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A case of heterozygous Fabry's disease with a short PR interval and giant negative T waves

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SUMMARY A 55 year old woman with heterozygous Fabry's disease presented with cardiac symptoms. The electrocardiogram showed a PR interval of 0·12 s and giant negative T waves, suggesting apical hypertrophic cardiomyopathy. Endomyocardial biopsy, however, revealed myelin like substances characteristic of Fabry's disease. Increasing thickness of the left ventricular wall was seen by echocardiography over a period of five years. A deficiency of α galactosidase activity in the leucocytes confirmed the diagnosis of Fabry's disease, although this patient had neither angiokeratoma or proteinuria.

The possibility of Fabry's disease should be considered in patients with cardiomegaly of unknown cause and the following electrocardiographic abnormalities: *(a)* a PR interval $\leqslant$0·12 s, *(b)* high voltage QRS complexes in the left precordial leads, and *(c)* giant negative T waves.

Fabry's disease is a sex linked recessive disease. Heterozygous female cases seldom show overt symptoms,[1] and there are no previous reports of any presenting with cardiac symptoms. We report a case of heterozygous Fabry's disease that was confirmed by endomyocardial biopsy.

Case report

A 50 year old woman was admitted to the hospital of Niigata University School of Medicine in November 1980. She had complained of anterior chest pain and easy fatigability since the summer of that year.

On physical examination we found no dermatological abnormality. Her blood pressure was 126/60 mm Hg. Heart sounds were normal and no heart murmur was audible. There was no ankle oedema. The electrocardiogram showed a PR interval of 0·12 s and giant negative T waves in leads V5 and V6 (fig 1a). The chest radiograph showed no abnormality and the cardiothoracic ratio was 0·46. On M mode echocardiogram the thicknesses of the interventricular septum and the left ventricular posterior wall were 0·9 and 1·0 cm respectively (fig 2). Cross sectional echocardiography showed slight hypertrophy of the left ventricular apical area. There was no proteinuria. Concentrations of serum urea nitrogen and serum creatinine were 14 mg/dl and 0·8 mg/dl respectively.

Because the electrocardiographic findings were suggestive of apical hypertrophic cardiomyopathy we performed right and left heart catheterisation. The cardiac index was 2·9 l/min/m^2 and left ventricular end diastolic pressure was 4 mm Hg. Coronary angiography showed no significant obstructive lesion. The left ventricular angiogram showed slight hypertrophy of the wall of the apical area. The left ventricular ejection fraction was normal (78%). Endomyocardial biopsy of the right side of the intraventricular septum showed slight hypertrophy (mean 19 μm) and a focal mild degree of disarray of muscle cells. In about two thirds of the muscle cells granules or ring like deposits staining with toluidine blue and basic fuchsin were present both in the perinuclear zone and between myofibrils. In plastic embedded material the granules were demonstrable by the Kurotaki method[2] and electron microscopy confirmed the presence of myelinoid lamellar inclusions. The biopsy findings were those of Fabry's disease.[3 4]

The patient did not visit our hospital for five years,

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but early in the summer of 1985 her anterior chest pain and easy fatigability became severe, with additional attacks of pain in the legs. She was readmitted to hospital in October with a one month history of fever. On physical examination, dry rales were heard at the base of both lungs and a fourth heart sound was audible. There was no ankle oedema. The chest *x* ray showed reticular shadows in both lower lung fields that were compatible with interstitial pneumonitis. The cardiothoracic ratio was 0·54 and slight cardiomegaly was seen. The electrocardiogram showed that septal Q waves, present on the electrocardiogram five years before (fig 1b), had disappeared. The echocardiogram showed that thickening of the interventricular septal wall and the posterior wall had increased to 1·4 and 1·5 cm respectively, with hypertrophy of the left ventricular wall, although there was no dilatation of the left ventricle (fig 2b). Her interstitial pneumonitis advanced and was accompanied with generalised convulsions and evidence of disseminated intravascular coagulation. The patient eventually died 32 days after admission to hospital.

At necropsy the heart weighed 540 g and the left ventricle showed concentric hypertrophy. There was hypertrophy and fibrosis of the myocardium, particularly in the ventricular septum. These findings are compatible with hypertrophy of the ventricular wall.

Alpha galactosidase activity was assayed by a fluorescence method with 4-meltylumbellibryl-D-galactopyranoside (Koch-Light) as a substrate. The α galactosidase activity of her leucocytes was 12·4 nmol/mg protein (normal (mean (SD)) 67·9 (16·2)).[5]

The patient's 27 year old daughter was found to be a carrier of the disease, although she was symptom free. Her electrocardiogram showed ST-T changes in leads II, III, and aVF.

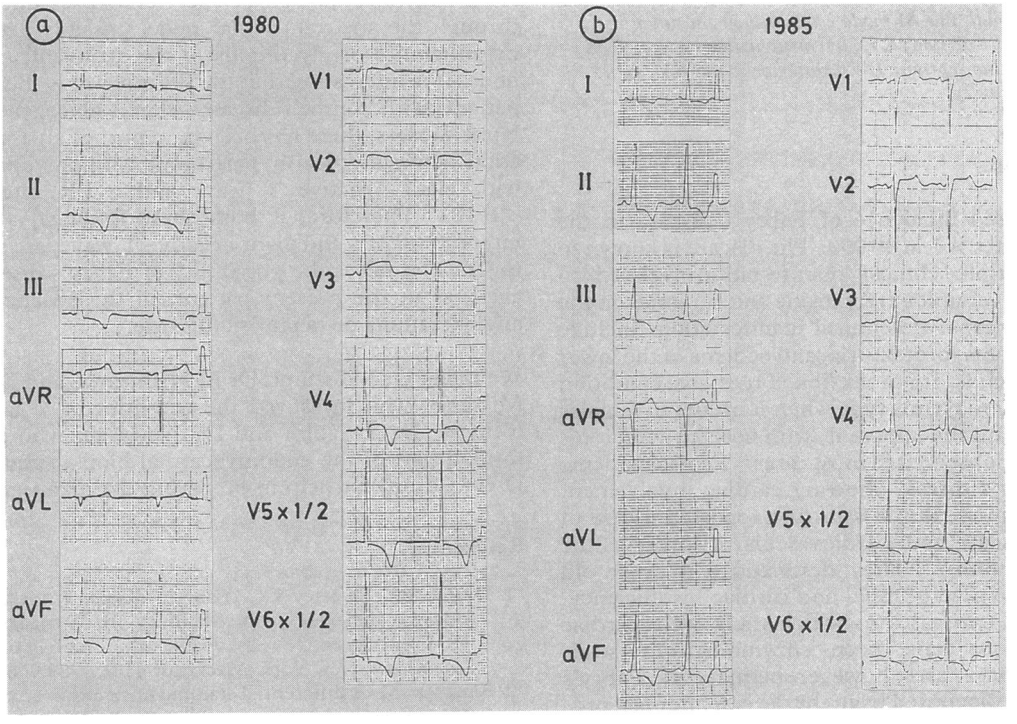

Fig 1 *An electrocardiogram. (a) recorded in 1980 showing a PR interval of 0·12 s and giant negative T waves in leads V5 and V6. There is no septal Q wave on the electrocardiogram (b) recorded in 1985; this was present 5 years before.*

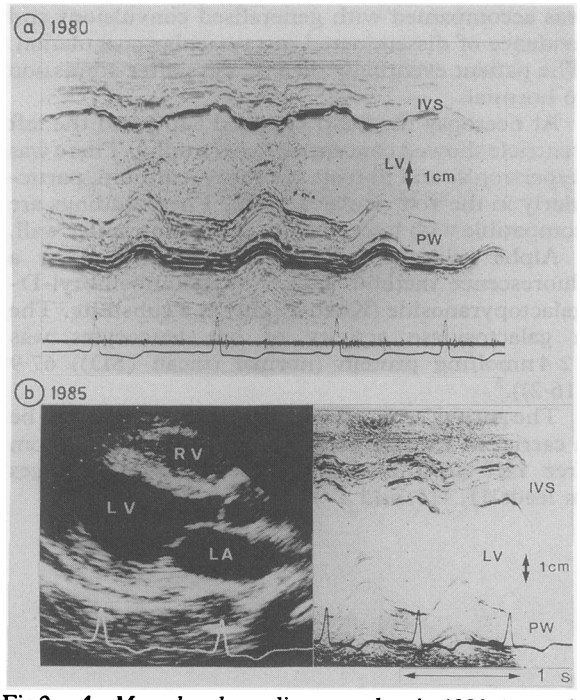

Fig 2 *An M mode echocardiogram taken in 1980 (a) and a cross sectional and M mode echocardiogram taken in 1985. LA, left atrium; LV, left ventricular cavity; IVS, interventricular septum; PW, posterior wall; RV, right ventricular cavity.*

Discussion

The reported incidence of Fabry's disease in the United States is 1 in 40 000. The disease is known to show multiple clinical manifestations related to deposits of ceramide trihexoside and ceramide in the systemic organs. Its clinical manifestations include angiokeratoma, proteinuria, and oedema of the lower legs and eyelids. It is a sex linked recessive condition and the heterozygous type when it occurs in females is rarely clinically apparent, with corneal symptoms alone being observed in most cases.[1] Female patients with Fabry's disease showing cardiac involvement are uncommon. Burda *et al* first reported a case of Fabry's disease with cardiovascular disorder as the main symptom.[6 7] They described a 47 year old woman who died of renal and cardiac insufficiency. Since then two cases in which there were cardiac manifestations have been enzymologically studied.[3 8] In these cases, however, hemizygotic Fabry's disease was diagnosed from the dermal findings, proteinuria, and family history. The mechanism of the occurrence of Fabry's disease as a sex linked recessive hereditary condition in females had been explained by the hypothesis of Lyon which states that one of the two X chromosomes in the cell is activated while the other is inactivated.[9] Indeed, Romeo and Migeon demonstrated two types of clone, one with normal α galactosidase activity and one with reduced α galactosidase activity in cultured skin fibroblasts from a patient with heterozygous Fabry's disease.[10]

The patient presented in this report had electrocardiographic findings suggestive of apical hypertrophic cardiomyopathy.[11 12] The echocardiograms and left ventriculograms obtained in 1980 showed only mild hypertrophy of the left ventricular apical wall, and Fabry's disease was first suspected because of the results of endomyocardial biopsy. The serial M mode echocardiograms showed increases in the thickness of the interventricular septum from 0·9 to 1·4 cm and the left ventricular posterior wall from 1·0 to 1·5 cm. The cross sectional echocardiograms obtained in 1985 also showed considerable concentric hypertrophy of the left ventricle. There has been no previous report describing such a progression of cardiac findings in Fabry's disease.

It has been reported that the PR interval is often $\leqslant 0{\cdot}12$ s in Fabry's disease.[13 14] According to Matsui *et al*,[8] the mechanism of this short PR interval is an electrophysiologically accelerated conduction through the atrioventricular node, possibly caused by adherence of glycolipids to the atrioventricular node. It is interesting that the PR interval is short in patients with Pompe's disease—that is glycogenosis. None the less, there has been no report of an association between apical hypertrophic cardiomyopathy with giant negative T wave and a PR interval $\leqslant 0{\cdot}12$ s. Therefore, if both these findings, a PR interval $\leqslant 0{\cdot}12$ s and giant negative T wave, are seen together, it raises the possibility of Fabry's disease, even, as in the present patient, in the absence of angiokeratoma or nephrotic disorder.

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References

1 Desnic RJ, Sweeley CC. Fabry's disease (α-galactosidase A deficiency). In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease*. New York: MacGraw-Hill, 1983:906–44.
2 Kurotaki M. A differential staining of semithin sections of epon-embedded tissue and a short review on the optical microscopy of plastic-embedded tissue. *Acta anat Nippon* 1972;47:237–50.
3 Broadbent JC, Edwards WD, Gordon H, Hartzler GO,

Krawisz JE. Fabry cardiomyopathy in the female confirmed by endomyocardial biopsy. *Mayo Clin Proc* 1981;**56**:623–8.
4 Rodorignez FH, Hoffmann EO, Ordinario AT, Baliga M. Fabry's in a heterozygous women. *Arch Pathol Lab Med* 1985;**109**:89–92.
5 Suzuki K. Enzymic diagnosis of sphingolipidosis. In: Ginsburg V, ed. *Methods in enzymology*. Vol 50. New York: Academic Press, 1978:456–98.
6 Burda CD, Winder PR. Angiokeratoma corpus diffusum universale in female subjects. *Am J Med* 1967;**42**:293–301.
7 Burda CD. The heart in Fabry's disease. *Am J Cardiol* 1969;**24**:95–110.
8 Matsui S, Murakami E, Takekoshi N, *et al*. Cardiac manifestations of Fabry's disease. Report of a case with pulmonary regurgitation diagnosed on the basis of endomyocardial biopsy findings. *Jpn Circ J* 1977;**41**:1023–36.
9 Lyon MG. Gene action in the X-chromosome of the mouse. *Nature* 1961;**190**:372–84.
10 Romeo G, Migeon BR. Genetic activation of the α-galactosidase locus in carriers of Fabry's disease. *Science* 1970;**170**:180–1.
11 Sakamoto T, Tei C, Murayama M, *et al*. Giant negative T wave inversion as a manifestation of asymmetric apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasonocardiographic study. *Jpn Heart J* 1976;**17**:611–9.
12 Yamaguchi H, Ishimura T, Nishiyama S, *et al*. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979;**44**:401–12.
13 Roudebush CP, Foerster JM, Bing OHL. The abbreviated PR interval of Fabry's disease [Abstract]. *Circulation* 1973;**48**(suppl IV):IV–210.
14 Mehta J, Tuna N, Moller JH, Densnick RJ. Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. *Am Heart J* 1977;**93**:669–76.

Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts was 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Pacing and electrophysiology

The 8th Annual Scientific Session, North American Society of Pacing and Electrophysiology will take place in Boston on 30 April to 3 May 1987. Further details from: NASPE, 13 Eaton Court, Wellesley Hills, MA 02181, USA.

Heart research

The 9th Annual Meeting of the International Society of Heart Research (ISHR), American Section, will be held in Boston on 8 to 12 September 1987. Inquiries to: Dr Joanne S Ingwall, Director, NMR Laboratory, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA.