CASE REPORT

Sisters with atypical Fabry's disease with complete atrioventricular block

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A 56 year old woman with severe right heart failure and complete atrioventricular block was referred to hospital for further examination. Symptoms and signs suggestive of Fabry's disease, such as corneal opacities, acroparaesthesias, hypohidrosis, and angiokeratoma, were not noted. Echocardiography showed a diffuse hypertrophic left ventricular wall and paradoxical movement of the interventricular septum. Cardiac catheterisation showed restrictive-type ventricular dysfunction. Left ventricular endomyocardial biopsy showed central vacuolar degeneration of myocytes with inclusion bodies, which had a concentric lamellar configuration under electron microscopy. This finding is specific for Fabry's disease. The patient's elder sister had experienced an almost identical clinical course and histological findings of myocardial cells on necropsy. In conclusion, two sisters were encountered displaying interesting cases of atypical Fabry's disease. Symptoms began with complete atrioventricular block and histological myocardial findings were specific for Fabry's disease.

Fabry's disease is a metabolic disorder caused by a deficiency of α galactosidase. Recently, several cases of the atypical variant of Fabry's disease characterised by left ventricular hypertrophy have been reported.[1–3] The prevalence of Fabry's disease is reportedly 3% in men, suggesting that it is not rare in that subset of the population.[1] As Fabry's disease is an X linked recessive disease, most affected women are heterozygotes, either asymptomatic or with only mild symptoms. A definitive diagnosis of Fabry's disease in women can therefore be particularly difficult to make.

CASE PRESENTATION

Case 1: younger sister

A 56 year old woman was referred to our hospital with severe right heart failure. Facial oedema had been present for 17 years. When she was 43 years old, atrial flutter and complete atrioventricular block developed and a ventricular inhibitor-type permanent pacemaker was implanted. When she was 51 years old, severe tricuspid regurgitation developed with major cardiomegaly. From that time, facial oedema, pretibial oedema, and ascites gradually worsened. On admission, her blood pressure was 122/72 mm Hg and heart rate was 60 beats/min and regular. A grade 3/6 systolic murmur along the left fourth intercostals space and apex and a grade 2/6 diastolic murmur at the lower sternum were heard, in addition to a third heart sound. Breath sounds were muffled and moist rales were audible at the right back. Hepatomegaly and leg oedema were observed. No other symptoms or signs suggestive of Fabry's disease (such as corneal opacities, acroparaesthesias, hypohidrosis, or angiokeratoma) were noted. Routine laboratory examinations showed liver dysfunction caused by congestion. α Galactosidase activity was 8.9 nM/h/ml (normal range 4.8–17.6 nM/h/ml). Chest radiography showed massive right pleural effusion and major cardiomegaly. Echocardiography showed a diffuse hypertrophic left ventricular wall (interventricular septum 13 mm) and paradoxical movement of the interventricular septum. Haemodynamic measurements under cardiac catheterisation showed an increased V wave in the right atrium, a dip and plateau pattern in the right ventricular pressure tracing, and increased right and left ventricular end diastolic pressures, both at 15 mm Hg. Left ventriculography showed impaired systolic function with akinesis of the inferior ventricular wall. Left ventricular ejection fraction was 47%. The endomyocardium of the left ventricle was biopsied. The biopsy specimen exhibited vacuolar degeneration in myocardial cells stained with haematoxylin and eosin (fig 1) and inclusion bodies stained with toluidine blue in the vacuoles (not shown). Electron microscopy identified concentric lamellar inclusion bodies (fig 2). On the basis of these results, atypical Fabry's disease was diagnosed. Despite various medications, she died of heart failure at 58 years of age.

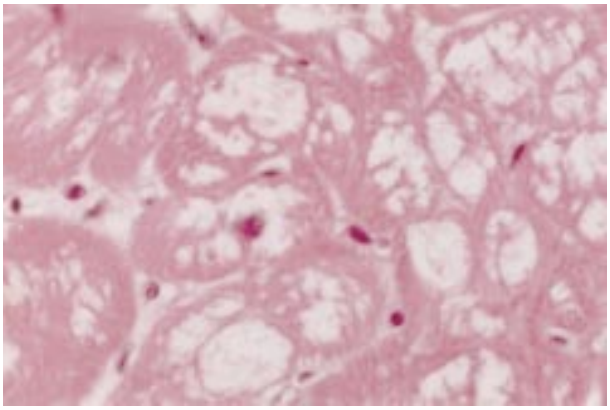

Figure 1 Optical microscopy showing vacuolar degeneration in myocardial cells. Inclusion bodies are present in vacuoles. Haematoxylin and eosin, original magnification ×460.

Case 2: elder sister

This patient had experienced an almost identical clinical course to that of her younger sister. Leg oedema was observed when she was 37 years old. At 41 years of age, she experienced complete atrioventricular block resulting in permanent pacemaker implantation. Congestive heart failure gradually deteriorated thereafter. At 55 years of age, she was admitted to our hospital with severe heart failure and died from the sepsis. Echocardiography had shown diffuse hypertrophic changes in the left ventricular wall (interventricular septum 12 mm) and paradoxical movement of the interventricular septum. A necropsy specimen displayed vacuolar degeneration in myocardial cells stained with haematoxylin and eosin, as did her younger sister's biopsy specimen. These findings confirmed a

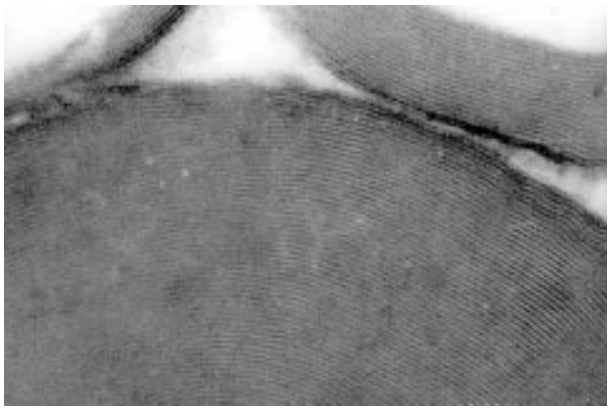

Figure 2 Electron microscopy showing concentric lamellar configuration consistent with inclusion bodies shown in vacuoles of myocardial cells. Lamellar arrangement is regular over a 5–6 nm interval.

diagnosis of atypical Fabry's disease. This diagnosis was made only after the younger sister's diagnosis.

DISCUSSION

We have presented the cases of two sisters with atypical Fabry's disease. In both cases, the initial signs were complete atrioventricular block, right side heart failure, and left ventricular hypertrophy. Very similar clinical courses were experienced. Cardiac biopsy or necropsy specimens histologically confirmed the diagnosis.

Conduction disturbances such as complete atrioventricular block or shortened PR interval have been reported in Fabry's disease.[4–6] In a case reported by Ikari and colleagues,[5] necropsy showed deposition of glycosphingolipids in the bundle of His and bundle branches, suggesting that accumulation in the conduction system may result in complete atrioventricular block. Although necropsy was conducted on the elder sister in our case, the conduction system was not histologically investigated with special stains.

The activity of α galactosidase was normal in the case of the younger sister. Hence, the final diagnosis was based on endomyocardial biopsy findings. In the elder sister's case, although α galactosidase activity was not examined, diagnosis was determined from similarities to the younger sister in clinical history and laboratory and pathological findings.

A clinical survey was conducted among their relatives. Although none displayed heart disease similar to these two sisters, two brothers in the family had experienced cerebrovascular accidents at 40 and 50 years of age, respectively. Cerebrovascular accident has occasionally been reported as a cardinal manifestation of Fabry's disease[7 8] and it is very possible that these two brothers have Fabry's disease.

Fabry's disease in two monozygous sisters has previously been reported.[9] However, there have been no reports of sisters presenting with Fabry's disease beginning with complete atrioventricular block. This case report offers valuable insight from both clinical and aetiological perspectives. Firstly, Fabry's disease must be considered in cases of cardiomegaly with heart block even in women. Secondly, histological examination of myocardial cells is necessary despite normal α galactosidase activity to confirm a diagnosis of Fabry's disease. Thirdly, family history can offer important clues towards diagnosis.

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