

Progressive cardiac involvement in a compound heterozygote Fabry patient: a case report

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Background

Fabry disease is an X-linked lysosomal storage disorder due to mutations in the gene encoding for alpha-galactosidase A, with subsequent accumulation of complex sphingolipids in multiple organs, including the heart. Female heterozygotes can develop cardiac involvement although this is usually milder and slower to progress compared with male hemizygotes.

Case summary

A 71-year-old woman with two separate pathological Fabry mutations (N215S, C202R; compound heterozygote) presented with progressive cardiac involvement despite enzyme replacement therapy (ERT) with Replagal, as demonstrated by troponin elevation and cardiovascular magnetic resonance (CMR) findings: moderate segmental left ventricular dysfunction with wall thinning, low myocardial native T1, and extensive late gadolinium enhancement with co-located increased T2.

Discussion

We report for the first time, a detailed cardiac phenotype using CMR in a compound heterozygote Fabry patient with progressive cardiac involvement despite ERT.

Keywords

Case report • Fabry • Cardiovascular magnetic resonance • T1 mapping

Learning points

- Women with Fabry disease may have cardiovascular involvement that tends to present later in life (in the sixth decade) and progress at a slower rate.
- The compound heterozygote genotype for Fabry disease is rare, but can present with a severe clinical phenotype.
- Cardiovascular magnetic resonance imaging is an important diagnostic modality for Fabry disease and can be used serially to demonstrate disease progression.

Introduction

Fabry disease is a rare X-linked lysosomal storage disorder due to mutations in the gene encoding for alpha-galactosidase A, with subsequent accumulation of complex sphingolipids (e.g. globotriaosylceramide, Gb3) in multiple organs.¹ Fabry disease can have a variety of phenotypes including neurological, cardiac, dermatological, and renal manifestations.

Despite being heterozygotes, women can be affected by the disease. However, generally women present later in life and progress slower than males (hemizygotes).² Cardiovascular complications are the leading cause of premature death in Fabry disease, including in females.^{1,2}

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Timeline

| Patient age | Patient events |
|-------------|--|
| 60 years | Diagnosed with Fabry disease <ul style="list-style-type: none"> Enzyme replacement therapy (ERT) commenced for 3 weeks and then ceased due to non-compliance |
| 66 years | Initial cardiac magnetic resonance (CMR) demonstrated: <ul style="list-style-type: none"> Moderate left ventricular hypertrophy Late gadolinium enhancement (LGE) ERT is recommended |
| 67–69 years | Recurrent paroxysmal atrial fibrillation necessitating pulmonary vein isolation on three occasions |
| 71 years | Serial CMR demonstrated: <ul style="list-style-type: none"> New moderate segmental systolic dysfunction Progressive extensive transmural LGE Raised troponin, brain natriuretic peptide, and mild decline in renal function noted on bloods at this time |

Case report

This is the case of a 71-year-old woman who was diagnosed with Fabry disease at age 60. She had normal renal function (eGFR 79 mL/min/1.73 m²), which deteriorated at a rate of -0.7 mL/min/1.73 m² per year during the subsequent 11 years. Genetic studies revealed the patient was a compound heterozygote with two separate mutations (N215S and C202R), one on each X chromosome. Her leucocyte a-gal activity was 0.111 nmol/min/mg protein (normal 0.7–3.3).

Diagnostic assessment

Initial cardiovascular magnetic resonance (CMR) at age 66, on a 3 T GE Healthcare MRI System, showed normal left ventricular (LV) cavity size (end diastolic volume 125 mL) and systolic function [LV ejection fraction (LVEF) 71%] with no regional wall motion abnormalities. It also showed moderate concentric LV hypertrophy [LVH; maximal wall thickness of 14 mm, LV mass (LVM) 203 g] and prominent papillary muscles. Dense mid-wall late gadolinium enhancement (LGE) was also evident in the classic basal inferolateral wall extending into the basal inferior wall, mid inferolateral wall, and apicolateral wall.

Interventions and outcomes

Enzyme replacement therapy (ERT) with Replagal (agalsidase alpha) was initially commenced, at age 60 but was discontinued after 3 weeks due to patient preference. Enzyme replacement therapy (Replagal) was recommenced at age 66 due to the CMR findings described above indicating cardiac involvement. Between the ages of 67 and 69 the patient had recurrent paroxysmal atrial fibrillation. Pulmonary

vein isolation was performed on three occasions and was complicated on the last attempt by pericardial effusion requiring a pericardial window.

Serial CMR (1.5 T Siemens Aera) at age 71 demonstrated (Figure 1):

a mildly dilated LV (LVEDV 160 mL) with moderate eccentric LVH—increased LMV (256 g) and maximal wall thickness of 17 mm in basal septum, but thinning of the basal-to-mid inferolateral and anterolateral walls (4 mm). New moderate segmental LV systolic dysfunction (LVEF 43%) with akinesis of the thinned segments. There was progressive extensive transmural LGE in the basal-to-mid inferolateral and anterolateral walls, extending into the apicoseptal, and apicolateral walls, plus mid-wall LGE in the mid septum. T1 mapping revealed low myocardial native T1 (using MODified Look-Locker Inversion recovery sequence) in the remote basal septum (889 ms; normal 1017 ± 37 ms). T2 mapping revealed increased T2 values in the LGE areas (59–63 ms; normal range 45 ± 6 ms) but normal T2 in the remote basal septum (48 ms).

Blood tests were significant for raised high sensitivity troponin I (126 ng/L; normal <14 ng/L), and elevated NT-pro BNP (193 pmol/L; normal <13 pmol/L), in the context of normal renal function (eGFR 72 mL/min/1.73 m²).

ECG showed sinus rhythm, LVH by Sokolov voltage criteria, incomplete left bundle branch block, and inferolateral T-wave inversion.

Discussion

This case reports for the first time, a detailed cardiac phenotype using CMR in a compound heterozygote Fabry patient with progressive cardiac involvement despite ERT.

Cardiovascular magnetic resonance was able to accurately detail the cardiac progression, namely—mild dilatation in LV cavity size (125–160 mL), increase in LVM (203–256 g), segmental thinning and akinesis of the LV with reduction in LV systolic function (LVEF 71–43%), and progression of LGE. The application of newer advanced tissue characterization techniques in the most recent scan showed—low T1 values in the septum representing sphingolipid storage, and high T2 values in the LGE areas coupled with elevated troponin levels suggesting myocardial inflammation.³

Usually, hemizygotic Fabry males demonstrate the classic disease features. However, it has been accepted for some time now that heterozygote females present with significant disease manifestations.^{2–4} The mechanism behind the variation in the severity of organ involvement in female carriers is thought to be as a result of X-linked inactivation.³ There is, to the authors' knowledge, only one case of a compound heterozygote and four cases of homozygotes (the same mutation on both X chromosomes) described in the literature regarding females with Fabry disease.^{5–7} Of these cases, two homozygotes presented without a clinical phenotype and the one female compound heterozygote had a mild non-cardiac variant.⁷

Interestingly, the index patient was diagnosed as a compound heterozygote after her 48-year-old son with classical Fabry disease carried a separate mutation (C202R) to that of the index patient and her sister (N215S) (Figure 2). The son has 'classic' Fabry disease with renal involvement (including a history of renal transplantation) plus cardiac

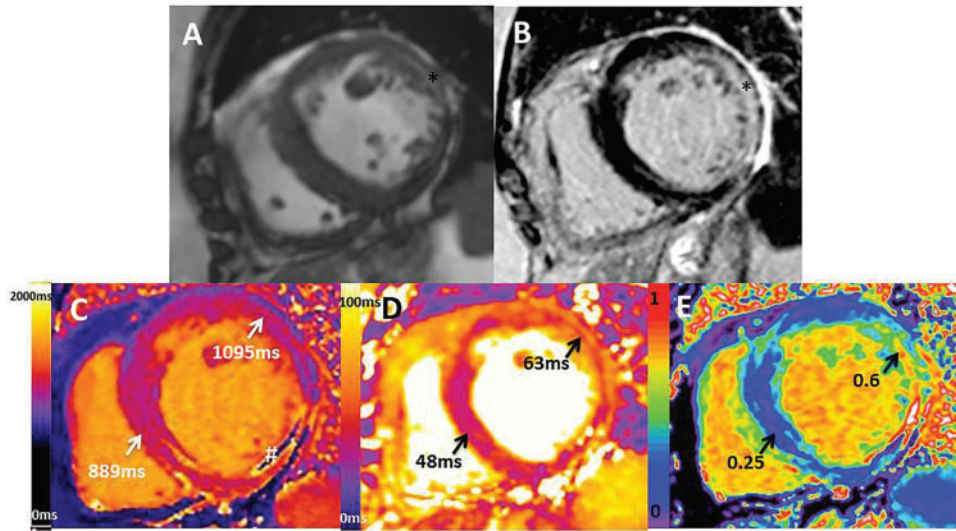


Figure 1 (A) Short-axis cine showing left ventricular hypertrophy but also thinning of the basal lateral wall (asterisk), (B) PSIR late gadolinium enhancement showing extensive late gadolinium enhancement (asterisk), (C) MOLLI T1 map showing low T1 in the septum, high T1 in the late gadolinium enhancement areas with a central core of very low T1 (#) suggesting possible fatty metaplasia, (D) T2 map showing normal T2 in the septum but high T2 in the late gadolinium enhancement area, (E) synthetic extracellular volume map showing normal extra-cellular volume in the septum and high ECV in the late gadolinium enhancement area.

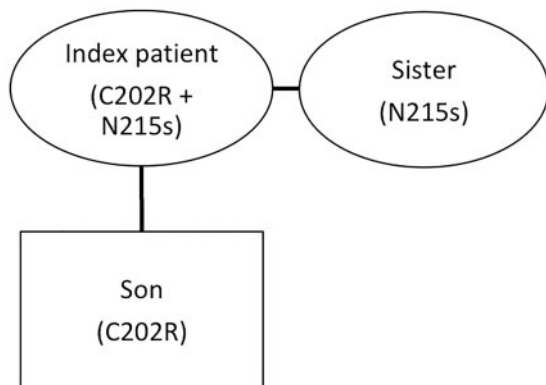


Figure 2 A family tree (abridged in order to preserve patient anonymity) demonstrating the key family members with their associated genetic mutations.

involvement. His leucocyte a-gal activity was 0.100 nmol/min/mg protein. His CMR revealed: normal LV cavity size with moderate concentric LVH of 16 mm and hyperdynamic LV systolic function (LVEF 84%). Low native T1 in septum, and pseudonormal native T1 in the basal inferolateral wall suggestive of inflammation/fibrosis (note: no gadolinium was administered to assess for LGE). The older sister passed away from a stroke.

Fabry disease can be subdivided into classical and non-classical presentations, with classical patients defined in males by presentation with neuropathic pain, angiokeratoma and cornea verticillata, and long-term complications with renal, cardiac, and central nervous system disease.⁸ The ‘cardiac variant’ of Fabry disease represents a non-classical subgroup where disease manifestations are usually limited solely to the heart.⁹ N215S is an example of this with the predominant reported cardiovascular manifestation being LVH.^{10,11} The mutation C202R has not been previously described in the literature but is highly likely to be a classical mutation as the index patient’s son has classic disease, and two other mutations at this site (C202Y and C202W) are reported to cause classic Fabry disease.^{12,13}

In our patient, the presentation is most like older males who carry the N215S mutation. This is most likely consistent with her genotype, as the C202R allele contributes comparatively less to overall enzyme activity, leaving her with enzyme mostly generated from the N215S allele. However, X-chromosome inactivation is likely to have left a proportion of her cells expressing alpha galactosidase from the C202R allele only, thus potentially explaining her more severe cardiac phenotype when compared with those with the N215S mutation alone.

Conclusion

We report for the first time, a detailed cardiac phenotype using CMR in a compound heterozygote Fabry patient with progressive cardiac involvement despite ERT.

Supplementary material

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

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

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

Conflict of interest: R.K. has received honorary from Sanofi-Genzyme. M.T. reports being on disease specific advisory boards of Sanofi-Genzyme and Shire Pharmaceuticals, without personal financial remuneration.

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