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CASE REPORT
Other

Ventricular tachycardia: a presentation of Fabry disease case report

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Background Fabry disease is an inherited rare metabolic disease caused by mutation in the *GLA* gene, encoding lysosomal enzyme alpha-galactosidase A. The disorder is a systemic disease that manifests as cerebrovascular and cardiac disease, chronic renal failure, skin lesion, peripheral neuropathy, and other abnormalities. Ventricular tachycardia as a Fabry disease presentation is very rare.

Case summary A 36-year-old man self-presented to a general practitioner complaining of episodes of shortness of breath together with a 6-month history of malaise. The 12-lead electrocardiogram (ECG) prompted a decision to transfer him immediately to a percutaneous coronary intervention (PCI) capable hospital under the suspicion of acute coronary syndrome. Whilst awaiting transport, he experienced acute onset of dyspnoea together with non-specific chest heaviness. A repeat ECG monitor strip showed ventricular tachycardia transforming to ventricular fibrillation. The patient was successfully defibrillated. Coronary angiography was performed upon arrival at hospital and demonstrated unobstructed coronary arteries. Transthoracic echocardiography revealed concentric left ventricular hypertrophy (LVH) and normal systolic function, with severe diastolic dysfunction. Magnetic resonance imaging (MRI) confirmed the LVH, and did not demonstrate any late gadolinium enhancement.

Discussion Our case illustrates the pivotal role of critical clinical thinking in the diagnosis of rare but treatable hereditary cardiomyopathy. The uncommon cardiac presentation of Fabry disease promotes further research linking different phenotypes of Fabry disease with different pathogenic mutations.

Keywords Fabry disease • Case report • Hypertrophic cardiomyopathy • Ventricular tachycardia • Alpha-galactosidase A • Metabolic disease

Learning points

- Male patients with the classic form of the disease have very low alpha-galactosidase A activity.
- In all male patients, diagnosis must be confirmed by enzyme assay in leucocytes and DNA sequence analysis.
- The activity of alpha-galactosidase A may be normal in female carriers.
- Diagnosis of Fabry disease in females can be only confirmed by molecular genetic testing.

Introduction

Fabry disease is considered to be a recessive X-linked disorder, manifesting predominantly in men.[1] The hallmark of Fabry disease is the age dependent pattern of a clinical presentation. The skin lesions in late childhood are followed by renal failure in early adulthood, then cardiac and cerebrovascular symptoms dominate in the middle age. We present a case of unusual cardiac manifestation of Fabry disease.

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Timeline

Timeline	Location	Investigation	Results of investigation	Intervention
Day 0	General practitioner's surgery	Obtaining of patient history	Unexplainable malaise and sudden episodes of shortness of breath at rest in the previous 6 months	Recording of ECG
Day 0	General practitioner's surgery	Electrocardiogram (ECG)	Suspicion of acute coronary syndrome without ST elevation	Decision to transfer patient to percutaneous coronary intervention (PCI) capable hospital
Day 0	General practitioner's surgery	Repeated ECG for acute onset of dyspnoea	Ventricular tachycardia transforming to ventricular fibrillation present on ECG	Defibrillation with one external 200 J biphasic discharge recovering sinus rhythm
Day 0	Hospital—coronary intensive care unit	Coronary angiogram	Angiography showed unobstructed coronary arteries	None
Day 0	Hospital—echocardiography laboratory	Transthoracic echocardiography	Echocardiography showed severe concentric left ventricular hypertrophy	Decision to perform dried blood spot test for Fabry disease
Day 3	Hospital—cardiogenetic consultation	Enzymatic dried blood spot test	Dried blood spot was positive test for Fabry disease	Decision to request enzyme assay and *GLA* gene analysis to confirm diagnosis of Fabry disease
Day 8	Hospital—standard cardiology ward monitored bed, electrophysiology heart team	Electrophysiology indication seminar	Decision to implantable cardioverter-defibrillator (ICD) in secondary prevention indication	ICD implantation
Day 126	Outpatient cardiogenetic clinic	Enzyme assay analysis	Confirmation of Fabry disease	Referral to the National Centre of Fabry Disease Programme for enzyme replacement therapy
Day 126	Institute of Inherited Metabolic Disorders	*GLA* gene analysis	Detection of pathogenic mutation c.902G>A (p.R301Q)	Mutation had been described previously in HGMD databases in patients with Fabry disease with cardiac involvement
Day 339	National Centre of Fabry Disease Programme for enzyme replacement therapy	Request for reimbursement of enzyme replacement therapy to the healthcare provider	Reimbursement for enzyme replacement therapy approved by healthcare provider	Commencing enzyme replacement therapy

Case presentation

A 36-year-old Caucasian man, life-long non-smoker, with no past medical history and no regular medication self-presented to a general practitioner complaining of sudden episodes of shortness of breath at rest together with unexplainable malaise in the previous 6 months. He reported no history of fever, chills, cough, diarrhoea, or vomiting. He denied any episodes of chest pain under any circumstances. On physical examination, he had a regular pulse (188 b.p.m.), with a blood pressure of 150/70 mmHg. The oxygen saturation was 100%. He had a normal jugular vein pressure and the heart sounds were normal. His chest was clear on auscultation. There was no peripheral oedema present.

A 12-lead electrocardiogram (ECG) showed sinus rhythm at a rate of 75 b.p.m., with a normal QRS axis and normal conduction intervals. There was concave ST segment elevation in leads V1 and V2. ST segment depression was present in leads I, II, aVF, aVL, and V3–V6. The T wave was biphasic in lead III. The precordial leads suggested left ventricular hypertrophy (LVH) according to the Sokolow-Lyon criteria. This ECG prompted a decision to transfer him immediately to a hospital under the suspicion of acute coronary syndrome without ST elevation. Whilst awaiting transport, he experienced acute onset of dyspnoea together with non-specific chest heaviness. A repeat ECG showed ventricular tachycardia transforming to ventricular fibrillation. The patient was successfully defibrillated with one external 200 J biphasic discharge. Coronary angiography was performed upon arrival at the hospital and demonstrated unobstructed coronary arteries. Laboratory tests showed normal renal function and electrolyte levels (sodium, potassium, and chloride). The Troponin T level was 46.0 ng/L (cut-off 14.0 ng/L). Transthoracic echocardiography

revealed concentric LVH without valvular disease or left ventricular outflow tract obstruction and normal left ventricular ejection fraction. Echocardiographic findings were notable for severe diastolic dysfunction. The patient stayed on the coronary care unit for 72 h, and then transferred to a monitored bed on the standard cardiology ward. He had no further episodes of ventricular tachycardia during the hospital stay. He was administered bisoprolol 2.5 mg per day and ramipril 2.5 mg per day. The indication for an implantable cardioverter-defibrillator (ICD) therapy was discussed and unequivocal consent was reached at the electrophysiology indication seminar. On the 8th day, the patient had an ICD fitted and he was discharged home after 24 h.

A cardiac magnetic resonance imaging (MRI) study confirmed the LVH, and did not demonstrate any late gadolinium enhancement. Within the differential diagnoses, we considered Fabry disease as a possible cause of concentric ventricular hypertrophy although the patient had no classical pain symptoms (acroparaesthesia and abdominal pain) or specific signs such as skin changes (angiokeratomas in lower abdomen, groin, gluteal regions, and anhidrosis). The screening dried blood spot test was positive for Fabry disease, confirmed by low plasma activity of alpha-galactosidase A. Genetic testing discovered the pathogenic mutation c.902G>A (p.R301Q); both the sister and daughter of the patient carried the pathogenic mutation. He was diagnosed with a cardiac manifestation of Fabry disease, and was referred to the National Centre of Fabry Disease Programme for enzyme replacement therapy. The enzyme replacement therapy has been started and the patient has been receiving it for almost 4 years (Fabrazyme 1 mg/kg i.v. every 14 days). He has had no ventricular tachycardia recorded or treated with ICD since its implantation.

Discussion

Fabry disease is an inherited rare metabolic disease caused by mutation in the *GLA* gene, encoding lysosomal enzyme alpha-galactosidase A. This enzymatic defect results in excessive accumulation of neutral glycosphingolipids in the cellular lysosomes.

There is a positive correlation between phenotype and degree of X-chromosome inactivation.[2] The disorder is a systemic disease that manifests as cerebrovascular and cardiac disease, chronic renal failure, skin lesion, peripheral neuropathy, and other abnormalities.[3]

The classic phenotype of Fabry disease in males is characterized by absent or severely diminished alpha-galactosidase A activity, which affects several organ systems. Acroparesthesias, diffuse angiokeratomas, abdominal pain crises, and heat intolerance are the leading presentations in late childhood and early adulthood. Dominant presentations in adulthood are those of renal (chronic kidney disease) followed by cardiac involvement (arrhythmias, heart failure with preserved ejection fraction)[4] and neurologic manifestations (stroke).[5]

The presented patient did not have renal involvement, which is the most common feature of Fabry disease in adulthood. The pathogenic mutation c.902G>A (p.R301Q) had been described previously in HGMD databases in patients with Fabry disease with cardiac involvement, without the involvement of other systems.[6]

A 'variant phenotype' of Fabry disease is related to patients with reduced alpha-Galactosidase A activity leading to a later onset of the manifestation of renal or cardiac symptoms. This delivers difficulties and misunderstanding in establishing the incidence and prevalence of Fabry disease in population, since the majority of data is reported in the Fabry male population. The reported unselected population prevalence of Fabry disease defined as number of affected males per 100 000 live births varies from 0.12 to 0.52.[7,8] If affected women would be considered in calculation, the prevalence of unselected population of Fabry disease would reach 1.29 per 100 000 live births.[8] The prevalence of Fabry disease can dramatically rise in the selected populations. In patients with unexplained LVH, the prevalence spans from 0.5%[9] to 3%.[10] Male end stage renal disease patients on haemodialysis are also a well-studied patient subgroup with a prevalence of 0.22%[11] to 1.2%.[12]

The cardiac presentation of Fabry disease is considered common in the literature. But if cardiac presentation would be defined as the first and the only clinical manifestation of Fabry disease, then there have been only a limited number of reported clinical cases or case series. The exceptions are the cohort studies from international registers established upon the arrival of enzyme replacement therapy. The international Fabry outcome survey[13] reported no patient with exclusively cardiac involvement among 714 patients. The leading symptoms were dyspnoea (23%) and chest pain (22%).

The dominant clinical sign of cardiac involvement is LVH. Unexplained LVH serves as an important prompt to consider Fabry disease and if diagnosed to initiate enzyme replacement therapy. Tissue Doppler imaging was found to be able to detect myocardial impairment prior to manifest LVH in Fabry patients with causal mutations without LVH[14] and in a larger cohort of patients with Fabry disease without LVH.[15]

Cardiovascular magnetic resonance (CMR) plays a pivotal role in the non-invasive differential diagnosis of LVH and cardiomyopathy in general.[16] Typical late gadolinium enhancement (LGE) distribution in the inferolateral basal or mid-basal segments,[17] low native T1 value,[18] and prolonged T2, particularly in areas of LGE are the hallmarks of Fabry disease on CMR. The amount of myocardial fibrosis assessed using CMR was found to be an independent predictor of incidence of malignant ventricular arrhythmias (non-sustained and sustained ventricular tachycardia, sudden cardiac death) in Fabry disease patients.[19]

The clinical manifestation with a possible association to ventricular tachycardia is syncope, showing an incidence of only 3%.[13] Unfortunately, this study does not report the number of patients with ICD therapy. In 2007, the Fabry Registry data reported[20] a 9% incidence of arrhythmia in 2187 enrolled patients of which only 74 were reported to have congestive heart failure (3.4%). Again, there are no data on the number of patients with ICD. Therefore, our case report would present a unique patient with cardiac manifestation of Fabry disease and possibly the 5th published case of sustained ventricular tachycardia as the sole manifestation of cardiac involvement of Fabry disease. The first published case was a Japanese woman corresponding to the complexity of Fabry disease.[21]

Conclusion

There are variable aetiologies of LVH in early adulthood. Our case illustrates the pivotal role of critical clinical thinking in the diagnosis of rare but treatable hereditary cardiomyopathy.[22] The uncommon

cardiac presentation of Fabry disease promotes further research linking different phenotypes of Fabry disease with different pathogenic mutations.

Genetic and molecular diagnosis is necessary for the confirmation of Fabry disease. In clinically unaffected individuals, there is an increased risk based on family history. Knowing the disease-causing mutation allows one to determine or exclude carriers. When a carrier status is diagnosed, family planning and prenatal diagnosis are enabled.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: none declared.

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