Caso clínico de diagnóstico “muito fácil” pelo ECG

Clinical case of “very easy” diagnosis by ECG

From Raimundo Barbosa Barros MD Nickname “ The fox”
Coronary Center Hospital de Messejana Dr. Carlos Alberto Studart Gomes Fortaleza-Ceará-Brazil

Final Comments and ECGs analysis by Andrés Ricardo Pérez-Riera M.D. Ph.D.
In Charge of Electro-vectorcardiogram sector – Cardiology Discipline – ABC Faculty – ABC Foudation – Santo André – São Paulo- Brazil

- **Mulher 41 anos foi admitida com história de angina e cansaço aos esforços.**

  Sem fatores de risco para doença arterial coronariana.

  Relata que vários membros da família são portadores da mesma doença.

  Qual o diagnóstico?

  Um abraço

  Raimundo Barbosa Barros "La raposa"

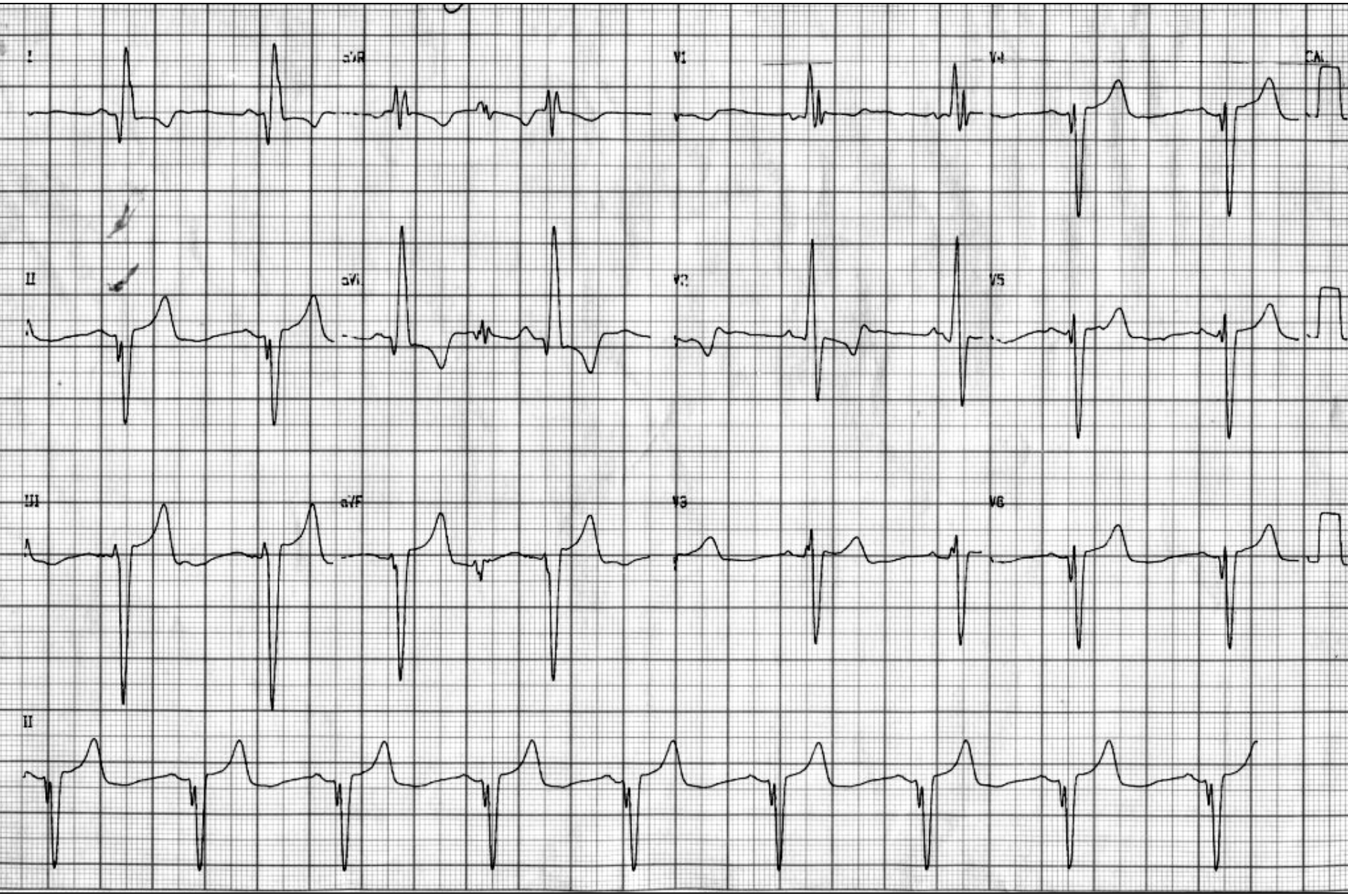
- Female 41 years old was admitted with a history of angina and fatigue on exertion.

  No risk factors for coronary artery disease.

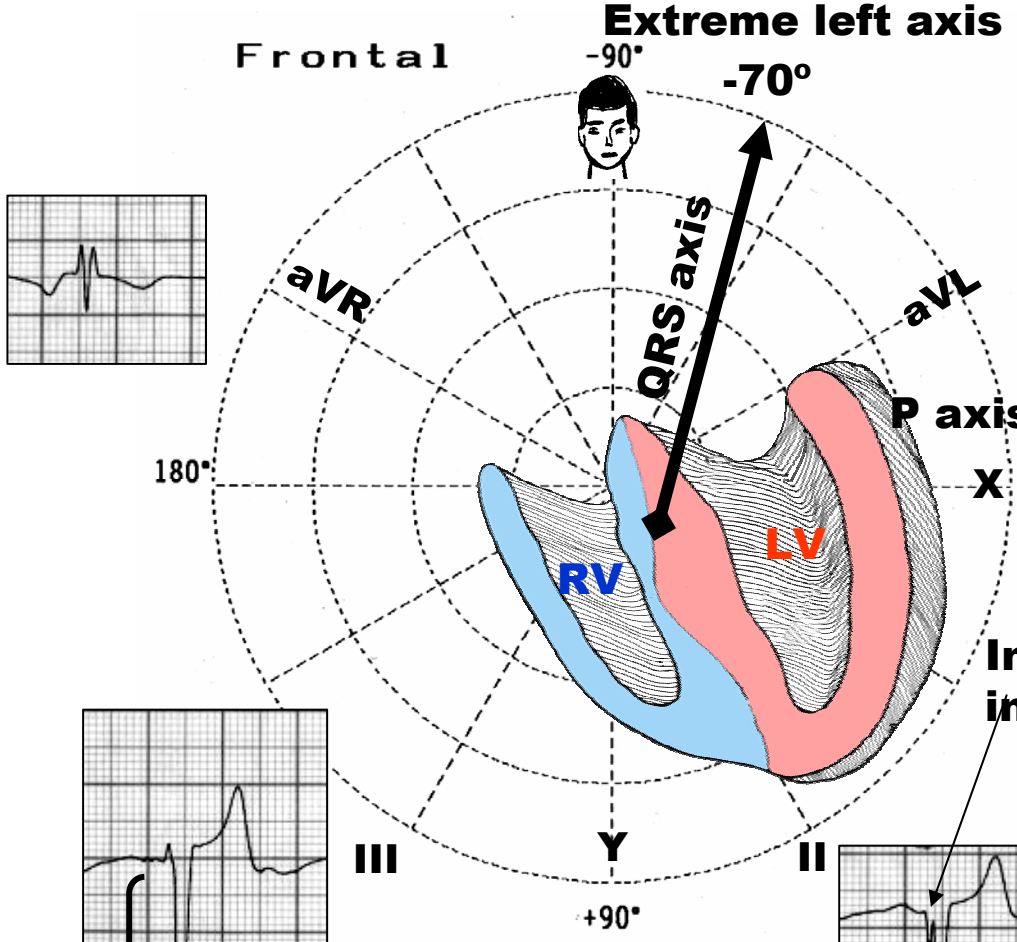
  Reports that several family members are carriers of the same disease. What is the diagnosis?

  A hug

  Raimundo Barros Barbosa "The Fox"


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

ECG FRONTAL PLANE



Extreme left axis deviation

P axis: -20°

LVH

ST-T abnormalities

Strain pattern

qR pattern

Broad QRS/T angle

Inactive electrically area in Inferior lead II?

SIII>15mm

= 28mm!!

LVH high voltage of the QRS complex

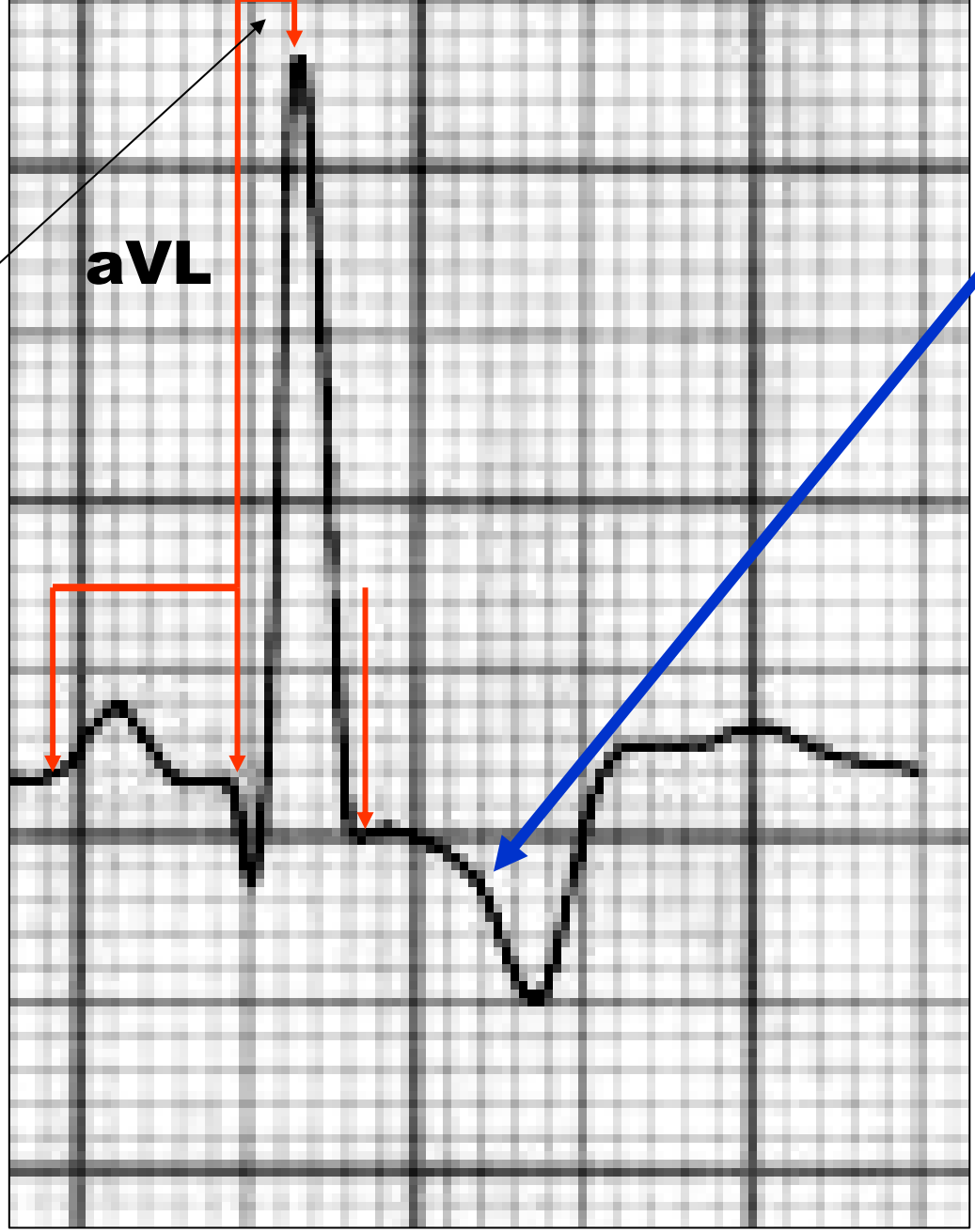
SIII>SII

aVF

LAFB Rosembaum type IV: LAFB associated to LVH

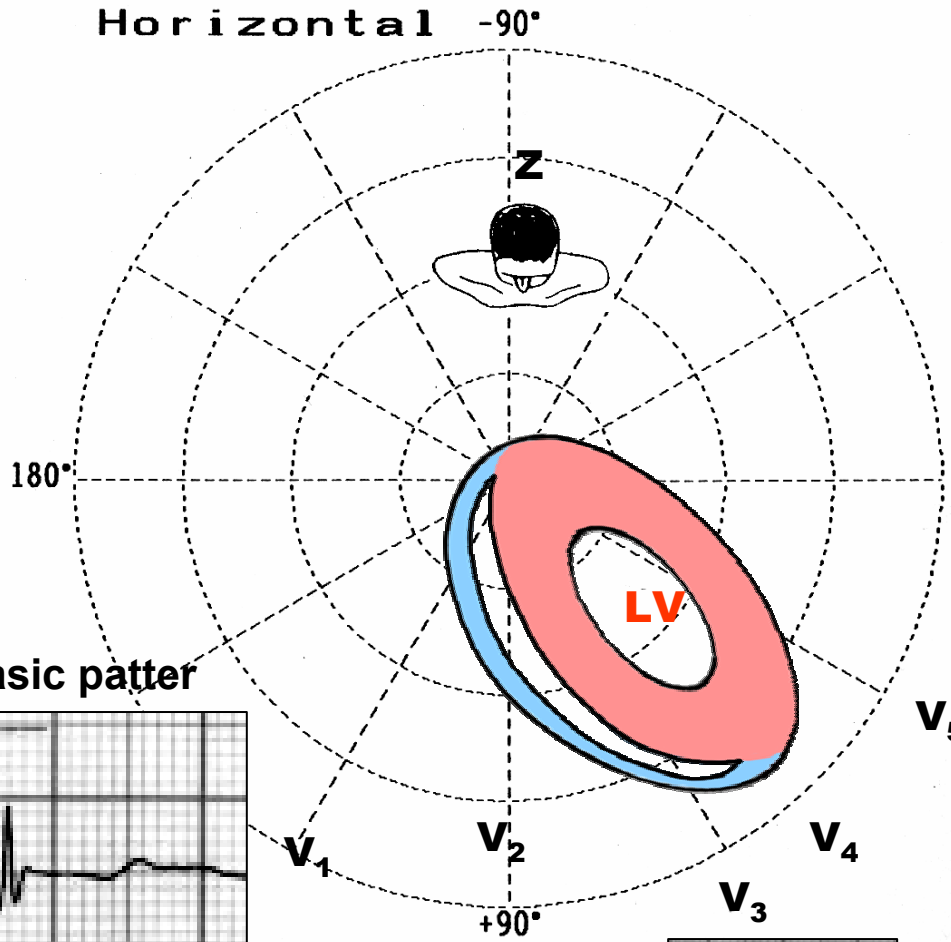
R peak time ≥ 50ms or Prolonged Ventricular Activation Time (VAT)

In later stages, of Fabry disease prolongation of the QRS complex (with or without a right or left bundle branch block morphology) may also be seen (24).

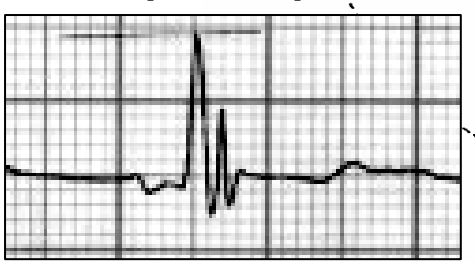


Strain pattern or secondary repolarization abnormality due to Left Ventricular Hypertrophy (LVH)
LVH Criteria based on the increase in QRS complex duration at the expense of a delay in the time of appearance of R wave apex: "R peak time" in the leads that are opposite to the LV, (I and aVL) or ventricular activation time (VAT).

PR or PQ interval = 200ms
QRS duration 150ms: prolonged: Severe > LV mass

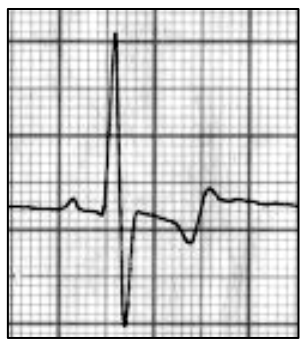


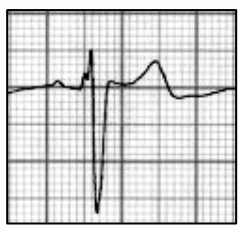
Tetraphasic patter

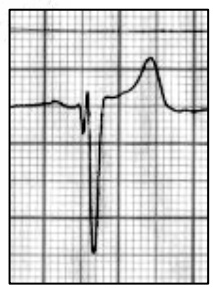


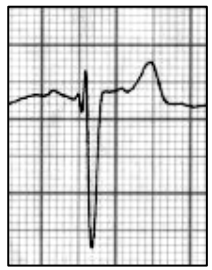
Prominent Anterior Forces V_1-V_2

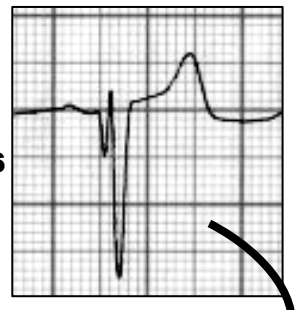
Suggestive Loss of the lateral forces not dorsal!!!(1) or septal hypertrophy











Suggestive Loss of the forces in the anterior apical wall

Queridos amigos del forum tratare de analizar el caso de mujer de 41 años del Dr Raimundo Barbosa Barros y del profe Andres Ricardo Perez Riera PHD
Este electro expresa una hypertrofica asimétrica, con alta probabilidas de ser obstructiva
El maximo engrosamiento del vent izquierdo esta el la base cardiaca y el septo superior
Las ondas Q iniciales en I ,II aVL V3 a V6 pertenecen al mismo vector con orientacion la derecha y abajo, probablemente por una hipertrofia del musculo papilar posteroinferior y el septo
Las ondas S muy profunda en III , II y aVF sugieren que la base del ventriculo izquierdo esta muy hipertrofiada Este fenómeno se acompania casi siempre con una desviacion del eje a izquierda, sugeriendo, que la cara anterior del ventriculo izquierdo se depolariza mucho mas lentamente que la cara posterior Porque es esto? Por 2 causas posibles: 1) la cara anterior esta muy engrosada y como tambien se sabe que las fibras de Purkinje som muy escasa y 2) porque hay una distribucion no homogenea entre el apex y la base de conexina 43 y las hipertrofias la enrarecen aun mas.
Las S profundas en v3 -v6 son profundas por tambien 2 causas 1)por la desviacion del eje a la izquierda y2) por la hypertrofia superior ,como bien se sabe que el apex es electricamente oponente a la base Porque las ondas negativas en aVL y I ? Mi experiencia dice que la hipertrofia de la base no unicamente es muscular ,sino tambien fibrotica(remodelacion electrofisiologica) El ST deprimido en V2 sugiere la sobrecarga sobre el septo alto, sugeriendo la etapa obstructiva de la evolucion de esta patologia (de paso sea dicho el MRI confirmara esta suposicion La onda P negativa en V1 sugieren que la auricula izquierda esta agrandada por la insuficiecia diastolica
Las ondas P son muy poco desarrolladas , posiblemente que estas estan sufriendo un proceso fibrotico.

CONCLUSION HIPERTROFIA SUBAORTICA OBSTRUCTIVA, CON SIGNOS DE REMODELACION ELECTROFISIOLOGICA EN LA BASE. TRATAMIENTO DEPENDE DEL GRADIENTE Y SI LA FALLA DEL ALIVIO MEDICAMENTOSO Y DEL MARCAPASO DERECHO, PROPONER UNA ABLACION DEL SEPTO

Un fraternal abrazo
Samuel sclarovsky

Final Diagnostic and Commentaries

By Andrés Ricardo Pérez-Riera M.D. Ph.D.

Professor Andrés, esta paciente é portadora de Doença de Fabry já confirmada com estudo genético.
Ecocardiograma: Ventrículo esquerdo = 42/25; Massa=500g; FE=72%. Dimensões cardíacas normais; hipertrofia ventricular esquerda concêntrica importante;
Gradiente na via de saída do ventrículo esquerdo =12,5mmHg.
Conclusão: O ecocardiograma transtorácico revelou severa HVE concêntrica com função sistólica normal.
Recrutamos todos os membros da família para realizar ecocardiograma e ECG pois há vários outros casos semelhantes na família.
Coronariografia normal.

Raimundo

Professor Andrés, this patient has Fabry disease. Confirmed diagnosis by genetic study.
Echocardiogram: LV = 42/25; Mass = 500g, EF = 72%. Normal cardiac dimensions,
Concentric severe left ventricular hypertrophy (LVH)
Gradient towards the LVOT = 12.5 mmHg.
Conclusion: Transthoracic echocardiography demonstrated marked concentric left ventricular hypertrophy and normal left ventricular systolic function.
We recruit all members of the family to perform echocardiography and ECG because there are other similar cases in the family.
Normal coronary angiography.
Raimundo

Fabry disease (FD), Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum or α-galactosidase

A deficiency is a rare X-linked recessive (inherited) lysosomal storage disease, which can cause a wide range of systemic symptoms.The disease is named after one of its discoverers, Johannes Fabry (June 1,1860 - June 29,1930).

The disturbance was first described in 1898(1) by Fabry in Germany and Anderson in England(2). 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 generalized 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 recognized in Egypt by Frank Cole Madden(6) (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.

1. **Fabry J. : *Ein Beitrag zur Kenntnis der Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae).* Archiv für Dermatologie und Syphilis, Berlin, 1898, 43: 187-200.**
2. **Anderson W. : *A case of " angio-keratoma".* British Journal of Dermatology, Oxford, 1898, 10: 113-117.**
3. ***Ueber einen Fall von Angiokeratoma circumscriptum am linken Oberschenkel.*Dermatologische Zeitschrift, 1915, 22: 1-4.**
4. ***Zur Klinik und Ätiologie der Angiokeratoma.*Archiv für Dermatologie und Syphilis, Berlin, 1916, 123: 294-307.**
5. ***Weiterer Beitrag zur Klinik des Angiokeratoma naeviforme (Naevus angiokeratosus).*Dermatologische Wochenschrift, Hamburg, 1923, 90: 339.**
6. **Madden FC. :*Papilliform lesions (lymphangiomata) of the scrotum.* British Medical Journal, 1912, 2: 302-304.**
7. **A. Pompen, M. Ruiter, H. J. Wyers:*Angiokeratoma corporis diffusum (universale) Fabry, as a sign of an unknown internal disease, two autopsy reports.* Acta Medica Scandinavica, Stockholm, 1947, 128: 234-255.**
8. **C. C. Sweeley, B. Klionsky: *Fabry disease: Classification as a sphingolipidosis and partial characterization of a novel glycolipid.* Journal of Biological Chemistry, Baltimore, 1963, 238: 3148-3150**

FD is an inherited lysosomal storage disorder caused by deficiency of the enzyme α-galactosidase A. The enzyme deficiency results in accumulation of glycosphingolipids in the lysosomes nearly all cell types and tissues leading to a multisystem disease.

A deficiency of the enzyme α galactosidase A (a-GAL A, encoded by GLA) due to mutation causes a glycolipid known as globotriaosylceramide (abbreviated as Gb3, GL-3, or ceramide trihexoside) to accumulate within the blood vessels, other tissues, and organs. This accumulation leads to an impairment of their proper function. The DNA mutations which cause the disease are X-linked recessive. The condition affects hemizygous males (i.e. all males), as well as homozygous, and in many cases heterozygous females. While males typically experience severe symptoms, women can range from being asymptomatic to having severe symptoms. This variability is thought to be due to X-inactivation patterns during embryonic development of the female.

Symptoms are typically first experienced in early childhood and can be very difficult to understand; the rarity of FD to many clinicians sometimes leads to misdiagnoses. Manifestations of the disease usually increase in number and severity as an individual ages.

Pain Full body or localized pain to the extremities (known as acroparesthesia) is common in patients with FD. Acroparesthesia in FD is believed to be related to the damage of peripheral nerve fibers that transmit pain. GI tract pain is likely caused by accumulation of lipids in the small vasculature of the GI tract which obstructs blood flow and causes pain.

Renal involvement

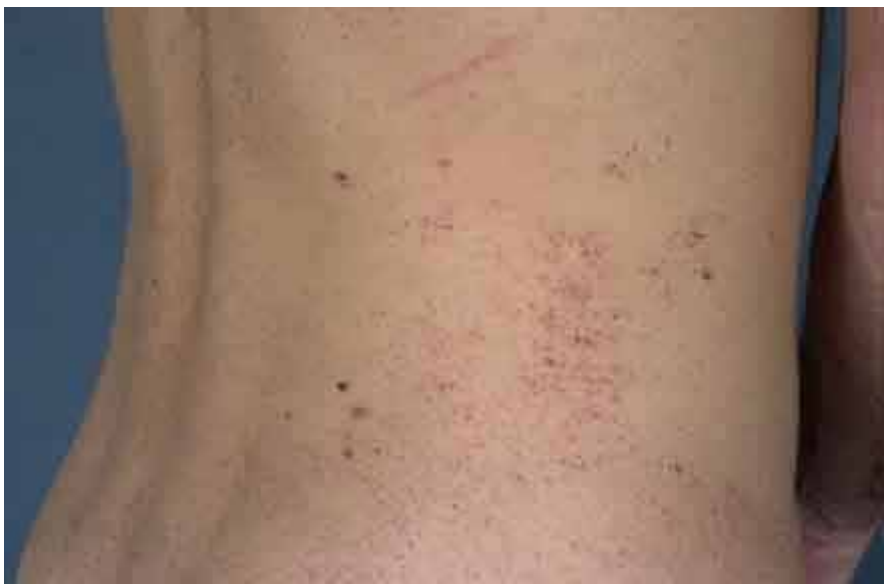
Kidney complications are a common and serious effect of the disease; renal insufficiency and renal failure may worsen throughout life. Proteinuria (which causes foamy urine) is often the first sign of kidney involvement. End stage renal failure in males can typically occur in the third decade of life, and is a common cause of death due to the disease.

Dermatological manifestations

Angiokeratomas in some of the typical locations: lower back , buttocks and flanks and restricted to a limited area: the umbilicus.

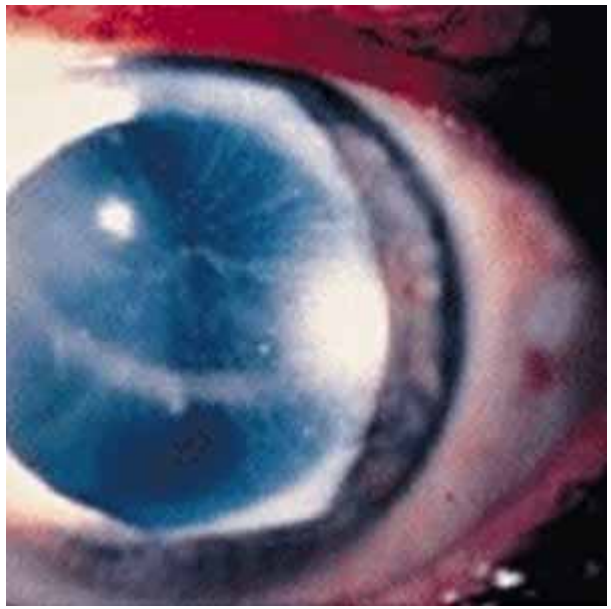
Angiokeratomas (tiny, painless papules that can appear on any region of the body, but are predominant on the thighs, around the belly-button, buttocks, lower abdomen, and groin) are a common symptom.

Anhidrosis (lack of sweating) is a common symptom, and less commonly hyperhidrosis (excessive sweating).Additionally, patients can exhibit Raynaud's disease-like symptoms with neuropathy (in particular, burning extremity pain).



Ocular manifestations

Cosmetic ocular involvement may be present showing cornea verticillata (also known as vortex keratopathy), i.e. clouding of the corneas. Keratopathy may be the presenting feature in asymptomatic carriers, and must be differentiated from other causes of vortex keratopathy (e.g. drug deposition in the cornea). This clouding does not affect vision.
Other ocular findings that can be seen include conjunctival aneurysms, posterior spoke-like cataracts, papilloedema, macular edema, optic atrophy and retinal vascular dilation.



Other manifestations;
Fatigue, neuropathy (in **particular, burning extremity pain**), cerebrovascular effects leading to an increased risk of stroke, tinnitus (ringing in the ears), vertigo, nausea, inability to gain weight, chemical inbalances, and diarrhea are other common symptoms.

Cardiac involvement

Occur when glycolipids build up in different heart cells; heart related effects worsen with age and may lead to increased risk of heart disease. Hypertension and cardiomyopathy are commonly observed in FD. Patients develop hypertrophic cardiomyopathy, arrhythmias, conduction abnormalities, and valvular abnormalities. Although FD leads to a complex clinical syndrome, the manifestations can be limited to the heart. The isolated cardiac variant of FD seems to be more common than previously thought: around 3-6% of male patients with LVH seem to suffer from this disease variant. Molecular biology and genetic engineering have enabled the development of enzyme replacement therapy in FD. Infusion of the enzyme preparation seems to be well tolerated and effective in catabolizing the lipid deposits. This enzyme replacement therapy could be one of the first examples for causal treatment of LVH. Therefore, early diagnosis of hypertrophy patients with the cardiac variant of FD is important. Unlike patients with the classical systemic FD entity, who present with multiple organ involvement, patients with a cardiac variant of FD are characterized mainly by LVH. Therefore, the cardiac variant of FD may be defined as a cardiomyocytic storage disorder, thus, mimicking the clinical features of especially non-obstructive HCM. In patients with unexplained LVH the diagnosis of a cardiac variant of Fabry disease is performed by light- and electron microscopic evaluation of endomyocardial catheter biopsy specimens and/or serologic investigations (decreased activity of alpha-galactosidase A in plasma or leucocytes). Between 4% and 8% of unselected patients with the clinical features of non-obstructive HCM have a cardiac variant of FD. In each patient with unexplained LVH concealed myocardial storage disease, especially cardiac FD has to be considered and should be ruled out or confirmed by endomyocardial catheter biopsy. This is important because of the recently reported α-galactosidase A enzyme replacement therapy in FD. Randomized, multicenter studies are mandatory to test the hypothesis that enzyme replacement therapy leads to a beneficial clinical effect in the cardiac variant form of FD and may prevent the progression of the disease in asymptomatic patients.(1)

1. **Beer G, Reinecke P, et al. Fabry disease in patients with hypertrophic cardiomyopathy (HCM).Z Kardiol. 2002 Dec;91:992-1002.**

Cardiomyopathy

Early ECHO studies of FD patients revealed increased LV wall thickness, confirmed by CRM imaging (1). The presence of LVH, along with coexistent valvular changes, correlate with the severity of FD (2). The increased wall thickness can be so marked that it may mimic HCM (3). The LVH is, usually not associated with significant systolic or restrictive diastolic dysfunction. In later stages of LVH, decreased LV end-diastolic volume leads to progressive impairment of diastolic filling, resulting in reduced stroke volume and cardiac output and, therefore, to a prerenal failure. Although prerenal failure may aggravate renal insufficiency, arterial hypertension will lead to a further increase in LV mass. The mechanism and pattern of cardiac hypertrophy in FD is different from that seen in Hypertensive Heart Disease (HHD), or other forms of infiltrative cardiac amyloidosis where extensive interstitial infiltration is encountered, whereas in FD, infiltration is caused by intracellular lysosomal deposits of Gb3. Furthermore, in FD patients with cardiac involvement there is ECG evidence of LVH marked by increased voltage, whereas low voltage is common in patients with other infiltrative cardiomyopathies (4). ECG voltage criteria for LVH correlates with LV mass assessed by ECHO in FD patients. Lysosomal deposits represent ≈ 1% of the increase in LV mass in FD (5), suggesting that additional mechanisms, such as an absolute increase in contractile proteins, myocyte volume, and thereby in LV muscle mass, might contribute to LVH. One potential mechanism could be disruption of myocardial architecture by the deposited lipid leading to myocyte disarray. Increased plasma endothelin-1 levels also may contribute. Increased muscle mass rather than myocardial interstitial infiltration may explain the absence of restrictive filling patterns.

1. **Goldman ME, Cantor R, Schwartz MF, et al: Echocardiographic abnormalities and disease severity in Fabry's disease. *J Am Coll Cardiol* 1986; 7: 1157–1161.**
2. **Linhart A, Palecek T, Bultas J, et al: New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J.* 2000; 139: 1101–1108.**
3. **Tanaka H, Adachi K, Yamashita Y, et al: Four cases of Fabry's disease mimicking hypertrophic cardiomyopathy. *J Cardiol* 1988; 18: 705–718,**
4. **Cohen IS, Fluri-Lundeen J, et al : Two dimensional echocardiographic similarity of Fabry's disease to cardiac amyloidosis: A function of ultrastructural analogy? *J Clin Ultrasound* 1983; 11: 437–41.**
5. ***Elleder M, Bradova V, Smid F, et al: Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. Virchows Arch Pathol Anat Histopathol 1990; 417: 449–455.***

Valvular Disease

Valvular changes in FD are believed to be caused by lipid deposition and fibrosis of valvular tissue (1). However, estimates of the incidence of valvular involvement in FD differ significantly. Many authors have suggested, that there is a high frequency of mitral valve prolapse (2;3), but a report did not confirm these findings (4). Nevertheless, minor structural abnormalities on both mitral and aortic valves are frequent. Mitral valve thickening or prolapse are seen in younger patients, whereas aortic valve and aortic root abnormalities typically appear in older patients.
Most of the patients with mitral valve abnormalities have thickened papillary muscles, accompanied by mild valvular regurgitation. In the advanced stage with progression of the cardiac involvement and left ventricular hypertrophy, there can be marked aortic root dilatation (4). Aortic regurgitation is not so rare in patients with FD. Enzyme replacement therapy has become the standard medical care for FD in recent years.(5) There are no differences in the incidence of valvular changes among hemizygotes and heterozygotes; both genders are affected equally. Severe valvular disease requiring surgical treatment is rare.

1. Becker AE, Schoorl R, Balk AG, van der Heide RM: Cardiac manifestations of Fabry's disease. Report of a case with mitral insufficiency and electrocardiographic evidence of myocardial infarction. *Am J Cardiol* 1975; 36: 829–835.
2. Sakuraba H, Yanagawa Y, Igarashi T, et al.: Cardiovascular manifestations in Fabry's diesease. *Clin Genet* . 1986;29: 276–283.
3. Goldman ME, Cantor R, Schwartz MF, Baker M, Desnick RJ: Echocardiographic abnormalities and disease severity in Fabry's disease. *J Am Coll Cardiol* 1986; 7: 1157–1161.
4. Linhart A, Palecek T, Bultas J, et al: New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000; 139: 1101–1108.
5. Choi S, Seo H, Park M, Fabry disease **with aortic regurgitation.** Ann Thorac Surg.2009 Feb;87:625-628.

Coronary Artery Disease

More than 50% of hemizygotes and heterozygotes complain of anginal chest pain (1;2). In many patients, there is ECG evidence of myocardial injury but no evidence of ischemic myocardial damage (3; 4). Endothelial dysfunction may also play a major role in the development of these symptoms, as endothelial cells from cardiac capillaries are heavily infiltrated. Endothelial dysfunction may be related to coronary vasospasm. An additional cause of angina is decreased coronary reserve associated with LVH (5). The major clinical manifestations of the disease result from the accumulation of the glycolipid substrate in endothelial cells, with eventual occlussion o the of small arterioles. The accumulation of the glycolipid occurs in the lissosome of the cardiac tissue and is responsible for the multipe cardiovasc manifestations.

When fixed coronary stenoses due to atherosclerosis occur, they are aggravated by dyslipidemia and hypertension, which frequently accompany chronic renal disease.

There are case reports of patients with FD who required coronary revascularization.

None patients have angiographically detectable coronary artery disease, although complain of chest pain. Cardiac catheterization is not routinely performed in patients with FD; therefore, the true incidence of large vessel coronary artery disease remains unclear. Likewise, whether there is a higher incidence of coronary disease among FD patients compared with age-matched controls is unknown.

1. ***MacDermot KD, Holmes A, Miners AH: Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet 2001; 38: 769–807,***
2. ***MacDermot KD, Holmes A, Miners AH: Anderson-Fabry diease: Clinical manifestations and impact of disease in a cohort of 98 hemizygote males. J Med Genet 2001; 38: 750–760,***
3. **Becker AE, Schoorl R, Balk AG, et al. Cardiac manifestations of Fabry's disease. Report of a case with mitral insufficiency and electrocardiographic evidence of myocardial infarction. 1975; *Am J Cardiol* 36: 829–835,**
4. **Mehta J, Tuna N, Moller JH, Desnick RJ: Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. *Am Heart J* 93: 699–705, 1977.**
5. **Linhart A, Palecek T, Bultas J, et al: New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000 139: 1101–1108,**

Conduction System Disease

In addition to accumulation of Gb3 in the myocardium and valves, deposits have been noted throughout the conduction system (1;2;.3). This accumulation predisposes to both tachy- and bradyarrhythmias. For example, patients exhibit increased susceptibility to supraventricular tachycardias, complete heart block, PVCs, and in later stages, prolongation of the QRS complex (with or without a right or left bundle branch block morphology our present case) may also be seen (3). Arrhythmias are implicated in the development of cardiac symptoms. For example, atrial fibrillation in association with diastolic LV dysfunction can rapidly aggravate signs and symptoms of congestive heart failure.

In patients with FD increasing age is associated with PR and QRS interval prolongation and left QRS axis deviation. Pacing for atrioventricular and sinus node disease is common and patients with QRS≥110 ms should be closely monitored for bradyarrhythmias.(4)

1. ***Ferrans VJ, Hibbs RG, Burda CD: The heart in Fabry's disease. A histochemical and electron microscopic study. Am J Cardiol 1969; 24: 95–110.***
2. ***Bannwart F: Fabry's disease. Light and electron microscopic cardiac findings 12 years after successful kidney transplantation. Schweiz Med Wochenschr 112: 1982;1742–1747.***
3. ***Mehta J, Tuna N, Moller JH, Desnick RJ: Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. Am Heart J 1977; 93: 699–705.***
4. ***O'Mahony C , Coats C, Cardona M, et al. Incidence and predictors of anti-bradycardia pacing in patients with Anderson-****Fabry disease****. Europace. 2011 Dec;13:1781-1788.***

This woman has a cardiac mass calculate by Echo of = 500g, consequently, she has a severe LVH
LVH is defined as all increase in LV mass above the values considered normal: 134 g/m^2 of body surface for men and 109 g/cm^2 for women with or without cavity dilatation.
In absolute terms the LV weight is from 120 to 240 g in men and 20% less in women: 100 to 200 g.
This term is used in echocardiography.

ADVANTAGES OF THE ECG FOR LVH DIAGNOSIS

1) Low cost;
2) Easy application in a great universe;
3) High specificity (close to 99%);
4) Simple diagnostic criteria;
5) Possibility of identifying ischemia, necrosis, arrhythmias and associated dromotropic disorders;
6) Independent from the experience of the observer and the quality of the equipment;
7)Irreplaceable in apical hypertrophic cardiomyopathy when revealing the typical giant negative T waves from V2 to V5 accompanied by positive voltage criteria.

DRAWBACKS OF ECG FOR LVH DIAGNOSIS

1) Low sensitivity: 20% to 60%. Only 3% of the general population and 5% of hypertensive patients show LVH in ECG;
2) Low specificity to determine the enlargement modality;
3) Inverse ratio between sensitivity and specificity of ECG criteria for LVH: the greater the sensitivity, the smaller the specificity and vice-versa;
4) Sensitivity and specificity are affected in concomitance of: RVH, MI, bundle branch block, and by use of drugs.

CLASSIFICATION AND ETIOLOGIES OF LVH

I) SYSTOLIC, OF PRESSURE OR CONCENTRIC HYPERTROPHY

- Hypertensive Heart Disease (HHD),
- Aortic Stenosis (AS): valvular, subvalvular and supravalvular.
- Coarctation of the aorta (Co. Ao.).

II) DIASTOLIC, OF VOLUME OR ECCENTRIC HYPERTROPHY

- Aortic insufficiency (AI).
- Mitral valve insufficiency (MVI).
- Patent ***ductus arteriosus*** (PDA)
- Ventricular septal defect (VSD), hemodynamic group II.
- Anemia.

III) PRIMARY OR HYPERTROPHIC/RESTRICTIVE CARDIOMYOPATHIES.

By myocardial diseases that dilate or hypertrophy the heart:

- Dilated cardiomypathy.
- Myocarditis.
- Non-obstructive Hypertrophic Cardiomyopathy (NO-HCM),
- Obstructive Hypertrophic Cardiomyopathy HCM
- Fabry Disease (FD)
- Amiloidosis
- Gaucher disease
- Hemochromatosis
- Glycogen storage disease
- Sarcoidosis
- Endomycardial fibrosis

THE CAUSES OF LVE ACCORDING TO THE AGE GROUP

I) INFANTS:

- Fibroelastosis;
- Tricuspid atresia;
- Single left ventricle;
- Pulmonary atresia without VSD;
- PAC in premature babies;
- Children of diabetic mothers;
- Severe aortic stenosis (AS);
- Pompes' disease.

II) CHILDREN:

- Ventricular septal defect (VSD);
- Persistence of arterial channel (PAC);
- Endocardial cushion defects;
- Aortic stenosis (AS);
- Coarctation of the aorta (Co.Ao);
- Hypertensive Heart Disease (HHD),

III) YOUNG PEOPLE:

- Athletes;
- Mitro-aortic injuries.
- Co.Ao;
- HHD
- Fabry Disease (FD)
- HCM.

IV) ADULTS:

- HHD;
- HCM
- AS;
- Amiloidosis
- Hemochromatosis
- Sarcoidosis.
- Mitro-aortic injuries;
- Myocardiosclerosis.

V) ELDERLY PEOPLE:

- HHD. Secondary;
- Myocardiosclerosis;
- HHD;
- Bivalvular AS.

Causes of LVH according to age range.

MAIN ECG FEATURES IN FABRY DISEASE

P wave: Atrial enlargement: present in 60% of cases.(1) In early stages P-duration is shorter than normal people. **PR or PQ interval:** A short PR interval (≤120 ms) is no rare. PR interval less than 140 ms is frequent The significant shortening of the PQ-interval in FD occurs because of a marked shortening of the P-wave duration, which in itself demonstrated a high sensitivity and specificity for early detection and treatment of this disease.(2). ECGs of 207 patients with FD were compared to echocardiograms. PQ-interval shortening and first-degree AV block could be found in only in14% 1.4%, respectively. Shortening of the PQ interval was not a common ECG finding in patients newly diagnosed with FD. (3). **QRS duration:** In patients with FD increasing age is associated QRS interval prolongation(5) **QRS axis:** In patients with FD increasing age is associated left QRS axis deviation. **Intraventricular conduction disturbance:** present between 20 to 35% of cases. The severity of conduction defects also increased with the duration of the disease process. **Left Ventricular Hypertrophy** with strain pattern is the rule ≈ 80% of cases. Positive Sokolow Lyon index ECG common with hypertrophic cardiomyopathy except that ECG showed depression of ST segment and inversion of T wave in leads I, aVL.(4) **pseudo Myocardial infarction pattern** Frequent.**Repolarization dispersion** is more pronounced in patients with FD(2)

1. **Mehta J, Tuna N, Moller JH,et al. Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. Am Heart J. 1977 Jun;93:699-705.**
2. **Namdar M, Steffel J, Vidovic M, et al. Electrocardiographic changes in early recognition of Fabry disease.Heart. 2011 Mar;97:485-90.**
3. **Namdar M, Kampmann C, Steffel J, et al PQ interval in patients with Fabry disease.Am J Cardiol.2010 Mar 1;105:753-756.**
4. **Bouvagnet P, Millat G, Rousson R, et al. Fabry disease among hypertrophic cardiomyopathy of genetic origin. Rev Med Interne.2010 Dec;31 Suppl 2:S233-237.**
5. ***O'Mahony C , Coats C, Cardona M, et al. Incidence and predictors of anti-bradycardia pacing in patients with Anderson-Fabry disease. Europace. 2011 Dec;13:1781-1788.***

A combination of symptoms, echo findings and ECG in unexplained LVH may help to differentiate amyloidosis, non-obstructive HCM and HHD from FD (1).
In a univariate analysis, four criteria are characteristic of FD

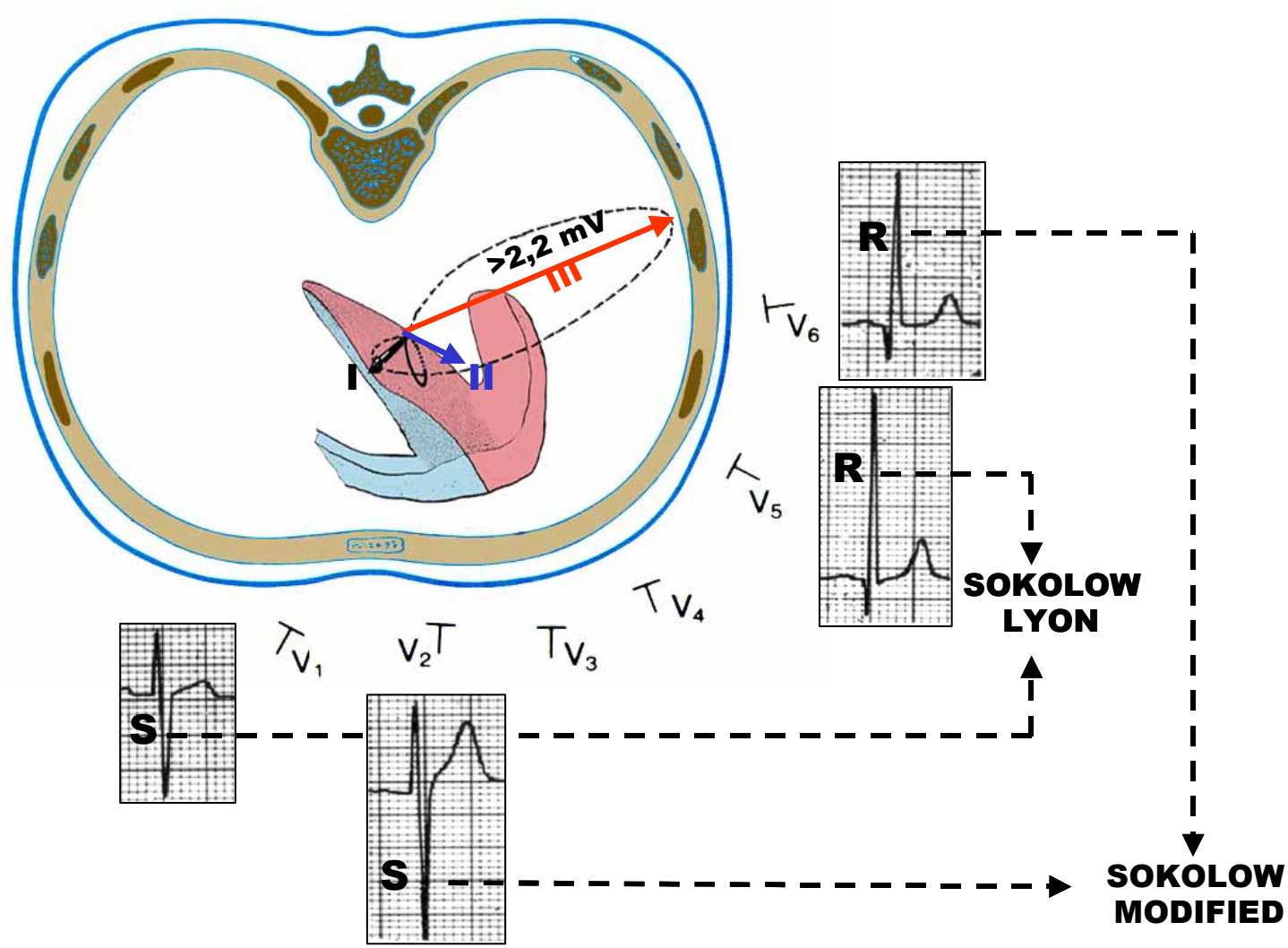
1. Acroparesthesia,
2. Anhydrosis,
3. Absence of hypertension
4. Presence of Sokolow criteria for LVH in the ECG (see next slide)
5. Absence of pericardial effusion
6. No papillary muscle anomaly.

Cardiac abnormalities in patients with FD were first described in the 1960s. In the 1990s a form of FD confined to the heart was reported; however, this variant is extremely rare and a more appropriate concept is of cardiac predominance of the disease in some patients. Up to 60% of males with classic FD have cardiac abnormalities, including LVH, valvular dysfunction and conduction abnormalities. Left ventricular mass and systolic function in patients with FD improve after 12 months of enzyme replacement therapy (ERT); however, many of the patients studied are relatively young and have mild cardiac abnormalities, suggesting that more research into the efficacy of ERT in older patients is necessary. Cardiac manifestations are common in patients with FD and are not confined to a 'cardiac variant' of the disease.

1. **Hoigné P, Attenhofer Jost CH, Duru F, et al Simple criteria for differentiation of Fabry disease from amyloid heart disease and other causes of left ventricular hypertrophy Int J Cardiol. 2006 Aug 28;111:413-422.**
2. **Shah JS, Elliott PM.; Fabry disease and the heart: an overview of the natural history and the effect of enzyme replacement therapy. Acta Paediatr Suppl. 2005 Mar;94:11-14**

SOKOLOW INDEX MODIFIED FOR LVH

S of V_2 + R of V_5 or $V_6 \geq 35$ mm



Modified Sokolow index for LVH.

Value of ECG in the differentiation LVH of Hypertensive Heart Disease (HHD), Non-obstructive Hypertrophic Cardiomyopathy (NO-HCM), Aortic Stenosis (AS), Amyloidosis, and Fabry Disease (FD)

LVH is a parameter associated with bad prognosis. Many different causes of LVH exist. Namdar et al (1) studied the value of common ECG parameters to differentiate FD, amyloidosis, and non-obstructive HCM, HHD and AS.

In 94 patients with newly diagnosed FD (n = 17), HHD (n = 20), amyloidosis (n = 17), AS (n = 20), and HCM (n = 20), common ECG parameters were analyzed and tested for their diagnostic value. A stepwise approach including the Sokolow-Lyon index, corrected QT duration, and PQ interval minus P-wave duration in lead II to overcome P-wave abnormalities was applied. A corrected QT duration <440 ms in combination with a PQ interval minus P-wave duration in lead II <40 ms was 100% sensitive and 99% specific for the diagnosis of FD, whereas a corrected QT duration >440 ms and a Sokolow-Lyon index ≤1.5 mV were found to have a sensitivity and specificity of 85% and 100%, respectively, for the diagnosis of amyloidosis and differentiation from HC, AS, and HHD. Moreover, a novel index ([PQ interval minus P-wave duration in lead II multiplied by corrected QT duration]/Sokolow-Lyon index) proved to be highly diagnostic for the differentiation of amyloidosis (area under the curve 0.92) and FD (area under the curve 0.91) by receiver operator characteristic analysis. The autors conclude that a combined analysis of PQ interval minus P-wave duration in lead II, corrected QT duration, and Sokolow-Lyon index proved highly sensitive and specific in the differentiation of FD, amyloidosis, and HCC compared to HHD and AS. Analysis of these easy-to-assess ECG parameters may be of substantial help in the diagnostic workup of these 5 conditions.

1. **Namdar M, Steffel J, Jetzer S, et al. Value of Electrocardiogram in the Differentiation of Hypertensive Heart Disease, Hypertrophic Cardiomyopathy, Aortic Stenosis, Amyloidosis, and Fabry Disease. Am J Cardiol. 2011 Nov 18. [Epub ahead of print]**

Echocardiography

Forty consecutive patients with an established diagnosis of Fabry's disease were submitted to echocardiographic evaluation by Mundigler et al(1).

Control population consisted of 40 patients with (HCM), 40 hypertensive patients with echocardiographic evidence of LVH, and 40 age- and gender-matched healthy subjects with no LVH. All HCM patients and FC with LVH and/or cardiac symptoms underwent cardiac catheterization with LV endomyocardial biopsy. Echocardiography showed in 83% of FD patients a binary appearance of endocardial border absent in all HCM, hypertensive, and healthy subjects. The sensitivity and specificity of this echocardiographic feature in detecting FD patients in study population were 94% and 100%, respectively.

The authors concluded that Echocardiographic binary appearance of LV endocardial border, reflecting endomyocardial glycosphingolipids compartmentalization, represents a sensitive and specific diagnostic hallmark of Fabry's disease cardiomyopathy.

1. **Mundigler G, Gaggl M, Heinze G, et al. The endocardial binary appearance ('binary sign') is an unreliable marker for echocardiographic detection of Fabry disease in patients with left ventricular hypertrophy. Eur J Echocardiogr. 2011 Oct;12: 744-749.**

Diagnosis

FD is indicated when associated symptoms are present, and can be diagnosed by a blood test to measure the level of α-galactosidase activity, however this may be misleading in female carriers due to the random nature of X-inactivation. Chromosomal analysis of the GLA gene is the most accurate method of diagnosis, and many mutations which cause the disease have been noted. Kidney biopsy may also be suggestive of Fabry Disease if excessive lipid buildup is noted.

Naturally, α-galactosidase A (a-GAL A) is likely to be present only at very low levels in the blood, particularly in males. In females, owing to X-inactivation patterns, levels are commonly normal even if the patient is not asymptomatic. The Sifap (stroke in young FD patients) project will investigate the relation between stroke and FD.

Misdiagnosis of FD. Pediatricians as well as internists commonly misdiagnose FD.

Treatment

Enzyme replacement therapy is now the treatment of choice for patients with Fabry disease, and preliminary results indicate promising effects not only on the renal and neurological manifestations of the disease but also on the cardiac manifestations. Until the 2000s, treatment of FD targeted the symptomatic effects. In 2001, two Enzyme Replacement Therapies (ERTs) were released: Agalsidase alpha (Replagal, manufactured by Shire) and Agalsidase beta (Fabrazyme, manufactured by Genzyme). These attempt to replace the deficient enzyme by means of infusion, most commonly, every two weeks. The cost of these drugs is problematic (approximately $250,000 US a year/patient) and remains a barrier to many patients in some countries. The infusion may be performed by the patient themselves, in the patient's home by a registered nurse, or at a medical facility. Enzyme replacement therapy is not a cure, but can allow normal metabolism and both prevent disease progression as well as potentially reverse symptoms. Pain in FD responds to ERT, but pain management regimens may also include analgesics, anticonvulsants, and non-steroidal anti-inflammatory drugs.