Letter

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Fabry disease – a genetically conditioned extremely rare disease with a very unusual course

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SUMMARY Fabry disease (FD) is a rare lysosomal storage disease. FD is caused by the presence of a deleterious mutation in the GLA gene encoding the enzyme alpha galactosidase A (αGAL A) on the X chromosome. The accumulation of Gb3 and lyso-GL-3 in nerve fiber cells, endothelium, vascular muscle cells, mesangial cells, podocytes, renal tubular epithelial cells and cardiomyocytes is the most important pathogenetic factor. The rate of disease progression depends on residual conserved enzymatic activity. In this article we present an example of a 25-year-old patient with FD with an initial asymptomatic course. The first manifestation of FD developed in the third decade of life. These include high blood pressure, urinary changes and grade V renal failure, requiring renal replacement therapy. The diagnosis was made very late, when renal failure and cerebro-cardiac complications occurred, including stroke and dangerous cardiac tamponade.

Keywords fabry disease, renal failure, cardiovascular complications

Fabry disease (FD) was first described in 1898 by two independent physicians: surgeon William Anderson and dermatologist Johannes Fabry. These authors demonstrated the association of skin lesions ("angiokeratoma corporis diffusum") with the risk of developing renal failure (*1,2*).

To date, more than 50 genetic lysosomal storage disorders (LSDs) have been identified, of which FD [OMIM number: 301500] is probably the most common. FD is caused by the presence of a deleterious mutation in the GLA gene [Xq22.1] encoding the enzyme alphagalactosidase A (αGAL A) on the X chromosome (*3,4*). FD is described as an ultra-rare disease, with a frequency of 1/40,000 in men and 1/117,000 in the female population (*5-7*). The rate of development of the disorder depends on the preserved residual enzymatic activity, *i.e*. the lower the enzyme activity, the earlier the manifestation of the disease and the faster its progression.

A 25-year-old Caucasian male, previously untreated, was admitted to the nephrology department for high blood pressure (BP > 200/120 mm Hg) and macroscopic hematuria. The patient's general condition was moderate, with no signs of pulmonary stasis or peripheral edema. Physical examination revealed mild redness of the throat, nasal mucus leakage, as well as caries, excessive body fat (BMI = 32 kg/m^2), and lower extremity varicose veins. No skin lesions were found. Laboratory tests performed showed mild anemia, prolonged activated partial thromboplastin time (APTT), very significantly elevated creatinine levels, as well as hematuria and proteinuria [5.4 g/L] (Table 1). Aminotransferase, gamma glutamyl transpeptidase (GGTP), alkaline phosphatase and bilirubin activities were normal. Ultrasound imaging of the urinary tract showed no significant abnormalities. The radiologist performing the examination also noted that the spleen was slightly enlarged (to 12.6 cm). Urine culture showed no bacterial growth. A cystoscopy was performed in which the source of bleeding was not visible and the bladder mucosa was smooth. Following treatment (etamsylate, tranexamic acid), hematuria resolved. During hospitalization, the patient required intensive hypotensive treatment due to repeated high blood pressure values (> 180/100 mmHg). In the following days, progressive weakness was observed, nausea appeared, and laboratory tests showed a further increase in creatinine levels and increased proteinuria to 24 g/L, increased metabolic acidosis and hyperkalemia. The patient was treated with renal replacement hemodialysis. There was no improvement in renal function during hospitalization, but there was a significant reduction in proteinuria and normalization of APTT.

Six months later the patient was hospitalized twice for dyspnea. The dyspnea was already present at rest, but clearly worsened after exertion. The electrocardiogram (ECG) was normal. Echocardiography shows that left

Table 1. Basic results of laboratory tests performed on the patient on admission to the nephrology department

White blood cells	Observed value	Normal value
Red blood cells	8.28 [10*3/uL]	4–10 [10*3/uL]
Hemoglobin	3.85 [10*6/uL]	4.2–5.4 [10*6/uL]
Platelets	11.5 g/L	14–18 g/L
Prothrombin time	147 [10*3/uL]	150–450 [10*3/uL]
Partial thromboplastin time	12.8 sec	11–16b sec
Creatinine	45.5 sec	28–40 sec
Natrium	868 µmol/L	< 130 µmol/L
Kalium	142 mmol/L	135–145 mmol/L
Phosphate	4.86 mmol/L	3.5–5.1 mmol/L
Calcium	1.7 mmol/L	< 1.6 mmol/L
Bicarbonate	2.35 mmol/L	2.25–2.55 mmol/L
Protein	19.2 mmol/L	22–26 mmol/L
Uric acid	55 g/dL	> 60 g/dL
C-reactive protein	669 umol/L	< 420 µmol/L
Antinuclear antibodies	0.79 mg/L	0-5 mg/L
Antineutrophil cytoplasmic antibodies	Negative	Negative
Urine - general examination	Negative reaction: acidic specific gravity: 1015 glucose: not detected protein: 5.4 g/L urobilinogen: normal bilirubin: negative ketone bodies: negative sediment: fresh and leached erythrocytes, very numerous ; leukocytes 2-5	Negative reaction: acidic specific gravity: > 1023 glucose: absent protein: absent urobilinogen: normal bilirubin: negative ketone bodies: negative precipitate: leukocytes < 5 erythrocytes 1-2

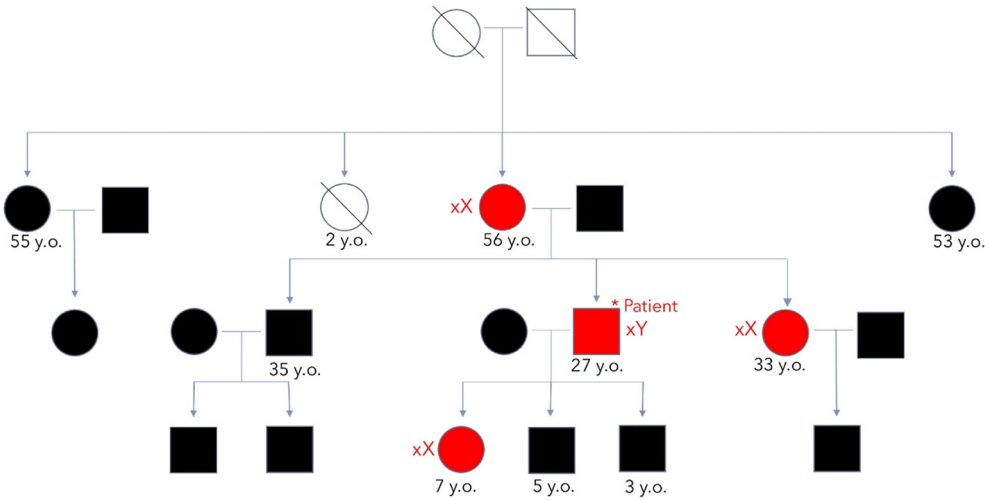

Figure 1. Inheritance of the c.109G> C mutation occurring in Fabry disease on the example of the patient's family. Red color - the presence of a mutation. Black color - no mutation. White - unaudited family members (deceased).

ventricular systolic fraction (LVEF) is normal and left ventricular diastolic fraction (LVDF) is abnormal. Cardiac echocardiography shows myocardial dilatation and thickening with a small amount of fluid in the pericardial sac (up to 3 mm).

A few months later, the patient was diagnosed with a dangerous cardiac tamponade manifested by unconsciousness and weakness in the course of hypotension. The pericardium was decanted, yielding 710 mL of bloody fluid. Subsequent histological examination of the pericardial fluid showed signs of acute chronic pericarditis secondary to uremia. A cardiac MRI was performed, which showed no pathology other than myocardial hypertrophy.

After several weeks, the patient was urgently admitted to the neurology department due to speech disorders and right hemiparesis. Central nervous system bleeding was ruled out, but cerebrovascular abnormalities were noted.

Taking into account the general clinical picture and the result of the consultation, FD was suspected. Blood was drawn from the patient (dry blood spot) to determine alpha-galactosidase activity. The test showed: alpha-galactosidase activity < 0.1 µmol/L/h; normal > 2.8 µmol/L/h, lyso-Gl-3 globotriaosylphingosine

concentration = 57.1 ng/mL; normal < 3.5 ng/mL. Genetic testing revealed the presence of the c.109G> C mutation (p.Ala37Pro). This finally confirmed the diagnosis of FD. In this situation, the patient started treatment with agalsidase alfa. Genetic testing in the patient's family confirmed the presence of the mutation in the patient's mother, sister, and daughter. The inheritance of the c.109G> C mutation found in FD in the patient's family is shown in Figure 1.

The first symptoms of the classic form of FD appear already in childhood. The most common symptoms observed at this time are: peripheral limb pain [acroparesthesia], angiokeratoma type skin lesions, hearing disorders and eye diseases such as cataract and keratopathy and others. In our patient, such symptoms were not present in childhood. In our patient, the first manifestation of the disease was renal failure with hypertension, proteinuria and hematuria. The cerebro-cardiovascular complications that we observed in the patient included stroke, the presence of left ventricular diastolic dysfunction and cardiac tamponade. Only one case of cardiac tamponade in a patient with FD was described (*8*). In conclusions, the patient presented with a very atypical course of FD - initial asymptomatic course. The diagnosis was made very late, when organ complications occurred.

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