



CASUISTIC PAPER

Fabry disease related nephropathy – case family report and literature review

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ABSTRACT

Introduction and aim. Fabry disease (FD) is a ultrarare storage disorder which causes irreversible damage to the brain, heart, and kidneys in young patients. The aim of our study was to draw clinician's attention to the need of considering FD in the differential diagnosis of kidney disorders.

Description of the case. We present the case of a 45-year-old man who has been misdiagnosed for several years with arterial hypertension with organ complications. He was referred to the nephrological ward due to chronic advanced kidney disease of unclear etiology. After 2 months of thorough differential diagnostics, based on the clinical course (past stroke, membranoproliferative glomerulonephritis (MPGN), left ventricular hypertrophy, paroxysmal limb pain) and conducted genetic examination, FD was confirmed. Then, screening tests were performed among the patient's family members, confirming the presence of the same mutation as in our patient in 4 women of which in 3 were diagnosed cardio-renal syndrome. The authors of other studies report glycolipid deposits in the kidney cells on a needle biopsy, usefulness assess podocyturia, globotriaosylceramide protein in the urine and renal parapelvic cysts in an ultrasound examination in diagnostic FD nephropathy.

Conclusions. This is the first case report to describe membranoproliferative glomerulonephritis in a patient suffering from FD. In patients with FD and the same genotype, kidney damage has a different phenotype.

Keywords. Fabry disease, kidney injury, membranoproliferative glomerulonephritis, rare disease

Introduction

Fabry disease (FD), also known as Anderson-Fabry disease, was first described in 1898 independently by the German dermatologist Johannes Fabry and the English dermatologist William Anderson due to the characteristic changes in patients with FD (angiokeratoma). FD is a rare, genetically determined metabolic disorder that dramatically reduces a patient's life expectancy. It

is inherited with the X chromosome and results from a mutation in the GAL gene in the Xq22 locus, which encodes the α -galactosidase (a-Gal) enzyme. Mainly men suffer from the disease, although it is believed that the clinical manifestation of the disease may occur even in 30% of heterozygous women.^{1,2} Whereas the manifestation of FD in heterozygous women may be as severe as in men, although some women are asymptomatic.³

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The disease phenotypes in women differ due to differences in residual enzyme activity and X-chromosome inactivation patterns.^{1,4,6} In the course of the disease, the activity of the α -Gal is reduced or absent. Testing the activity of the α -Gal in the blood of patients may be helpful in detecting FD. In the heterozygous women, due to the random inactivation of the X chromosome, the result of this test is often inconclusive in the female population. Therefore, molecular testing in women with suspected or positive family history of FD is obligatory.¹

The lack or reduced activity of α -Gal causes the accumulation of large amounts of sphingolipids in the lysosomes of various types of cells of the heart, kidneys, skin, eyes, central nervous system and digestive system, which in turn triggers a cascade of cellular damage and may lead to various clinical symptoms.^{1-5,7,8} Fabry deposits in cells are histopathologically defined as membrane-like lamellar deposits called myeloid bodies or zebras. In studies of kidney biopsies under electron microscopy, electronically dense osmophilic inclusions referred to as lamellated bodies (myelin-like bodies, myeloid bodies, zebra bodies) are also observed in the lysosomes of podocytes, epithelial cells of the distal tubules and in arterioles FD nephropathies.⁹ The most characteristic symptoms of FD include episodes of very severe pain in the distal parts of the limbs, hyperhidrosis, heat intolerance, clouding of the lens and cornea, left ventricular hypertrophy, damage to the kidneys with proteinuria, skin lesions (angiokeratoma).^{1,5} Moreover, patients suffer from gastrointestinal disorders and have a significantly increased risk of ischemic stroke or small fiber peripheral neuropath.^{3,7,8} Kidney injury and cardiovascular complications are the main causes of death in FD patients. The clinical picture of the disease changes with the patient's age.^{6,7,10} Almost all complications resulting from the occurrence of FD are non-specific, which makes them clinically indistinguishable from other similar abnormalities often observed in the course of civilization diseases. In undiagnosed and untreated patients with FD, organ damage progresses with the patient's age, gradually deteriorating the patient's quality of life, leading to organ failure and premature death.^{6,10}

Both symptomatic treatments are used in the treatment of FD.^{1,11} Conventional management depends on the clinical manifestation of the disease and consists in administering painkillers, antiarrhythmic drugs as well as cardio- and nephroprotective drugs, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers.¹ Patients with end-stage renal disease may undergo renal replacement therapy.⁶

Currently, a specific therapy for Fabry disease is the replacement of the missing enzyme with recombinant human α -Gal (enzyme replacement therapy; ERT).^{1,7,6} It has been confirmed that the early initiation of treatment is of great importance for the improvement of the qual-

ity of life and the patient's prognosis (alleviation of neuropathic pain, reduction of gastrointestinal symptoms, reduction of myocardial hypertrophy, stabilization of renal function).³

Before starting ERT treatment, a comprehensive evaluation of the organ involvement in FD is necessary.

Prenatal diagnosis involving the determination of enzymatic activity or DNA testing in chorionic villus or cultured amniotic cells can be considered only in male foetuses for ethical reasons.¹

Although the direct cause of FD has been known for many years, the pathomechanisms leading to multi-organ disorders have not yet been fully elucidated.

The gradual deposition of glycosphingolipids in kidney patients leads to a progressive deterioration of renal function with proteinuria, decrease of glomerular filtration rate (GFR) and hypertension. Fabry nephropathy (FN) probably begins with elevated albuminuria or proteinuria. These abnormalities in the results of urine tests in the classic form of the disease manifest themselves from childhood. A progressive decline in the GFR may begin at an early age and progress to end-stage renal failure, which is one of the main causes of premature mortality in patients with FD.^{6,7,13} Considering the high survival rate of patients after transplantation, kidney transplantation is the treatment of choice in patients with end-stage renal disease in the course of FD. Unfortunately, despite numerous studies, little is known so far about the long-term results, overall patient survival or the possible role of ERT after transplantation.⁶

Aim

The diagnosis of FD is a problem for clinicians because of its little characteristic symptomatology. It happens, that patients around the of 40 start dialysis for secondary of hypertension renal failure, but the true diagnosis is FD.

The aim in the first part of our study, was described a case of a patient with FD, with particular emphasis on kidney injury in the course of this disease. Despite having a kidney biopsy performed on the patient, nephrologists in our team wondered, what was behind the diagnosed glomerulopathy. On the other hand, our patient concealed some of the symptoms due to prolonged hospitalization. The case report of a patient with FD presented in the manuscript, in whom arterial hypertension with organ complications was indiscriminately diagnosed for several years, confirms that it is necessary to repeat the existence of this disease according to the old Latin rule: *repetitio mater studiorum est*.

In the second part of the study, family members of the patient were analysed for the presence of FD and kidney injury. In the last part of our study, we correlated our clinical data with the available data from the literature on the symptomatology and pathomechanisms of kidney damage in the course of FD.

Material and methods

The patient's medical history was analyzed retrospectively with FD that was genetically confirmed. The genetic test was performed using the dry blood drop test.

Retrospective data on FD gene penetration in the patient's family were collected. Then, routine medical, physical, laboratory and imaging examinations necessary to assess kidney function in the population of 4 patients from the patient's family with diagnosed FD were prospectively performed.

In addition, the medical database (Medline, PubMed) was reviewed using keywords (Fabry disease, rare disease, enzyme replacement therapy, α -galactosidase A, lysosomal disease, storage disease) to obtain information on the symptomatology and pathomechanisms of kidney damage in the course of the FD. A Total of 48 English-language papers published between 2000 and 2021 were analysed. All the 7 selected publications are original research papers.

Description of the case

A 45-year-old patient with chronic kidney disease, hypertension, epilepsy, after an ischemic stroke of the right hemisphere at the age of 44, was admitted to the department with a nephrological profile due to chronic kidney disease in stage G4 (according to KDIGO 2012) with unclear etiology diagnosed in the nephrology clinic.¹⁴ On admission, the patient reported pain in the upper limbs of paresthesia nature, periodic chest pain, anhidrosis, hearing loss and periodic diarrhoea. During hospitalization, systemic diseases of the connective tissue, chronic infectious diseases, neoplastic diseases (also in the field of hematology) and thrombotic microangiopathy were excluded. The patient had bilateral permanent sensorineural hearing loss, and the histopathological examination of the kidney biopsy showed the features of advanced chronic membranous-proliferative nephropathy. Figures 1 and 2 show the results of a light microscopic examination of a patient's kidney biopsy. Due to the lack of improvement after the applied conservative treatment as well as rapidly increasing parameters of kidney failure and uremic symptoms, the patient was qualified for renal replacement therapy using intermittent hemodialysis. For this purpose, a vascular catheter was implanted into the right internal jugular vein and the first hemodialysis procedure was performed. The psychiatrist diagnosed the patient with depression.

In addition, FD tests were performed using the dry blood drop test. The results of tests with a dry blood drop of the patient showed: no activity of the α -Gal, high concentration of Lyso-GL-3 (112.3 ng/ml; normal <3.5 ng/ml), the presence of a nonsense genetic mutation -c.679C > T (p. (Arg227Ter)).

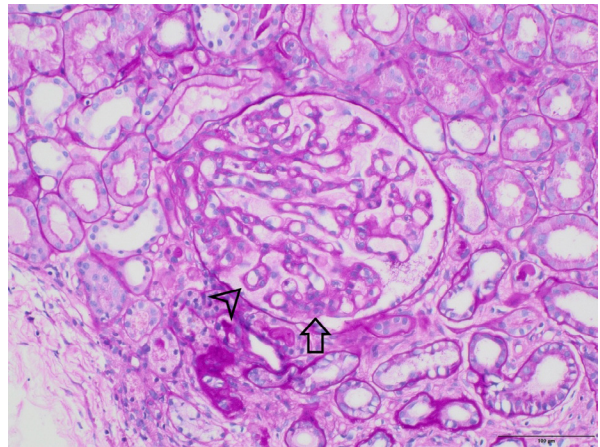


Fig. 1. Glomerulus with focus of mesangial hypercellularity (arrow) and thickening of glomerular basement membrane (arrowhead) (PAS stain, 200X)

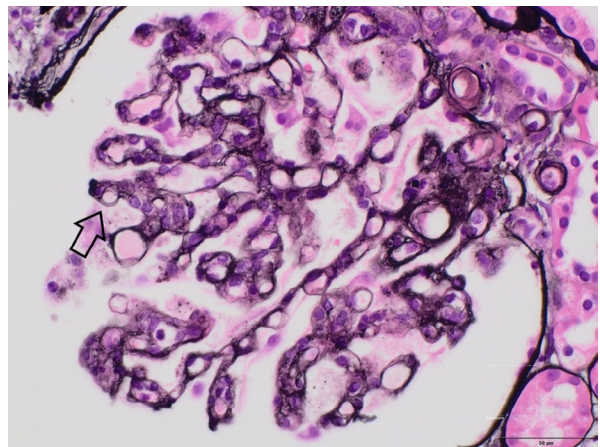


Fig. 2. Glomerulus with thickening of glomerular basement membrane with double contours (arrow) (Silver stain, 400X)

After obtaining the results of the above-mentioned studies, the interview with the patient was deepened. He revealed from early childhood a characteristic rash on the lower abdomen and thighs (angiokeratoma), he suffered from paroxysmal burning pains in the feet and hands, appearing periodically. In addition, the patient suffered from sudden abdominal pain of unknown origin, accompanied by diarrhoea and vomiting. From childhood, he had a big problem with tolerance of physical effort, which often prevented him from integrating with a group of peers. The patient also pointed out that the symptoms worsened mainly when he was in high temperatures. At that time, he felt exceptional weakness, and at the same time lack of sweating was characteristic. Edema in the limbs did not begin to appear in the patient until around the age of 40, when the characteristics of kidney damage appeared. During the consultation, the cardiologist performed cardiac echocardiography, which showed signs of left ventricular hypertrophy

and assessed the patient's 5-year risk of sudden cardiac death at 4.6% and qualified the patient for cardioverter-defibrillator (ICD) implantation in the primary prevention of sudden cardiac death. Moreover, the consulting neurologist, based on the physical, subjective and ENG results, diagnosed the patient with a history of ischemic stroke and peripheral polyneuropathy. The patient is currently undergoing enzyme replacement therapy. He regularly receives intravenous infusions of α -Gal at a dose of 0.2 mg per kg body weight from every 2 weeks. In addition, he continues treatment with chronic hemodialysis (treatments 3 times a week for 4 hours) on the arteriovenous fistula created on the left forearm. In the diagnostic and therapeutic plan of the patient, after ICD implantation, it is planned to qualify the patient for kidney transplantation. The patient's wife is considering donating the kidney to her husband.

The patient also noted that his grandfather (mother's father) also suffered from burning pain in his limbs. The patient's grandfather died around the age of 50.

The results of genetic tests of the patient's family confirmed the presence of the mutation characteristic of FD in another 4 people (all people are women).

In addition, it is known that the patient's mother, his aunt, and sister suffer from hypertrophic cardiomyopathy, while the 20-year-old niece was diagnosed with the symptoms of mitral valve prolapse syndrome. The patient's nephew and cousin are healthy.

Figure 3 shows the genetic tree of a family with FD.

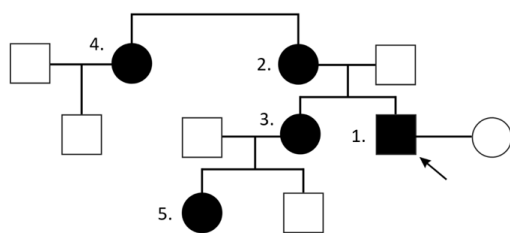


Fig. 3. Genetic tree of a family with Fabry disease (1. Patient, 2. Patient's mother, 3. Patient's sister, 4. Patient's aunt, 5. Patient's niece)

Table 1 shows the results of selected genetic and enzymatic tests together with the assessment of kidney damage in individual people with Fabry disease in the family.

Based on a review of the literature available in medical databases, it was observed that the most frequently described pathology in the course of FD are parapelvic cysts, podocyturia even without an increase in creatinine or albuminuria, and also glomerulonephritis in the course of podocytopathy, including focal segmental glomerulosclerosis (FSGS).

Table 2 provides an overview of selected studies on the types of kidney disease in patients with FD. Only clinical research studies were selected.

Table 1. Results of selected genetic and enzymatic tests together with the assessment of kidney damage in individual people with FD in the family.

	Genetic mutation	α -Gal [mmol/L/h]	Lyso-GL-3 [ng/ml]	CKD ^a	Cause of CKD
1 patient	nonsense type – c.679C>T (p.(Arg227Ter))	0*	112.3 [#]	G4/A3	MPGN
2 patient's mother	Nonsense type – c.679C>T (p.(Arg227Ter))	3.8*	6.6 [#]	G2/A2	CRS type II
3 patient's sister	Nonsense type – c.679C>T (p.(Arg227Ter))	1.4*	17.0 [#]	G1/A2	peripelvic cyst
4 patient's aunt	Nonsense type – c.679C>T (p.(Arg227Ter))	2.3*	12.2 [#]	G1/A2	CRS type II
5 patient's niece	Nonsense type – c.679C>T (p.(Arg227Ter))	2.8*	8.9 [#]	n	n

^a Abbreviations: # – norm <3.5 ng/ml; * cut-off value = 2.8 mmol/L/h; n – no irregularities; & – stage of CKD according KDIGO 2012 [14]; α -Gal – alpha-galactosidase enzyme activity; CRS – cardio-renal syndrome; MPGN – membranoproliferative glomerulonephritis

Discussion

The presented clinical case deserves a comment due to the very late diagnosis of a genetic disease affecting many zones of the patient's life. Due to the rarity of the disease and the multi-symptomatic course of FD, it is rarely considered in the differential diagnosis. The presence of cardiovascular complications in young people without concomitant classic risk factors for these diseases and the appearance of renal failure of unclear etiology should be an indication for testing for FD. Despite confirmation of the same mutation, the nephrological phenotype in FD may be different. This heterogeneity in the symptoms of kidney injury in FD may be related to the gender, α -Gal activity, and age of the patients, although environmental influences may also be involved in the symptomatology of FN.

Based on the case study of our patient with FD and his family, and based on the available literature, the following causes of nephropathy can be found in patients with FD:

- glomerulopathies associated with damage to the podocytes,
- other glomerulopathies (such as membranous-proliferative nephropathy found in our patient),
- distal renal tubular acidosis,
- Fanconi syndrome,
- cardio-renal syndrome.²¹

In some patients hyperfiltration is described. Whereas hyperfiltration is most often estimated using eGFR calculation formulas based on serum creatinine.

Table 2. The overview of selected studies on the types of kidney disease in patients with FD^a

Authors	Year of publication	Research method	Conclusions
Ries et al ¹⁰	2004	prospective MRI and CT imaging of the kidneys	<ul style="list-style-type: none"> multiple cysts in the renal sinuses are characteristic the cause of the cysts is unknown
Pisani et al ¹³	2018	USG of the kidneys	<ul style="list-style-type: none"> renal parapelvic cysts were detected in 28.9% of people with FD vs 1.1% of people in the control group (p < 0.001)
Fall et al ¹⁵	2016	analysis of patient urine cells using cytopspin slides stained for podocalyxin, claudin-1 and Dapi	<ul style="list-style-type: none"> patients with FD have increased podocyturia even in the absence of proteinuria and albuminuria podocyturia correlates with the clinical severity of FN
Auray-Blais et al ¹⁶	2020	dry stain analysis from the urine of patients - by liquid chromatography / tandem mass spectrometry	<ul style="list-style-type: none"> increased concentrations of Gb3 in urine were observed in 13.6% of patients with FN CKD or other comorbidities may be associated with an increase in urine Gb3 concentration (all the patients)
Yeniçerioglu et al ¹⁷	2016	genetic analysis in people, who were not dialyzed, with α -Gal-A enzyme activity ≤ 1.2 $\mu\text{mol/l/h}$ in the dry blood drop test	<ul style="list-style-type: none"> FD should be considered in the differential diagnosis of CKD of unknown etiology
Mauer et al ¹⁸	2014	kidney biopsy from 12 untreated women with FD aged 8-63	<ul style="list-style-type: none"> there is an association between podocyte mosaicism and podocyte damage in FD patients the kidney biopsy, which provides information about podocyte mosaicism, can help stratify women with FD for their risk of kidney disease and help make treatment decisions
Ortiz et al ¹⁹	2008	sectional retrospective evaluation of eGFR, albuminuria and proteinuria in 1,262 adult patients (677 females) from the Fabry registry	<ul style="list-style-type: none"> proteinuria, although an early complication, may not be evident in patients with advanced CKD a significant proportion of women suffer from moderate to severe kidney involvement in FD
Siegenthaler et al ²⁰	2017	eGFR, left ventricular myocardial mass index	<ul style="list-style-type: none"> CRS was associated with a high risk to develop cardiovascular complications and death a focus on cardio-reno-protective therapies is crucial

Abbreviations: CKD – chronic kidney disease; CT – computer tomography; eGFR - estimated glomerular filtration rate; FN – Fabry nephropathy; lyso-Gb3 – globotriaosylsphingosine; MRI - magnetic resonance imaging; USG – renal ultrasonography

In patients with FD, we also observe a sarcopenia caused by the persistence of chronic inflammation in the body of these patients, secondary to damage to muscle cells overloaded with lysosomal proteins. Evaluation of eGFR estimated based on serum creatinine concentration, which is dependent on muscle mass, is another reason why in the evaluation of eGFR in patients with FD we should use a different biomarker, such as serum cystatin C (CysC). In our nephrology department, we observe that the eGFR estimated based on blood creatinine in patients with FD may be overstated by up to 60 ml/min in relation to the eGFR estimated based on serum CysC (118 vs. 44 ml/min/1.73m²).

Currently, a specific therapy for Fabry disease is the replacement of the missing enzyme with recombinant human α -Gal (enzyme replacement therapy; ERT).^{1,7,6} The current approach is ERT with intravenous agalsidase-alpha or agalsidase-beta administered every 2 weeks and oral chaperone therapy with migalastat.²²

It has been confirmed that the early initiation of treatment is of great importance for the improvement of the quality of life and the patient's prognosis and stabilization of renal function.³ However, the efficacy of therapy and its diagnostic role in FD is not easy to determine in the paediatric population, as paediatric patients relatively rarely undergo renal biopsy.²³

Conclusion

Patients with Fabry disease should be under the care of a multidisciplinary medical team that should include a nephrologist.

Declarations

Funding

The study did not require funding.

Author contributions

Conceptualization, N.K. and A.G.B.; Methodology, K.M.C.; Investigation, S.T., K.M.C. and A.G.B.; Writing – Original Draft Preparation, N.K. and A.G.B.; Writing – Review & Editing, N.K. and A.G.B.; Supervision, A.G.B.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data may be made available to interested persons at the request of the corresponding author via e-mail.

Ethics approval

All subjects gave informed consent to the inclusion prior to participating in the study. The study has been ap-

proved by the Bioethics Committee at the University of Rzeszow No 2018/06/10.

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