Quando Pensare al Fabry?

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Cardiologia SUN-Ospedale Monaldi

Napoli, 16 Aprile 2015

Disclosures

Advisory Board Genzyme
Advisory Board Biomarin
Editor in Chief Cardiogenetics

Che cos'è la Malattia di Fabry?

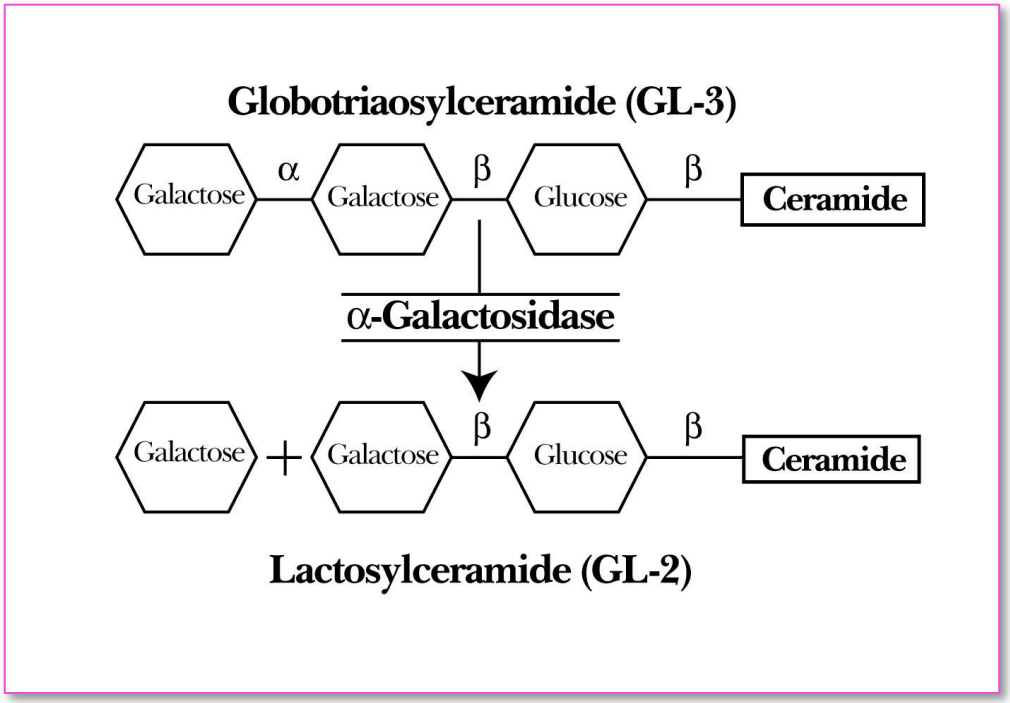
Quando pensare al Fabry?

Perche' pensare al Fabry?

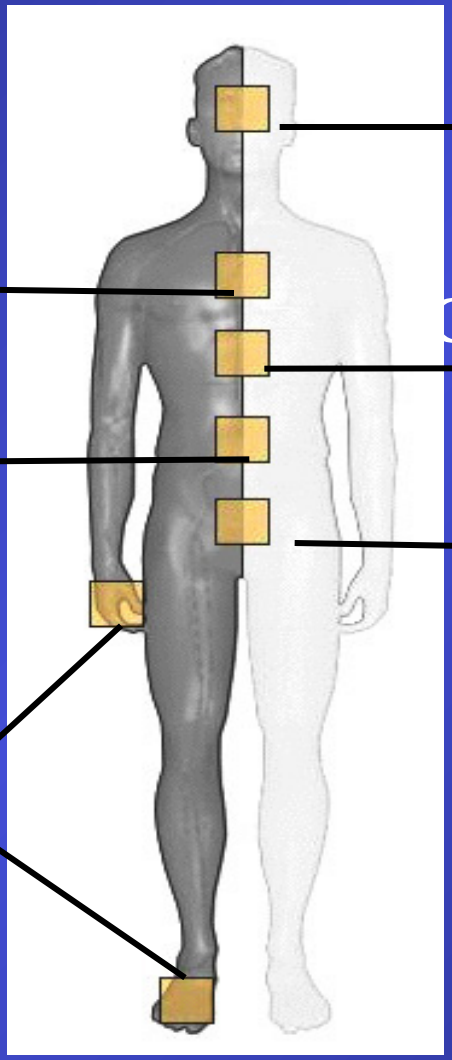
Che cos'è la Malattia di Fabry?

ANDERSON FABRY DISEASE

Fabry disease (FD) (OMIM 301500) is a rare X-linked disorder in which globotriaosylceramide and other glycosphingolipids accumulate within lysosomes because of insufficient activity of α-galactosidase A.



Signs and Symptoms



Eyes

celebrovascular disease

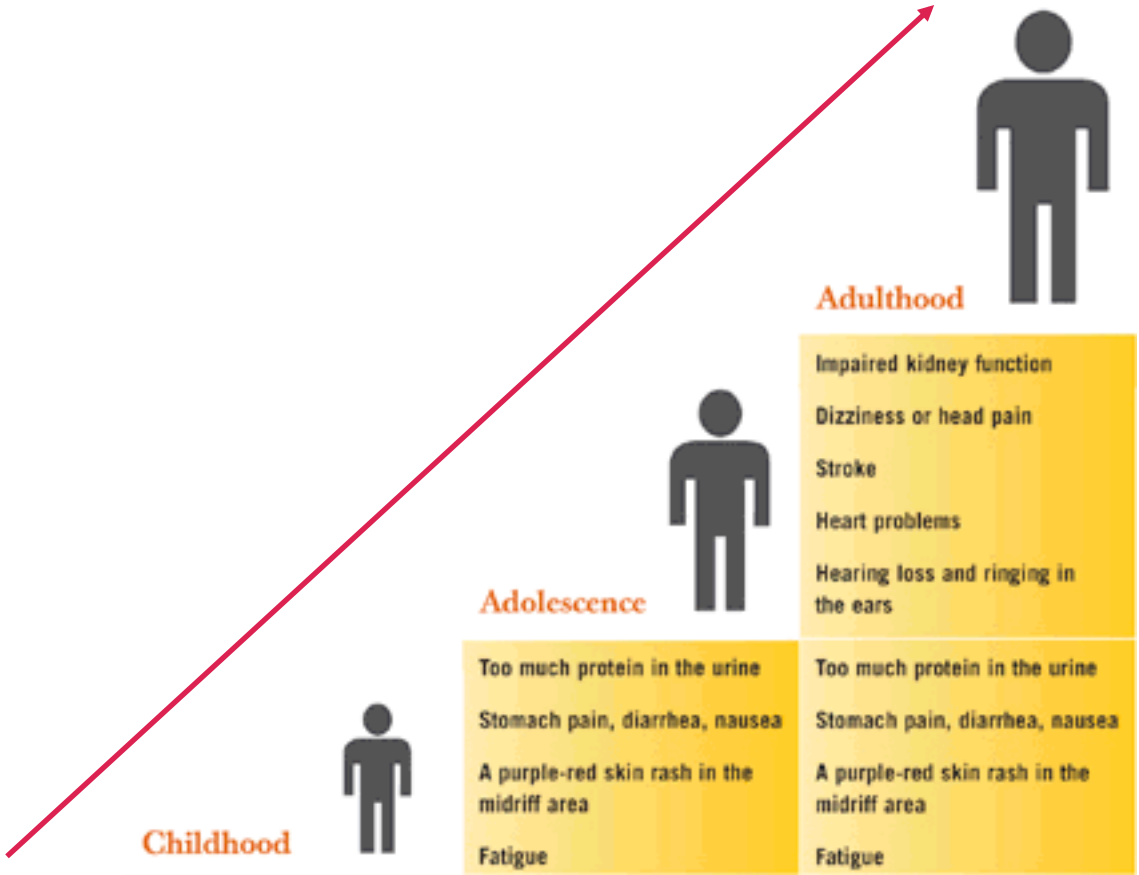
Heart

Gastrointestinal involvement

Kidney

Skin

acroparesthesia



Childhood	Adolescence	Adulthood
		Impaired kidney function
		Dizziness or head pain
		Stroke
		Heart problems
		Hearing loss and ringing in the ears
	Too much protein in the urine	Too much protein in the urine
	Stomach pain, diarrhea, nausea	Stomach pain, diarrhea, nausea
	A purple-red skin rash in the midriff area	A purple-red skin rash in the midriff area
	Fatigue	Fatigue
Periods of intense pain radiating throughout the body	Periods of intense pain radiating throughout the body	Periods of intense pain radiating throughout the body
Burning, tingling pain in the hands and feet	Burning, tingling pain in the hands and feet	Burning, tingling pain in the hands and feet
Impaired sweating	Impaired sweating	Impaired sweating
Corneal clouding or whorling	Corneal clouding or whorling	Corneal clouding or whorling
Frequent fevers	Frequent fevers	Frequent fevers
Heat and cold intolerance	Heat and cold intolerance	Heat and cold intolerance
Psychological issues (depression)	Psychological issues (depression)	Psychological issues (depression)

Malattia di Fabry

Patologia cardiovascolare

- Accumulo di glicosfingolipidi (Gb3) in:
  - Miocardiociti
  - Cellule endoteliali
  - Cellule muscolari lisce

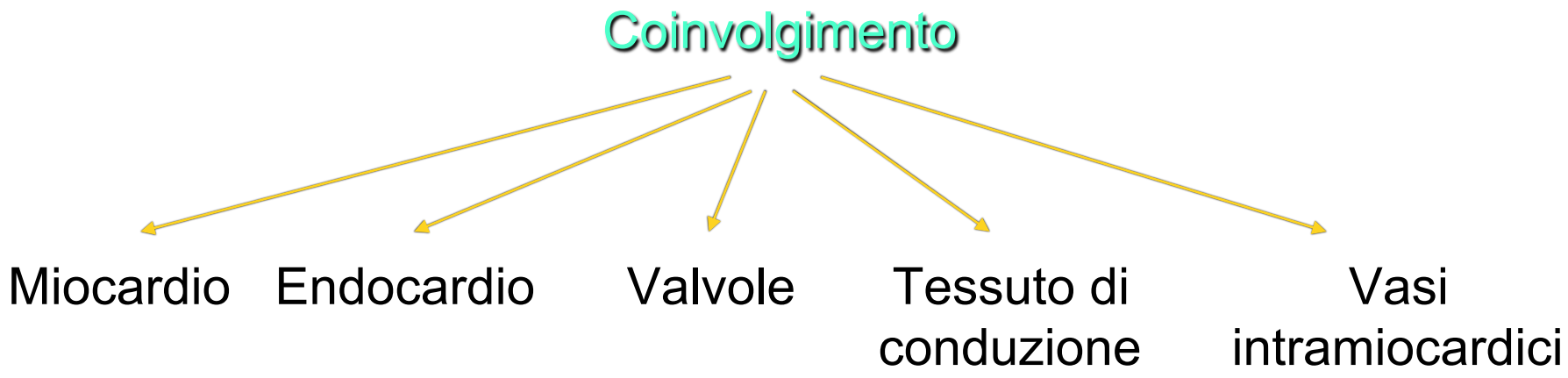
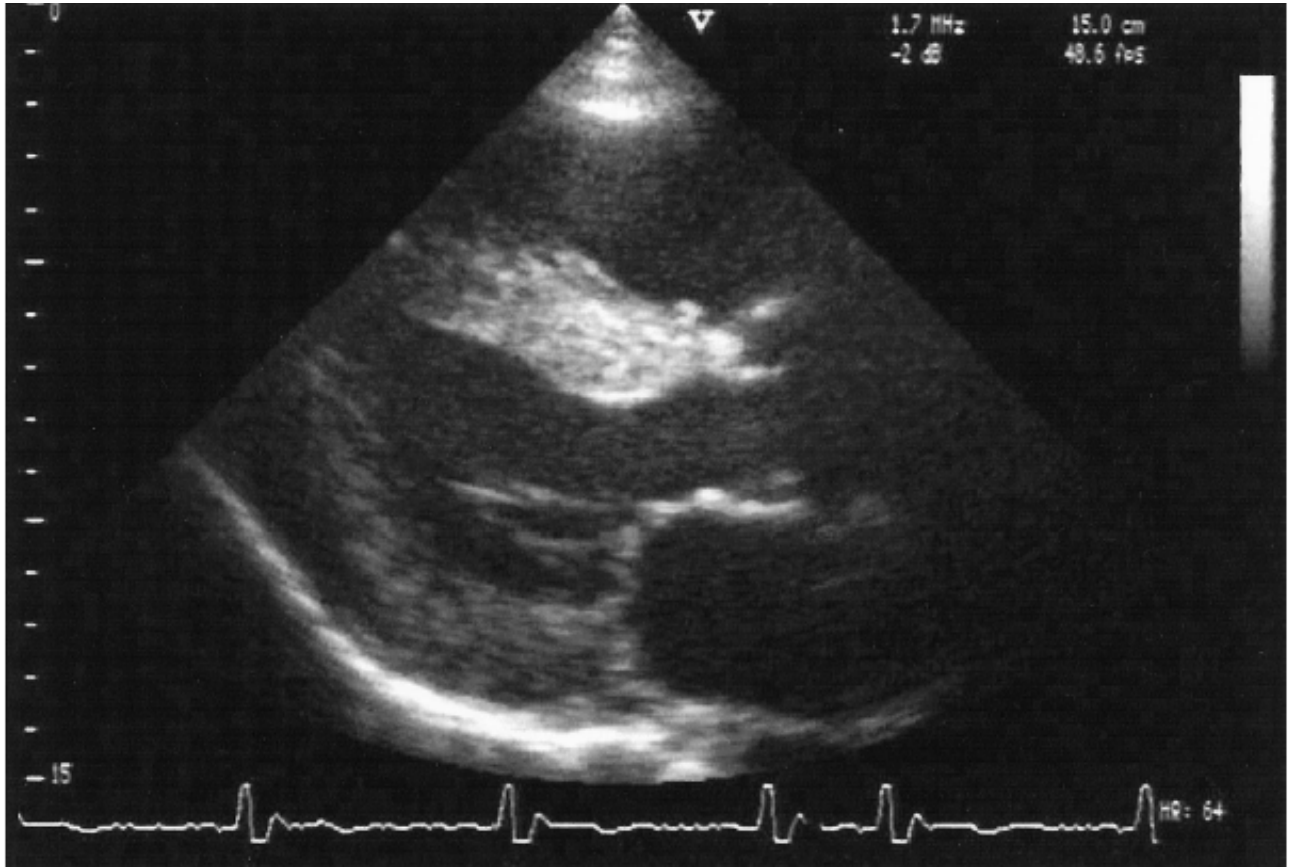


TABLE 3. Echocardiographic Features in Anderson-Fabry Patients

Patient	LVWT, mm	LA, mm	LVED, mm	LVES, mm	Pattern	E Wave, m/s	A Wave, m/s	IVRT, ms	Deceleration Time, ms	Fractional Shortening, %	Valve Abnormalities
1	21	46	50	33	Concentric	0.9	0.7	72	158	34	Normal
2	24	56	52	30	Concentric	0.6	0.5	90	216	42	Normal
3	20	46	53	27	Concentric	0.9	0.5	81	233	49	Mild MR
4	26	44	47	31	Concentric	0.6	1.0	130	147	34	Mild MR, AR
5	14	34	44	26	Concentric	0.7	0.7	88	264	41	Mild MR
6	19	47	40	28	Asymmetric	1.0	Paced/AF	84	193	30	Normal

LVWT indicates maximum left ventricular wall thickness; LA, left atrium; LVED, left ventricular end-diastolic dimension; LVES, left ventricular end-systolic dimension; AF, atrial fibrillation; IVRT, isovolumic relaxation time; MR, mitral regurgitation; and AR, aortic regurgitation.

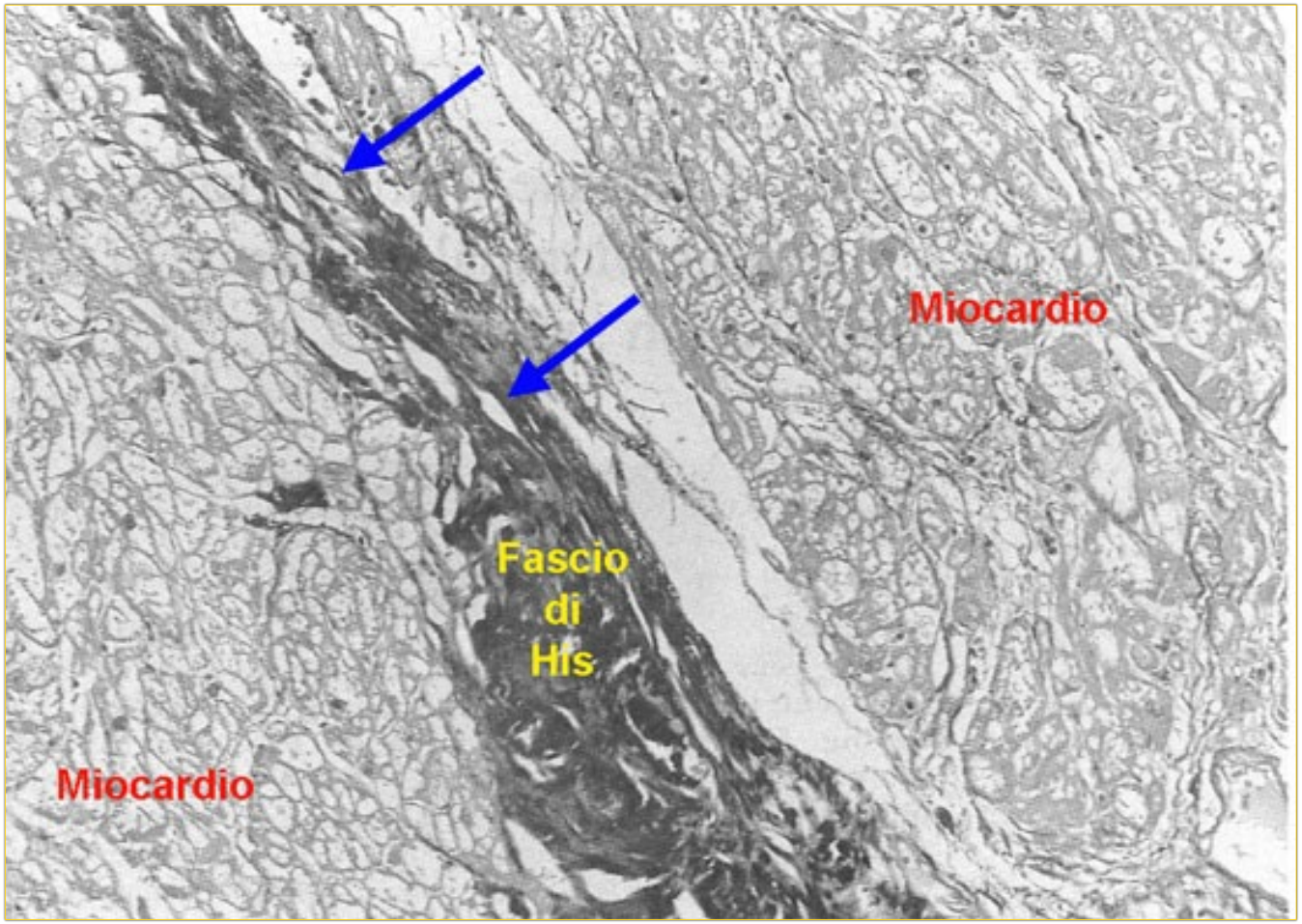


Anderson-Fabry disease should be suspected in male pts, with concentric LVH, and inheritance consistent with X-linked disease.

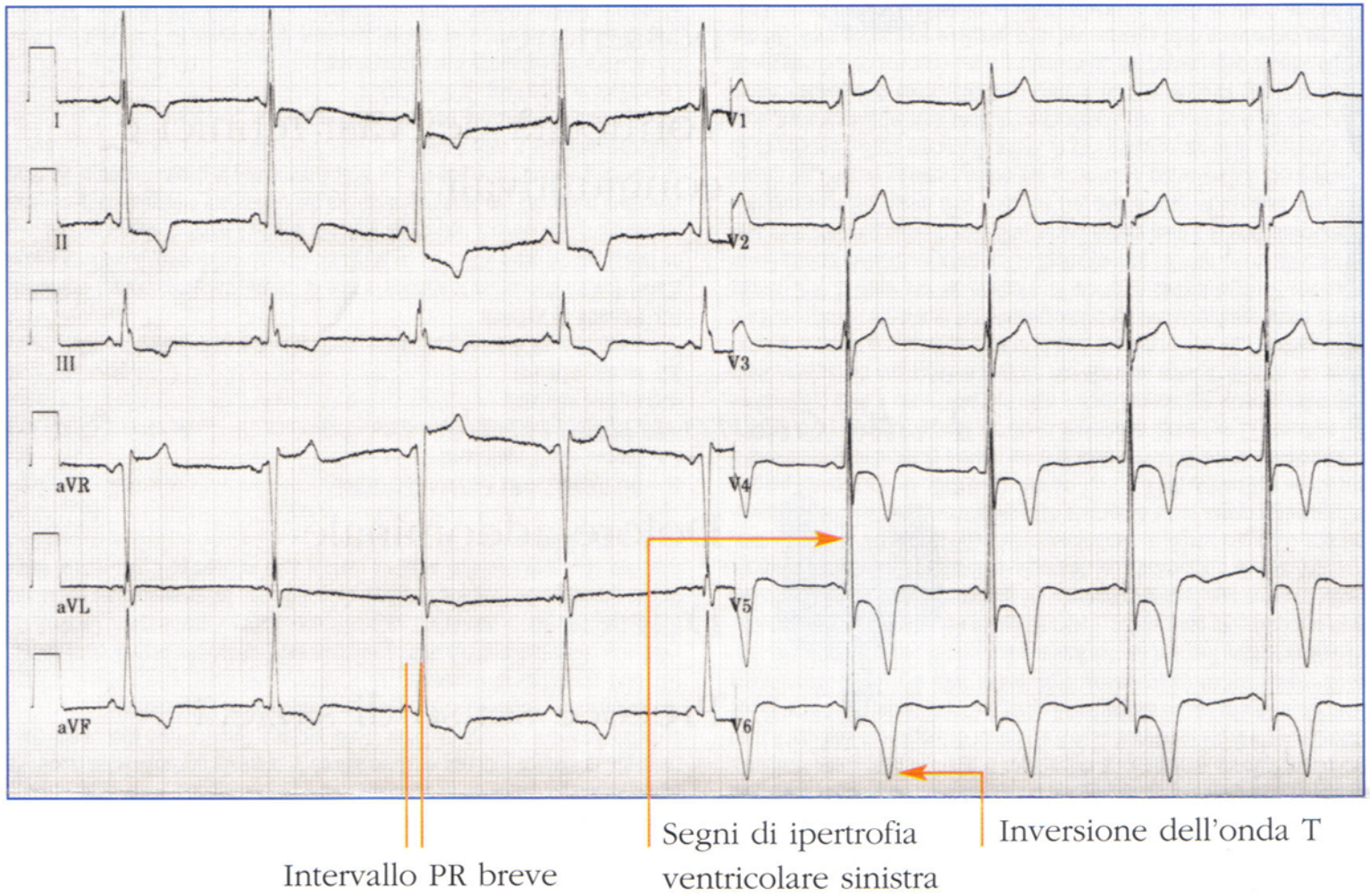
Sachdev B, et al . Circulation 2002

LVH/HCM
50-60% AFD males
30% AFD females

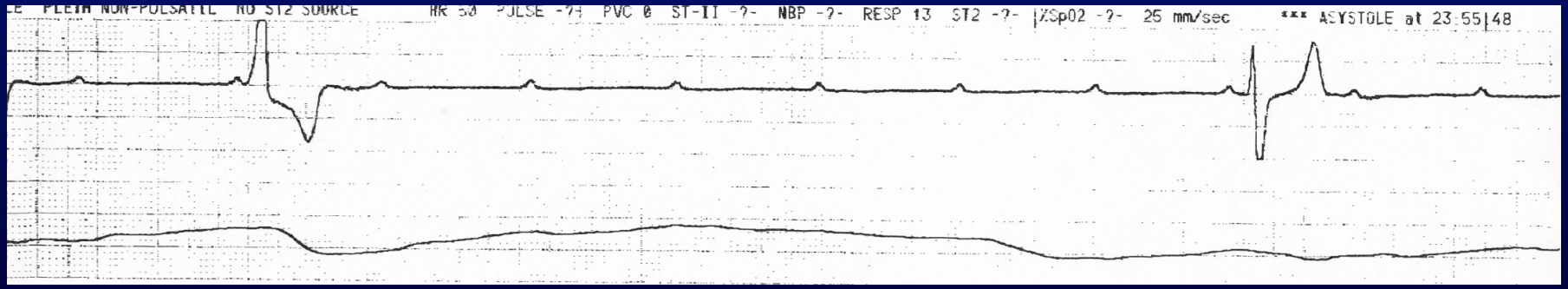
Tessuto di conduzione



Modificata da Ikari et al, Br Heart J 1992



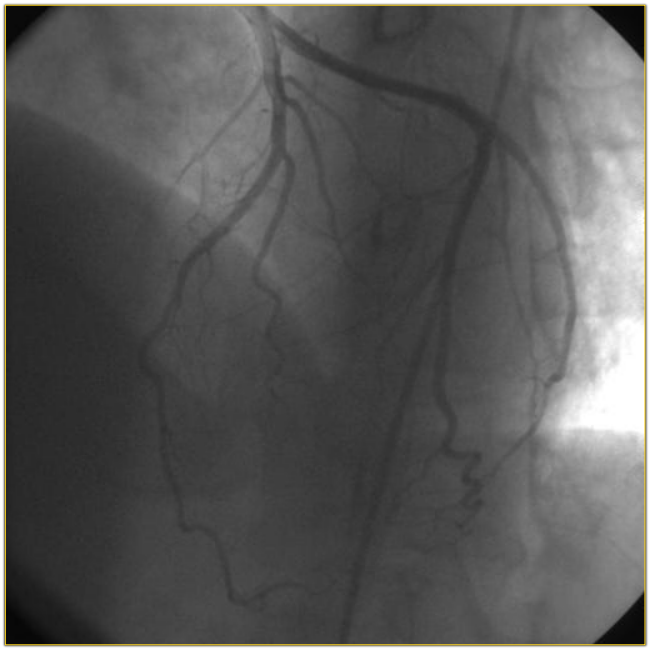
ECG di paziente affetto da Malattia di Fabry. Adattato da Linhart, 2006.[8]

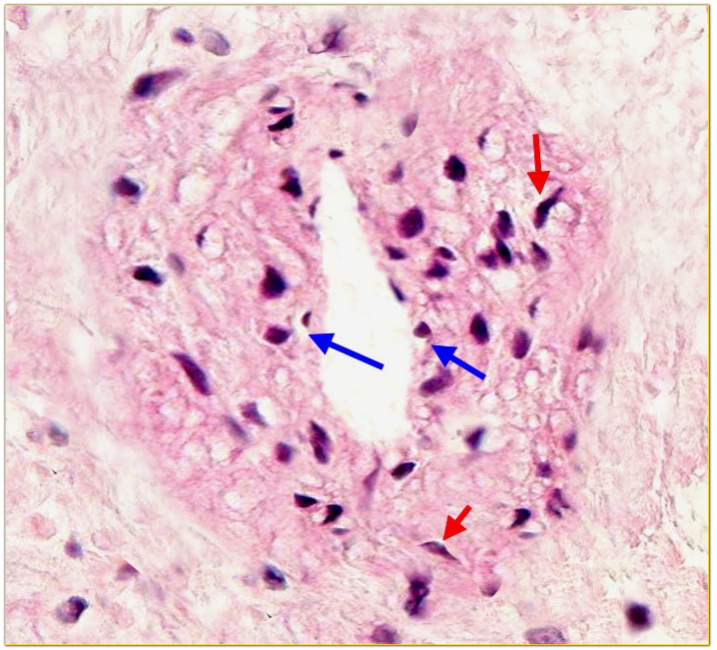


Courtesy of Prof. Elliott, The Heart Hospital, UCL

Vasi intramiocardici - Microcircolo

Uomo, 58 anni, angina da sforzo con ↓ ST



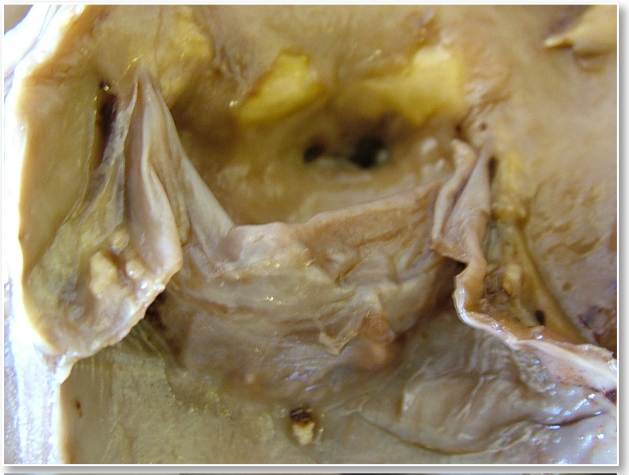


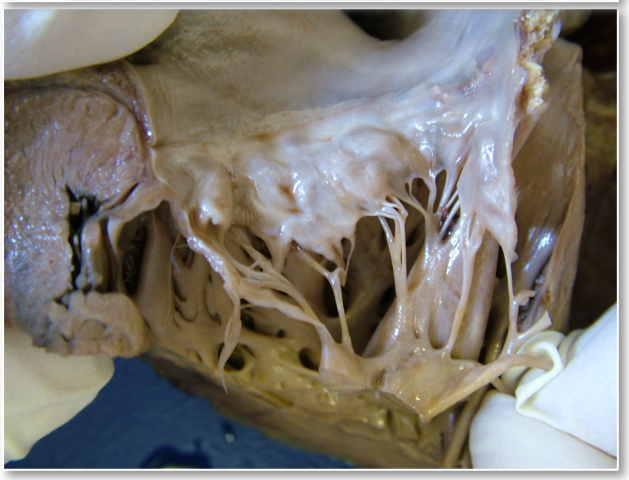
Le coronarie epicardiche risultano indenni (sinistra). Le arteriole contenute nella biopsia endomiocardica del ventricolo sinistro (destra, ematossilina-eosina) presentano vacuolizzazione delle cellule endoteliale (frecce blu) e delle cellule muscolari lisce (frecce rosse)

Angina
(13–23% of patients)

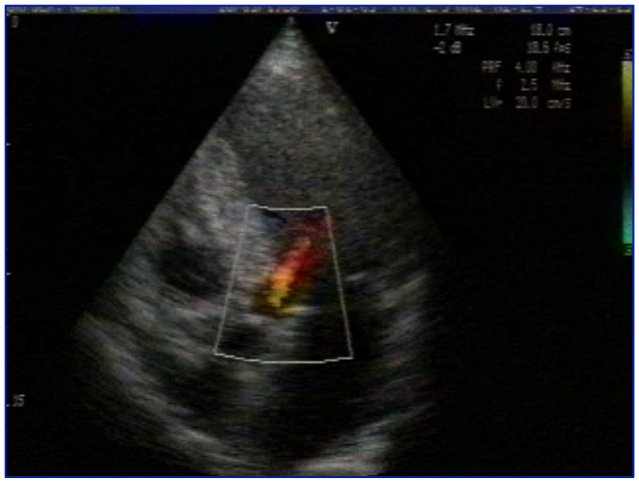
IMA
(2% of patients)

Valve Disease in AFD

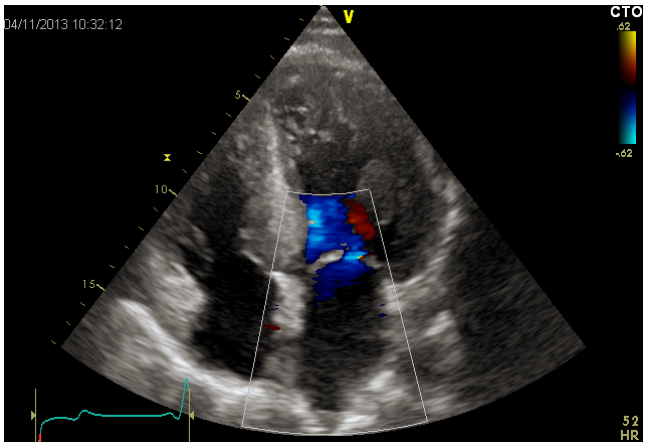




Courtesy of Prof Elliott & Dr. Sheppard



AV=15%



MV=50%

[Cardiogenetics 2013; 3:e3]

Take home message

Although Gl3 storage is present in valve tissue, valve abnormalities are only mild.

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Echocardiography in Fabry disease

[Cardiogenetics 2013; 3:e3]

Markus Niemann, Frank Weidemann

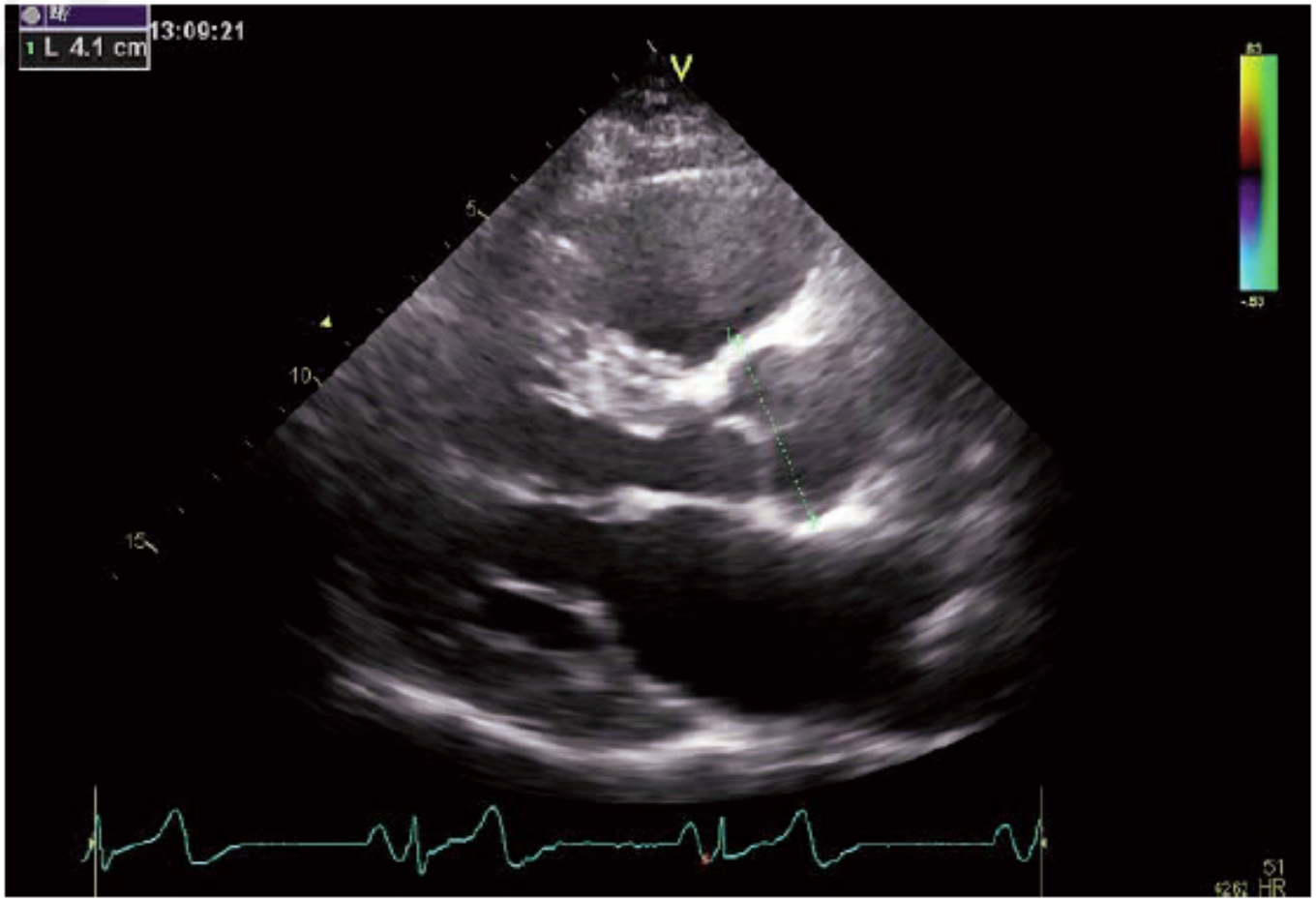


Figure 1. A parasternal long axis view of a Fabry patient's heart. Please note the mildly dilatated aortic root and left atrium.

European Heart Journal (2010) **31**, 347–353
doi:10.1093/eurheartj/ehp426

Aortic remodelling in Fabry disease

Frédéric Barbey[1*†], Salah D. Qanadli[2†], Christoph Juli[3], Noureddine Brakch[4], Tomáš Palaček[5], Elena Rizzo[2], Xavier Jeanrenaud[6], Boris Eckhardt[7], and Aleš Linhart[5]

Aortic dilation at the sinus of Valsalva was found in 32.7% of males and 5.6% of females; aneurysms were present in 9.6% of males and 1.9% of females. No aortic dilation was observed in the descending aorta. Dilation appeared to be independent from cardiovascular risk factors.

idered as a cardiovascular disease that affects the heart and arteria

Quando pensare al Fabry?

Diagnosi

2014 version

Fabry Disease in the recent ESC Guidelines on Hypertrophic Cardiomyopathy

www.escardio.org/guidelines

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

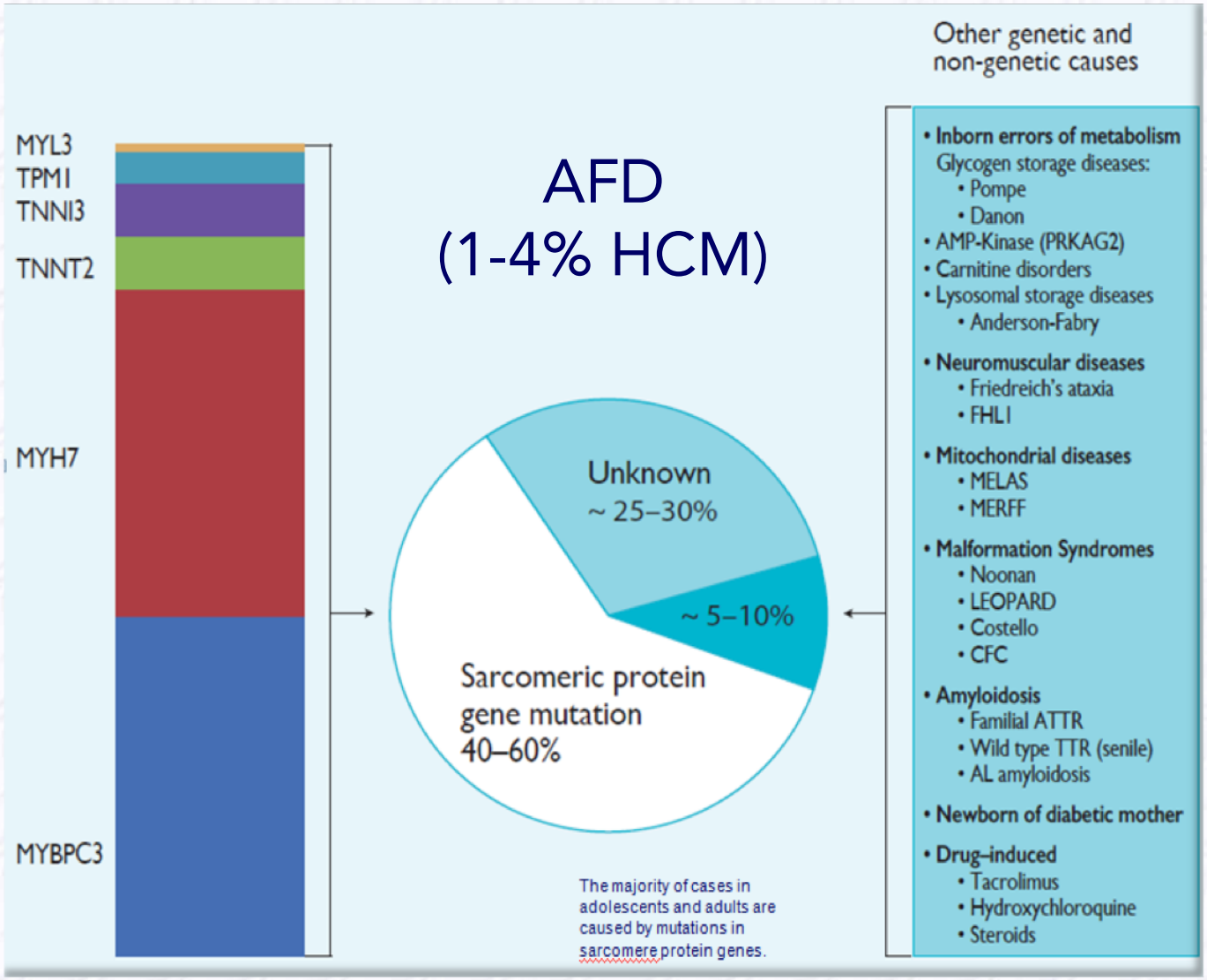
EUROPEAN SOCIETY OF CARDIOLOGY®

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

Authors/Task Force members: Perry M. Elliott (Chairperson) (UK), Aris Anastasakis (Greece), Michael A. Borger (Germany), Martin Borggrefe (Germany), Franco Cecchi (Italy), Philippe Charron (France), Albert Alain Hagege (France), Antoine Lafont (France), Giuseppe Limongelli (Italy), Heiko Mahrholdt (Germany), William J. McKenna (UK), Jens Mogensen (Denmark), Petros Nihoyannopoulos (UK), Stefano Nistri (Italy), Petronella G. Pieper (Netherlands), Burkert Pieske (Austria), Claudio Rapezzi (Italy), Frans H. Rutten (Netherlands), Christoph Tillmanns (Germany), and Hugh Watkins (UK).

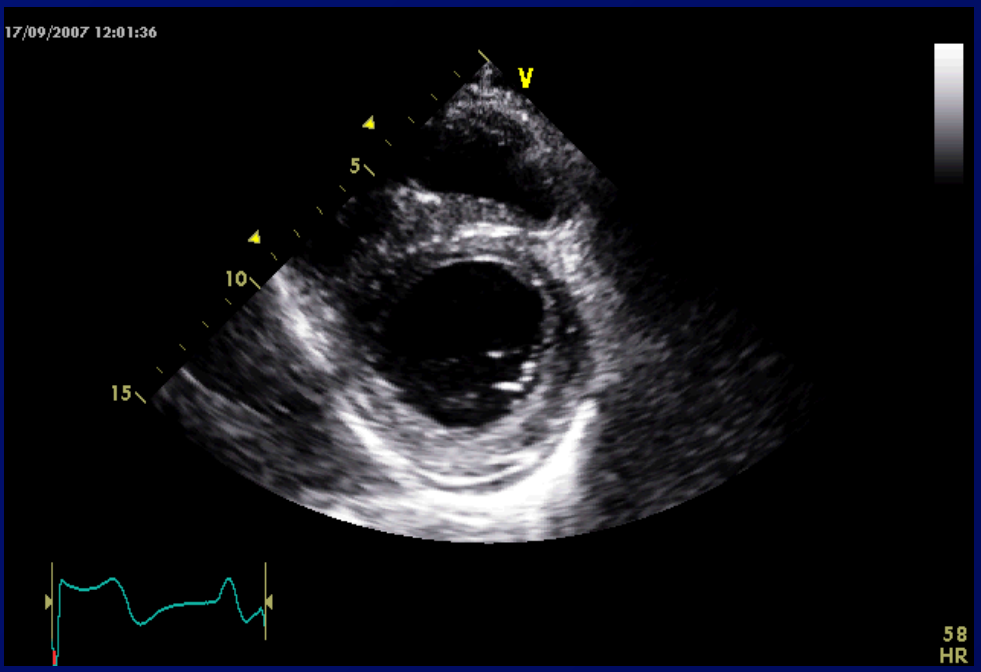
Additional Contributor: Constantinos O'Mahony (UK).

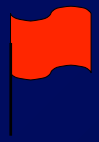
European Heart Journal (2014):doi:10.1093/eurheartj/ehu284



European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Sarcomeric HCM
vs
Fabry

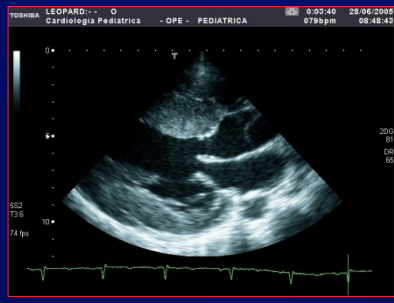




✓Concentric Hypertrophy

✓Right Ventricular Hypertrophy (50-75%)

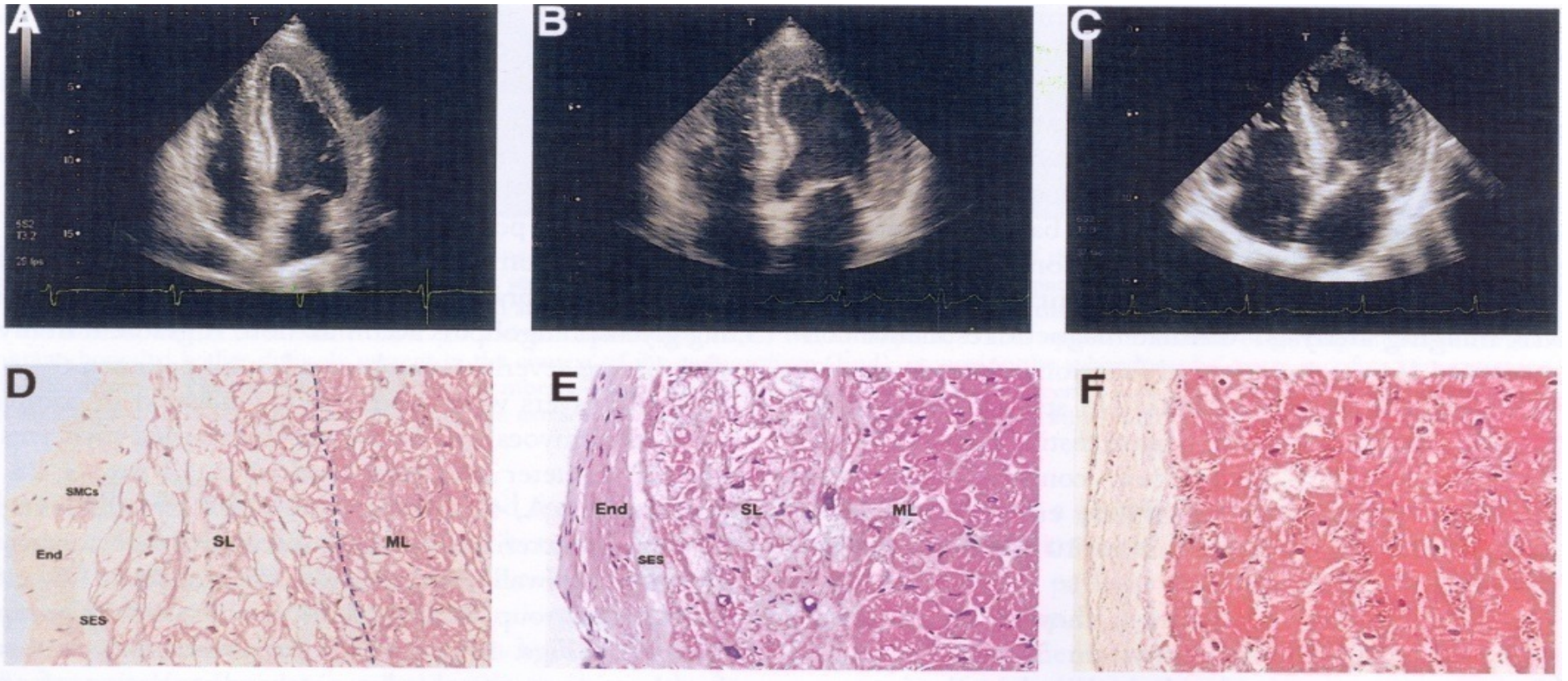
✓No LVOT obs (rare; latent?)



Sarcomeric HCM vs Specific Disease

✓Disease Markers

The “Binary Sign” in Fabry Disease



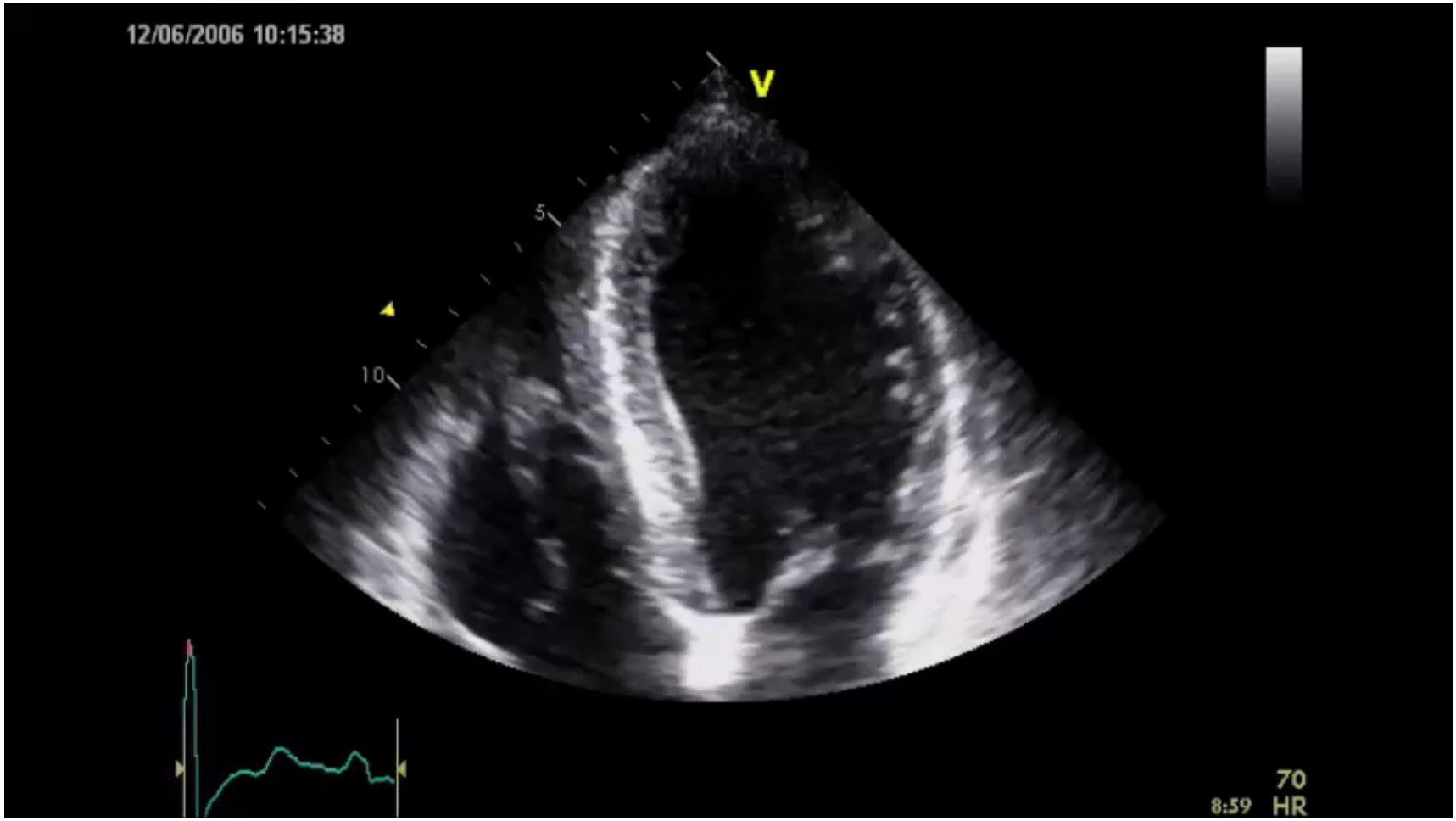
Sensitivity= 94%

Specificity= 100%

“…the binary appearance to reflect an endomyocardial glycosphingolipids compartmentalization, consisting of thickened glycolipid-rich endocardium, free glycosphingolipid subendocardial storage, and an inner severely affected myocardial layer with a clear subendocardial-midwall layer gradient of disease severity.

Pieroni, JACC 2006

www.cardiogenetics.it



Nieman M, Weidemann F. Cardiogenetics 2013; 3:e3.

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doi:10.1016/j.jacc.2008.02.046

The Binary Endocardial Appearance Is a Poor Discriminator of Anderson-Fabry Disease From Familial Hypertrophic Cardiomyopathy

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Andre Keren, MD,† Philip J. Lee, DM, FRCPCH, FRCP,‡
Derralynn Hughes, MA, DPhil, MRCP, MRCPath,§ Atul Mehta, MA, MD, FRCP, FRCPath,§
Perry Mark Elliott, MBBS, MD, FRCP, FACC, FESC*

London, United Kingdom; and Jerusalem, Israel

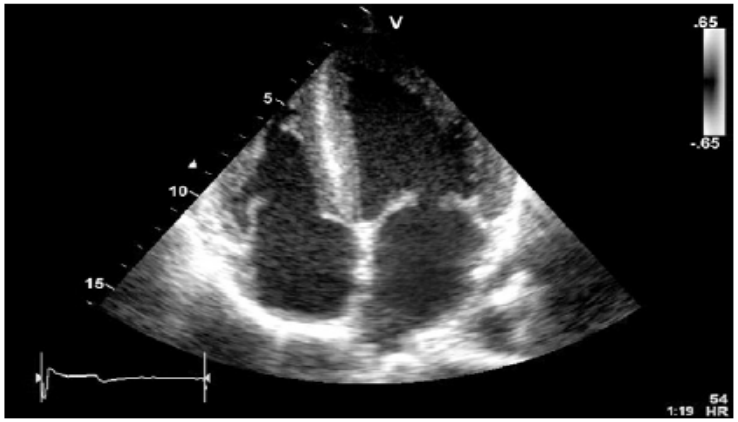


Figure 1 Apical View of a Patient With Anderson-Fabry Disease

Left ventricular hypertrophy is present with no binary endocardial appearance.

Table 2 Sensitivity and Specificity of the Binary Endocardial Appearance

		Maximum LVWT		
		<15 mm	≥15 mm	Overall
AFD	No. of patients	5	9	14
	Binary sign	1	4	5
	Sensitivity	20%	44%	35%
HCM	No. of patients	4	10	14
	Binary sign	0	3	3
	Specificity	100%	70%	79%

Cardiogenetics 2013; volume 3:e3

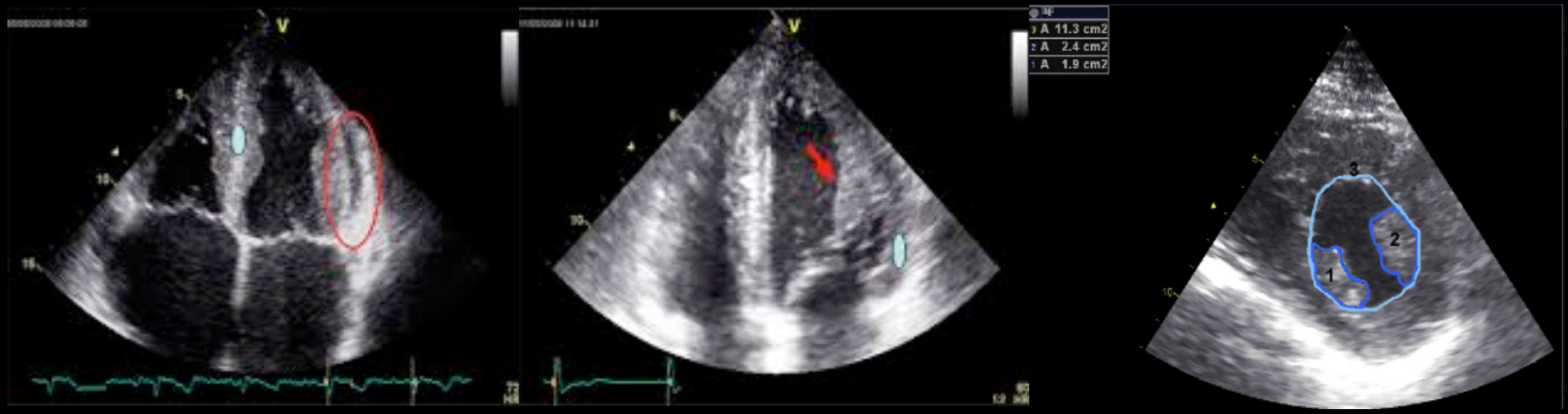
Take home message

Prominent papillary muscles are typical.

pagepress:

Echocardiography in Fabry disease

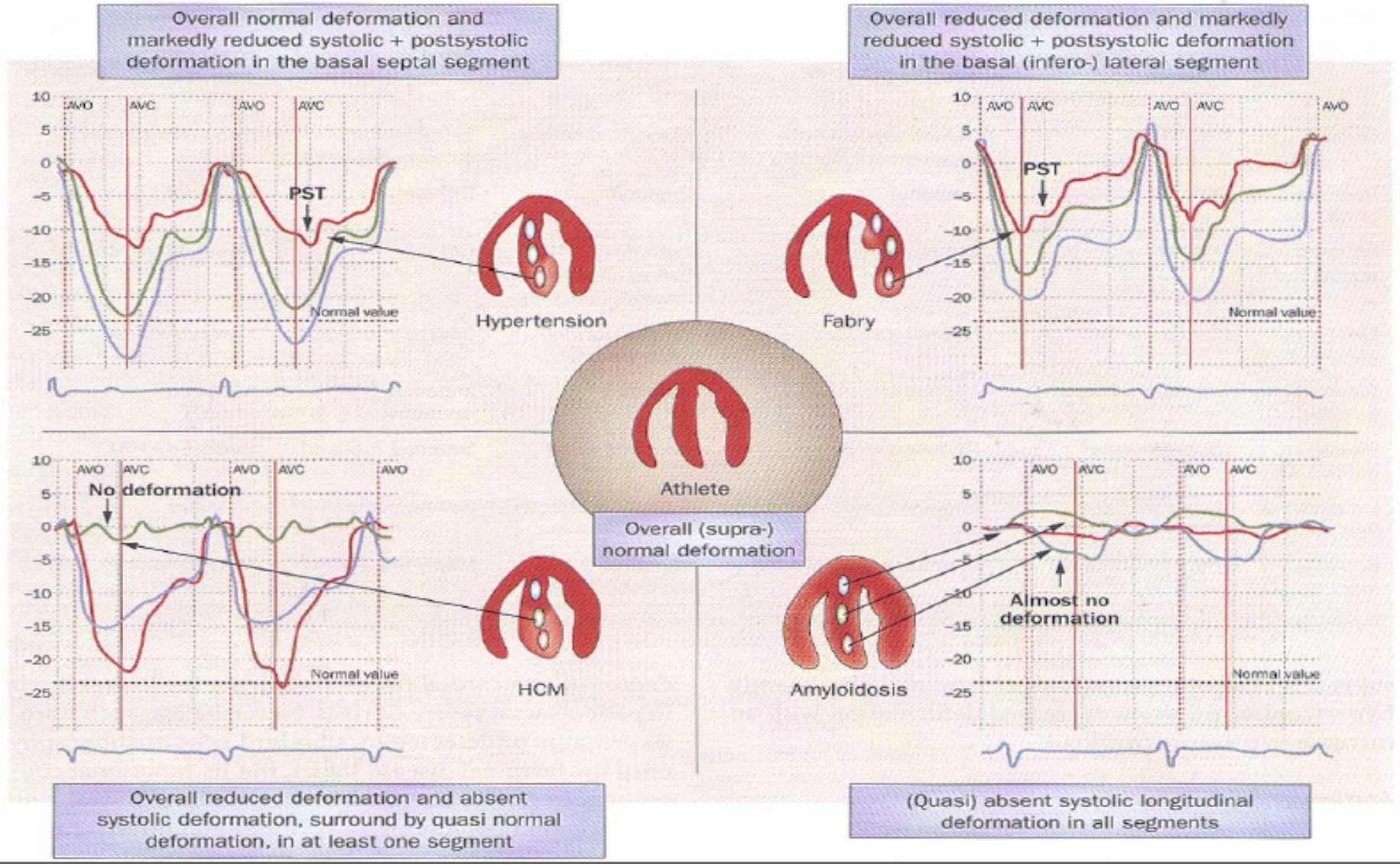
Markus Niemann, Frank Weidemann

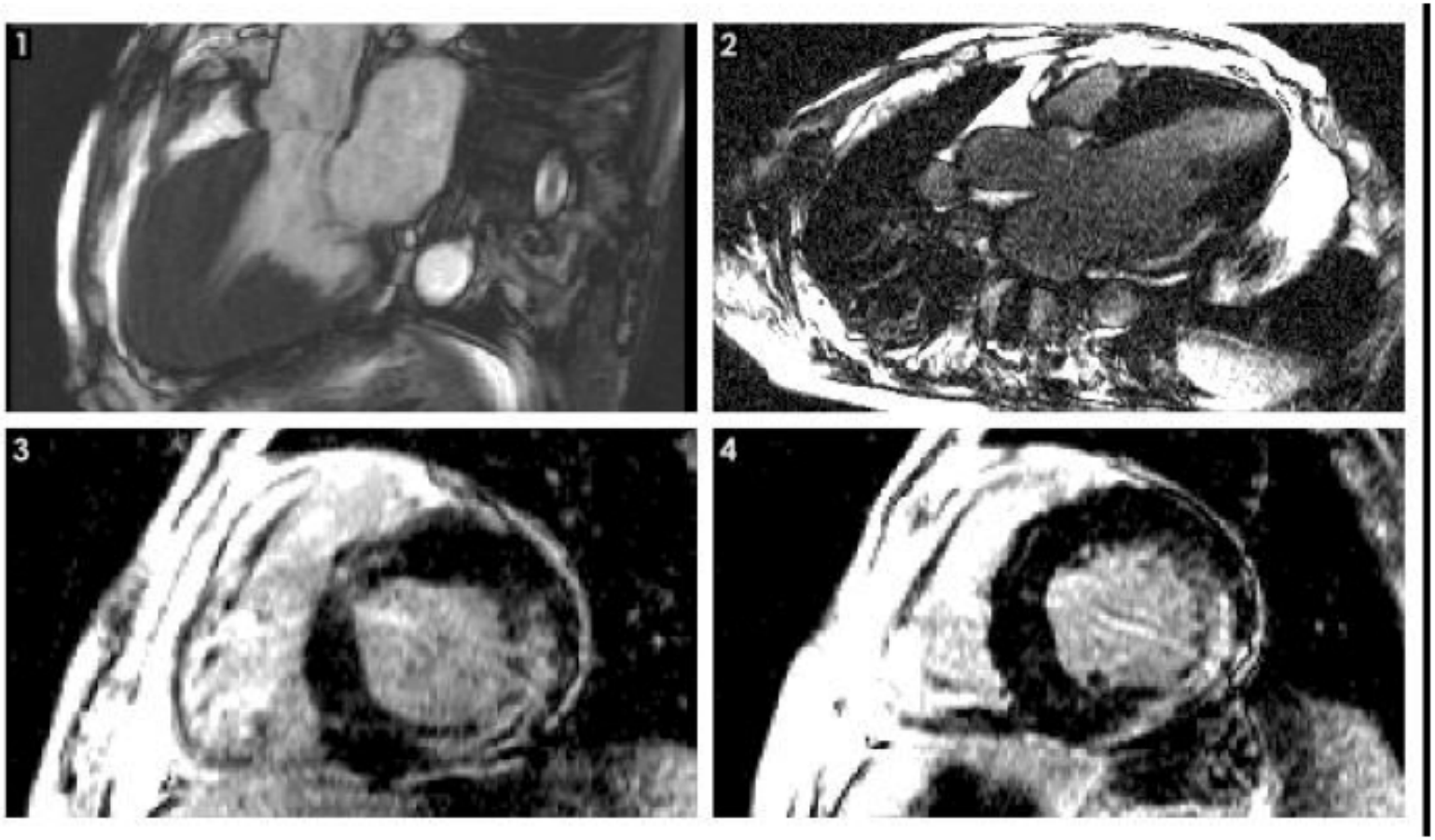


"In a recent study it could be shown that the absolute papillary muscle area as well as the ratio of the papillary muscle area and the left ventricular circumference is enlarged in AFD"

Ultrasound Med Biol 2011;37:37-43.

New Echo Technologies





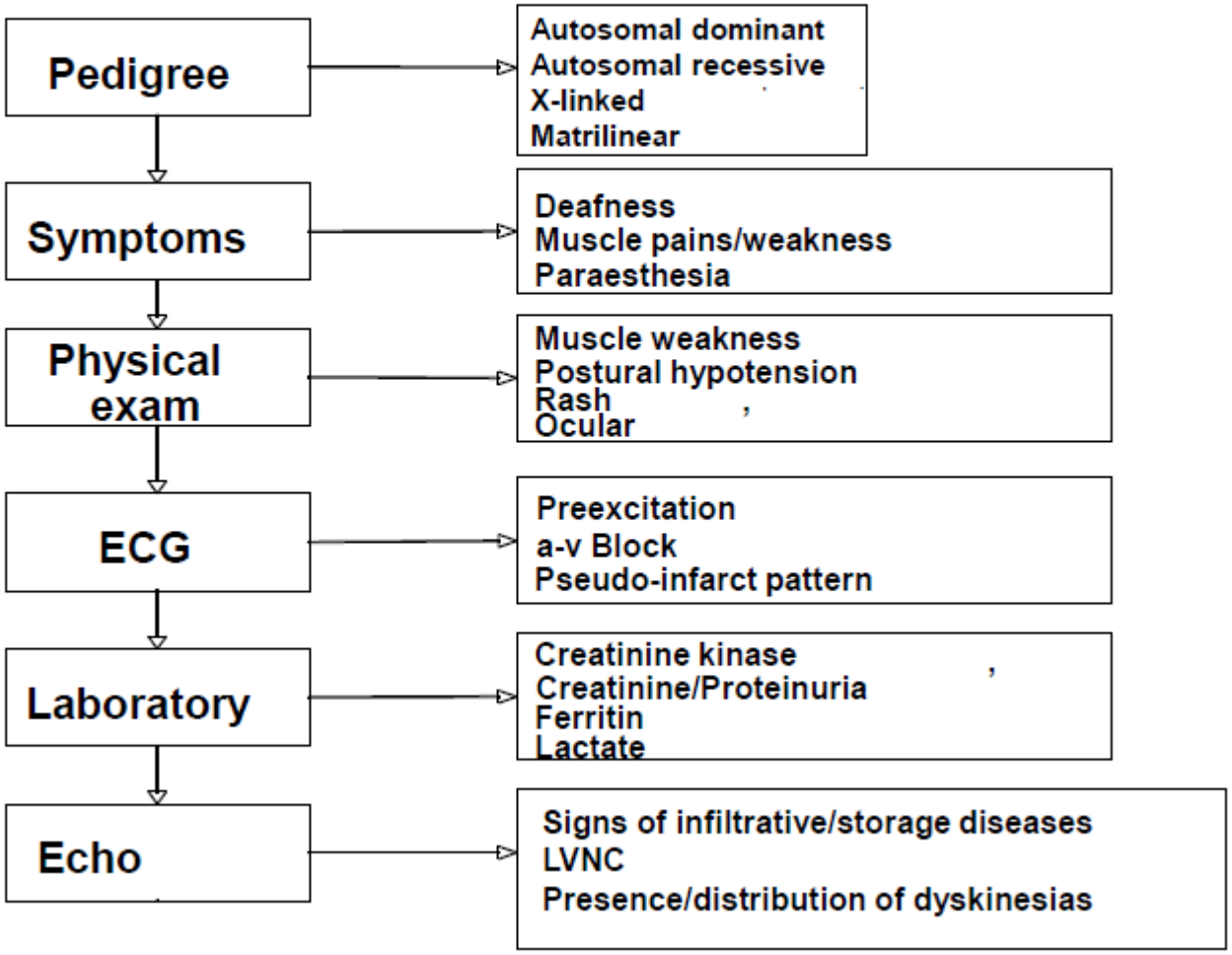
Moon J et al. Eur Heart J 2003;24: 2151

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Rare Cardiomyopathies: is all imaging?

"Well, we've had the results of your tests Mr Fittock, and I have to tell you that you have nothing famous."

The red flags approach



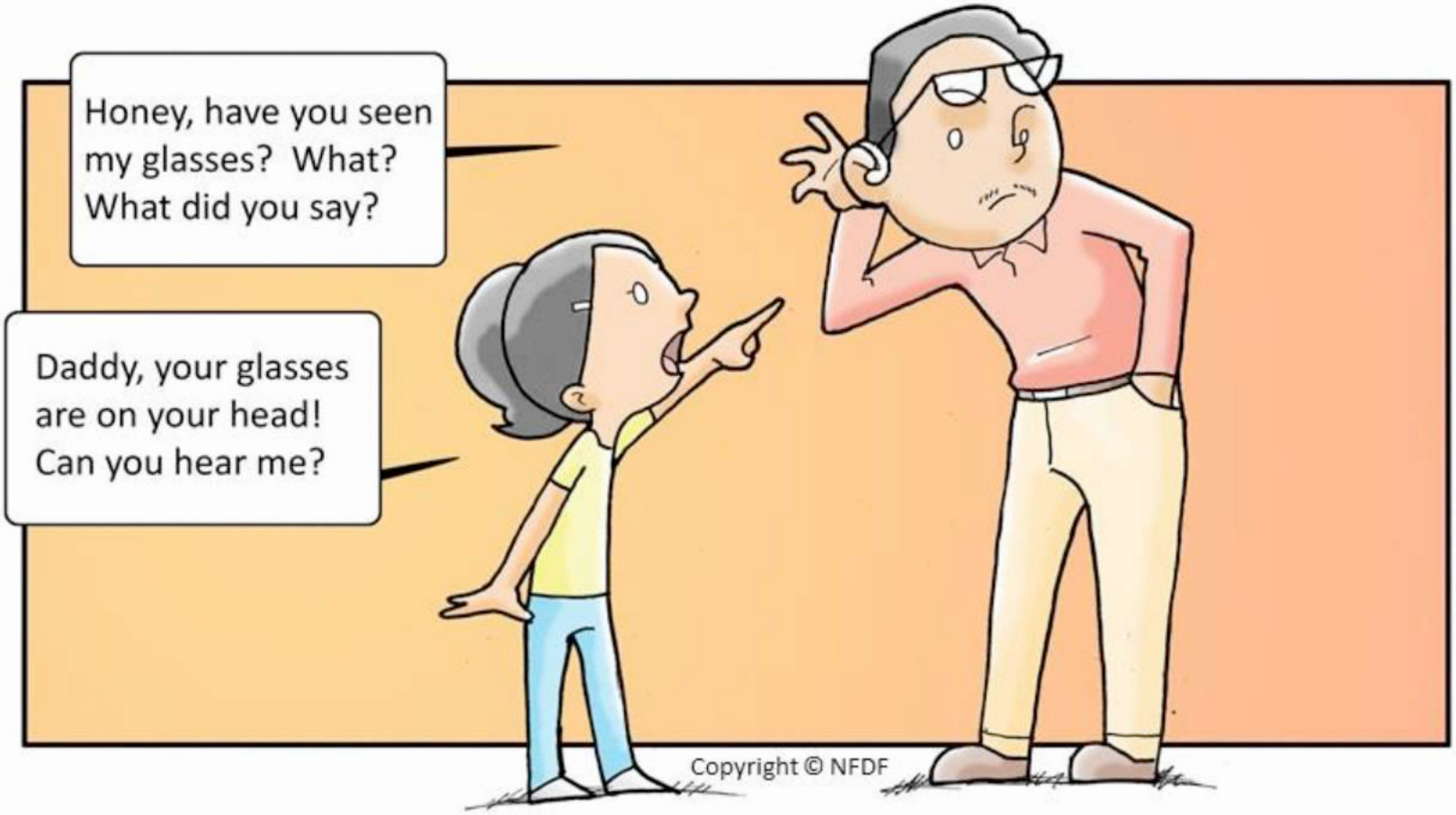
Claudio Rapezzi, 2010

Table 3 Examples of signs and symptoms suggestive of specific diagnoses (modified from Rapezzi et al.[67])

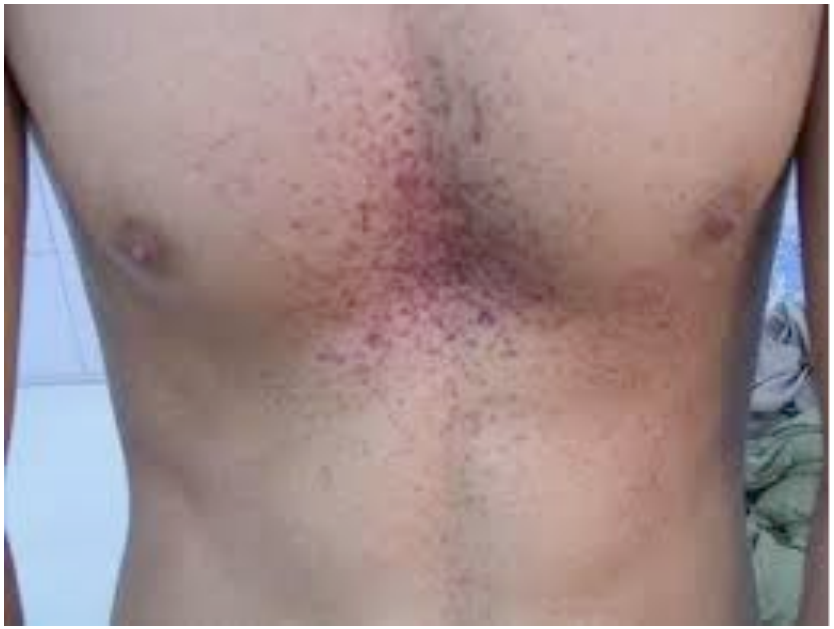
Symptom/sign	Diagnosis
Learning difficulties, mental retardation	• Mitochondrial diseases • Noonan/LEOPARD/Costello syndrome • Danon disease
Sensorineural deafness	• Mitochondrial diseases (particularly with diabetes) • Anderson-Fabry disease • LEOPARD syndrome
Visual impairment	• Mitochondrial diseases (retinal disease, optic nerve) • TTR-related amyloidosis (cotton wool type vitreous opacities) • Danon disease (retinitis pigmentosa) • Anderson-Fabry disease (cataracts, corneal opacities)
Gait disturbance	• Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	• Amyloidosis • Anderson-Fabry disease
Carpal tunnel syndrome	• TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	• Mitochondrial diseases • Glycogen storage disorders • FHL1 mutations • Friedreich's ataxia
Palpebral ptosis	• Mitochondrial diseases • Noonan/LEOPARD syndrome • Myotonic dystrophy
Lentigines/café au lait spots	• LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	• Anderson-Fabry disease

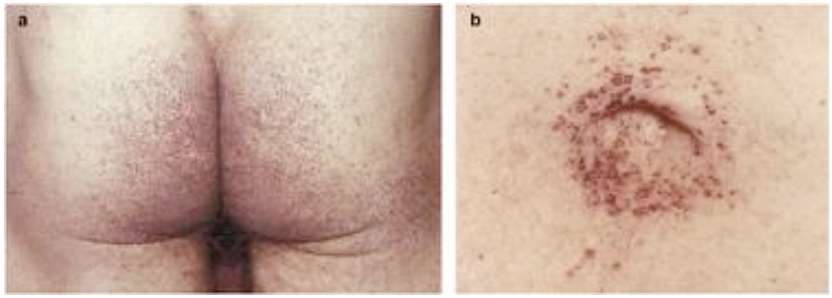
European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

People with Fabry disease tend to lose things!



Common audiology symptoms include tinnitus and progressive or sudden hearing loss. Acute hearing loss is about 60 times more prevalent than in the general population. The onset of progressive hearing loss usually begins in men and women in the 2nd and 4th decades of life respectively. Use of hearing aids is common. Dizziness and vertigo (spinning dizziness) are also common symptoms of Fabry disease.





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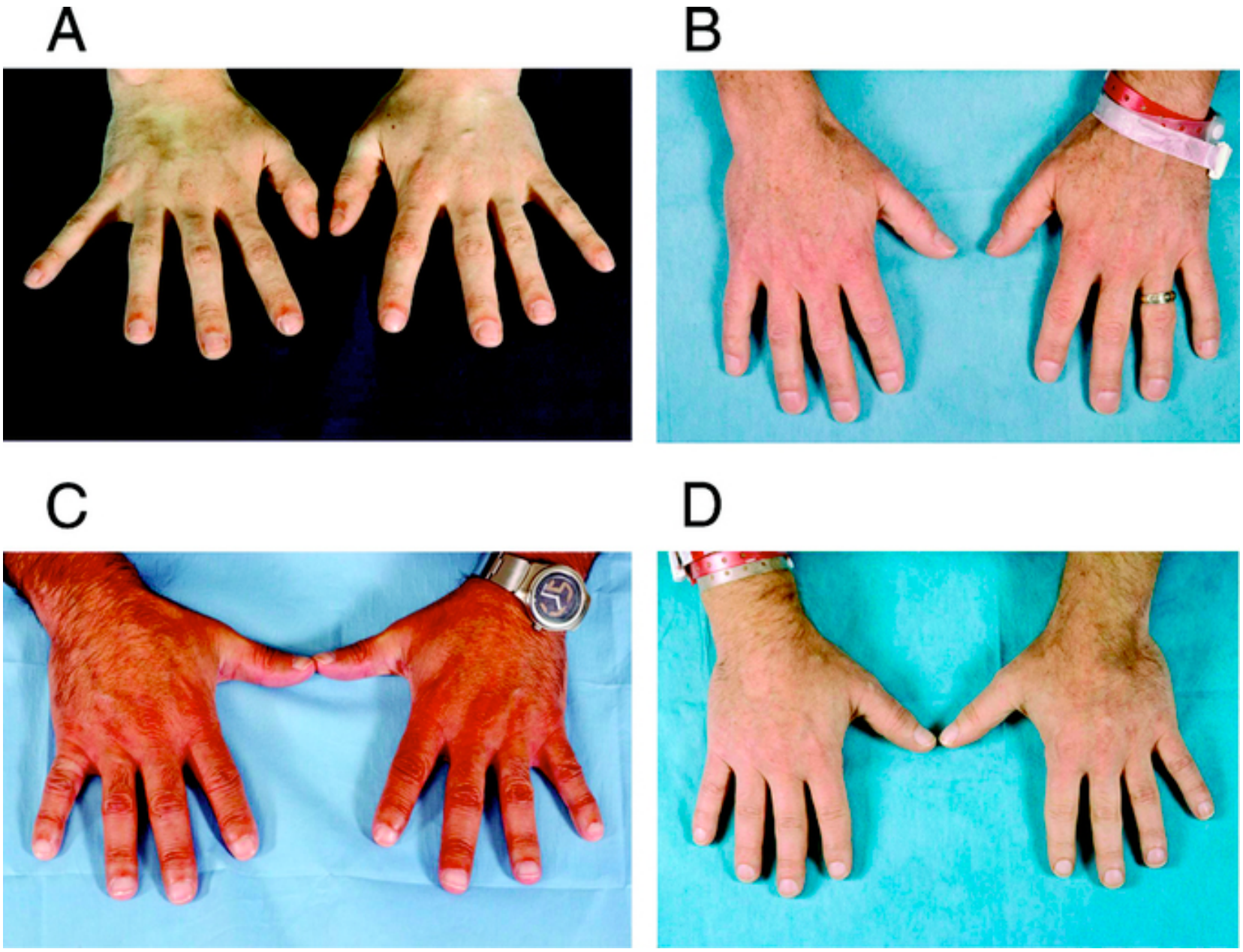
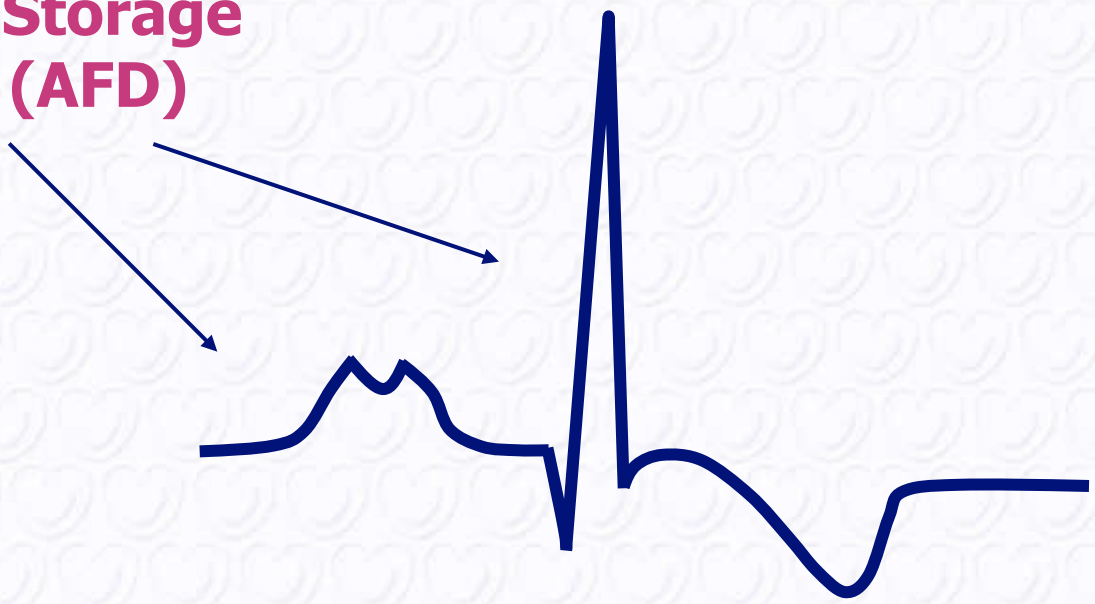


Digital findings: A) normal; B-D) illustrate short fingers and broad fingertips.

ECG abnormalities in cardiomyopathies

Glycogen Storage Disease (AFD)



Courtesy C. Rapezzi

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Recommended Laboratory Tests

Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy	
Test	**Comment**
Haemoglobin	Anaemia exacerbates chest pain and dyspnoea and should be excluded whenever there is a change in symptoms.
Renal function	Renal function may be impaired in patients with severe left ventricular impairment. Impaired GFR and proteinuria may be seen in amyloidosis, Anderson-Fabry disease and mitochondrial DNA disorders.
Liver transaminases	Liver tests may be abnormal in mitochondrial disorders, Danon disease and ß-oxidation defects.
Creatine phosphokinase	Serum creatine phosphokinase is raised in metabolic disorders such as Danon and mitochondrial disease.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

DIAGNOSIS

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Recommended Laboratory Tests

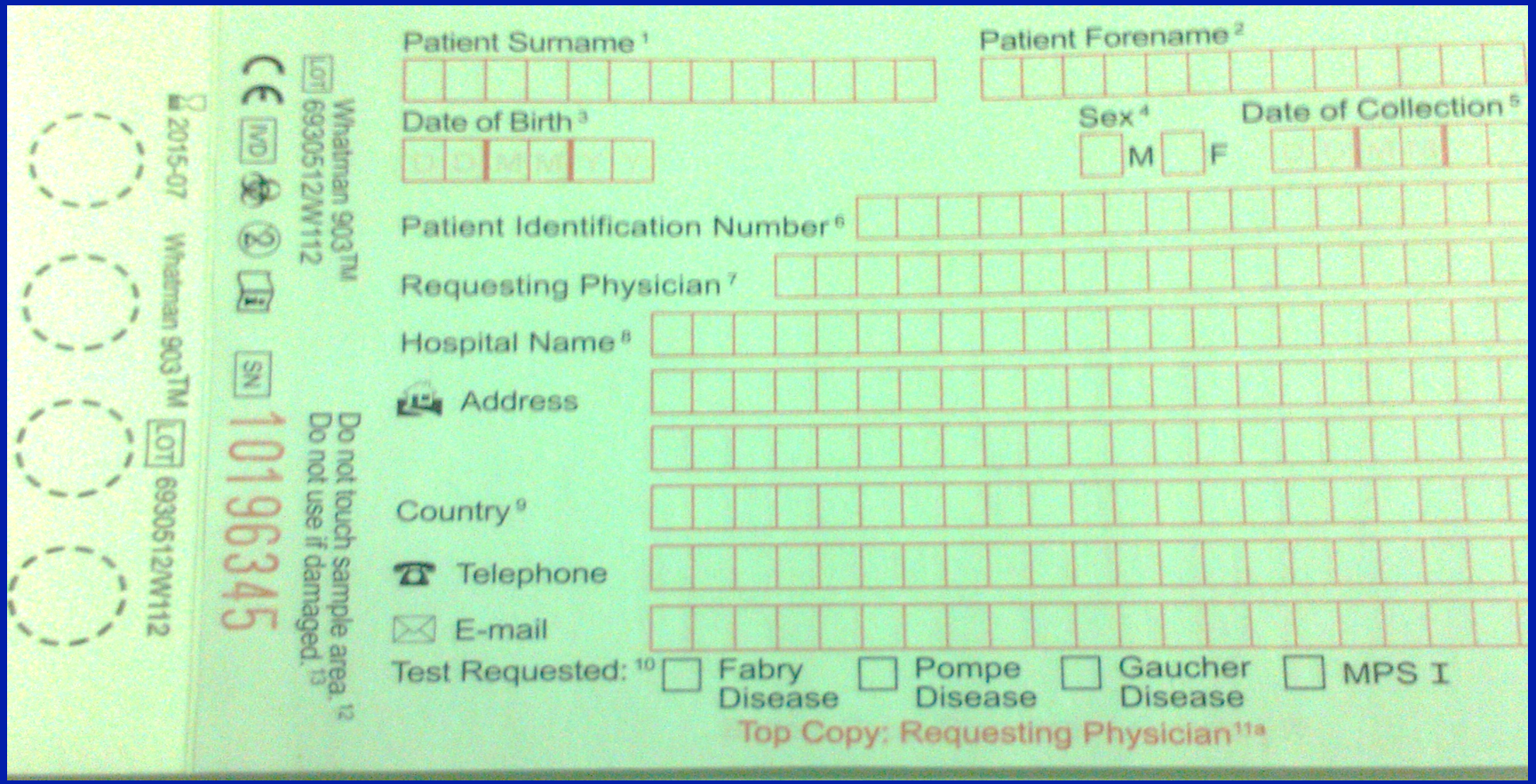
Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy (cont.)	
Test	**Comment**
Plasma/leucocyte alpha galactosidase A (in men aged >30 years)	Low (<10% normal values) or undetectable plasma and leucocyte alpha galactosidase A is present in male patients with Anderson-Fabry disease.[a] Plasma and leucocyte enzyme levels are often within the normal range in affected females and so genetic testing may be considered if clinically suspected.
Serum immunoglobulin free light chain assay, serum and urine immunofixation, and urine electrophoresis	Should be considered if amyloidosis is suspected from history and non-invasive tests. Confirmation of the diagnosis usually requires histological analysis.
Fasting glucose	May be elevated in some mitochondrial DNA disorders and low in fatty acid and carnitine disorders.
Brain natriuretic peptide and troponin T	Elevated plasma levels of BNP, NT-proBNP and troponin T are associated with higher risk of cardiovascular events, heart failure and death.
Thyroid function tests	Should be measured at diagnosis and monitored every 6 months in patients treated with amiodarone.
Plasma Lactate	Elevated in some patients with mitochondrial disorders.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Screening dei pazienti con ipertrofia ventricolare/ cardiomiopatia ipertrofica

- ✓ Sesso maschile
- ✓ Età insorgenza IVS/CMI $\geq$ 40 anni
- ✓ Assenza di familiarità per CMI con modalità di trasmissione autosomica documentata
- ✓ Assenza di mutazione nota per CMI sarcomerica

Screening dei pazienti con ipertrofia ventricolare/ cardiomiopatia ipertrofica



Left Ventricular Hypertrophy

Concentric thickening of the LV wall (≥13 mm on echo)

- Hypertrophic cardiomyopathy, sarcomeric mutations or unknown gene
- Aortic stenosis
- Hypertension
- Athletic heart
- LV non-compaction
- Obesity
- Infiltrating cardiomyopathies
- Metabolic disorders
- Syndromal

Focus on Fabry disease

History, examination, ECG, urine analysis

- **History:** Childhood neuropathic pains, abdominal cramps and diarrhea, hypohidrosis, fatigue. Depression.
- **Family history:** Premature stroke, renal failure, cardiomyopathy, sudden death. Absence of male-to-male transmission.
- **Examination:** Angiokeratoma, cornea verticillata, proteinuria, hearing loss.
- **ECG:** Short PR interval (young age), AV block (older age), voltage criteria for LVH, ST segment changes, T wave inversion.

Consider Fabry disease (α-galactosidase A deficiency)

- **For males:** α-galactosidase A deficiency testing: whole blood assay or dry blood spot
- **For females:** genetic testing for Fabry mutation

Note: It is important to consider formal blood/genetic testing for Fabry disease even if there are no red flags or diagnostic pointers and the LVH remains truly unknown.

Perche’ pensare al Fabry?

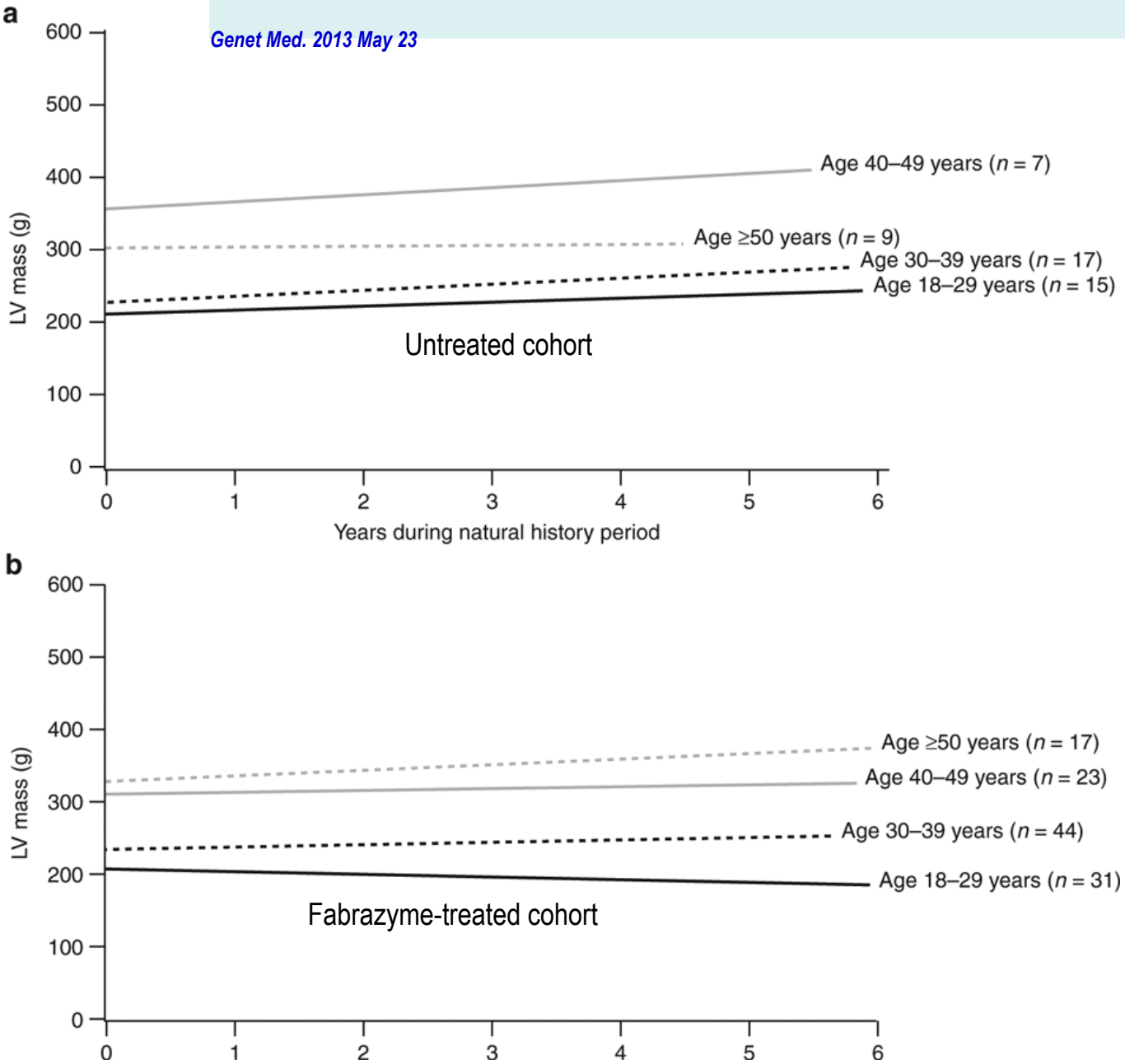
Perche’ dovrei fare la diagnosi di una malattia rara?

ANDERSON FABRY: 1: 40,000

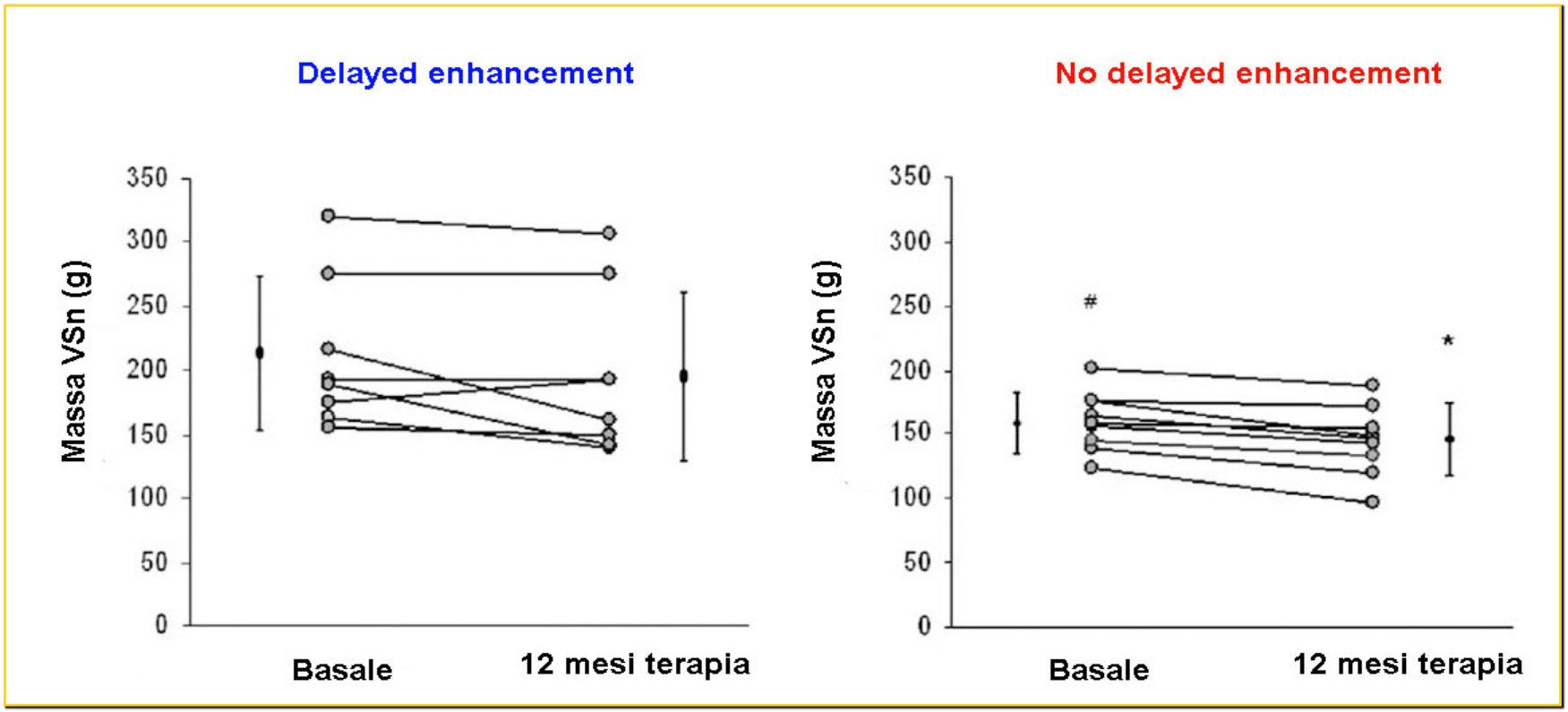
Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry Registry

Germain DP, Weidemann F, Abiose A, Patel MR, Cizmarik M, Cole JA, Beitner-Johnson D, Benistan K, Cabrera G, Charrow J, Kantola I, Linhart A, Nicholls K, Niemann M, Scott CR, Sims K, Waldek S, Warnock DG, Strotmann J

Genet Med. 2013 May 23



EFFICACIA TERAPIA



La terapia enzimatica risulta meno efficace nei pazienti con maggior massa ventricolare sinistra e presenza di delayed enhancement !!!

Modificato da Beer et al. Eur Heart J 2005

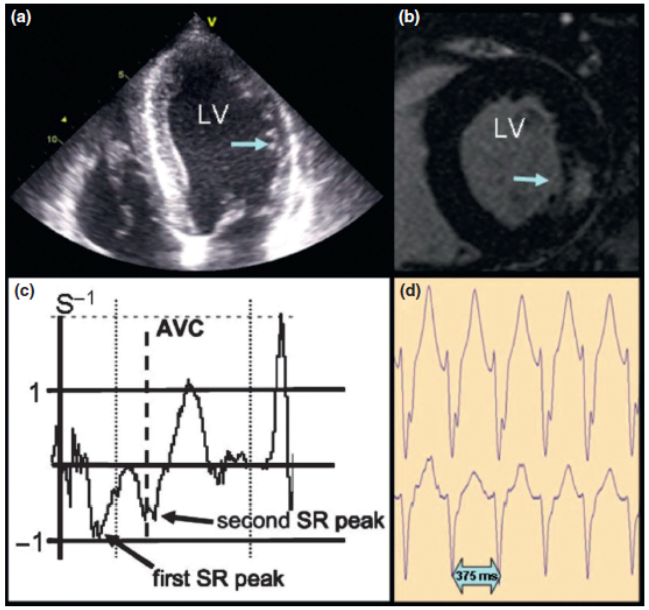
Original Article

Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12077

Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications

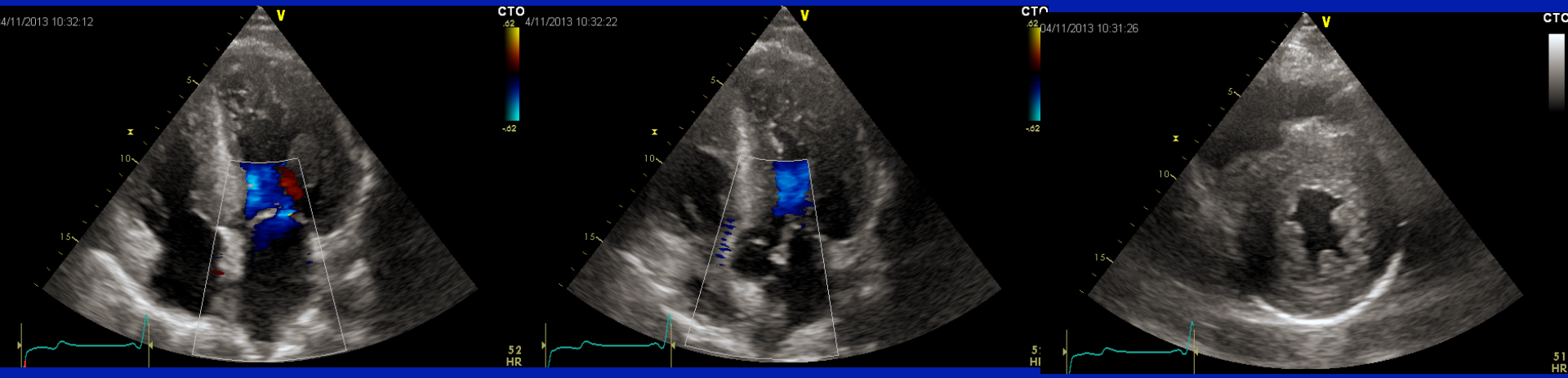
F. Wejdemann[1,2,*], M. Niemann[1,2,*], S. Störk[1,2], F. Breunig[1], M. Beer[3], C. Sommer[4], S. Herrmann[1,2], G. Ertl[1,2] & C. Wanner[1,2]



- Left Ventricular Mass
- Myocardial Fibrosis
- Ventricular Arrhythmias

P.G. 63 anni

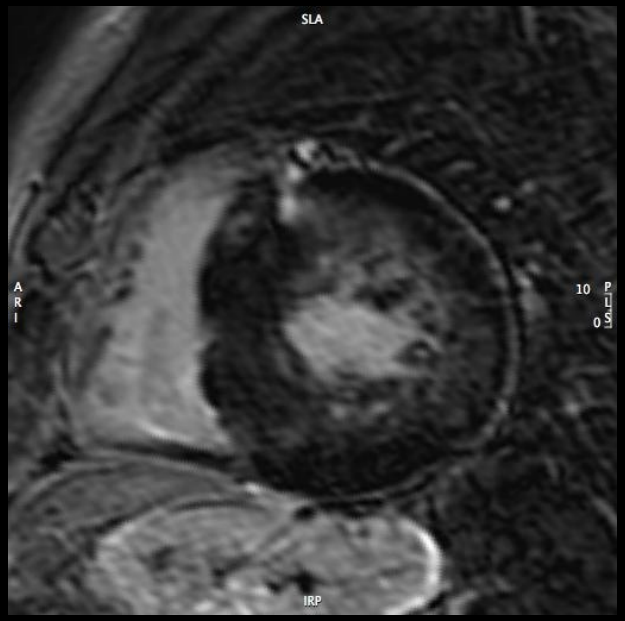
Isolated Cardiac Involvement (Atypical AFD)

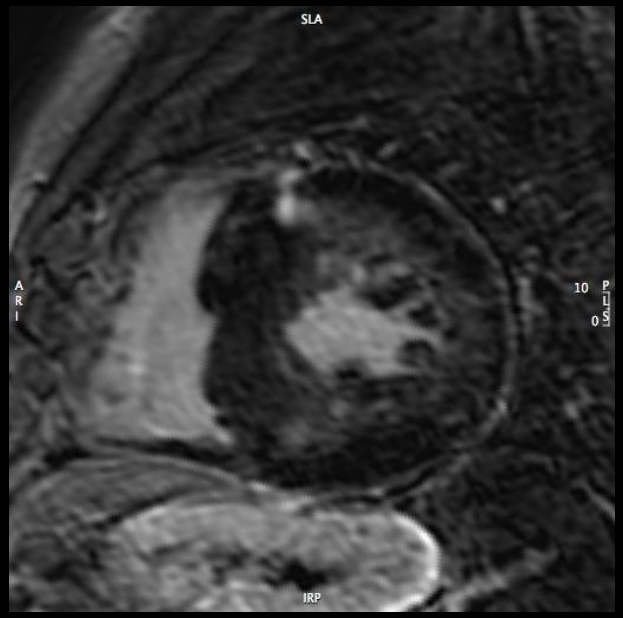


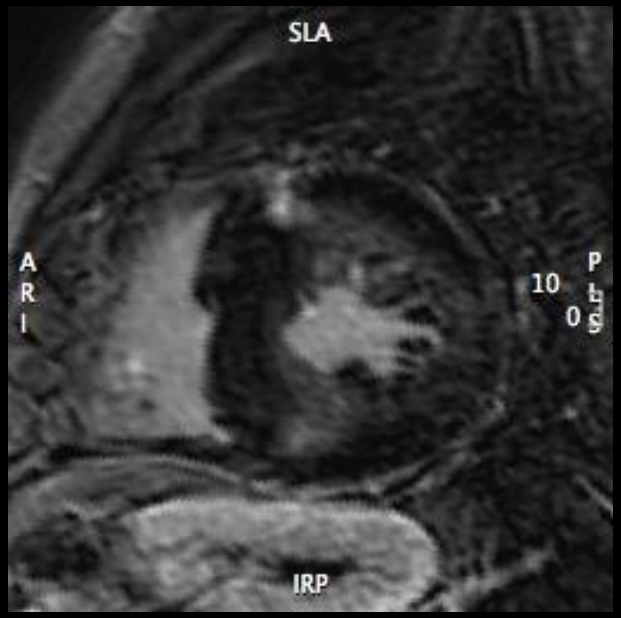
No history of pain/gastrointestinal
No skin disease
No renal involvement
No neurological involvement

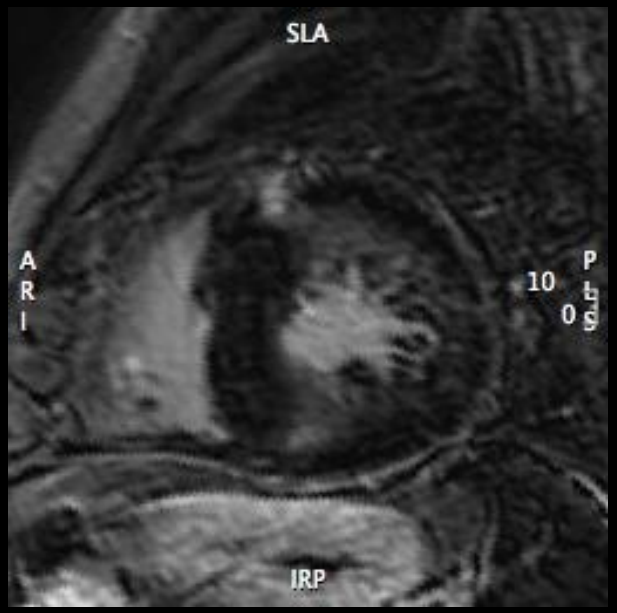
Alpha-GAL=0

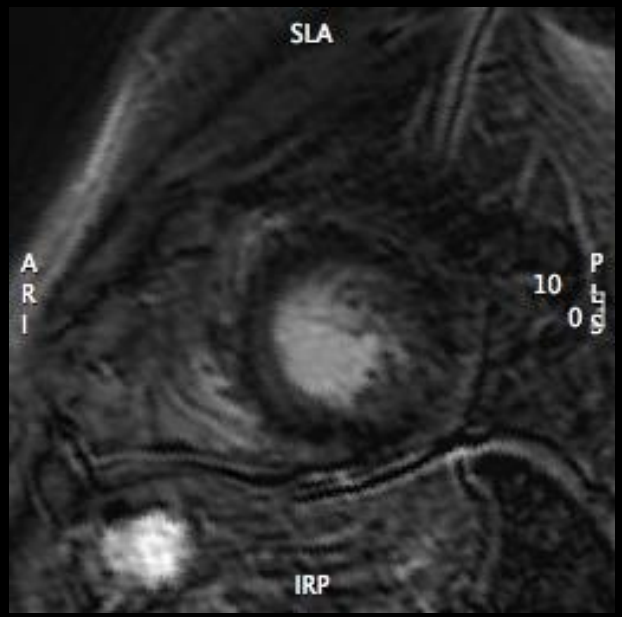
R301G (GLA)











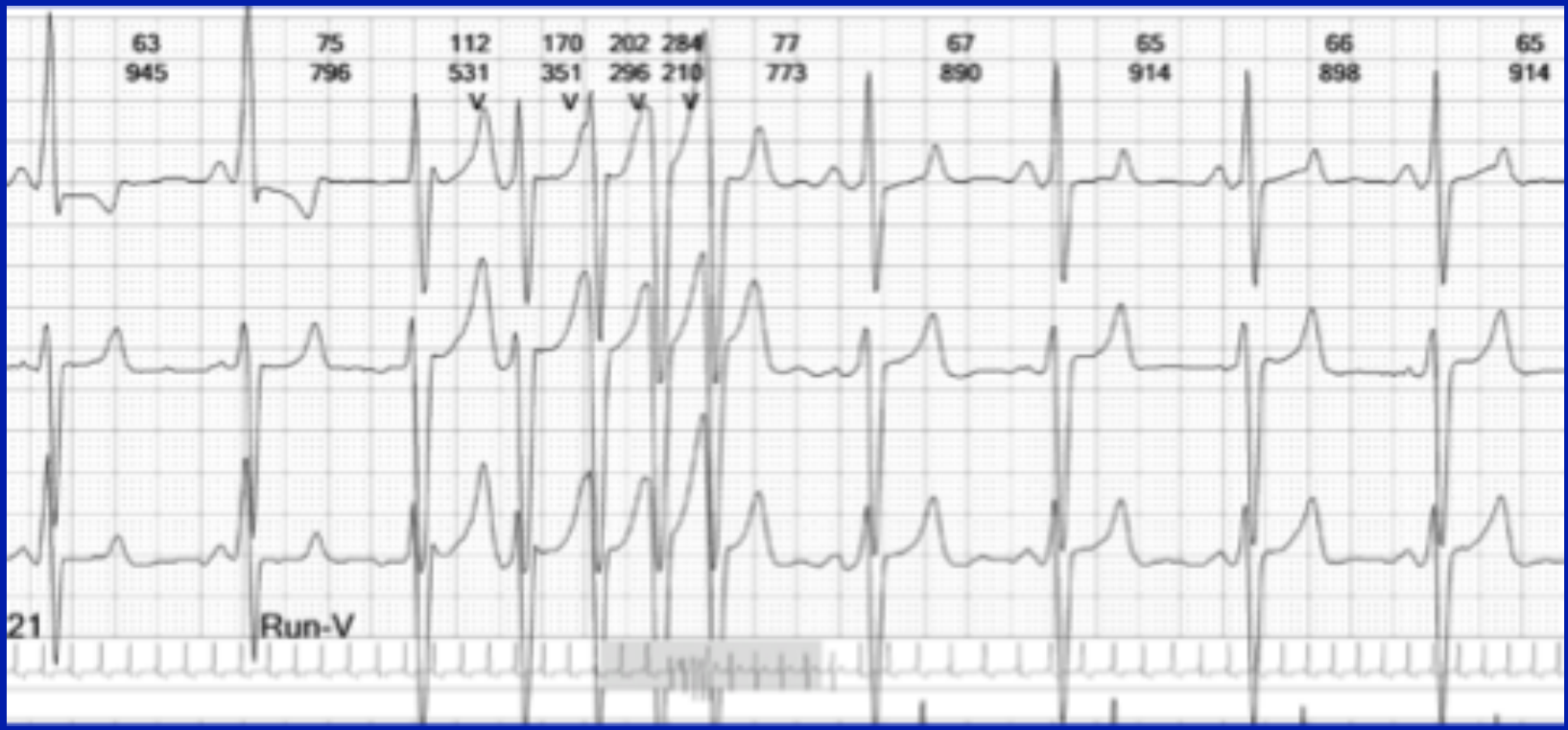
Concentric LVH

MWT=27mm

LVMI=209g/m2

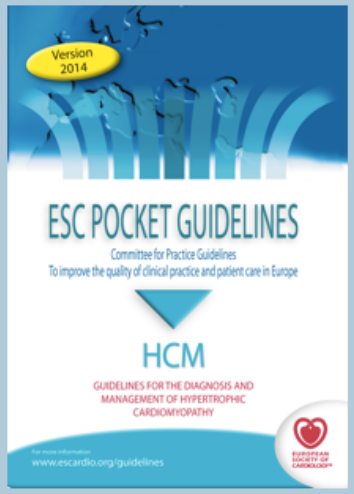
LGE=diffuse

Ecocardiogramma



Episodes of NSVT (Holter 24h + Stress Test)

HCM Risk-SCD Calculator



Age	**Years**	*Age at evaluation*
Maximum LV wall thickness	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	
ESC recommendation:	

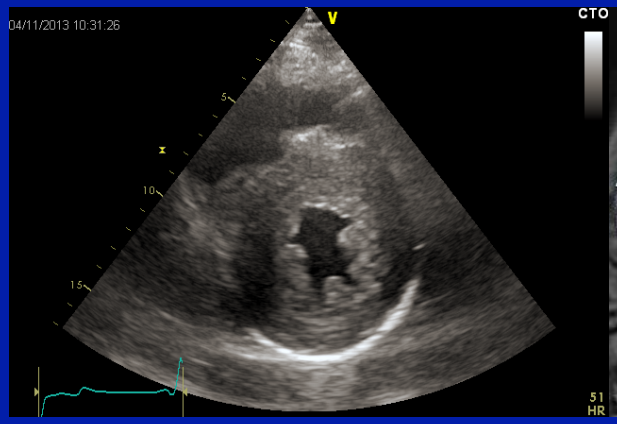
Reset

2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy (Eur Heart J 2014 – doi:10.1093/eurheartj/ehu284)

O'Mahony C et al Eur Heart J (2014) 35 (30): 2010-2020

HCM Risk-SCD should not be used in:

- ***Paediatric patients (<16 years)***
- ***Elite/competitive athletes***
- ***HCM associated with metabolic diseases (e.g. Anderson-Fabry disease), and syndromes (e.g. Noonan syndrome).***
- ***Patients with a previous history of aborted SCD or sustained ventricular arrhythmia who should be treated with an ICD for secondary prevention.***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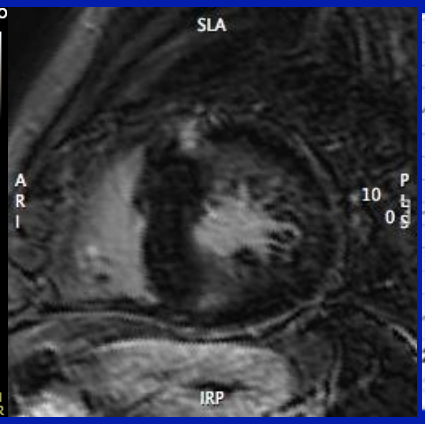
CTO
51
HR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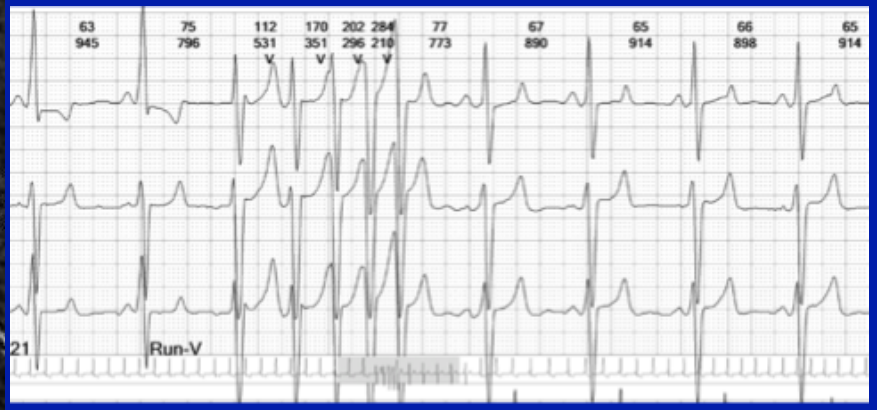
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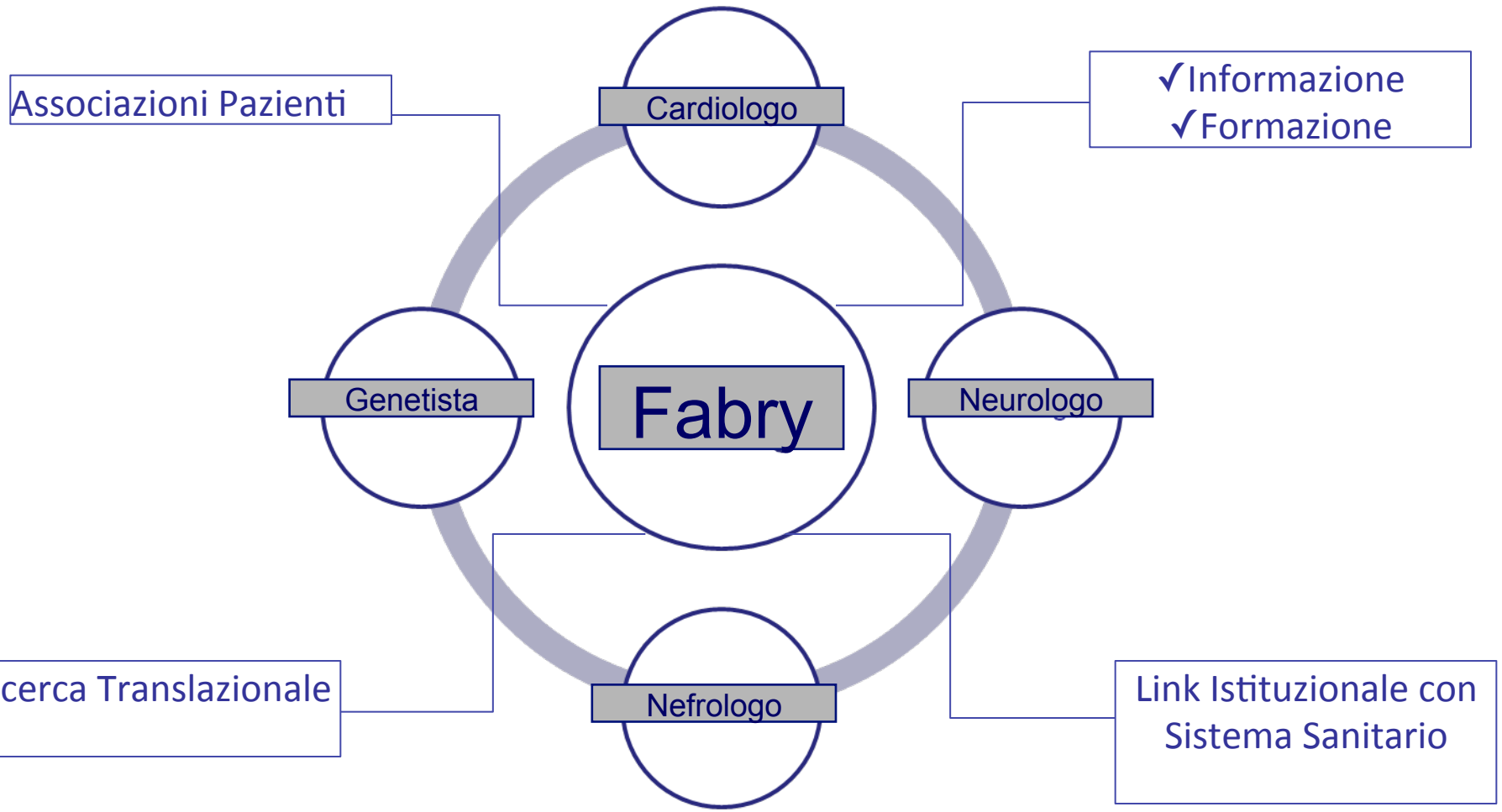
AICD

TAKE HOME


Associazioni Pazienti
Cardiologo
✓Informazione
✓Formazione
Genetista
Fabry
Neurologo
Ricerca Translazionale
Nefrologo
Link Istituzionale con Sistema Sanitario

TAKE HOME

Il ruolo del Cardiologo nella malattia di Fabry

Diagnosi
(territorio!)

Management
(centri riferimento)

Abstract

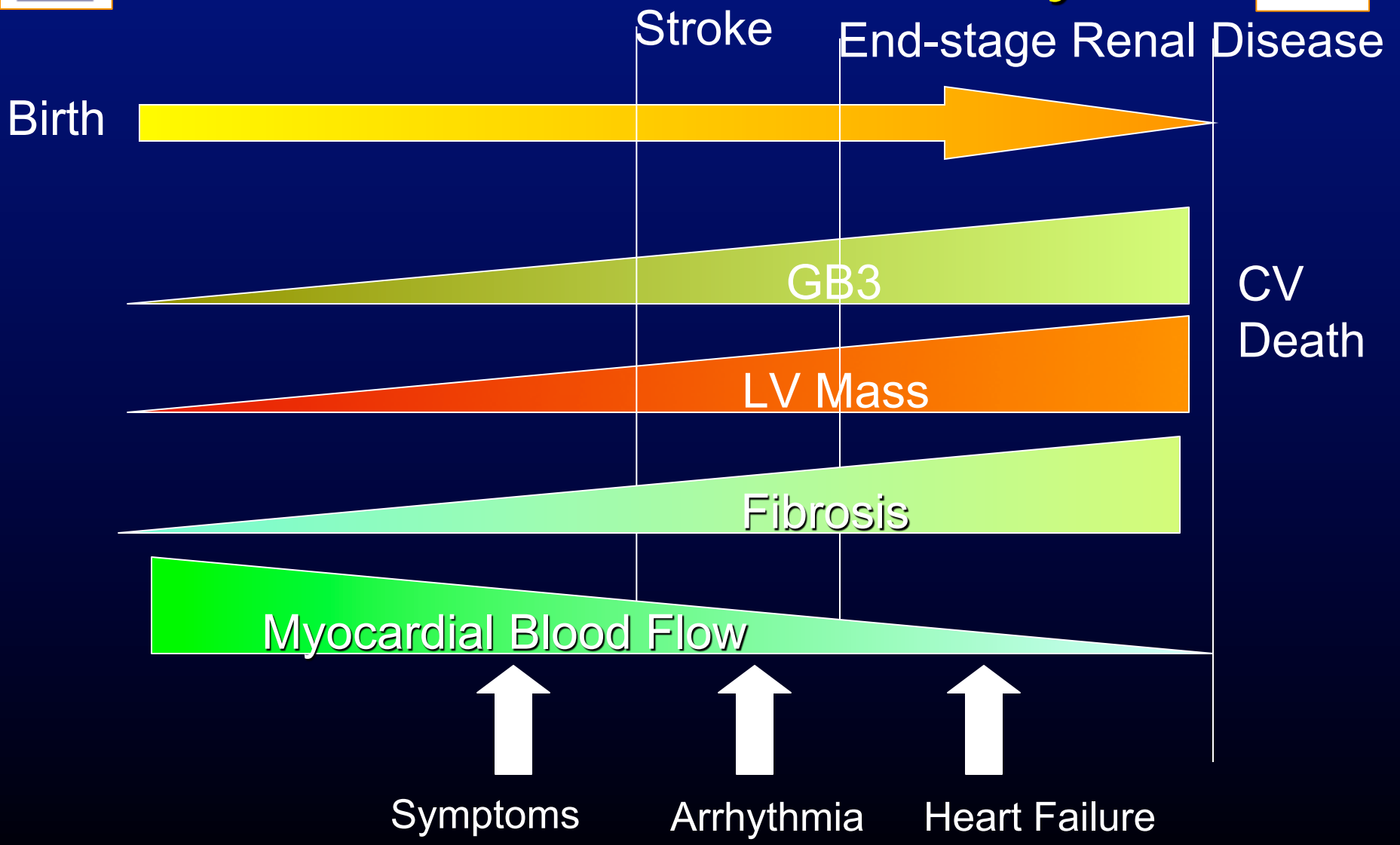
Purpose: 1) To identify morphometric characteristics in hemizygous patients with Fabry disease a treatable lysosomal storage disorder caused by the deficiency of α-galactosidase A where morphological abnormalities have occasionally been mentioned, but have never been investigated systematically. 2) To devise a quantitative method to evaluate dysmorphic abnormalities in Fabry disease.

Method: Cross-sectional, single center, independent dysmorphology assessment by a panel of three clinical geneticists, based on standardized medical photography. Population: consecutive hemizygous patients with Fabry disease (N = 38) unselected for the features assessed, mean age 38 ± 10.8 years (range: 10–60), recruited for neuropathic pain into enzyme replacement therapy trials.

Results: The following dysmorphic features were identified (in order of descending frequency): periorbital fullness, prominent lobules of the ears, bushy eyebrows, recessed forehead, pronounced nasal angle, generous nose/bulbous nasal tip, prominent supraorbital ridges, shallow midface, full lips, prominent nasal bridge, broad alar base, coarse features, posteriorly rotated ears, and prognathism. Extremity features included broad fingertips, short fingers, prominent superficial vessels of hands, 5th digit brachydactyly, and 5th digit clinodactyly. Narrow anterior-posterior chest diameter was noted. Ten core features were statistically defined. Cronbach's alpha measuring internal consitency was 0.62. Light's kappa for global inter-rater variability was 0.26 while Cohen's kappa allowing pair-wise rater comparison varied between 0.08–0.48.

Conclusions: Patients with Fabry disease share common morphological characteristics of the face, trunk, and extremities. Some of these features are subtle as documented by the inter-rater variability. Awareness of these features may facilitate the diagnosis of patients with Fabry disease, and identification of affected family members.

AFD: Natural History



Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants

Finding	Comment
Extreme superior ("North West") QRS axis deviation	Seen in patients with Noonan syndrome who have severe basal hypertrophy extending into the RV outflow tract.
Giant negative T wave inversion (>10 mm)	Giant negative T wave inversion in the precordial and/or inferolateral leads suggests involvement of the LV apex.
Abnormal Q waves ≥40 ms in duration and/or ≥25% of the R wave in depth and/or ≥3 mm in depth in at least two contiguous leads except aVR	Abnormally deep Q waves in the inferolateral leads, usually with a positive T wave, are associated with an asymmetrical distribution of LVH. Q waves of abnormal duration (≥40 ms) are associated with areas of replacement fibrosis.
Coved ST-segmentelevation in lateral chest leads	Some patients with apical or distal hypertrophy develop small apical aneurysms, sometimes associated with myocardial scarring. These may only be detectable on CMR, ventriculography or contrast echo, and are occasionally associated with ST-segment in the lateral chest leads.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Cardiac Magnetic Resonance Imaging

CMR should be considered in patients with HCM at their baseline assessment if local resources and expertise permit.

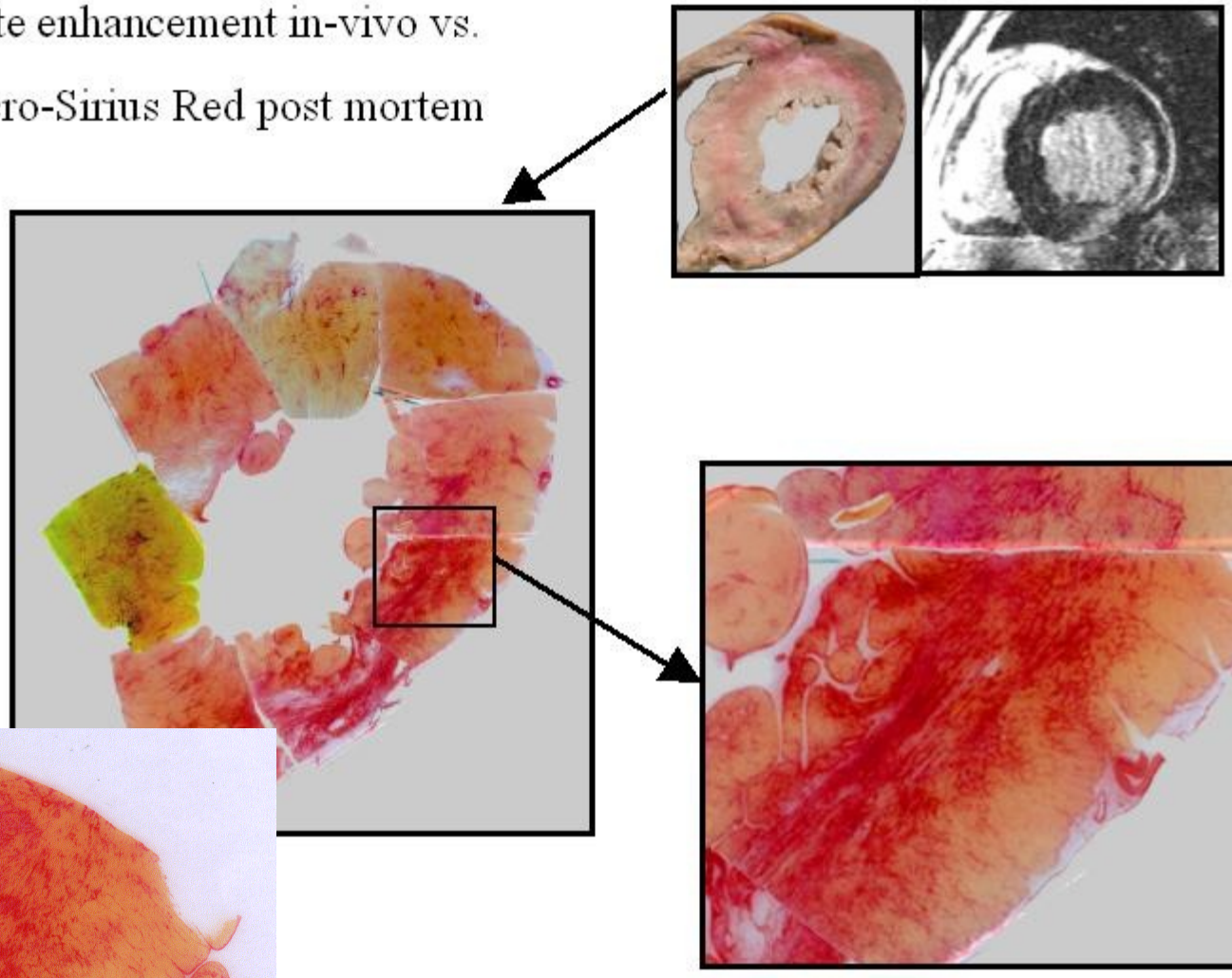
Value of Cardiac CMR:

- LV morphology and function
- Myocardial fibrosis
- Differential Diagnosis

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Late enhancement in-vivo vs.

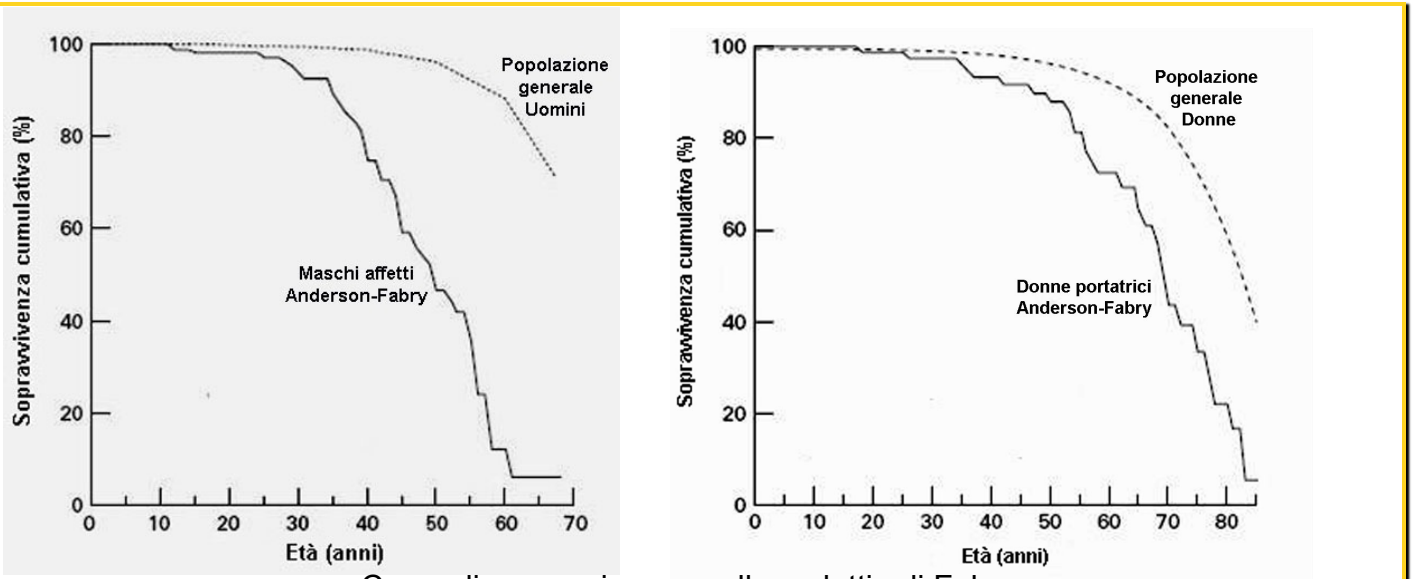
Picro-Sirius Red post mortem



Moon et al. J Cardiovasc Magn Reson. 2006;8:479-82.

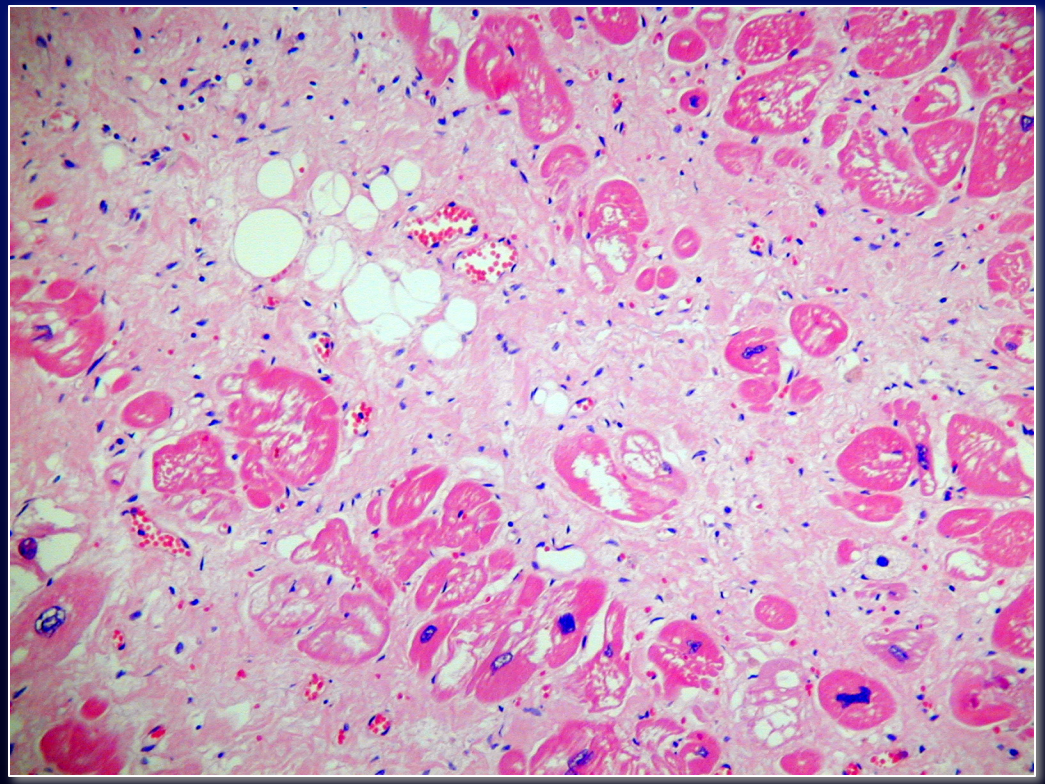
Epidemiologia

- L'età media al decesso è di circa 45 anni per gli uomini e 55 anni per le donne
- Le prime cause di morte sono il danno renale e cardiaco



Curve di sopravvivenza nella malattia di Fabry.
Maschi emizigoti (sinistra) e donne eterozigoti (destra).

AFD: Fibrosis



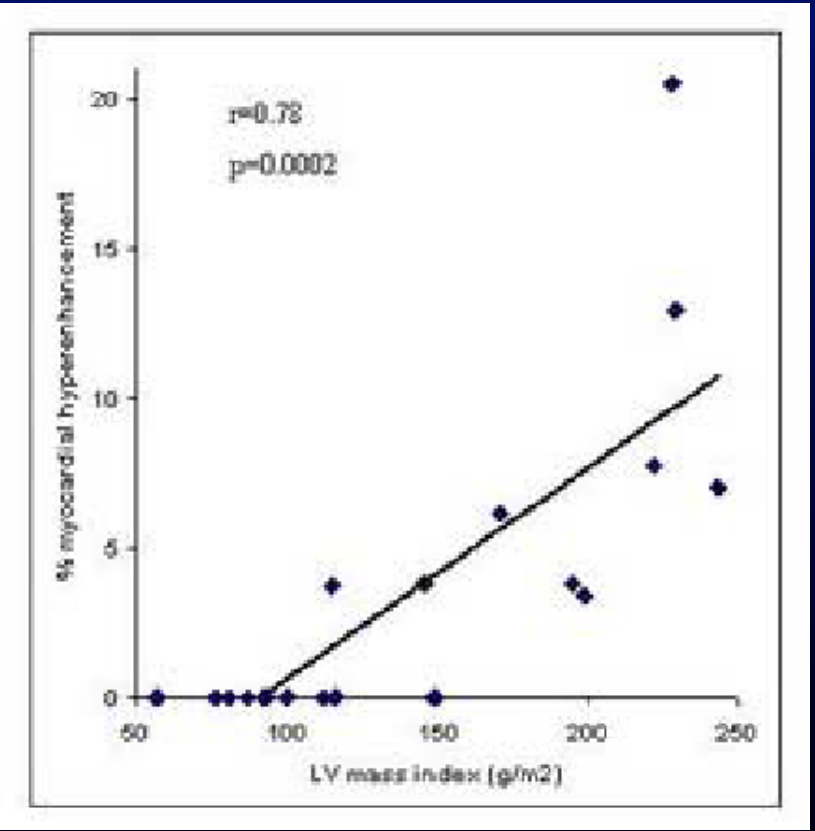
Courtesy of Dr. Sheppard: RBH

CMR in AFD

18 men (43±14 yrs)
9 (50%) had hyperenhancement
(3.4-20.6%)
% related to LVM (r=0.78, p=0.0002)

8 women (48±12 yr)
4 (50%) hyperenhancement (4.6%)

In 12 (92%) baso-lateral segments



Moon J et al. Eur Heart J 2003

Genetic Testing

Web Table 2: Main genes associated with familial hypertrophic cardiomyopathy (Online Mendelian Inheritance in Man OMIM phenotypic series, 192600)[21]

Protein	Gene	Location	MIM gene	Frequency
Myosin-7 (ß-myosin heavy chain)	MYH7	14q11.2	160760	10–20%
Myosin-binding protein C, cardiac-type	MYBPC3	11p11.2	600958	15–30%
Troponin T, cardiac muscle	TNNT2	1q32.1	191045	3–5%
Troponin I, cardiac muscle	TNNI3	19q13.42	191044	<5%
Tropomyosin alpha-1 chain	TPM1	15q22.2	191010	<5%
Myosin regulatory light chain 2, ventricular/cardiac muscle isoform	MYL2	12q24.11	160781	
Myosin light chain 3	MYL3	3p21.31	160790	1%
Actin, alpha cardiac muscle 1	ACTC1	15q14	102540	
Cysteine and glycine-rich protein 3, muscle LIM protein	CSRP3	11p15.1	600824	
Titin	TTN	2q31.2	188840	<5%
Cardiac phospholamban	PLN	6q22.31	172405	
5'-AMP-activated protein kinase subunit gamma-2	PRKAG2	7q36.1	602743	1%
Alpha galactosidase A (Anderson Fabry disease)	GLA	Xq22.1	300644	1–3%
Lysosome membrane associated protein 2 (Danon disease)	LAMP2	Xq24	309060	0.7%–2.7%

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

J Inherit Metab Dis (2010) 33 (Suppl 3):S385–S387
DOI 10.1007/s10545-010-9194-3

CASE REPORT

Case report: long-term outcome post-heart transplantation in a woman with Fabry's disease

Flavia Verocai · Joe Thomas Clarke · Robert M. Iwanochko

Abstract Fabry's disease is an X-linked recessive disorder that results from the deficiency of alpha-galactosidase A and causes the accumulation of globotriaosylceramide (Gb3) in different tissues. It leads to a rare form of cardiomyopathy which may be complicated by end-stage heart failure and need to heart transplant. Our group described the first case of heart transplant in a woman with cardiomyopathy secondary to Fabry's disease about 12 years ago. There was uncertainty in regards to the possibility of recurrence of the disease as previously documented in kidney transplant recipients and long-term outcomes. In this report, 14 years after transplant, this woman is still alive and there is no evidence of Fabry's disease in any of the endomyocardial biopsies. Heart transplantation can be recommended for Fabry's patients with end-stage cardiomyopathy.

Genetic Testing

Recommendations on genetic testing in probands

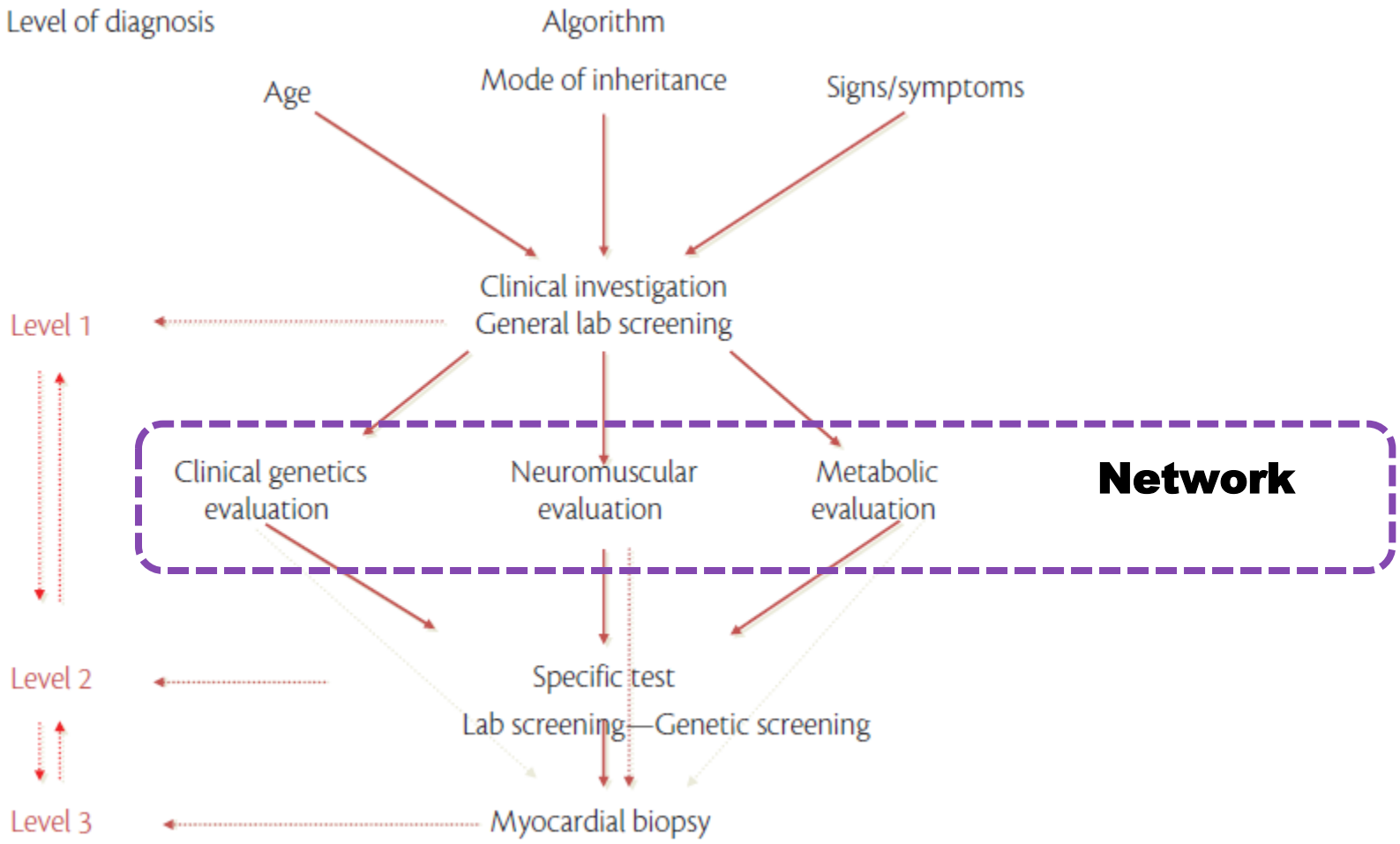
Recommendations	Class[a]	Level[b]	Ref.[c]
Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.	I	B	24,175 178–180
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.	I	C	168,172,183
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.	I	B	36–40, 43–46,67
Genetic testing in patients with a borderline[d] diagnosis of HCM should be performed only after detailed assessment by specialist teams.	IIa	C	168
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.	IIa	C	181,182

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Endomyocardial Biopsy

Recommendations for endomyocardial biopsy		
	Class[a]	Level[b]
Endomyocardial biopsy may be considered when the results of other clinical assessments suggest myocardial infiltration, inflammation or storage that cannot be confirmed by other means.	IIb	C

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284



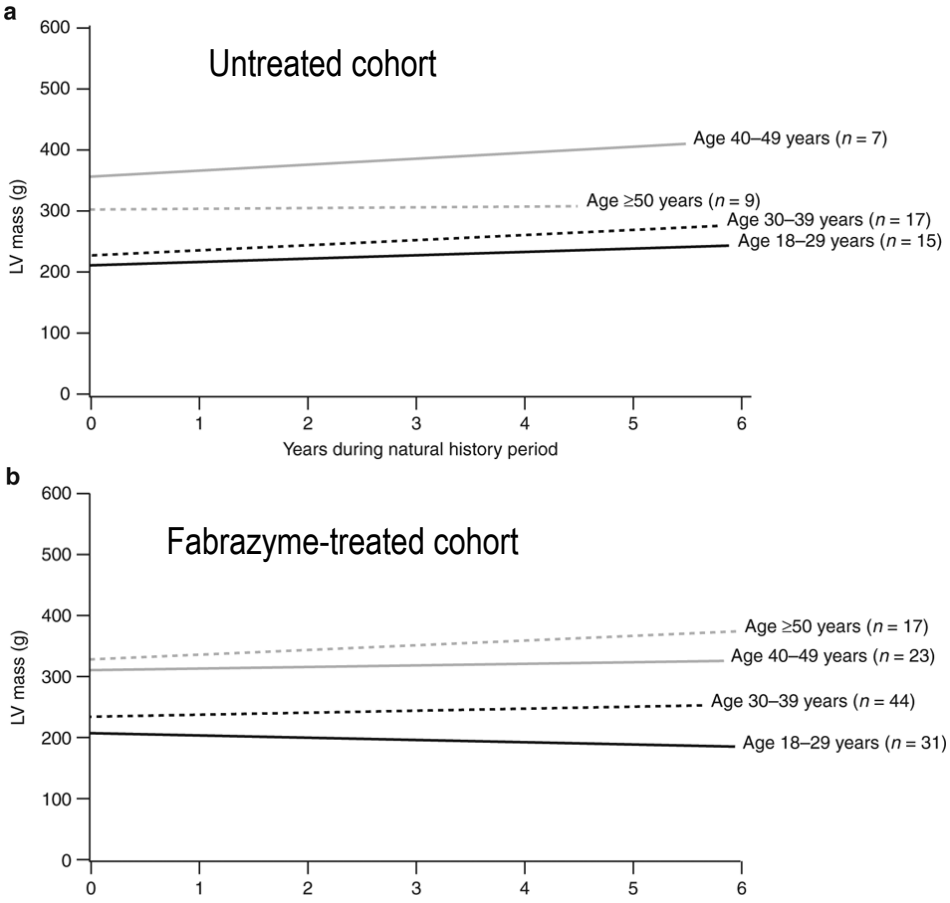
The genetics of heart failure

Giuseppe Limongelli and Perry M. Elliott

Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry Registry

Germain DP, Weidemann F, Abiose A, Patel MR, Cizmarik M, Cole JA, Beitner-Johnson D, Benistan K, Cabrera G, Charrow J, Kantola I, Linhart A, Nicholls K, Niemann M, Scott CR, Sims K, Waldek S, Warnock DG, Strotmann J

Genet Med. 2013 May 23



	LVM slope (g/year) ± SEM	*P* value
Age 18–29 years		
During untreated period (*n* = 15)	9.5 ± 2.36	
During treatment (*n* = 31)	−3.6 ± 1.62	
Difference in LVM slope	−13.0 ± 2.72	<0.0001
Age 30–39 years		
During untreated period (*n* = 17)	8.4 ± 3.55	
During treatment (*n* = 44)	2.8 ± 2.20	
Difference in LVM slope	−5.6 ± 4.12	0.1760
Age 40–49 years		
During untreated period (*n* = 7)	13.4 ± 6.63	
During treatment (*n* = 23)	3.4 ± 2.87	
Difference in LVM slope	−10.0 ± 7.21	0.1691
Age ≥50 years		
During untreated period (*n* = 9)	0.4 ± 9.41	
During treatment (*n* = 17)	7.7 ± 4.48	
Difference in LVM slope	7.3 ± 10.33	0.4843

LVM, left-ventricular mass; SEM, standard error of mean.

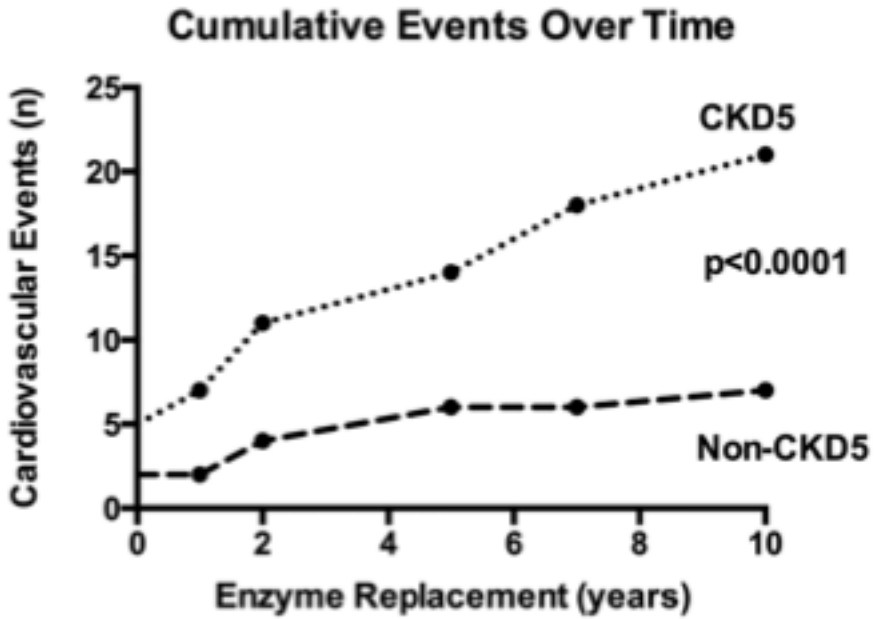
Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry Registry

Germain DP, Weidemann F, Abiose A, Patel MR, Cizmarik M, Cole JA, Beitner-Johnson D, Benistan K, Cabrera G, Charrow J, Kantola I, Linhart A, Nicholls K, Niemann M, Scott CR, Sims K, Waldek S, Warnock DG, Strotmann J

Genet Med. 2013 May 23

- LV mass progressively increased in untreated males aged 18–29, 30–39 and 40–49 years.
- Fabrazyme *significantly improved* LV mass if treatment was started between the ages 18–29 years (early stage of Fabry cardiomyopathy).
- Fabrazyme *stabilized* LV mass if treatment was started between the ages 30–39 and 40–49 years.

Cuore-Rene: Le Relazioni Pericolose!



Number of Patients at Risk						
Time (yr)	0	1	2	5	7	10
Non-CKD5	15	15	15	14	12	12
CKD5	10	10	10	9	7	6

Figure 2 Cumulative cardiovascular events while on enzyme replacement. Cardiovascular events included death, cardiac arrest, coronary artery stenting, conduction defect, pacing device insertion or severe valve defect. CKD5, chronic kidney disease stage 5.

Talbot AS, *et al*. *Heart* 2014;**0**:1–7. doi:10.1136/heartjnl-2014-306278

The disturbance was first described in 1898 by Fabry in Germany and Anderson in England. Anderson's patient was a male aged 39 years who had an eruption on his trunk, genitals and proximal limbs. He recorded that the patient had been afflicted since childhood and that varicose veins, rectal bleeding and albuminuria had developed. Anderson termed the condition "angiokeratoma" and suggested that there might be generalised changes in the vascular system. Fabry conducted independent studies of an affected boy. In his article Fabry used the designation "purpura haemorrhagica nodularis". A further case was recognised in Egypt by Frank Cole Madden (1873-1929) in 1912 and the condition was mentioned again by Fabry in 1915 under the title "Angiokeratoma corporis naeviforme". Fabry retained his interest in the disorder and published the autopsy findings after his patient's death in 1930.

Echocardiography: Differential Diagnosis

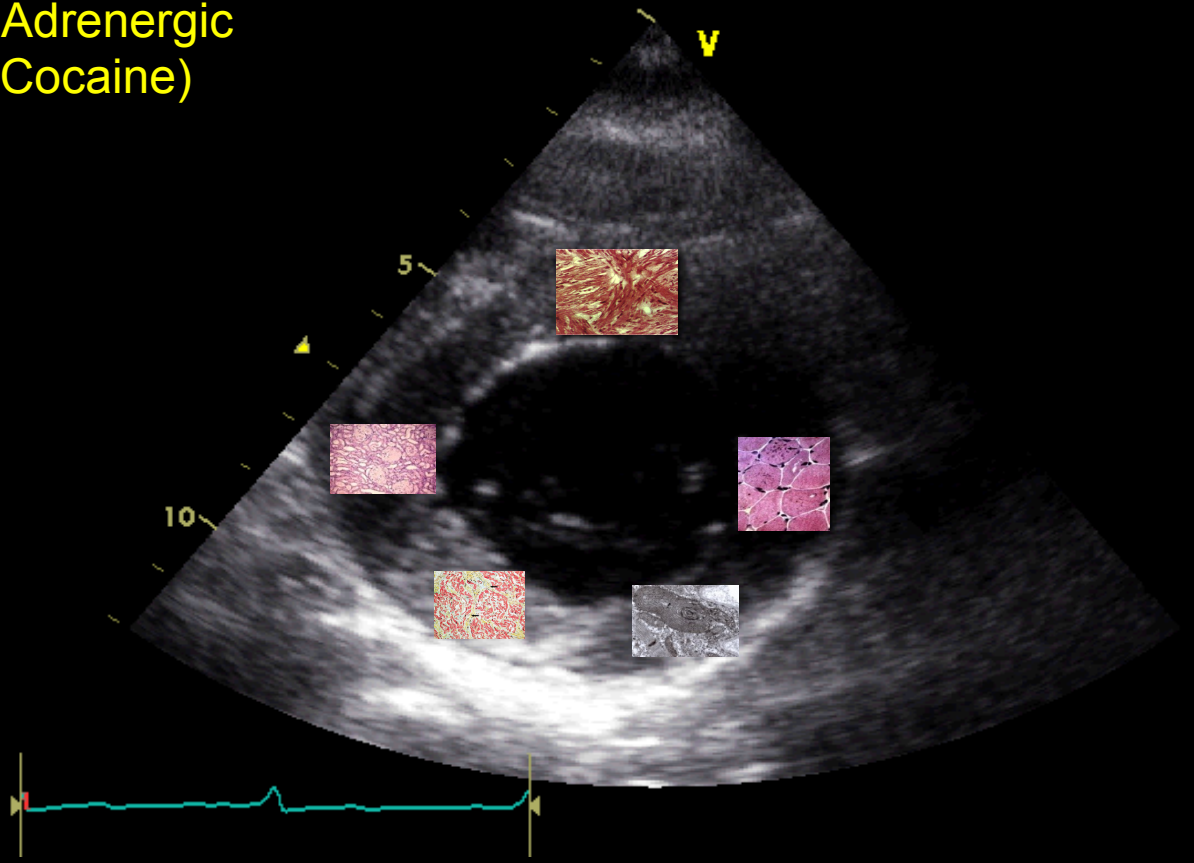
Interpret images in context of clinical features and other tests

Echocardiographic features that suggest specific aetiologies[a]	
Finding	**Specific diseases to be considered**
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2-D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

HCM?

Sarcomeric, Adrenergic
Overtone (Cocaine)



Noonan

Pompe/Fabry

Costello

Mitochondrial

Cardiogenetics 2013; volume 3:e3

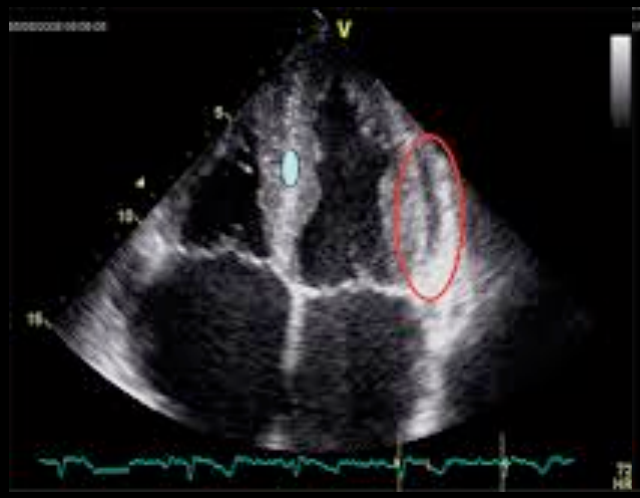
Take home message

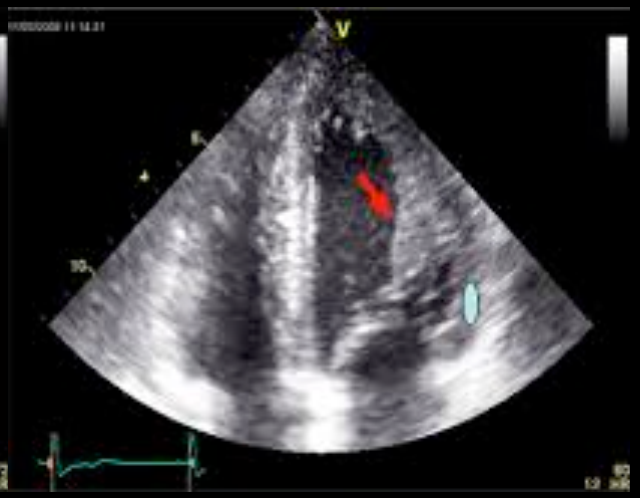
Prominent papillary muscles are typical.

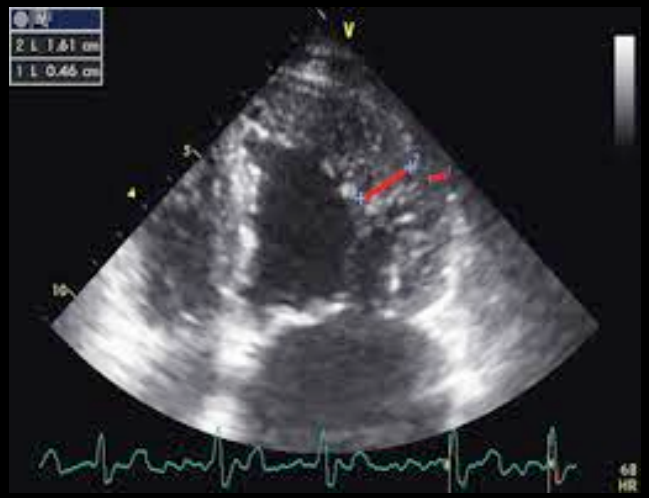
pagepress:

Echocardiography in Fabry disease

Markus Niemann, Frank Weidemann



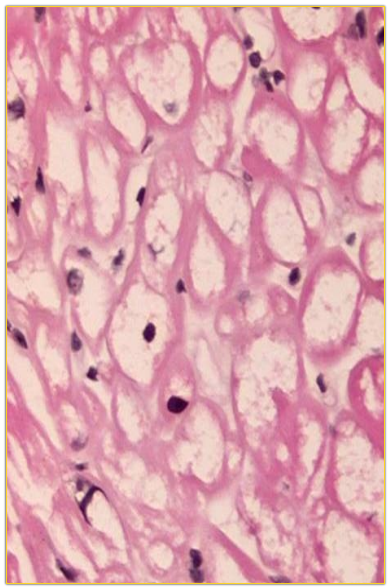


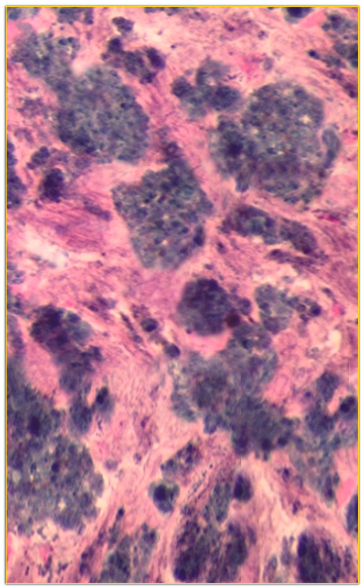


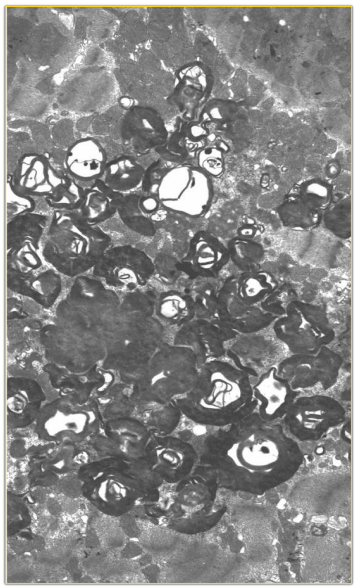
"In a recent study it could be shown that the absolute papillary muscle area as well as the ratio of the papillary muscle area and the left ventricular circumference is enlarged in AFD"

Ultrasound Med Biol 2011;37:37-43.

Miocardio







Vacuoli glicosfingolipidici

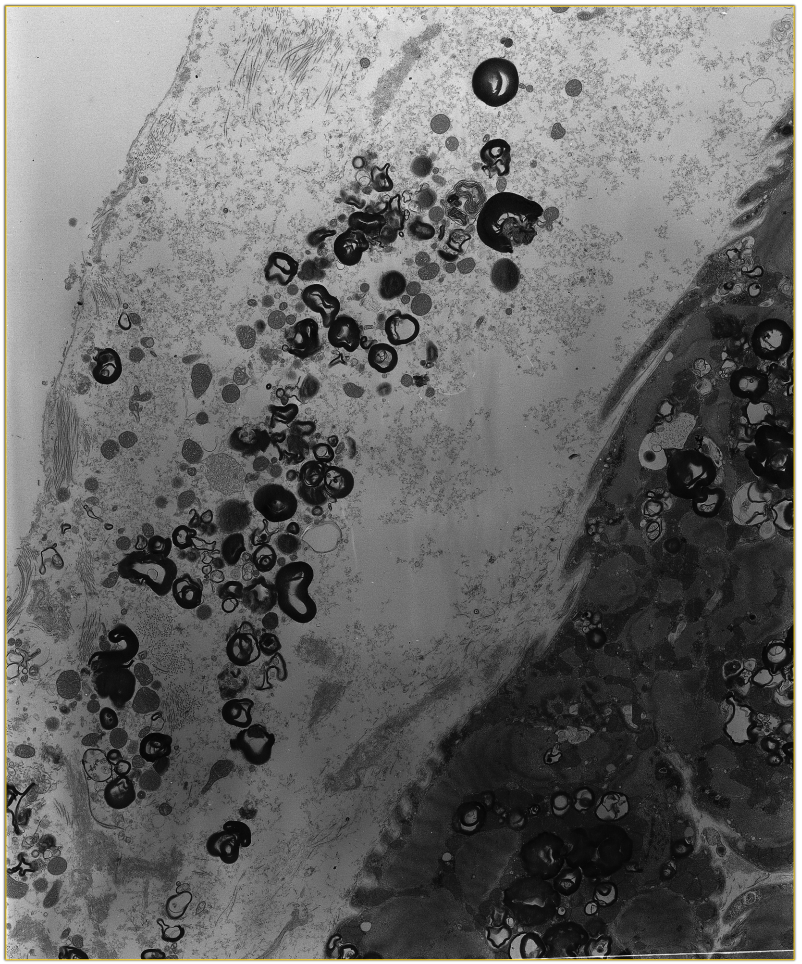
Ipertrofia miocardica (GB3 → Attivazione geni ipertrofia)

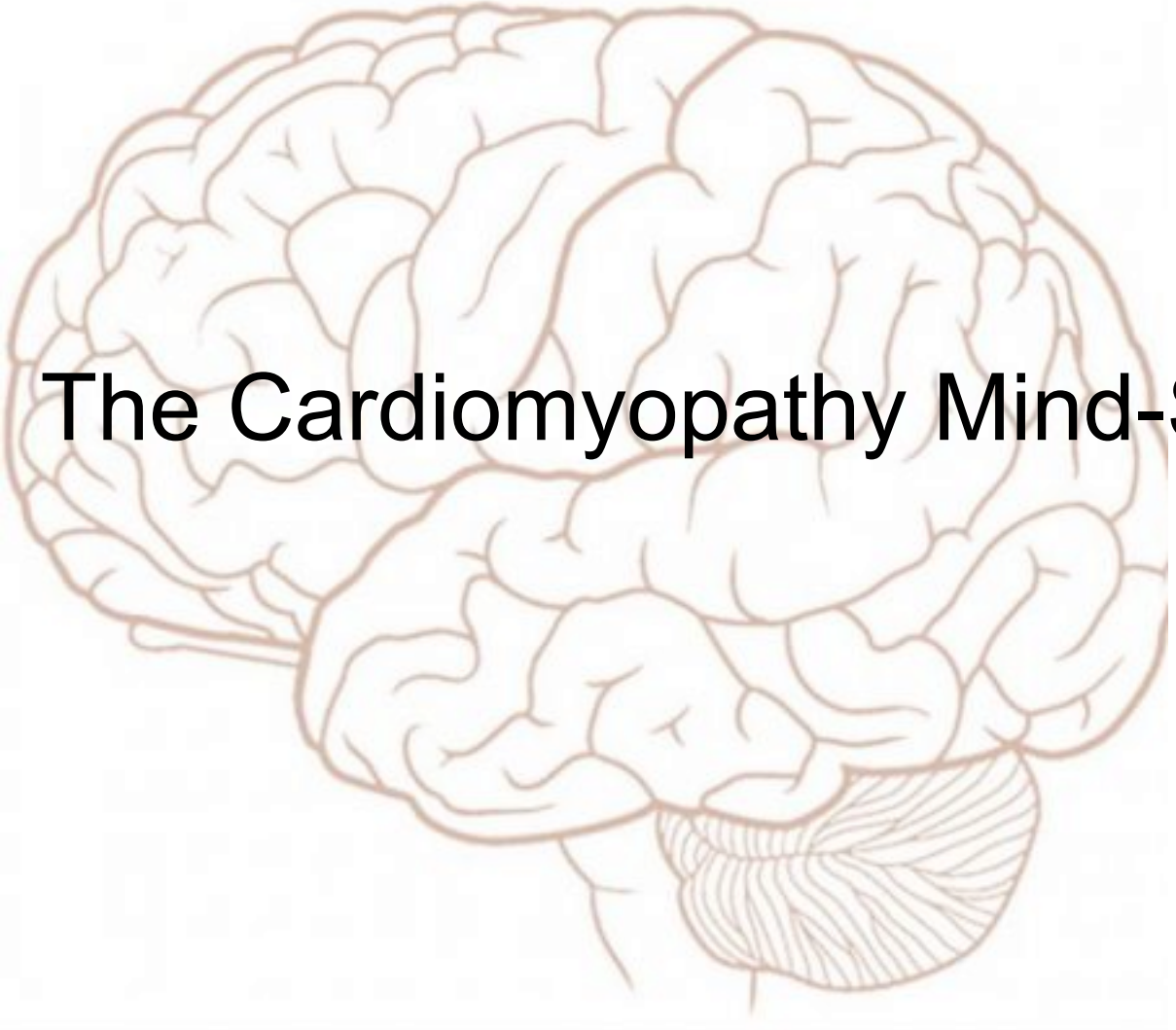
Ispessimento pareti cardiache

Endocardio

- Ispessimento fibroso con accumulo di Gb3 in:
  - Cellule endoteliali e cellule muscolari lisce
  - Valvole
  - Interstizio

Contribuisce alla disfunzione diastolica





The Cardiomyopathy Mind-Set

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

HCM: Definitions

Increased left ventricular wall thickness not solely explained by abnormal loading conditions

ADULTS:

- *LV wall thickness ≥15 mm in one or more LV myocardial segments measured by any imaging technique*

CHILDREN:

- *LV wall thickness more than two standard deviations above the predicted mean (z-score >2)*

European Heart Journal (2014):doi:10.1093/eurheartj/ehu284

Echocardiography
A Journal of Cardiovascular Ultrasound and Allied Techniques

DOI: 10.1111/j.1540-8175.2012.01704.x

Echocardiography

Gruner C et. al

Systolic Myocardial Mechanics in Patients with Anderson–Fabry Disease with and without Left Ventricular Hypertrophy and in Comparison to Nonobstructive Hypertrophic Cardiomyopathy

LVH+ and NOHCM had similarly lowered global LS compared to no

global CS was observed in AFD LVH+, whereas it was significantly in

HCM, AFD patients with/without LVH lost their normal base-to-apex

Ries M et al. Genetics in Medicine 2006; 8: 96–101

Table 1

Prevalence of morphometric findings in a cohort of 38 hemizygous patients with Fabry disease

Physical features	Present	Absent	N
Periorbital fullness[a]	87%	13%	38
Prominent lobules of the ears	68%	32%	38
Bushy eyebrows[a]	66%	34%	38
Acute nasal angle[a]	61%	39%	38
Shallow midface	61%	39%	38
Generous nose/bulbous nasal tip[a]	58%	42%	38
Recessed forhead	55%	45%	38
Prominent supraorbital ridges	55%	45%	38
Full lips[a]	50%	50%	38
Prominent nasal bridge	50%	50%	38
Broad alar base[a]	36%	63%	38
Coarse features[a]	29%	71%	38
Posteriorly rotated ears	11%	89%	38
Prognathism	5%	95%	38
Broad fingertips[a]	58%	42%	38
Short fingers[a]	43%	57%	37
Prominent superficial vessels (hands)	30%	74%	37
5th digit brachydactyly	14%	86%	37
5th digit clinodactyly	3%	97%	37
Narrow AP chest diameter[a]	74%	26%	23

The prevalences are given in median percentage of N patients. The presence or absence of a trait was independently scored by a panel of three clinical geneticists.

[a]Core features as suggested by the principle component analysis in the dendrogram (Figure 2) are printed in italics.

[redacted]

[redacted]

Sesso: M

Esame: ECOGRAFIA TIROIDEA

ECO TIROIDE

Tiroide di normali dimensioni ad ecotessitura
finemente inomogenea assenza di lesioni focali
presenza di linfonodi reattivi satelliti
con diam 10/21mm
lobo dx ap 15mm dt14mm dl 43mm
lobo sn ap 13mm dt 12mm dl 38mm
vol 7,8cc
trachea in asse

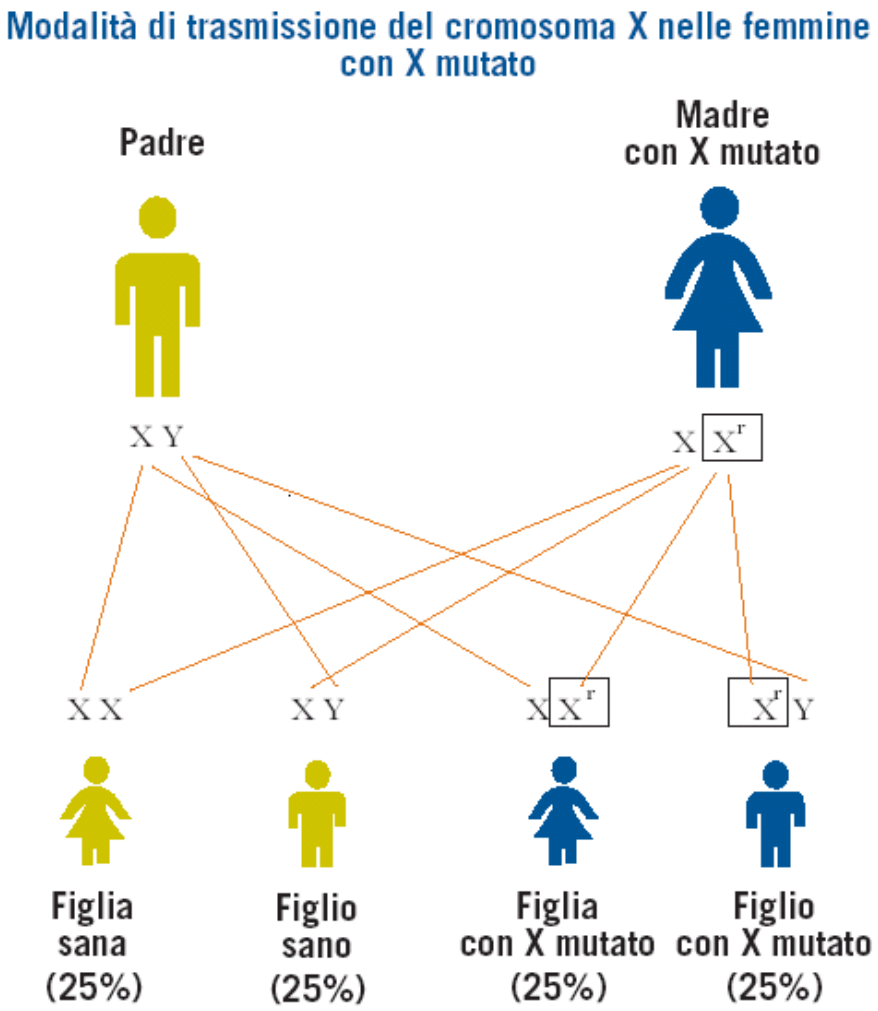
ECO ADDOME

Assenza di liquido in c. addominale,gastrite

Fegato normovolumetrico ad ecostruttura omogenea
lieve steatosi assenza di lesioni focali margini
regolari; colecisti alitiasica ; vbi e vbe non
dilatate; regolare per decorso e calibro l'asp
la cava ele sovraepatiche
Pancreas regolare per dimensioni ed ecostruttura
assenti ectasie del wirsung
Milza regolare per dimensioni ed ecostruttura
Reni in sede nei limiti volumetrici inferiori
parenchimi nei limiti ,assenza di masse ne' calcoli
o segni di stasi
rene dx e sn. dl 90mm
Assenza di masse surrenaliche
Prostata piccola (vol 7cc) con echi capsulari
integri
Vescica a pareti regolari assenza di lesioni
parietali aggettanti ne' calcoli

ECO SCROTALE

Testicoli retrattili ipotrofici ad ecostruttura
finemente inomogenea assenza di lesioni focali
testicolo dx. vol. 5cc testicolo sn. 4,4cc
epididimi lievemente ispessiti con cisti cefalica
sn. di 7mm e dx. di 5mm e 2mm
assenza d'idrocele
si segnala cardiopatia dilatativa FE 48%

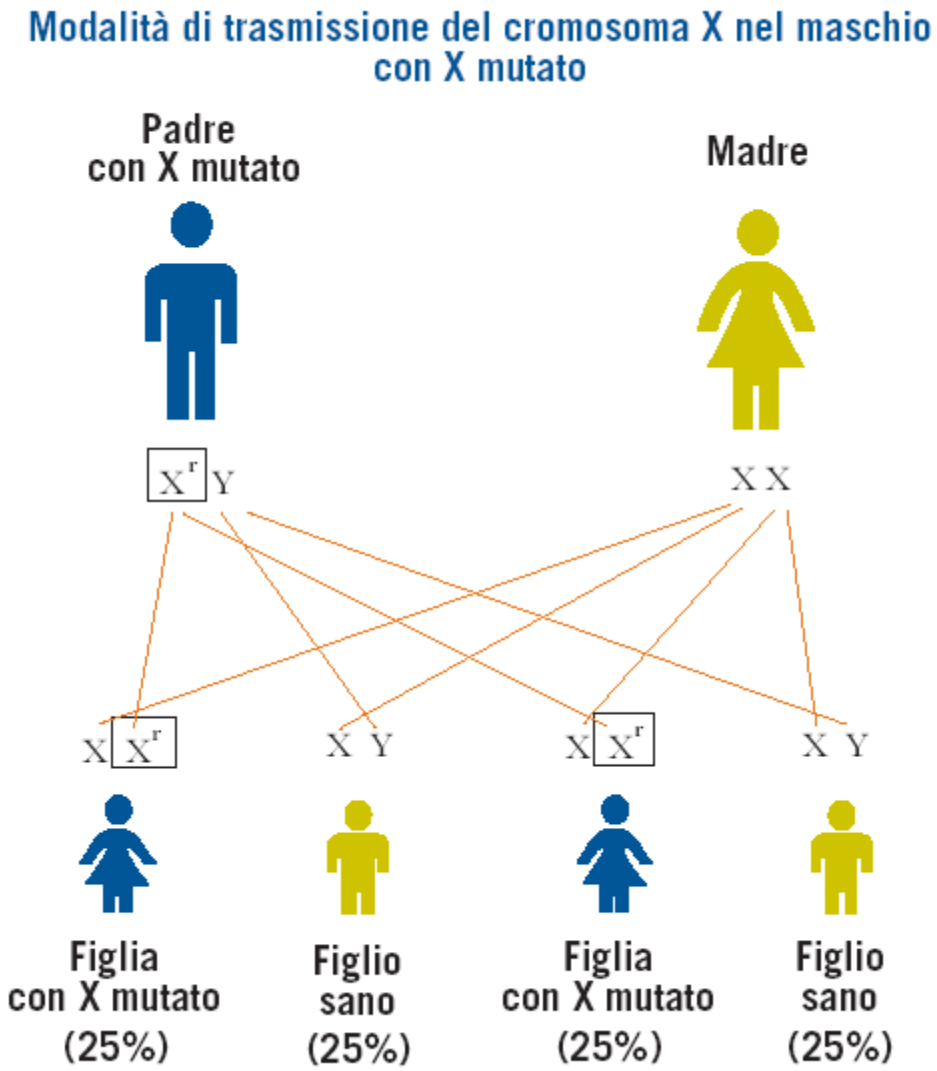


Elaborato da Desnick et al. ([7])

•Le femmine eterozigoti hanno il 50% di possibilità ad ogni gravidanza di trasmettere il gene ai propri figli maschi e femmine.

•La femmina affetta può aver ricevuto il gene sia dal padre che dalla madre[7]

La femmina eterozigote manifesta diversi gradi di coinvolgimento patologico che vanno dalla scarsa alla piena espressione della malattia[2]



Elaborato da Desnick et al. ([7])

- Il maschio affetto dalla Malattia di Anderson-Fabry trasmette la malattia a tutte le figlie femmine ma a nessuno dei figli maschi

- Il maschio riceve il gene mutato unicamente dalla madre[7]

Il maschio emizigote presenta sempre la malattia[2]

Cardiac Involvement

HYPERTROPHIC CARDIOMYOPATHY

Management of symptoms -
ERT
-BB/CCB if LVOT obs or diastolic dysfunction;
-antifailure therapy if HFREF
-diuretics if HFPEF
-prevention of ventricular arrhythmias (AICD?)

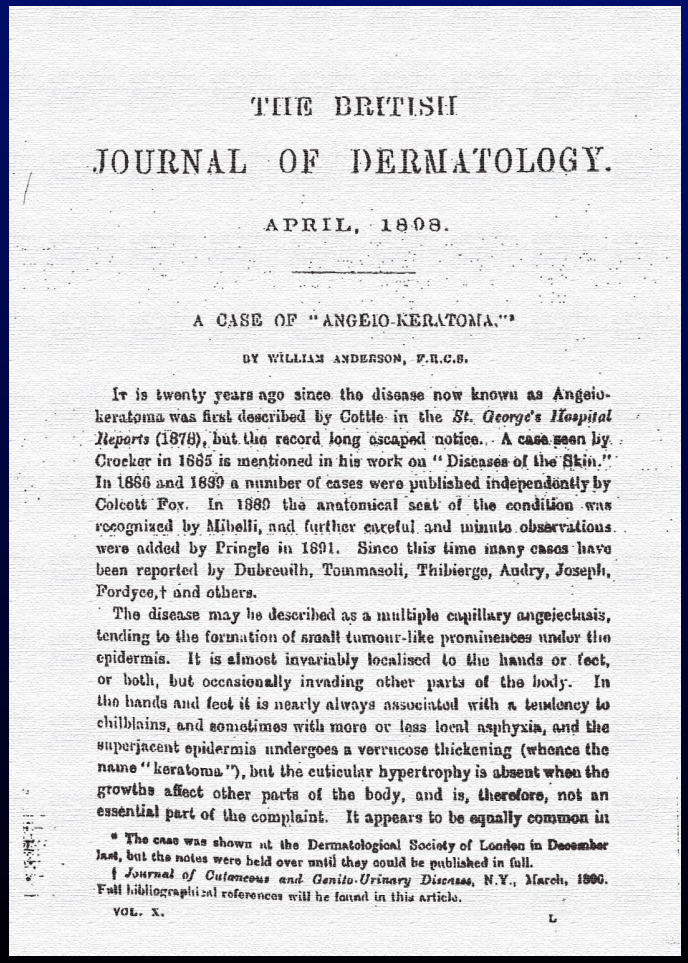
Progressive Conduction Disease

Atrioventricular Blocks
-EP study
-PMK implantation

Microvascular Dysfunction

Chest pain with Normal Coronary Arteries
-Calcium Channel Blockers

William Anderson (1842–1900)



THE BRITISH

JOURNAL OF DERMATOLOGY.

APRIL, 1898.

A CASE OF "ANGEIO-KERATOMA."*

BY WILLIAM ANDERSON, F.R.C.S.

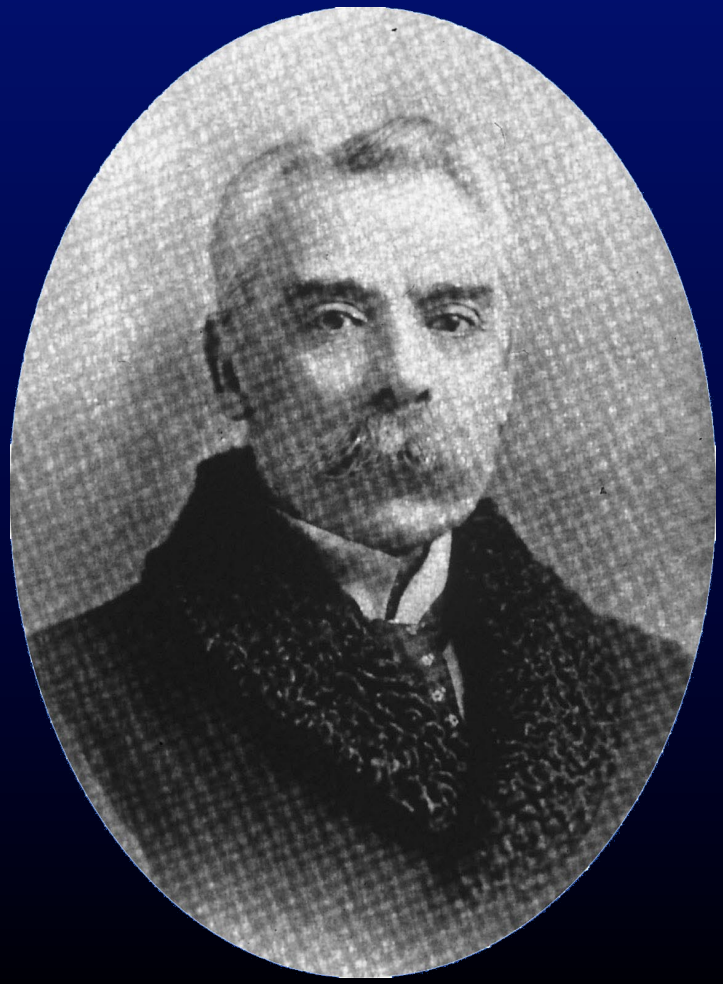
It is twenty years ago since the disease now known as Angeio-keratoma was first described by Cottle in the *St. George's Hospital Reports* (1878), but the record long escaped notice. A case seen by Crocker in 1865 is mentioned in his work on "Diseases of the Skin." In 1886 and 1889 a number of cases were published independently by Colcott Fox. In 1889 the anatomical seat of the condition was recognized by Mibelli, and further careful and minute observations were added by Pringle in 1891. Since this time many cases have been reported by Dubreuilh, Tommasoli, Thibierge, Audry, Joseph, Fordyce,† and others.

The disease may be described as a multiple capillary angiectasis, tending to the formation of small tumour-like prominences under the epidermis. It is almost invariably localised to the hands or feet, or both, but occasionally invading other parts of the body. In the hands and feet it is nearly always associated with a tendency to chilblains, and sometimes with more or less local asphyxia, and the superjacent epidermis undergoes a verrucose thickening (whence the name "keratoma"), but the cuticular hypertrophy is absent when the growths affect other parts of the body, and is, therefore, not an essential part of the complaint. It appears to be equally common in

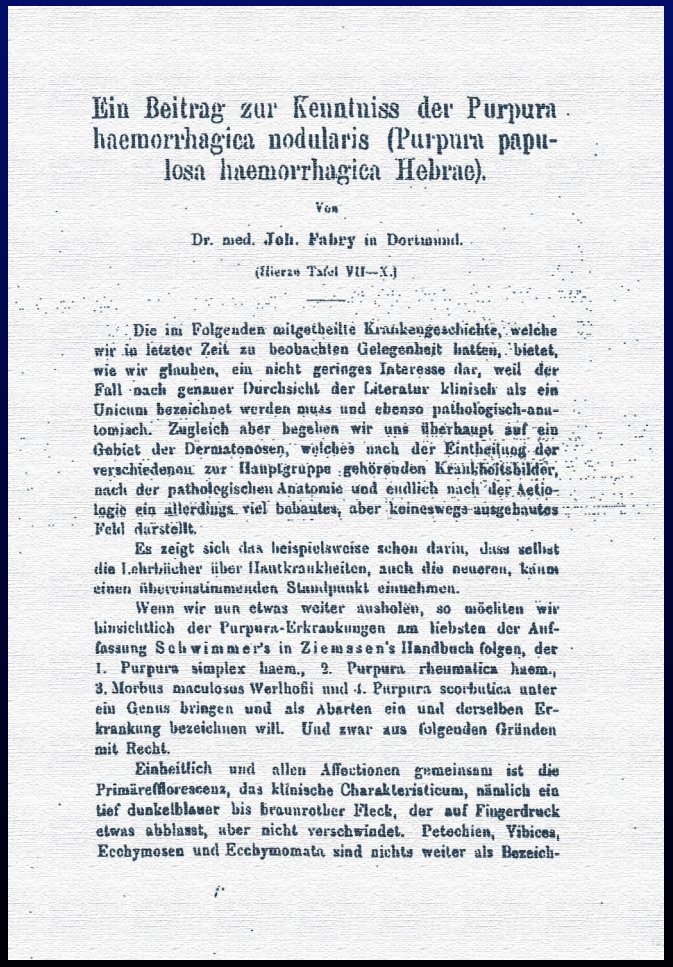
* The case was shown at the Dermatological Society of London in December last, but the notes were held over until they could be published in full.

† *Journal of Cutaneous and Genito-Urinary Diseases*, N.Y., March, 1896. Full bibliographical references will be found in this article.

VOL. X. L



Johannes Fabry (1860–1930)



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

Von

Dr. med. Joh. Fabry in Dortmund.

(Hierzu Tafel VII—X.)

Die im Folgenden mitgetheilte Krankengeschichte, welche wir in letzter Zeit zu beobachten Gelegenheit hatten, bietet, wie wir glauben, ein nicht geringes Interesse dar, weil der Fall nach genauer Durchsicht der Literatur klinisch als ein Unicum bezeichnet werden muss und ebenso pathologisch-anatomisch. Zugleich aber begeben wir uns überhaupt auf ein Gebiet der Dermatonosen, welches nach der Eintheilung der verschiedenen zur Hauptgruppe gehörenden Krankheitsbilder, nach der pathologischen Anatomie und endlich nach der Aetiologie ein allerdings viel bebautes, aber keineswegs ausgebautes Feld darstellt.

Es zeigt sich das beispielsweise schon darin, dass selbst die Lehrbücher über Hautkrankheiten, auch die neueren, kaum einen übereinstimmenden Standpunkt einnehmen.

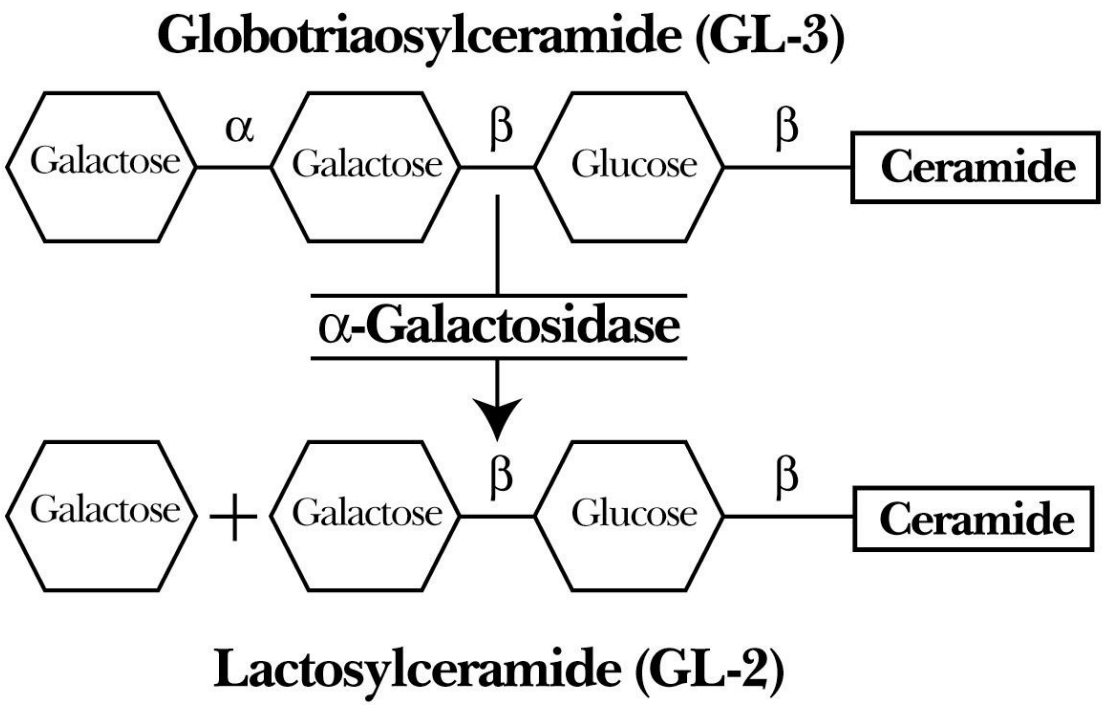
Wenn wir nun etwas weiter ausholen, so möchten wir hinsichtlich der Purpura-Erkrankungen am liebsten der Auffassung Schwimmer's in Ziemssen's Handbuch folgen, der 1. Purpura simplex haem., 2. Purpura rheumatica haem., 3. Morbus maculosus Werlhofii und 4. Purpura scorbutica unter ein Genus bringen und als Abarten ein und derselben Erkrankung bezeichnen will. Und zwar aus folgenden Gründen mit Recht.

Einheitlich und allen Affectionen gemeinsam ist die Primäreffloreseenz, das klinische Charakteristicum, nämlich ein tief dunkelblauer bis braunrother Fleck, der auf Fingerdruck etwas abblasst, aber nicht verschwindet. Petechien, Vibices, Ecchymosen und Ecchymomata sind nichts weiter als Bezeich-

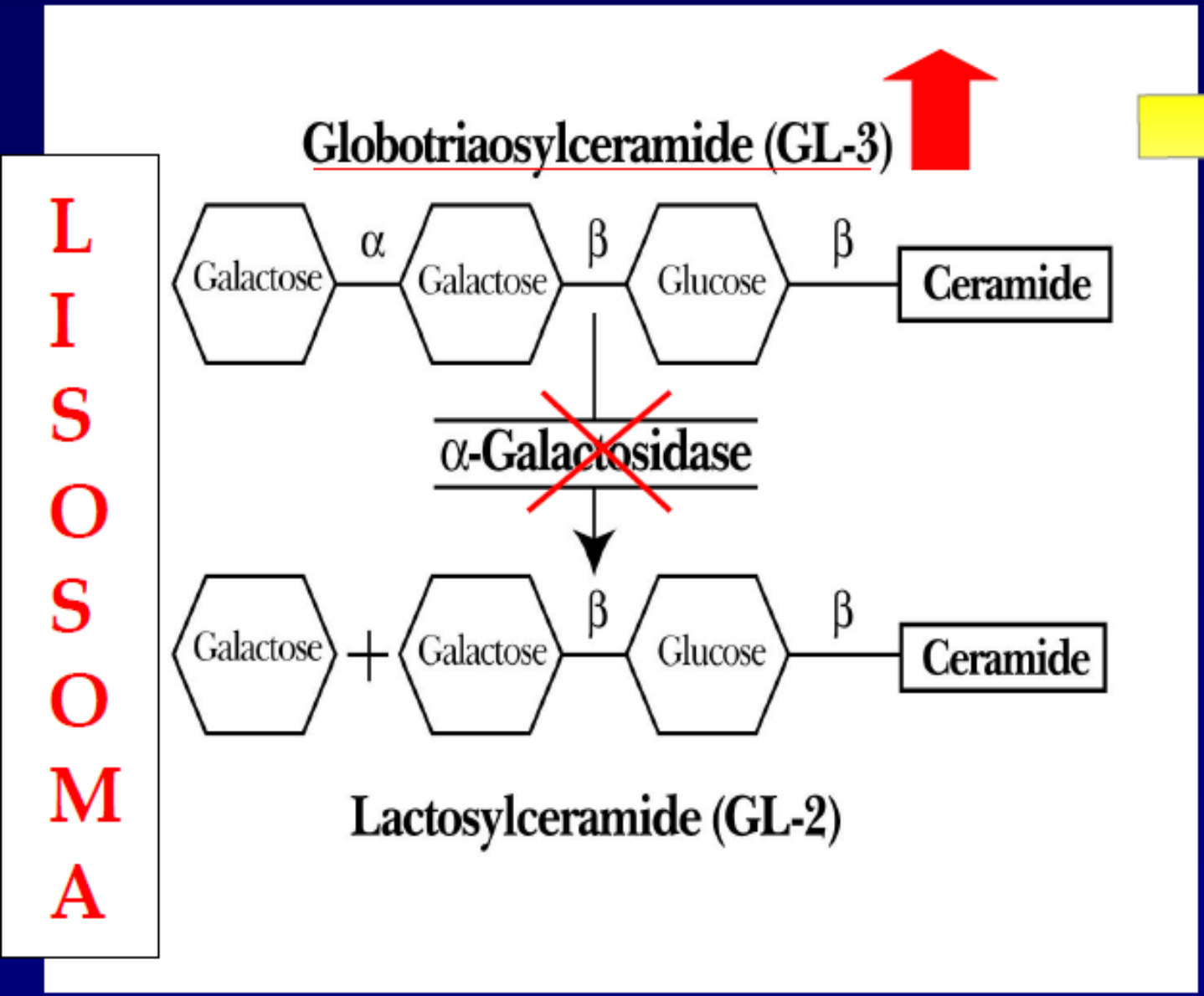
La Malattia di Fabry

- Malattia lisosomiale caratterizzata dal deficit dell'enzima α-galattosidasi A
- Progressivo accumulo di glicosfingolipidi all'interno delle cellule di vari tessuti
- Trasmissione di tipo X-linked recessiva
- Gene dell'α-galattosidasi A localizzato sul braccio lungo del cromosoma X (Xq22)
- Le mutazioni geniche causano un'instabilità dell'mRNA o un enzima severamente troncato con un'attività enzimatica marcatamente ridotta

Metabolic Pathway

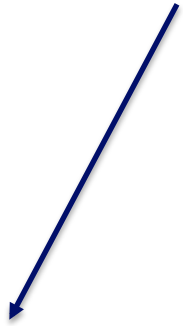


Difetto metabolico e malattia di Fabry



Accumulo sfingolipidi endotelio vascolare

Il ruolo del Cardiologo nelle malattie rare



“Spoke”

(specialista d’organo, all’interno di una gestione multidisciplinare)

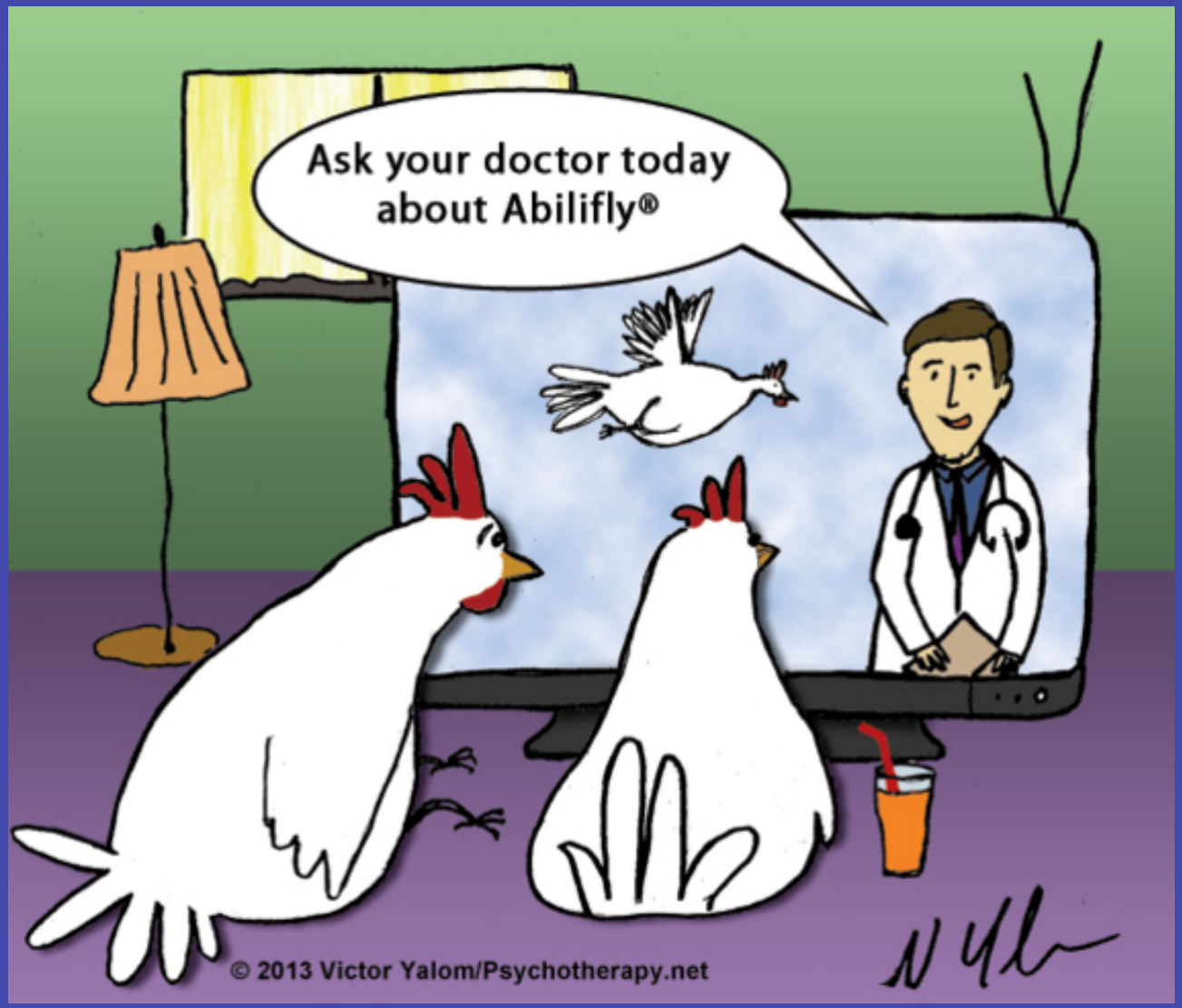
“Caregiver”

(in particolare, nelle patologie genetiche/ non genetiche dell’adulto, con il coinvolgimento del cuore come prevalente o unico!)

FHC and Anderson-Fabry CM:differential diagnosis

	Anderson-Fabry CM	FHC
Inheritance	X-linked-recessive	AD
Non cardiac features	Angiokeratoma, acroparesthesias, HTN, proteinuria, renal failure	no
Cardiac features	concentric LVH, ASH less common ECG: short PR, high LV voltage	ASH or not ECG:LVH
Biochemistry	Low plasma alpha-galactosidase A	no
EMB	Histology:glycosphingolipid deposits in lysosomes	Disarray,
Gene defects	alpha-galactosidase A	Sarcomeric

Therapy: Patient's Expectations



pagepress

Anderson-Fabry, the *histrionic disease*: from genetics to clinical management

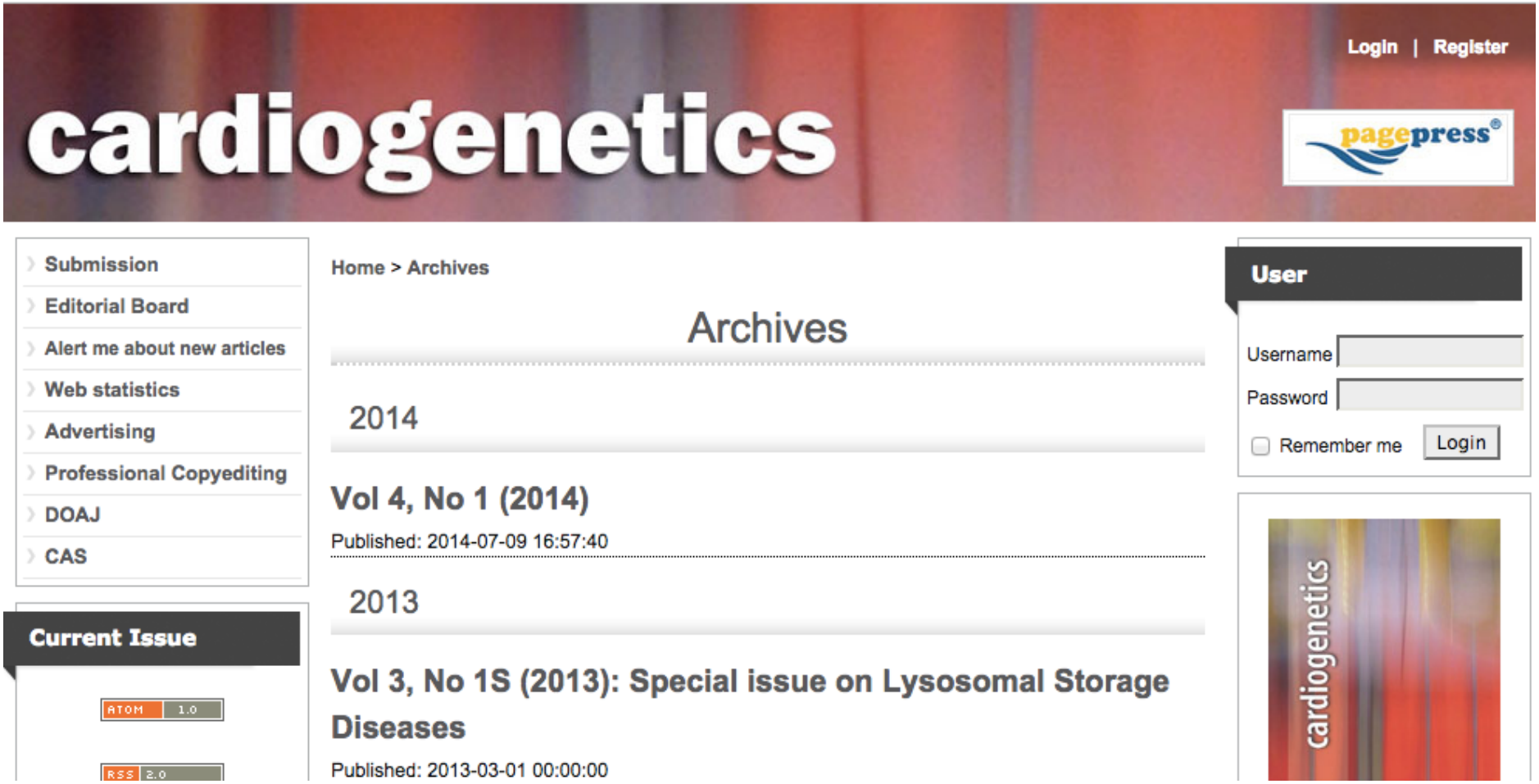
Franco Cecchi,[1] Benedetta Tomberli,[1,2] Amelia Morrone[3,4]

[1]Department of Clinical and Experimental Medicine; [2]Department of Heart and Vessels, Referral Center for Cardiomyopathies, Careggi Hospital; [3]Department of Neurosciences, Psychology, Pharmacology and Child Health, University of Florence; [4]Molecular and Cell Biology Laboratory, Paediatric Neurology Unit, Neuroscience Department, Meyer Children's Hospital, Florence, Italy

Treatment: when & who?

Table 2. Priority stages for treatment in naïve male and female patients with Anderson-Fabry disease.

Children	Adults
High priority	
Neuropathic pain unresponsive to optimal medical therapy	Neuropathic pain unresponsive to optimal medical therapy
Persistent microalbuminuria	Normal or mild to moderate reduction of renal function (GFR 30-90 mL/min)
Proteinuria >250 mg/day	Proteinuria >300 mg/day
Left ventricular mass index >90th percentile (age adjusted)	LVH without extensive fibrosis (on MRI)
TIA/stroke or white matter lesion on MRI	Cerebrovascular disease
-	Disease onset <50 years
Intermediate priority	
Age onset >50 years	➔ Less severe disease
LVH with fibrosis Severe renal dysfunction (GFR<30 mL/min)	➔ Less reversible disease
Low priority	
Severe cardiac or CNS disease (end stage)	
Multiple organ failure	
Other comorbidities with reduction of life expectancy <1 year	
Very mild multiorgan disease (*e.g.* normal renal function, no LVH, neuropathic pain well controlled by conventional medical therapy)	



www.cardiogenetics.it

TAKE HOME

- Enzyme replacement therapy (ERT) is the therapy of choice in patients with Anderson Fabry Disease

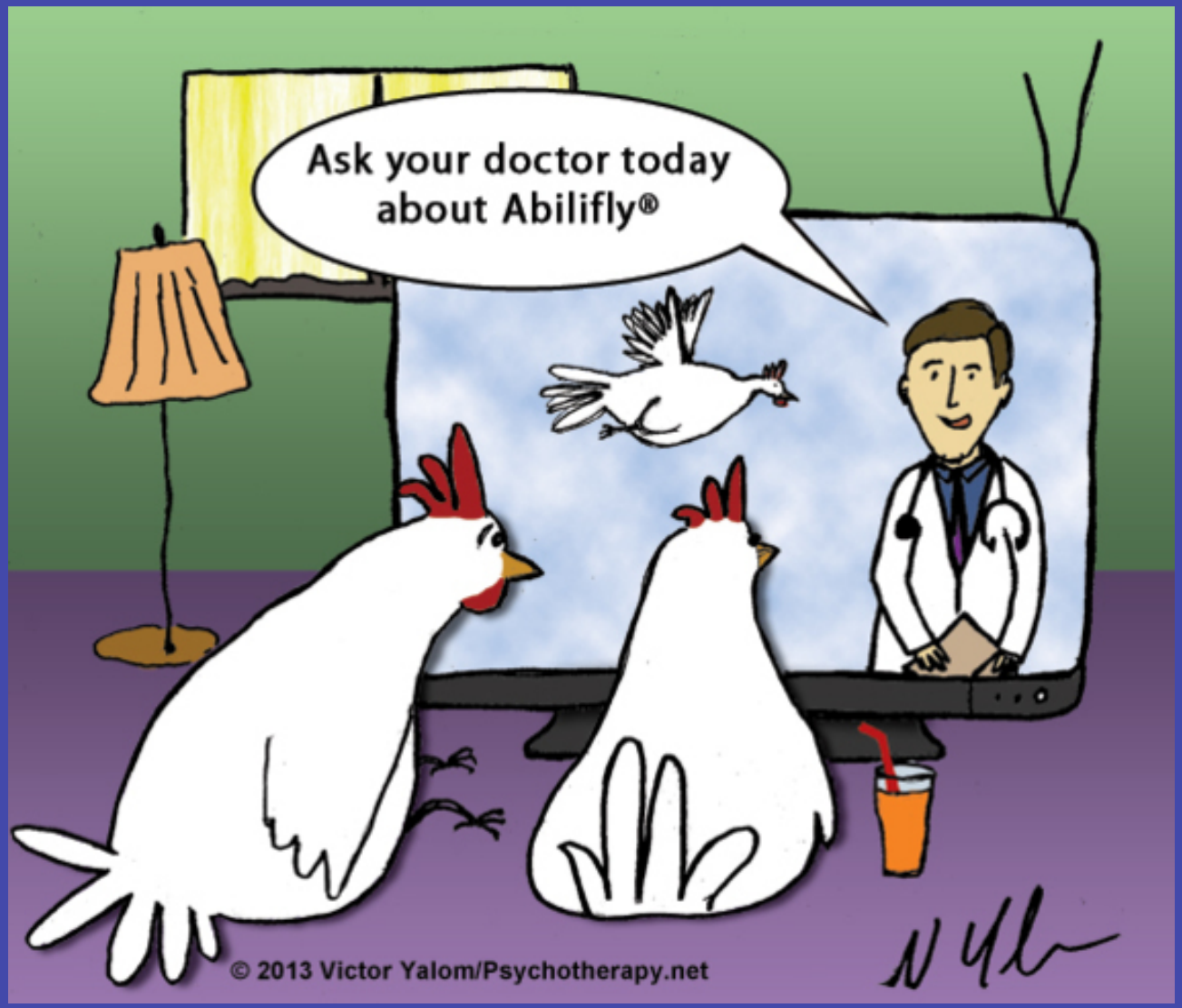
- Fabrazyme *significantly improved* LV mass if treatment was started during the early stage of Fabry cardiomyopathy (patients aged <30 years).

- Long-term *stabilization* of LV mass can be achieved if males are started on Fabrazyme treatment between 30 and 50 years of age.

- Although LV mass may continue to increase in patients started on treatment at age >50 years due to pre-existing advanced cardiac disease with replacement fibrosis, Fabrazyme may provide benefits with regard to clinical symptoms and involvement in other organs in such patients.

- <u>Realistic cardiac treatment expectations</u> should be set based on thorough cardiac evaluation at treatment baseline, preferably including assessment of myocardial fibrosis (no Registry data available) which is an important predictive factor of cardiac treatment response.

Therapy: Patient's Expectations



Fabry's Disease:

FABRY'C (*replace S with C*)

- **F**oam cells / **F**ebrile episodes
- **A**lpha galactosidase **A** deficiency / **A**ngiokeratomas
- **B**urning pain in hands & feet "Peripheral neuropathy" / **B**oys
- **R**enal Failure
- **Y**X genotype (Male, X-linked recessive)
- **C**eramide trihexoside *accumulation* / **C**ardiovascular disease

www.medical-institution.com

Ambulatorio di Genetica Cardiovascolare e Malattie Rare- AO Monaldi - AO Colli (2001-2013)

Cardiologo (AOM)

Genetista-Metabolista (Federico II)

Laboratorio Certificato (CEINGE)

726 pazienti

Diagnosi nota: 529

Diagnosi in corso: 197