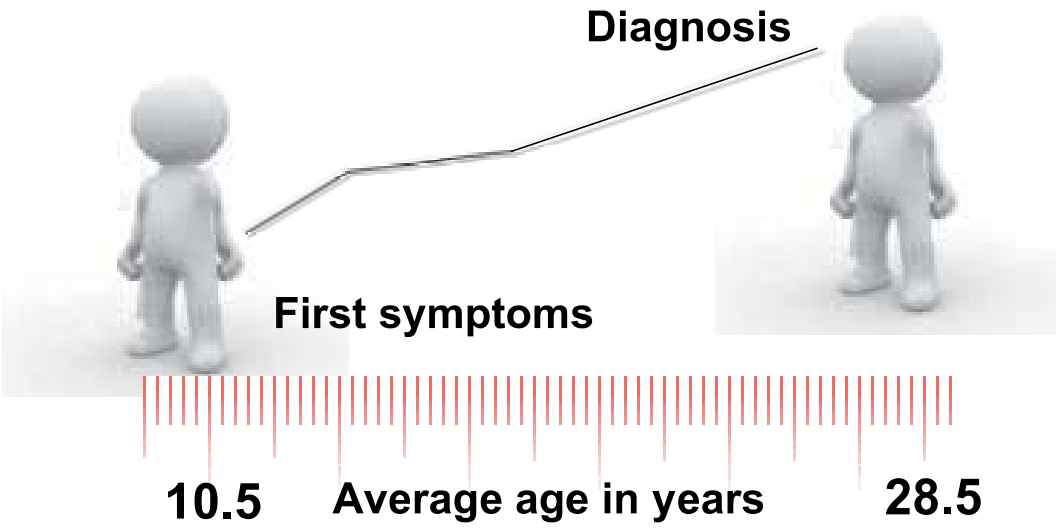
ERRORI DIAGNOSTICI PIÙ COMUNI IN ETÀ PEDIATRICA

- Febbre reumatica
- Artrite reumatoide
- Dolori di crescita

- Sindrome del colon irritabile
- Appendicite acuta
- Colica renale

Dtsch Arztebl Int 2009; 106(26): 440–7

RITARDO DIAGNOSTICO..



Ritardo diagnostico di circa 20 aa e numerose visite mediche..

J Inherit Metab Dis (2007) 30:184–192

ESISTE UNA TERAPIA..

Enzyme replacement therapy for Anderson-Fabry disease (Review)

El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC

Cochrane Database of Systematic Reviews 2016, Issue 7.

RESEARCH ARTICLE

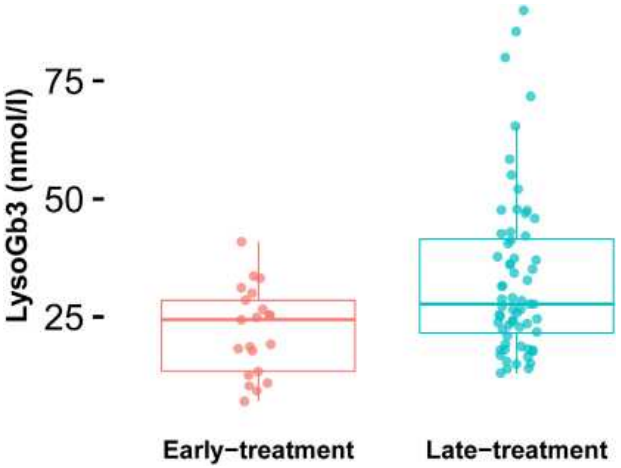
Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies

Regina El Dib[1,2]*, Huda Gomaa[3], Alberto Ortiz[4], Juan Politei[5], Anil Kapoor[2], Fellype Barreto[6]

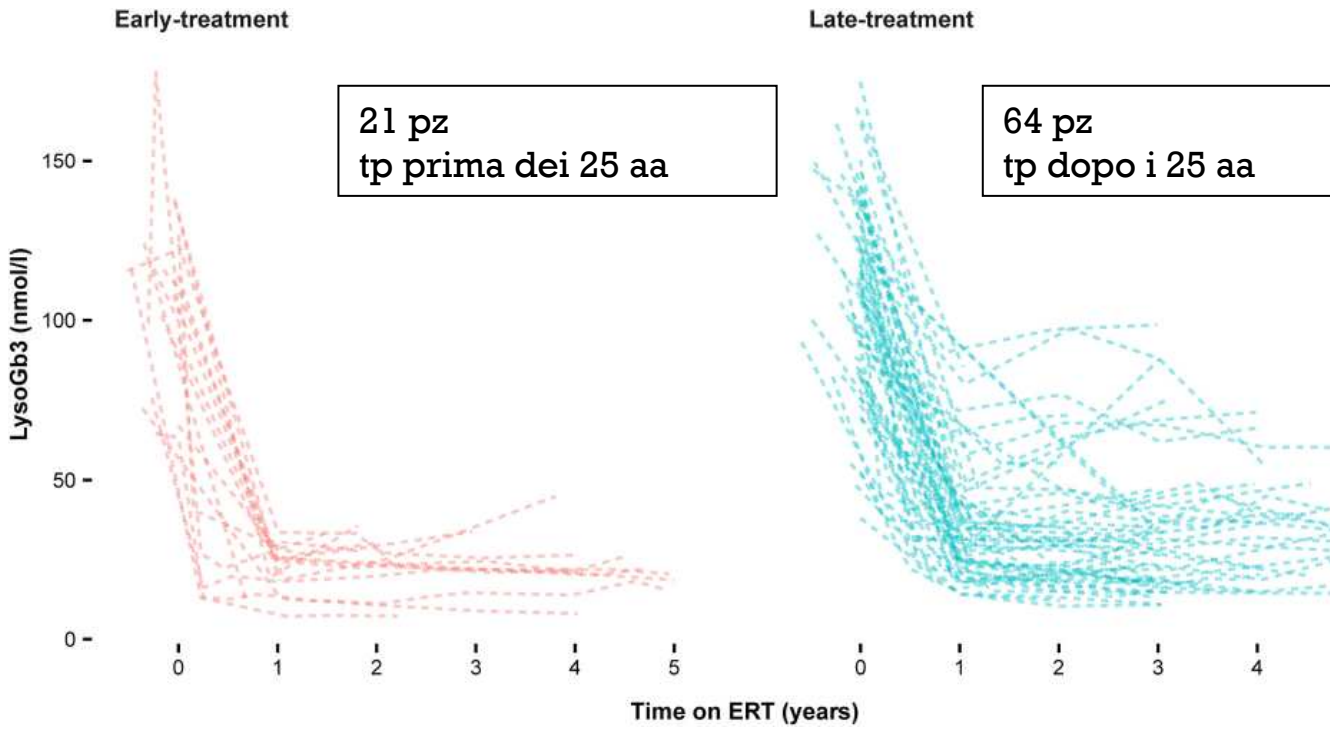
PLOS ONE March 15, 2017

Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease

Maarten Arends [a,*], Frits A. Wijburg [b], Christoph Wanner [c], Frédéric M. Vaz [d], André B.P. van Kuilenburg [d], Derralynn A. Hughes [e], Marieke Biegstraaten [a], Atul Mehta [e], Carla E.M. Hollak [a], Mirjam Langeveld [a]



Dopo 1 aa di tp



Molecular Genetics and Metabolism xxx (2017) xxx–xxx

SCREENING NEONATALE ESTESO

- Spettrometria di massa tandem
- Diagnosi precoce, preclinica di numerose malattie metabolico (fino a 60)

- Obbligatorio in tutta Italia (legge n°167/2016)

I PRINCIPI BASILARI DELLO SCREENING NEONATALE

La malattia deve:

1. Avere un'incidenza relativamente alta
2. Produrre un danno irreversibili prima che sia riconosciuta per sintomi e segni
3. Avere una storia naturale ben conosciuta
4. Avere un trattamento disponibile, non particolarmente costoso ed efficace se iniziato precocemente
5. Avere un test di screening relativamente poco costoso con un'altissima sensibilità (pochi falsi negativi) ed un'alta specificità (pochi falsi positivi e quindi pochi ritest)

MALATTIA DI ANDERSON-FABRY

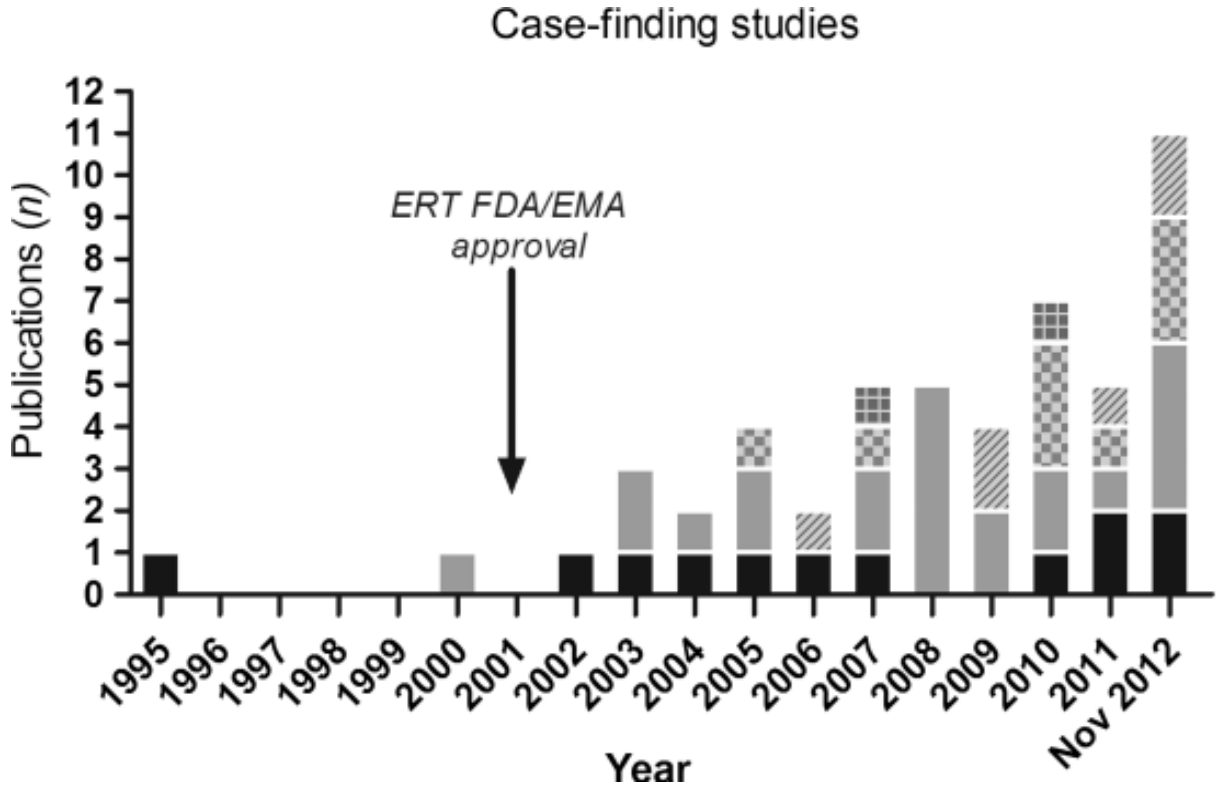
TEMPI MATURI PER LO SCREENING NEONATALE

- Poi non così rara
- Sintomi e segni aspecifici (diagnosi ritardata la normalità)
- Esistono numerosi casi di malattia di Fabry ad esordio tardivo e con sintomatologia sfumata (non facili da diagnosticare)
- Esiste una terapia efficace capace di modificare la storia naturale

A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance

L van der Tol,[1] B E Smid,[1] B J H M Poorthuis,[2] M Biegstraaten,[1]
R H Lekanne Deprez,[3] G E Linthorst,[1] C E M Hollak[1]

Incidenza stimata in passato
1:40.000 -1: 60.000 maschi



Prevalenza di varianti del ge GLA

0,6%

0,04%

J Med Genet 2014;**51**:1–9

A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance

L van der Tol,[1] B E Smid,[1] B J H M Poorthuis,[2] M Biegstraaten,[1]
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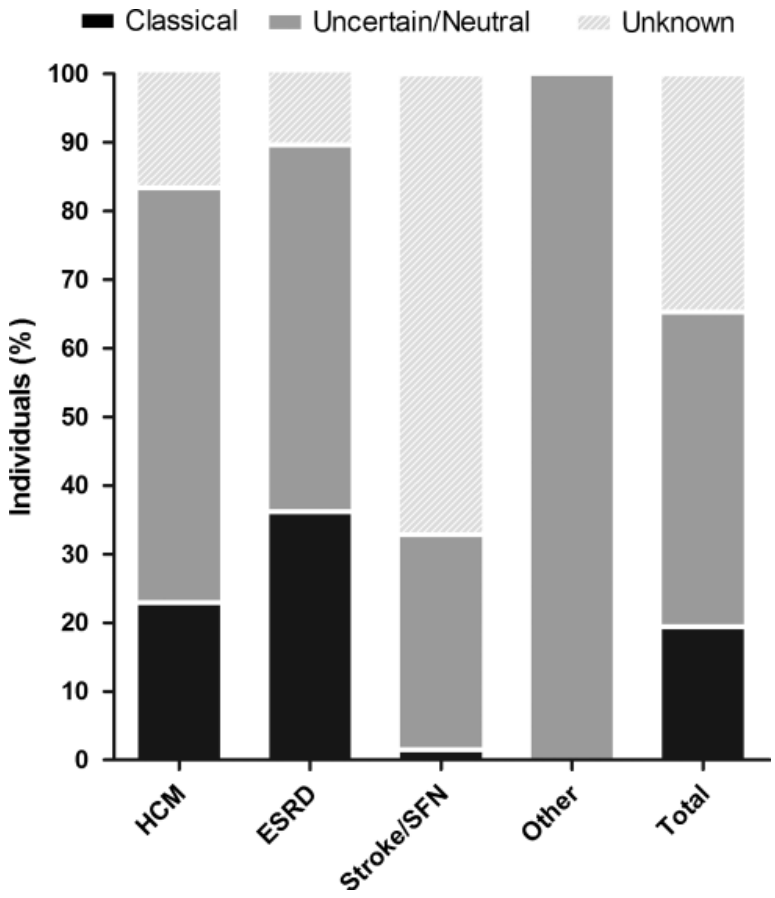


J Med Genet 2014;**51**:1–9

SCREENING NEONATALE IN ITALIA

High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening*

Marco Spada, Severo Pagliardini, Makiko Yasuda, Tur
Hitoshi Sakuraba, Alberto Ponzone, and Robert J. De

The American

Prevalenza 0,03%
12casi/37.000:
1 mutazione classica/11
mutazioni ad esordio tradivo

Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy.

Burlina AB[1], Polo G[2], Salviati L[3,4], Duro G[5], Zizzo C[5], Dardis A[6], Bembi R[3,4], Desnick RJ[7], Burlina AP[8].

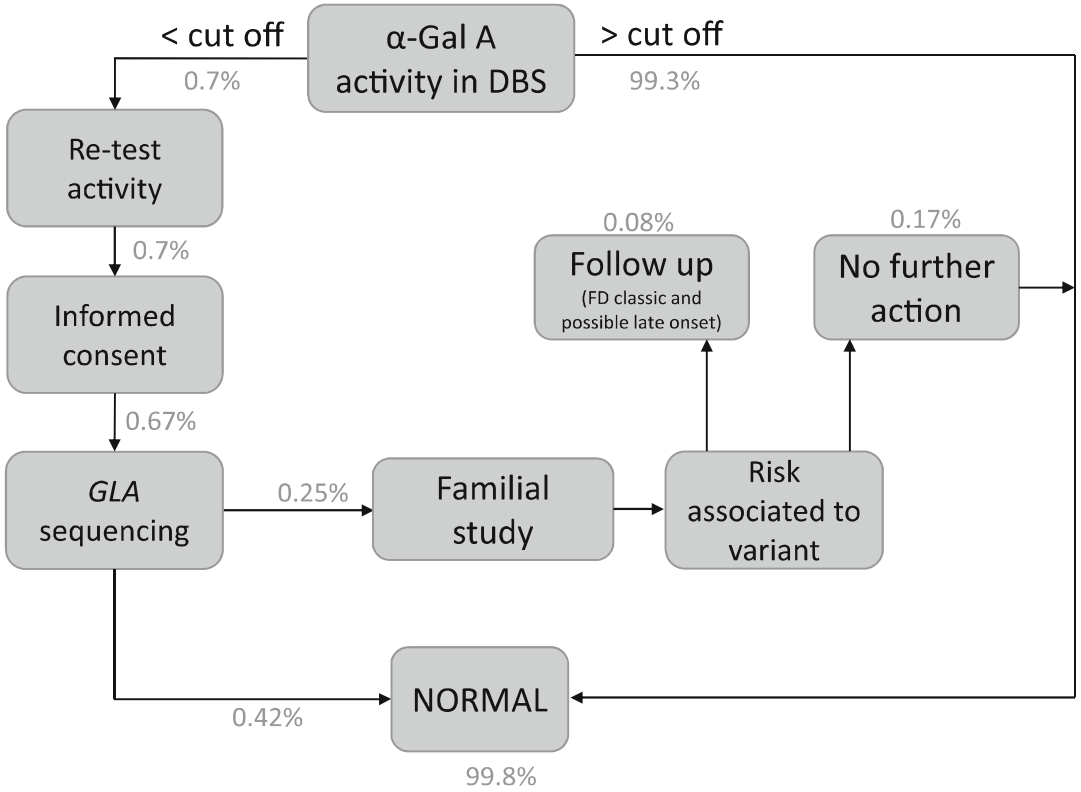
Prevalenza 0,01%
5 casi/44.400

J Inherit Metab Dis. 2017 Nov 15

ORIGINAL ARTICLE

Newborn screening for Fabry disease in the north-west of Spain

Cristobal Colon[1] · Saida Ortolano[2] · Cristina Melcon-Crespo[2,3] · Jose V. Alvarez[1] · Olalla E. Lopez-Suarez[1] · Maria L. Couce[1] · José R. Fernández-Lorenzo[2,3]



- La prevalenza di MF con fenotipo classico nei neonati maschi della Galizia è dello 0,013%
- Metodo: PPV=1,47%, accuratezza 99,12%, tasso di falsi positivi 0,88%
- Sono state identificate 10 varianti di GLA di incerto significato clinico.

Eur J Pediatr (2017) 176:1075–1081

PROBLEMI NUOVI (SECONDARI AD UNA DG PRECOCE E PRECLINICA)..

- Identificazione di forme attenuata
- Identificazione di condizioni di significato incerto
- Identificazione non malattie

- Necessità di preparare protocolli di trattamento
- Chi dobbiamo trattare? Quando iniziare il trattamento?

- Necessità di creare network tra centro specialistico/punto nascita e PdS