

## ELECTRONIC LETTER

## Clinical presentation in female patients with Fabry disease

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We write in support of the article by MacDermot *et al.*,<sup>1</sup> which described the clinical manifestations and impact of disease in a cohort of 60 obligate carrier female patients with Fabry disease. Fabry disease is a lysosomal storage disorder resulting from a deficiency of the enzyme  $\alpha$ -galactosidase A ( $\alpha$ -Gal A). Deficient concentrations of the enzyme result in an accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3), in the viscera and vascular endothelium throughout the body, causing multiple manifestations. Fabry disease is considered to be an X linked recessive disorder, in which symptoms in carriers are expected to be rare and, if present, very mild. However, the article by MacDermot *et al.* is one of several publications reporting that many heterozygous female patients display classical symptoms of Fabry disease.<sup>1-5</sup> Overall, symptomatology is usually more severe in hemizygous male patients with Fabry disease, but disease expression can vary widely in both sexes. Some female carriers remain asymptomatic and have normal concentrations of  $\alpha$ -Gal A, whereas some experience more severe manifestations of disease. This variability can be both between and within families and is thought to be partly the result of Lyonisation, a process that results in one X chromosome in some or all cells of the female embryo being randomly inactivated. Thus, female carriers are essentially a mosaic of normal and mutant cells in varying proportions.<sup>6</sup>

In view of this, a review of the medical records of 11 female patients with Fabry disease (derived from eight families) being monitored at the Edouard Herriot Hospital, Lyon was undertaken to evaluate the clinical range of their disease.

## METHODS

Eleven patients were selected from all the female patients with Fabry disease currently being monitored in Lyon, on the basis that complete clinical and paraclinical data (including renal function (inulin clearance), cardiac, and ophthalmic investigations) were available for all 11 patients.

## RESULTS

Two sisters and their mother (patients 7, 8, and 9 in table 1) were diagnosed during a family study, which was undertaken because the sisters had a brother affected by Fabry disease. The two sisters were not diagnosed until the ages of 18 and 25 years, and their mother was not diagnosed until 52 years of age. Three patients (1, 2, and 10) had no family history of Fabry disease, two of whom were diagnosed by kidney biopsy at 20 and 23 years of age after proteinuria was detected. Despite having very severe symptoms, two female patients (5 and 6) were considered to have psychosomatic disease and were only later diagnosed with Fabry disease during a family study. Two patients (3 and 4) were obligate carriers (affected father). The grandmother (patient 11) of one of these obligate carriers (patient 4) was also included in the analysis. Therefore, the age at which a formal diagnosis of Fabry disease was made varied widely in the group. Leucocytic  $\alpha$ -Gal A activity ranged from 4–50% of normal for all patients assessed. Results of mutation analysis are shown in table 1.

## Key points

- Although Fabry disease is an X linked recessive disorder, many heterozygous female patients display classical disease symptoms.
- Overall, symptomatology is more severe in hemizygous males, but disease expression can vary widely in both sexes.
- In female patients, phenotypic variability is thought to be partly the result of Lyonisation.
- In the current series of 11 female patients with confirmed Fabry disease, diagnosis was often delayed.
- Some female patients developed severe manifestations of disease, including cardiac and renal complications.
- Large prospective studies of female patients with Fabry disease ascertained through pedigree and DNA analysis are warranted so that the natural history of the disease in this population of patients can be explored.

**Table 1** Results of mutation analysis undertaken in 11 female heterozygotes with Fabry disease

Patient	Genotype
1	R342X
2	Not found
3	D313Y + G411D
4	S78X
5	N224D
6	R227X
7	R227X
8	R227X
9	R227X
10	1033 del Tec
11	S78X

The most common symptom of the disease found among the case series was acroparaesthesia, a severely debilitating symptom in Fabry disease, commonly impacting on patients' daily activities and, consequently, quality of life. Six patients had experienced this symptom between 4 and 11 years of age, whereas in two acroparaesthesia was first experienced during adolescence. The other three patients did not report any neuropathic pain. Ocular abnormalities were recorded in seven female patients, typically manifesting as corneal dystrophy or tortuosity of conjunctival and retinal vessels or both. Six female patients had angiokeratomas, small, raised, dark red skin spots found almost universally among hemizygous male patients, but these were not extensive.

**Abbreviations:**  $\alpha$ -Gal A,  $\alpha$ -galactosidase A; GL-3, globotriaosylceramide

Vertigo, a cochleovestibular symptom of Fabry disease, was recorded in six patients and was accompanied by acute hearing loss in two female patients and chronic dizziness in another. Other signs and symptoms experienced by the case series included abdominal pain and diarrhoea (n=3), chronic aesthenia (n=6), depression (n=5), febrile crises and heat or exercise intolerance (n=6), and phlebitis (n=1), all of which are often experienced by hemizygous male patients.

Cardiovascular abnormalities were recorded in five female patients. These included valvulopathy (n=5) and severe hypertrophic cardiomyopathy (n=4), occurring in the fourth, fifth, or sixth decades. Renal dysfunction, sometimes severe, was detected in eight female patients in this group. Two patients experienced terminal renal insufficiency and, as a result, one received kidney transplantation at 29 years and the other needed haemodialysis at 26 years and a renal transplantation at 41 years. Proteinuria was first detected in these two women at 20 and 23 years of age. In the other six patients, renal insufficiency was moderate to severe, as indicated by proteinuria and decreased inulin clearance. One woman had a capsulothalamic stroke at 39 years of age. Pulmonary complications were also recorded in two patients, and included chronic obstructive bronchopneumopathy in one and pulmonary embolism in the other.

## DISCUSSION

A review of this series of 11 female patients with Fabry disease corroborates other publications<sup>1-3</sup> that have reported manifestations of Fabry disease in a higher than expected proportion of female carriers. However, it is acknowledged that case reports and case series are open to ascertainment bias. Carriers are not usually clinically evaluated unless they present with serious complications of Fabry disease. Therefore, the patients reviewed here cannot be considered representative of the entire female Fabry population. Nevertheless, the current patient series suggests that many female patients are not protected from the severe manifestations of Fabry disease and that residual  $\alpha$ -Gal A activity (4-50% of normal in the patients reviewed) does not prevent accumulation of GL-3. Moreover, female carriers do not always have mild manifestations of disease, as is widely thought, and there is broad clinical heterogeneity in this population of patients.

To enable us to learn more about why the female phenotype varies so widely, studies involving heterozygous female patients presenting with the classical symptoms of Fabry disease are warranted. Also, to determine the true frequency of

symptoms in female carriers, many female patients ascertained through pedigree and DNA analysis would need to be examined. Only then can the current published estimates<sup>7</sup> of the frequency of various manifestations be verified or challenged.

Greater awareness that female carriers often experience the manifestations of Fabry disease has the potential to reduce misdiagnosis or delayed diagnosis and should lead to increased access to genetic counselling for female carriers. Increasing clinical evidence that Fabry disease often affects female carriers also raises two important questions: (1) whether all female relatives of an affected male patient should be scrutinised; and (2) when to initiate enzyme replacement therapy in female patients. Knowledge of carrier status can enable the patient and clinician to be watchful for disease symptoms, even if they seem healthy when carrier status is confirmed.

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