UDC: 616-056.7
DOI: https://doi.org/10.2298/VSP200228071C

Fabry disease in Serbia – current status and future perspectives

Fabrijeva bolest u Srbiji – trenutno stanje i buduće perspektive

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Key words:
fabry disease; genetic diseases, inborn; diagnosis; signs and symptoms; therapeutics; serbia.

Ključne reči:
fabrijeva bolest; nasledne bolesti; dijagnoza; znaci i simptomi; lečenje; srbija.

Introduction

Fabry disease (FD) (OMIM 301500) is a rare, X-chromosome-linked, slowly progressive lysosomal storage disorder [1]. The estimated prevalence of FD is very hard to establish and affects 1 in 40,000–117,000 newborns worldwide [2]. FD was first described in 1898 by two dermatologists, William Anderson and Johannes Fabry. It is hence sometimes referred to as Anderson-Fabry disease [3, 4].

The aim of this paper was to shed some light on this disease, which is profoundly under-recognized in our country, and to provide insight into the current status of FD in Serbia as well as to give future perspectives on this matter (planning of screening procedures and management issues).

Fabry disease – basic characteristics

In FD, as a consequence of a genetic variation in the *GLA* gene, an impairment of enzyme α-galactosidase A (AGAL) activity occurs. It leads to the accumulation of glycosphingolipids in various cell types. The finding of globotriaosylceramide (Gb3) in biopsy specimens from affected organs is essential from a diagnostic point of view. For this purpose, it is necessary to perform an electronic microscopic examination of the affected tissue, which demonstrates Gb3 accumulations as intracellular inclusions ("myeloid bodies" or "zebra bodies"). On the other hand, globotriaosylsphingosine (Lyso-Gb3), the deacylated form of Gb3, is very important not only as a diagnostic but also as a prognostic biomarker in FD, which should be measured in bodily fluids during the treatment of FD patients [5]. In contrast to other X-chromosome-linked diseases in which females can only be carriers, a disease of different severity can develop in FD females. The clinical picture of female patients with pathologic genetic variation largely depends on how the X chromosome is inactivated. In addition, it is a consequence of mosaicism of wild-type *GLA* gene and pathologic type *GLA* gene in their cells [6, 7]. Due to the manner of inheriting FD, all children of affected mothers have a 50% chance of inheriting the genetic variation. However, in the case of an affected father, daughters and not sons will inherit the pathologic genetic variation.

There are more than 1,000 genetic variations in the *GLA* gene (The Human Gene Mutation Database, www.hgmd.cf.ac.uk). Many of these genetic variations are pathogenic and lead to classic or late-onset forms of FD. Other genetic variations have uncertain clinical significance, and some variations are probably benign [5, 7, 8]. We can assort FD as an attenuated lysosomal storage disorder by knowing the fact that patients can live well into adulthood. Nevertheless, it poses a substantial burden on the lives of FD patients, with an estimated lifespan of 15–20 years shorter in classic hemizygous male patients and 5–10 years in classic heterozygous female patients. The leading causes of death in FD patients nowadays are cardiovascular disorders [9, 10].

There are two major forms of FD: classic form and late-onset variants.

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In patients with a classic form of the disease, the accumulation of glycosphingolipids starts practically *in utero*. The classic form of FD is characterized by absent or residual enzyme activity (AGAL < 1%) and abundant accumulation of Gb3 in various cells. Typically, the disease clinically manifests itself in patients during childhood with acroparesthesia. Neuropathic pain is the most frequent clinical symptom of FD, occurring in over 80% of males and 60% of females. The pain is usually aggravated during exercise, in febrile states, or a warm environment. It can last for days and sometimes be so excruciating that it disables the patient (so-called Fabry crises). That is often coupled with sweating disturbances, usually hypo- or anhydrosis, which makes this condition even worse. In addition, during childhood, eye changes can ensue, with *cornea verticillata* being the most prominent but still nonspecific for FD. Diagnosis is quite simple, with a slit lamp examination. It does not impair vision. A premature cataract is also one of the eye manifestations of FD, accompanied by tortuosity of retinal blood vessels on fundoscopic examination. During childhood and teenage years, skin changes so that angiokeratoma becomes prominent. Its localization is mainly around the umbilicus and inner thighs ("bathing trunk region"); it represents small red to purple papules composed of surface blood vessels (dilated capillaries). Gastrointestinal dysmotility is another important part of the FD spectrum. Usually, it manifests as postprandial pain, bloating, cramping, diarrhea, or constipation [11]. Bearing in mind all the aforementioned, rather nonspecific symptoms and signs, all FD patients generally experience a diagnostic odyssey before establishing a proper diagnosis. Initially, more than 25% of FD patients have a wrong diagnosis, ranging from different psychiatric disorders, across irritable bowel syndrome and fibromyalgia to multiple rheumatologic conditions [12]. During adulthood, patients with FD may experience serious target organ damage [11].

Kidneys are rather important target organs for FD patients since most patients with the classic form of FD have a kidney disorder, and untreated patients with classic FD usually develop end-stage renal disease (ESRD) into their 50s [13]. Accumulation of intracellular Gb3 inclusions in various kidney cells starts very early. Podocytes are terminally differentiated cells with restricted capability for regeneration. Their loss eventually leads to glomerulosclerosis [14]. Albuminuria, as the first sign of kidney disease, can be found very early, during childhood. Later overt proteinuria ensues but is rarely above 1 g/day. Some authors have found that podocyturia significantly impacts the diagnosis of Fabry nephropathy since it commences before proteinuria and can be an early sign of disease [15]. Ultrasound examination of kidneys is a crucial part of nephrology workup. With this technique, we can find the existence of parapelvic cysts in FD patients [16]. They are nonspecific for FD but can allege us to think about FD in our patients. Urine cytological examination is usually underestimated in our clinical practice but can be important, even though nonspecific. In FD patients, we can find mulberry cells (distal tubular epithelial cells in which Gb-3 has accumulated) or Maltese crosses (with polarized light microscopy – glycosphingolipid laden epithelial cells) in urinary sediment specimens that can lead us to FD diagnosis [14, 17]. Kidney biopsy is a vital part of the diagnostic and prognostic workup for many kidney diseases, including Fabry nephropathy. An essential part of kidney biopsy examination should be electronic microscopy (EM). Characteristic EM findings on kidney biopsy are myeloid bodies, also called "zebra bodies", which resemble the accumulation of glycosphingolipids in renal cells. These changes are characteristic of FD but can also be found in patients who are on certain medications, such as amiodarone, antimalarials, fluoxetine, and other drugs, or can be related to lithium ingestion [18]. The most usual finding on light microscopy examination in the case of FD is the one that resembles focal segmental glomerulosclerosis, a nonspecific consequence of podocyte loss. Before that, vacuoles in podocytes and distal tubular cells can be found [19].

Cardiac involvement in FD patients is a very important issue since 40–60% of FD patients will have some form of cardiac involvement during the course of their disease. The most prominent cardiac manifestation is left ventricular hypertrophy (LVH) (Figures 1 and 2), which is partly a

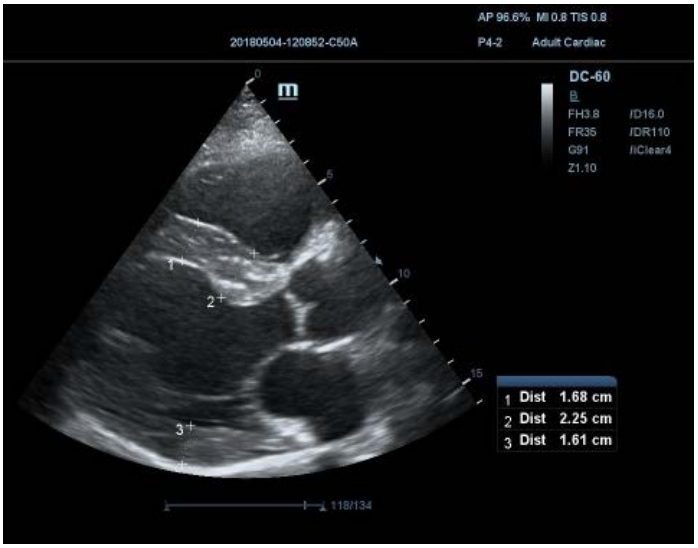

Fig. 1 – Echocardiographic image of Fabry disease patient – interventricular septum (IVS) in diastole 1.68 cm, posterior left wall (PLW) d 1.61 cm: hypertrophic cardiomyopathy.

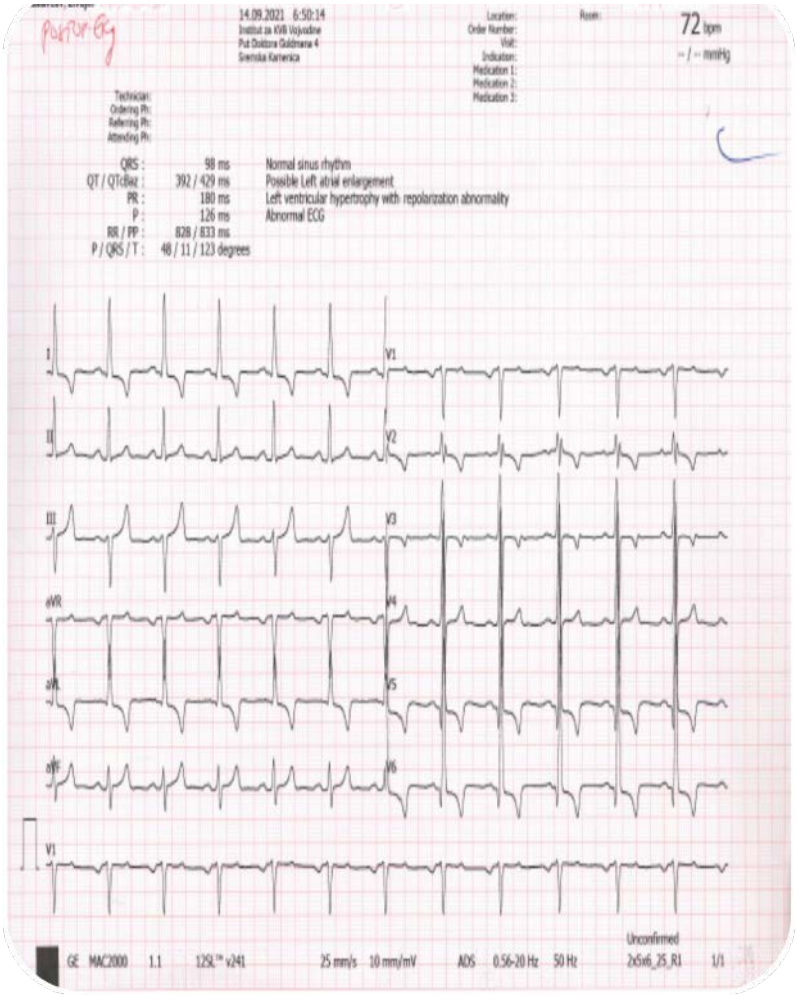

Fig. 2 – Electrocardiogram of Fabry disease patient (left ventricular hypertrophy).

consequence of glycosphingolipid accumulation, but some other mechanisms are also responsible for hypertrophic changes in the myocardium. Accumulated Gb3 triggers processes that lead to some signaling pathways affecting the functional impairment of myocytes. Aside from that, other mechanisms like inflammatory changes in the heart tissue can be responsible for the prominent hypertrophy of the myocardium [20]. It is usually concentric and leads to an increase in left ventricular mass over time. Along LVH, patients with FD may have conduction abnormalities, bradyarrhythmias, supraventricular and ventricular tachyarrhythmias, valvular disorders, dysfunction of cardiac microcirculation, and cardiac fibrosis which is best visualized with magnetic resonance imaging [21]. The posterolateral wall of the left ventricle is the predominant site for fibrosis development. Patients with FD usually suffer from heart failure with preserved ejection fraction, but the global longitudinal strain is impaired. Arrhythmias in FD patients can often be intermittent, so the preferred way of diagnosis is to perform a 48-hour ECG Holter monitoring [22].

Besides the peripheral and autonomous nervous system, another important site for FD manifestations is the central nervous system (CNS). The main CNS manifestations are cerebrovascular ("cerebral vasculopathy"), psychiatric, and cognitive disorders and vestibulocochlear nerve dysfunction. Cerebrovascular manifestations usually affect patients aged 15–55 years and range from ischemic strokes, transitory ischemic events, cerebral hemorrhage, cerebral venous thrombosis, dissection of cervical arteries, and white matter lesions (cerebral microangiopathy) (Figure 3). Stroke is one of the leading causes of death in FD patients. In addition, affection of large blood vessels, predominantly of the vertebrobasilar region [dolichoectasia (Figure 3), calcifications], is often found in FD patients. Psychiatric disorders comprise a spectrum of manifestations that vary from developmental difficulties (learning disabilities) and stress problems due to chronic pain and multisystemic affection to high rates of depression with suicidal intentions and neuropsychologic involvement with dementia. The affection of the eighth cranial nerve is manifested in vertigo, tinnitus, and deafness [23, 24].

Late-onset variants of FD usually manifest themselves with heart (cardiac variant) and kidney (renal variant) involvements that are similar to those in classic FD patients but manifest clinically somewhat later in the life of patients than in the classic form of FD. These patients generally lack all aforementioned signs and symptoms of the classic form of FD, aside from the affected organs [11].

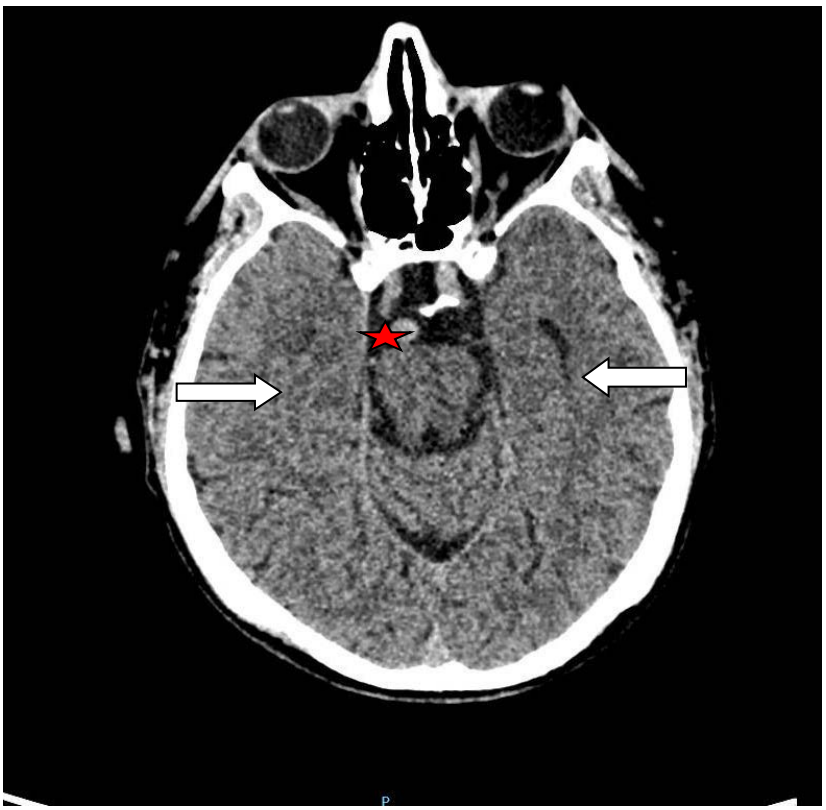

Fig. 3 – Computed tomography (CT) finding: white matter lesions (arrows) and ectasia of the right basilar artery (red asterisk).

Fabry disease in Serbia

According to the last census, Serbia has a population of 7,186,862 inhabitants [25] and only 17 established cases of FD so far, 7 males and 10 females, from 7 families. One adult male patient receives treatment with enzyme replacement therapy (ERT) at the University Clinical Center of Serbia in Belgrade, and three patients receive ERT at the University Clinical Center of Vojvodina in Novi Sad. Four patients have received approval for ERT from the Ministry of Health of the Republic of Serbia and are waiting for the therapy. According to the known epidemiological data, this is not a proper number of FD patients.

There are many reasons for such a low number of registered FD patients in Serbia. Patients with the same genetic variation from the same family can have a completely different phenotype of the disease. For instance, male and female patients can have very different clinical presentations because female patients experience the phenomenon of X chromosome inactivation. Therefore, our male patient with classic FD genetic variation, c.871G>C (Ala291Pro), has a full-blown disease presentation with acroparesthesia, premature cataract, proteinuric end-stage renal disease, left ventricular hypertrophy, basilar artery ectasia, and white matter lesions. On the other hand, his four years older sister with the same genetic variation of the *GLA* gene only has mild proteinuria with preserved renal function, mild left ventricular hypertrophy, and *cornea verticillata*. Furthermore, patients of the same gender can have a very heterogeneous phenotype of the disease, and that can be a diagnostic problem on its own. However, in our opinion, the main problem in establishing a diagnosis of FD in Serbia is the lack of awareness among our physicians regarding rare diseases in general, among them FD. A particularly complex problem is represented by the existing difficulties in testing possibilities for FD in Serbia. One of the ways we could raise awareness about FD undeniably is to present this rare disease to the scientific and physician auditorium with papers like this. We should all bear in mind the clinical picture of classic or late-onset FD patients described in the previous text and think about it in differential diagnosis while taking care of our patients. As we already mentioned, there are some essential rules in diagnosing an FD patient. It relies largely on the gender of our patients.

The most common way of finding a new FD patient is high-risk population screening. It stands for screening among patients on renal replacement therapy, especially for those with unknown causes for ESRD and younger than 50 years of age (female patients regardless of age), but also among patients with unknown causes of chronic kidney disease of any grade [26, 27]. Moreover, high-risk population screening is implicated in patients with hypertrophic cardiomyopathy of unknown origin [28] and patients with cerebrovascular accidents [29] under 55 years of age (so-called cryptogenic cerebrovascular accidents).

In previous years in our country, there have been only a few sporadic attempts at hemodialysis population screening for FD. Those attempts include only a few hundred hemodialysis patients without any success in finding a patient with FD (unpublished data, personal communication). So

far, there has been no published data on screening for FD in Serbia, and most of the FD patients in Serbia have been diagnosed on a clinical suspicion basis. There are numerous publications on screening programs for FD in a high-risk group population, with different results depending on the type of population screened and the types of genetic changes that were established. In a meta-analysis by Doheny et al. [30], they established that the prevalence of FD in hemodialysis patients is 0.21% of males and 0.15% of females, in cardiac screening, 0.94% males and 0.9% of females, and in stroke patients, 0.13% of males and 0.14% of females. Family screening is the most important part of the process of discovering FD patients. It should be done for every index FD case due to the estimation that for every new FD patient, we could expect to find other 3–5 patients through family screening [5]. Ideally, genetic counseling should be a vital part of managing FD patients and their families. Most of their work should be based on genetic testing *per se* but also on the commentary of the finding and prenatal family consultations. In our country, there is a possibility for genetic counseling.

The first patient was diagnosed in 2009 in Novi Sad with a classic FD genetic variation c.334C>G (R112G). After establishing the diagnosis of FD, he moved to Australia, where he received ERT until 2018 when he moved back to Serbia. In the first 6 months after coming back to Serbia, he received ERT through a donation of agalsidase alfa from the pharmaceutical industry and, after that time, through the approval of the Ministry of Health Commission for Rare Diseases of the Republic of Serbia. This patient has 3 relatives with established FD who are living abroad. The second patient from Novi Sad has already been described, with classic FD genetic variation, c.871G>C (A291P). This patient has been on agalsidase beta therapy since 2017 after approval from the Ministry of Health Commission for Rare Diseases of the Republic of Serbia. He experienced cadaveric kidney transplantation at the beginning of 2019 without a break in ERT treatment, and he received ERT regularly after the successful kidney transplantation. Several patients have been diagnosed with FD after a family screening was performed upon establishing FD diagnosis in proband cases. The number of detected FD patients is certainly below the real one.

Under the auspice of the Nephrology Association of Serbia, high-risk population screening among the hemodialysis patient population of Serbia is underway. There are 63 dialysis centers in our country, with around 6,500 patients on chronic hemodialysis programs [31]. We intend to test male dialysis patients with unknown causes of ESRD below 50 years of age and female dialysis patients with unknown causes of ESRD regardless of their age. According to the last annual report of the Registry of Kidney Disease Patients in Serbia [30], 8.1% of our patients on renal replacement therapy have an unknown cause of ESRD, in 19.1% of them, the cause of ESRD is some form of glomerulonephritis, while 13.5% of our patients on renal replacement therapy are categorized as "other" for the cause of their ESRD (Table 1). We should all bear in mind that kidney presentation of FD is proteinuria and slowly progressive chronic kidney disease. A gold standard for a proteinuric kidney disorder is ultrasound-guided percutaneous kidney biopsy. Due to the lack of performance of electronic microscopy of biopsied tissue, there is a great risk of misinterpreting findings as focal and segmental glomerulosclerosis and missing some FD diagnoses by reporting these patients to have glomerulonephritis as the cause of their ESRD. Looking back on all this data, the importance of dialysis population screening in Serbia is only getting stronger.

Table 1

Prevalence per million population (PMP) and percentage of the causes of end-stage renal disease (ESRD) in Serbia [31]

Diagnosis	PMP	%
Hypertension	195.3	24.4
Glomerulonephritis	153.1	19.1
Diabetes mellitus	131.8	16.5
Other	107.7	13.5
Pyelonephritis	84.8	10.6
Unknown	64.7	8.1
Polycystic kidney disease	53.6	6.7
Renovascular disease	8.6	1.1

The first step in the diagnostic algorithm for male patients suspected of FD is enzyme (AGAL) activity testing. Usually, affected hemizygous males with classic FD have absent or substantially reduced enzyme activity levels (< 1%), while in heterozygous female patients with classic FD, due to random X-chromosome inactivation, enzyme activity levels may be just slightly reduced or even normal. In order to establish the exact genetic variation of the *GLA* gene, the next step for male patients with reduced enzyme activity and all female patients suspected of having FD is genetic testing. The genetic study is "*conditio sine qua non*" for suspected female FD patients. Measurement of biomarkers in the blood (Lyso-Gb3), urine (Gb3), or affected tissue (Gb3) can help in establishing the diagnosis and in the management and prognosis of FD patients. In classic FD patients (males more than females), levels of these biomarkers are substantially elevated. The easiest way to test for FD is with dried blood spot (DBS) testing, in which a few drops of blood are enough for the enzyme, biomarker, and genetic testing.

With this screening program, we hope to find some new FD patients. The most important result of our screening program should be the acknowledgement of new, previously unrecognized patients with FD through family screening that will follow (Figure 4). In these patients, implementing adequate and timely therapy could prevent or slow down target organ damage. Moreover, having a genetic variation running in the family would allow for proper genetic counseling of future parents from the affected families.

Contemporary FD therapy is directed toward enzyme replacement. Nowadays, there are two forms of agalsidase enzyme on the market, agalsidase alfa and agalsidase beta.

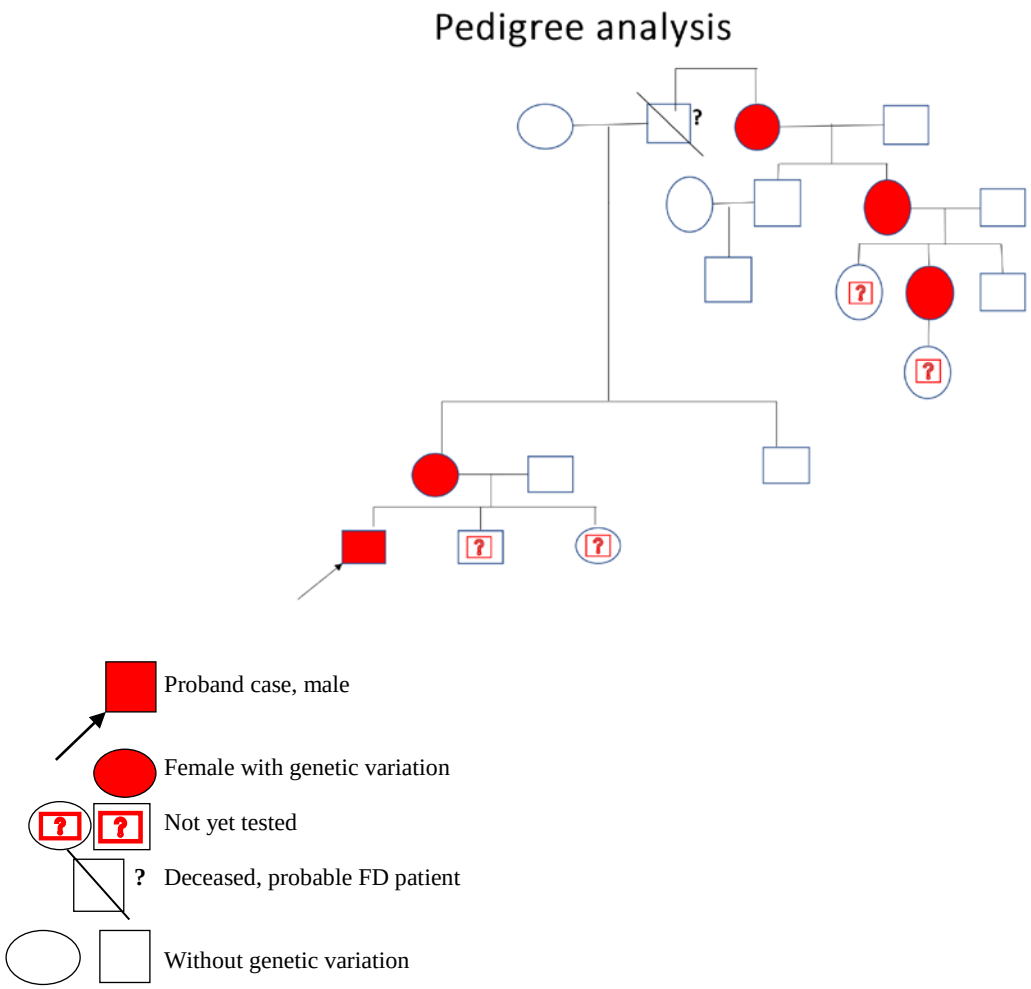

Fig. 4 – Pedigree analysis in Fabry disease.

Both enzyme forms have a place in the treatment of FD patients and are administered as *iv* infusions every 14 days. The dosage for agalsidase alfa is 0.2 mg/kg of body weight, and for agalsidase beta, 1 mg/kg of body weight. For some amenable genetic variations in the *GLA* gene, we can also use chaperone therapy with oral medication, migalastat [32]. Nevertheless, we cannot ignore adjunctive and supportive treatment for FD patients, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, pain control medications, anti-arrhythmic drugs or devices, renal replacement therapy, etc.

Since 2017, enzyme replacement therapy has been available for treating FD patients in Serbia. Both preparations, agalsidase alfa (Replagal®, Takeda) and agalsidase beta (Fabrazyme®, Sanofi Genzyme), are available and registered in our country. For every FD patient eligible for enzyme replacement therapy, physicians need to prepare adequate documentation that comprises a complete enzyme, biomarker, and genetic workup and the complete clinical phenotype of a patient as well. The physicians then present it to the Ministry of Health Commission for Rare Diseases of the Republic of Serbia, which approves therapy for patients in need.

Conclusion

FD is an orphan disease, but patients with it should not be the ones. Predominantly, the paper's role is to promote awareness about this rare, X-chromosome-linked, slowly progressive lysosomal storage disorder that can equally affect males and females. Major target organs in FD are the kidneys, heart, and nervous system. Until now, 17 FD patients have been diagnosed in Serbia, but the number of affected people is probably larger. There are many reasons for such a low number of registered FD patients in Serbia. One of the main reasons for such a situation is certainly a very heterogeneous phenotype of FD. However, the main problem in diagnosing this disease is the lack of awareness among physicians regarding rare diseases in general and especially difficulties in testing possibilities for FD in Serbia. A high-risk population screening program among the hemodialysis patient population of Serbia is underway. The aim of the program will be to detect new patients, give more objective data regarding the prevalence of FD in Serbia, and establish the basis for family screening. In newly detected patients, implementing adequate and timely therapy could prevent or slow down the occurrence of target organ damage.

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Received on February 28, 2020
Revised on June 28, 2022
Accepted on June 30, 2022
Online First July 2022