Letter to the Editor

Early cerebral manifestations in a young female with Fabry disease with skewed X-inactivation

To the Editor:

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of the enzyme alpha-galactosidase A (αGal A). Accumulation of globotriaosylceramide (Gb3) in different cell types eventually leads to renal insufficiency, cardiomyopathy and central nervous system (CNS) involvement (1). CNS involvement is mainly characterized by white matter lesions (WMLs) and strokes (2, 3). Several cohort studies revealed that females with FD often do develop clinical manifestations, although the disease generally follows a milder course (4–7). WMLs and strokes have been reported in young males with FD (8–10), but not in young females.

In this letter, we report the enzymatic, biochemical and molecular characteristics of a young female patient with FD who had signs of CNS involvement from the very early age of 13 years. The proband was the patient’s grandmother, diagnosed with FD after the evaluation of unexplained renal insufficiency. Patient’s aunt, mother and sister were subsequently also diagnosed with FD. The patient had several early signs and symptoms of FD: minor acroparesthesia during exercise, a few angiokeratoma on the trunk, cornea verticillata and bilateral high-frequency hearing loss. Renal and cardiac assessments were normal. Brain magnetic resonance imaging (MRI) at the age of 15 years showed a 4-mm periventricular WML on T2 and fluid-attenuated inversion recovery (FLAIR) images near the right posterior horn (Fig. 1a). In retrospect, this lesion was already present on the MRI performed at the age of 13 years. Intravenous enzyme replacement and antiplatelet therapy was started. One year later, a hemorrhagic infarction was present in the left globus pallidus (Fig. 1b) without any symptoms. Risk factors for cardiovascular disease only revealed a history of cigarette smoking. Fibrinogen, clotting factor VIII, antithrombin deficiency, lupus anticoagulant, factor II mutation, factor V Leiden mutation, protein C and S deficiency, elevated lipoprotein(a), anticardiolipin and homocysteine were all normal.

The patient’s mother suffered from amaurosis fugax at the age of 22 years and had a lacunar infarction on MRI FLAIR imaging of the right cerebellar hemisphere at the age of 45 years. The patient’s aunt had periventricular WMLs on brain MRI at the age of 48 years and echocardiography showed mild left ventricular hypertrophy. The patient’s 7 years older sister had no clinical signs or symptoms. αGal A activity, measured in leukocytes (11), was strongly reduced (1.8 ng/mmol/h) in the young female. Plasma globotriaosylphosphoglycerine (lysoGb3), the decylated form of Gb3, was markedly elevated (99 nmol/ml; Table 1) (12).

A mutation in the GLA gene, associated with a classic FD phenotype (13, 14) (c.1025G>A; p.R342Q) was found in this family. Sequencing all exons and flanking intron/exon boundaries revealed no other mutations in the girl. X-chromosome inactivation was studied in leukocytes, using polymorphic markers at the androgen receptor locus and two methylation sensitive restriction enzymes (HpaII and CfoI) (15). We found 100% skewed X-inactivation of the paternal wild-type allele in the patient (III.1) whereas in her
Intercellular transfer of explanation for phenotypic variation in females. Lack of metabolic cross-correction could be another could not be confirmed in another study (18). Lack of metabolic cross-correction have been proposed to explain the variable disease penetrance in heterozygotes with X-linked diseases (16). It has been suggested that disease severity in female Fabry patients correlates with the X-inactivation pattern (17–21). Dobrovolny et al. showed that heterozygotes who preferentially expressed the mutated allele tended to have a more rapid clinical evolution of the disease (17). However, this could not be confirmed in another study (18). Lack of metabolic cross-correction could be another explanation for phenotypic variation in females. Intercellular transfer of αGal A and metabolic cross-correction have been reported in vitro (22), but this mechanism might be insufficient to prevent the Gb3 storage in some cells and organs of Fabry heterozygotes. Alternatively, αGal A deficient cells may produce a metabolite that affects αGal A competent cells. Recently, it was shown that lysoGb3, produced in αGal A deficient cells, inhibits residual αGal A activity. In addition, lysoGb3 promotes smooth muscle cell proliferation and alters podocyte behavior in vitro, both cell types involved in FD (12, 23).

In conclusion, we report a hemorrhagic infarction in a young female Fabry patient. The 100% skewed X-inactivation in this girl may explain this remarkable early and severe phenotype. She had an exceptionally high plasma concentration of lysoGb3, whereas in most heterozygotes lysoGb3 is low at birth and gradually increases with age (24). High plasma lysoGb3 levels in male Fabry patients correlates with a high risk for development of WML (24).

Our findings support the inclusion of brain imaging by MRI for assessment and follow-up of Fabry patients from an early age and independent of gender.

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