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ABSTRACT

Fabry disease (FD) belongs to the group of lysosomal storage diseases (LSD), which are characterised by insufficient activity of enzymes responsible for the intra-lysosomal breakdown of various substrates. The result is an uncontrolled accumulation of by-products of cellular metabolism. Lysosomal storage diseases are inherited diseases, transmitted mainly in an autosomal recessive fashion. In the absence of a positive family history, an early diagnosis can often be missed. In addition, the age of clinical manifestation can range from infancy to adulthood — a distinction is made between severe "classic" variants of the disorders, presenting in childhood, and forms with late onset. Some of the conditions in this group may not show typical signs of tissue storage, such as liver and spleen enlargement, especially in subtypes associated with neurodegenerative changes.

The aim of the Expert Opinion of the Polish Cardiac Society and the Polish Forum for Fabry Disease is to summarise the current knowledge on FD, present advances in diagnosis and therapy and disseminate known diagnostic and therapeutic algorithms for this group of patients.

INTRODUCTION

Fabry disease, also known as Anderson-Fabry disease (FD), and also as lysosomal enzyme alpha-galactosidase A (α-GAL A) deficiency, is a rare, genetically determined, lysosomal storage disease (LSD) caused by the absence or deficiency of the α-GAL A enzyme responsible for the hydrolysis of neutral glycosphingolipids, leading to their accumulation in plasma and in the lysosomes of cells of many organs [1, 2].

The classification of LSD was initially based on the type of substrate/ deposit accumulating in the tissues, such as sphingolipidosis (GM2 gangliosidosis, Fabry disease and Gaucher disease), mucopolysaccharidosis or glycosaminoglycan build up (Hunter syndrome, Hurler syndrome or Hurler–Scheie syndrome) [1–3].

The current classification takes into account the assessment of a defect in the protein itself. For example, deficiency of β-hexosominidase A or α-galactosidase A are associated with

Tay–Sachs disease (TSD) and FD, respectively; in turn, faulty transmembrane transport, which results in suppression of the egress of metabolised substrates from lysosomes, is a cystinosin defect and the cause of cystinosis. Many of the storage disease names still in use are eponyms in honour of the physician/scientist who first provided a clinical description of the condition (Gaucher disease, Morquio syndrome or Niemann–Pick disease) [3, 4].

Fabry disease as one of the LSDs is an X-chromosome-linked hereditary disorder with severe cardiovascular, nephrological and neurological manifestations that occurs as a result of a defect in α-GAL A enzyme function [1].

Fabry disease is caused by a point mutation in the *GLA* gene encoding the lysosomal protein α-GAL A, which is one of the enzymes responsible for the hydrolysis of neutral glycosphingolipids. When α-GAL A malfunctions, glycosphingolipids are deposited in the cells — this process is called storage, which is why FD is classified as LSD. The breakdown of fatty substances, sphingolipids, into smaller components that provide the body with energy is disturbed. There is an accumulation of the substrate globotriaosylceramide (Gb3) in the autonomic nervous system, as well as in the organ of vision, kidneys and cardiovascular system. The classic form, occurring in males, with α-GAL A enzyme activity below 1%, usually has its onset in childhood or adolescence.

To date, nearly a thousand mutations of pathogenic variants within the *GLA* gene have been described, among which there are pathogenic variants responsible for the development of the full-blown, so-called classic form of the disease (complete absence of or reduced enzymatic activity <5%), pathogenic variants responsible for the development of the late-onset form (partially preserved enzyme activity), variants of uncertain (clinical) significance (VUS), for which no mutation–symptom relationship has been unequivocally demonstrated, and so-called benign polymorphisms [5, 6].

The disease-causing mutation is linked to the X chromosome, so the so-called classic FD mainly affects men; women are often asymptomatic carriers of the defective gene variant [6–8].

The basis for diagnosis, in addition to clinical symptoms, are enzyme assays, the results of which show a defect in the activity of the enzyme under investigation, and molecular analysis — genetic testing for mutations in the *GLA* gene, which is particularly important in the diagnosis of FD in women. Regarding genetic diagnosis, it should be noted that some sequence alterations that are uncommon or have not been previously described may not be clinically significant. The interpretation of VUS variants remains a challenge, and it is therefore recommended that molecular testing be performed by specialised and certified laboratories.

The prevalence of the classic form of the disease is approximately 2.5/100,000 (1/40,000 in men, 1/117 000 in women) — statistics are for the Caucasian race. In Poland, the incidence does not exceed 30 cases per year. Based on newborns screening, it is estimated that the actual prevalence of the disease (both classic and late-onset forms) is approximately 10 times higher [9, 10].

FABRY DISEASE IN CHILDREN

It is now known that the first symptoms of FD can occur as early as the foetal, infant and early childhood period. Due to the high non-specificity of the clinical picture, the final diagnosis is usually established after several or more years of a "diagnostic odyssey" following the onset of symptoms (on average after 15 years), whereas early diagnosis of FD is key to reducing morbidity and mortality as well as limiting complications and improving quality of life.

The clinical picture of FD in children and adolescents (Table 1)

Typical signs of FD in children and adolescents include lower limb pain, abdominal pain, diarrhoea, sweating disorders or intolerance to heat or cold. These symptoms can often be misinterpreted as common, harmless complaints and are often associated with "growing pains", irritable bowel syndrome, inflammatory bowel disease, fibromyalgia, or systemic connective tissue diseases. The average age of onset of FD symptoms in boys is 6 years old and in girls 9 years old. These data refer to children from a patient population with a positive family history of FD [11].

Dysmorphia is caused by deposition of unmetabolised macromolecular substances and becomes more pronounced as the disease progresses. The most common sign of dysmorphia is coarse facial features (so-called Fabry face), which include a prominent periorbital region, recessed forehead, bushy eyebrows, prominent lobules of the ears, bulbous nose, acute nasal angle with a marked bridge, shallow midface, full lips and prognathism. Signs of extrafacial dysmorphia include wide fingertips, shortened fingers, prominent vessels on the palmar surface, brachydactyly and clinodactyly of the 5th finger, and shortened AP dimension of the thorax [12].

Neuropathic pains are among the earliest symptoms of FD in children (60%–80%). They often remain a leading factor in reducing quality of life, which is associated with a significant increase in prevalence of psychiatric disorders (depression, anxiety, adjustment disorders, suicidal behaviour). Pain is usually localised distally in the limbs, with predominance of the lower limbs (acroparesthesias). Severe episodes of neuropathic pain are referred to as

“Fabry crises”, starting in the feet and hands and ascending proximally. Pain crises are very often triggered by sudden temperature changes, fever, stress, infections, fatigue and physical exercise. Pain episodes are not accompanied by external signs of inflammation (i.e., swelling, redness or tenderness), but periodically may be accompanied by fever and elevated ESR. Incidents of acute pain and chronic pain in the absence of other symptoms of the disease are one of the most challenging psychological aspects of the disease for the patient at a young age [13–15].

Neuro-otological symptoms in the form of hearing loss, up to and including deafness, tinnitus and dizziness are associated with changes in the microcirculation of the cochlear and vestibular structures, as well as neuropathy of the vestibulocochlear nerve.

Structural brain changes in the course of FD in children and adolescents can be visualised by brain MRI. Early detection of white matter abnormalities with ischaemic/haemorrhagic morphology that are clinically silent (without stroke) may favour the decision to initiate treatment. Ischaemic lesions are visible as hyperintense foci in FLAIR and T2-weighted sequences and as hypointense foci in T1-weighted images. In the study by Marchesoni et al. ischaemic lesions were present in about 16% of patients, predominated in heterozygous girls, affected the area supplied by the anterior cerebral vascularisation circle and were already visible in 13-year-old patients. The youngest described patient with subcortical white matter ischaemic foci was 8 years old. Among the “healthy, asymptomatic population”, small, diffuse and non-specific white matter ischaemic lesions occur in about 7% and are considered the so-called broad norm of brain images. The more than 2-fold higher frequency of these lesions in FD patients probably indicates their pathological nature, requiring further observation [16, 17].

Sweating disorders (hypo- and anhidrosis) are common in hemizygous patients (50%–90%) and less common in heterozygous females (up to 30%) with FD. In addition to reduced sweating, some patients (predominantly females) may develop hyperhidrosis. The symptoms start in childhood and adolescence with heat intolerance, dry skin and episodes of fever of unknown cause. The cause is the accumulation of Gb3 in the peripheral nervous system, the endothelium of the vessels surrounding the eccrine glands and in the eccrine cells themselves, which interferes with the autonomic system response.

Gastrointestinal symptoms affect about 20% of boys at 5 years of age and about 10% of girls at 9 years of age, with increasing symptoms as the condition progresses. The most common symptom remains abdominal pain and diarrhoea, which usually occurs after a meal. The manifestation may also include constipation, which is more common in girls, as well as

nausea and vomiting. The painful sensations are described as bloating, cramps, burning and are related to food intake. Chronic dyspepsia is often the cause of weight loss and significantly reduces the quality of life of a child with FD. Gastroenterological complications are mainly related to neuropathic changes in the neurogastroenteric system and also depend on pathological remodelling of the smooth muscle layer. In addition, impaired peristalsis is a determinant of a state of dysbiosis in the gut, and Gb3 accumulation in autonomic ganglion cells and vascular endothelium also promotes inflammatory processes in the gut. An additional pro-diarrhoea factor is the disturbance of bile acid metabolism associated with dysfunction of the enterohepatic circulation [18, 19].

Ocular manifestation of FD mainly concerns vortex keratopathy (vortex-like deposits, CV, *cornea verticillata*), which is diagnosed in the majority of hemizygotes and more than 70% of heterozygotes, and is therefore considered one of the pathognomonic signs of FD. Corneal changes have been described as early as in a 22-week-old foetus, in infancy or early childhood and occur in most patients in the 1st decade of life. Vortex-like cornea results from the accumulation of Gb3 deposits in the basal layer of the corneal epithelium, visible under a slit-lamp during ophthalmic examination. In the absence of characteristic keratopathy changes on slit-lamp examination, extending the diagnostics with corneal confocal microscopy reveals intracellular Gb3 inclusions in epithelial cells. It is important to remember that although this type of corneal degeneration is typical of the course of FD, the use of certain drugs (amiodarone, indomethacin, aminoquinolones: chloroquine, hydroxychloroquine) can also be the cause of vortex keratopathy. Other ophthalmic pathologies in FD are Gb3 deposits within the lens which are the cause of posterior subcapsular cataract (so called Fabry cataract), and tortuous and aneurysmal pattern of conjunctival and retinal vessels. Tortuous conjunctival and retinal vessel lesions can also occur in fucosidosis and GM1 gangliosidosis, while cataracts can occur in mannosidosis and other LSDs. Until recently, it was thought that ophthalmic problems usually did not cause deterioration of visual acuity and remained asymptomatic. It is now accepted that symptoms in the form of impaired night vision (twilight blindness, nyctalopia), blurred vision, impaired contrast sensitivity or the “halo” symptom around light sources may be the result of glycosphingolipid storage. In addition, Gb3 inclusions accumulating in the pterygopalatine ganglion and parasympathetic fibres innervating the lacrimal glands may cause secretory disturbances (anhidrosis/hypohidrosis) and may be the cause of “dry eye” syndrome, pain or eye fatigue (asthenopia), and are significantly more common in FD patients. A full ophthalmic examination using slit lamp or corneal confocal microscopy in the youngest children is a valuable and essential screening element in the diagnosis of FD prior to enzymatic and

molecular confirmation. Ocular involvement is also an indicator of the severity of the disease and is a sign of changes in the vasculature and autonomic system, especially when there are concomitant cardiac and renal complications [20, 21].

Skin lesions — because of the characteristic skin lesions of FD, it has been referred to in the past as diffuse angiokeratoma of the trunk (*angiokeratoma corporis diffusum*) [22]. Angiokeratoma (AK), in addition to vortex keratopathy, sweating disorders and pain crises, is a typical manifestation of FD, appearing in the 1st decade of life and occurring in the majority of patients (60%–90% of boys and 40%–75% of girls). In hemizygous patients, lesions appear between 5 and 8 years of age, but may initially manifest singly and go unnoticed or be misdiagnosed. The angiokeratoma foci are formed by small (1–5 mm) hyperkeratotic angiomatous papules, which do not fade on pressure, are purplish-brown in colour and may present in isolated or disseminated form. In FD, a disseminated form of the lesions is observed, which localise between the umbilicus and the knees (the so-called swimming trunk area), but isolated eruptions do occur. Angiokeratomas are also encountered in other LSDs (sphingolipidoses: GM1 gangliosidosis; glycoproteinoses: aspartylglycosaminuria, fucosidosis, sialidosis, β-mannosidosis; multiple enzyme deficiencies: galactosialidosis). AK-type lesions are often polymorphic with papillary elements, which can be interpreted as viral infection, hemangioma or vasuclar granuloma. A very important element of differential diagnosis is the dermatoscopic examination. The typical area of AK in FD is the umbilical region, particularly its fundus, which should always be carefully examined, as should the genitourinary organ area. Other skin symptoms in FD include telangiectasias (the second skin manifestation after AK), oral mucosal lesions, Raynaud's phenomenon, lymphoedema and hypotrichosis. Patients with severe AK foci and/or telangiectasias usually present with greater organ complications. Symptomatic therapeutic management includes laser therapy, cryotherapy, electrocoagulation and dermatosurgery. The inclusion of enzyme replacement therapy (*ERT*) reduces the number of Gb3 deposits in the skin [22, 23].

Renal damage in the form of albuminuria or proteinuria is observed in FD patients in the 2nd decade of life. However, the results of clinical trials indicate that the processes of pathological and irreversible renal remodelling start already in childhood and before the appearance of albuminuria. The initial sign of glomerular dysfunction in teenagers is hyperfiltration (glomerular filtration rate [GFR] >135 ml/min/1.73 m^2), accompanied by albuminuria, proteinuria and then a progressive decline in GFR values. Glomerular hyperfiltration is a relatively common symptom in young patients who rarely present with chronic kidney disease. An important investigation, especially in patients with the atypical renal

form of FD, is microscopic urine analysis, which may show podocytes, sphingolipid-overloaded endothelial cells resembling a “Maltese cross” or mulberry-shaped erythrocytes. In addition, podocyturia may antedate proteinuria and is therefore accepted to be a biomarker of asymptomatic renal damage [24].

FABRY DISEASE IN WOMEN

Due to the mode of inheritance (linked to the X chromosome), it was originally thought that FD affected only men and that women were only asymptomatic carriers of the mutation. This false view still persists today among some clinicians, leading to a significant delay in making a correct diagnosis and thus starting effective treatment [25–28]. The disease can develop in women not only in extremely rare cases, i.e. in the presence of mutations in both alleles or monosomy of the X chromosome (Turner syndrome), but it also affects heterozygous women.

The clinical picture of the disease in women depends on the type of pathogenic mutation and also on an epigenetic process involving silencing (inactivation) of one of the X chromosomes. X-chromosome inactivation (XCI) is a phenomenon that occurs during early embryogenesis, resulting in the balancing of the expression levels of genes located on the X chromosome, irrespective of sex [29–32].

In females, in a random manner, one of the chromosomes is switched off (inactivated) and passed on to the daughter cells in the form of the so-called Barr body. The assumption was that XCI proceeds randomly, i.e. in 50% of cells the paternal X chromosome is inactivated, and in 50% of cells the X chromosome inherited from the mother is inactivated (50:50). Now it is known that XCI relatively often has a so-called asymmetric, non-random course, with preferential inactivation of only one parental chromosome (e.g. 70:30). Furthermore, the level of asymmetric inactivation in the same woman can vary, depending on the type of tissue tested (30:70; 50:50; 70:30).

Asymmetric inactivation is not clinically relevant in women who do not carry the mutation (are healthy).

Heterozygous women with FD present a very wide range of clinical phenotypes depending on the type of mutation and the extent of X-chromosome inactivation. There can be classic phenotypes with a full-blown form of the disease already in childhood, non-classic (late-onset) phenotypes in which non-specific symptoms predominate, usually occurring in the 4th–5th decade of life and usually affecting a single organ, and completely oligosymptomatic or asymptomatic phenotypes where the woman is only a carrier of the mutation.

For this reason, one must be particularly vigilant during the diagnostic process carried out for women. In the case of clinically significant suspicion of disease, genetic testing to confirm the presence of the pathogenic variant is necessary in addition to determination of enzyme activity and plasma concentration of the Gb3 marker (in some cases these concentrations are not abnormal). Special care should be provided to young, asymptomatic women in whom the presence of the defective allele has been confirmed during family screening, as in their case the symptoms of the disease may occur at a later time.

The treatment regimen for patients with FD is independent of sex. The choice of optimal specific therapy (ERT, chaperone therapy) and symptomatic treatment should depend on the type of mutation, patient preference and the presence and severity of organ complications.
Special attention is required for female patients of childbearing age, for whom effective contraceptive methods are recommended during the period of causal treatment, but it should be remembered that pregnancy and lactation are temporal contraindications to this treatment [33–38].

So far, there has been no evidence that the presence of the disease significantly affects the fertility of patients. The rate of possible complications in women during pregnancy and childbirth is observed to be comparable to that of the general population. There are few scientific reports indicating the possibility of reduced reproductive performance in men, as a result of lowered or absent sperm count in semen (oligospermia/azoospermia), severe pain (crisis) or depressive disorders [39–42]. Heterozygous women have a 50% probability of passing on a pathogenic variant to their offspring, regardless of the sex of the child [42].

FABRY DISEASE IN THE ELDERLY

Fabry disease is characterised by a long-term, long-lasting course due to the persistence of the metabolic defect. Two basic phenotypes of FD: the classic form with onset in childhood and progressive multi-organ damage, and a later onset phenotype with limited organ involvement, manifesting in middle age, determine the picture of the disease in older patients. The diagnosis of the later-onset variant may be delayed due to the lack of clear external signs such as acroparesthesia and angiokeratoma [43]. In all FD phenotypes, the natural ageing process can be difficult to distinguish from FD-specific complications, which themselves become more severe and frequent with age. Elderly patients, aged over 50 years, represent a small proportion of patients eligible for ERT, with the majority of treated elderly patients being women [43].

When deciding whether to start or continue long-term ERT in patients with FD aged 50 years or older, one should consider the potential benefits of treatment compared to the costs for

the healthcare system and the patients' quality of life. Factors to consider when starting ERT in elderly patients are shown in Table 2

As FD is a progressive disease, the severity of the disease and the degree of organ involvement increase with age. Several recent reports indicate that ERT in patients with advanced disease has limited efficacy [42, 43], particularly if implemented in the presence of severe cardiac fibrosis, renal failure or central nervous system ischaemia. Starting or continuing ERT in FD patients with aged 75 years or older may not be beneficial in terms of life expectancy and raise doubts about cost-effectiveness [40, 43].

The cardiac and renal signs and symptoms observed in the FD patient population aged 50 years or older are generally non-specific and may reflect the natural ageing process. Hearing loss, an affliction that often comes with natural ageing, is an independent predictor of cardiac, renal and cerebrovascular complications.

The delayed diagnosis is also due to the fact that patients aged between 50 and 74 years have a limited number of symptoms characteristic of FD. Angiokeratoma and tortuous ocular vessels, which may facilitate diagnosis, are more common in younger patients than in older age groups.

When deciding whether to start/continue ERT at an advanced age, one should consider the FD form — whether it is classic or late-onset.

The age of onset in patients with cardiac variant of FD is in the 6th–8th decade of life [43]. As already indicated, cardiac events in this group may be related to FD, but mainly to the ageing process. If one considers that the main value of ERT is to prevent distant cardiovascular incidents that result from lifelong accumulation of deposits in cells and secondary organ pathology, then the value of ERT in this population may be limited. At the same time, in patients with severe FD symptoms that cannot be alleviated with conventional therapy, ERT could make a difference. There are many indications that time (number of years since the onset of symptoms or diagnosis) may be a better predictor of ERT-resistant disease than age alone [43].

CLINICAL PICTURE AND CARDIOLOGICAL DIAGNOSIS

Myocardial involvement is the most common cause of mortality and impaired quality of life in patients with FD. Almost two-thirds of patients report cardiac symptoms. Accumulation of sphingolipid deposits affects all heart cells — cardiomyocytes, conduction system cells, valvular fibroblasts, vascular smooth muscle cells and vascular endothelial cells — and leads to damage. There is a thickening of the heart walls, including the left ventricle (LV), which at a certain stage of the disease meets the criteria for hypertrophy (increase in LVMI, i.e. left

ventricular mass index). Changes occur in the conduction system, coronary vessels and valvular system. Myocardial damage begins early in the course of the disease, progressing subclinically for a long time before significant symptoms appear. It is usually diagnosed already at the stage of left ventricular hypertrophy [44–47].

Myocardial hypertrophy in FD is found in 88% of men and 20% of women. The hypertrophy is concentric, usually without narrowing of the outflow tract, and is particularly severe in the area of the posterior and inferior walls of the left ventricle [47–53]. Restriction-type filling obstruction, characteristic of other storage diseases, is rare in FD. Diastolic dysfunction of the slow relaxation type predominates. As the disease progresses, LV systolic function also becomes impaired and full-blown congestive heart failure develops. The cardiological diagnostic algorithm is shown in Table 3. In the cardiological diagnosis of patients with cardiac wall hypertrophy, family history can be an important element pointing towards an FD diagnosis. Apart from the intuitive questions related to a family history of cardiovascular disease, it seems important that the cardiologists inquire about other clinical presentations (e.g. neurological or nephrological) among family members related to the patient.

Electrocardiography (ECG) — reveals the following changes [52, 53]:

— features of LV hypertrophy with deep negative T waves,

— shortened PQ interval in the early stage of the disease, which is associated with the loss of the “electrical insulator” function of the fibrous ring between the atria and ventricles,

— conduction disturbances at different levels of the conduction system,

— supraventricular and ventricular arrhythmias,

— features of cardiac ischaemia that can lead to acute coronary syndromes and cerebrovascular events in young people,

— ECG changes characteristic of valvular heart defects.

In recent years, ECG-based scoring systems have been proposed to substantiate the diagnosis of FD with a hypertrophic cardiomyopathy phenotype FD-ECG Score). Although shortening of the PR interval is most often due to accelerated conduction via physiological pathways (Figure 1), co-occurrence of FD with typical pre-excitation syndromes has also been described. Therefore, in patients with FD and shortened PR it seems reasonable to perform electrophysiological tests to exclude pre-excitation syndrome.

The treatment of arrhythmias and conduction disturbances in patients with FD does not generally differ from the recommendations given in the guidelines of cardiological scientific societies. An unresolved issue is the assessment of the risk of sudden death in patients with Fabry cardiomyopathy. The risk calculators popularly used in hypertrophic cardiomyopathy

(e.g. HCM Risk-HCM Score or AHA HCM SCD Score), according to their developers, should not be used in the FD patient population. Reports on the analysis of interventions involving the implantation of implantable cardioverter-defibrillators in FD patients, among others, suggest that these very patients are at higher risk of ventricular arrhythmias. For this reason, risk stratification of sudden cardiac death should be individualised in FD patients.

Echocardiography is an essential step in the diagnostic algorithm and monitoring of therapeutic effects in patients with suspected FD. It is necessary to use all available examination techniques: 2D, M-mode, Doppler, tissue Doppler echocardiography (TDE; tissue Doppler imaging [TDI]) and strain analysis (Figure 2). The examination protocol should include assessment of: morphology, size of both systolic and diastolic function of the left and right ventricles, atria, great vessels, assessment of the valvular apparatus of the heart, estimated pulmonary circulation pressure and assessment of the pericardium [54–57].

— **2D transthoracic imaging** — the characteristic features of cardiomyopathy in FD on 2D imaging is left and/or right ventricular myocardial thickening, once secondary causes have been excluded. An important differentiating feature between cardiomyopathy in FD and hypertrophic cardiomyopathy (HCM) is LV morphology with concentric thickening of its walls without narrowing in the outflow tract. It is extremely important to assess both the wall thickness of individual LV segments and to calculate left ventricular mass (LVM) and LVMI values. It is necessary to determine all indices of LV diastolic dysfunction. In more advanced stages of the disease, reduced systolic function is present. The classic echocardiographic picture in FD corresponds to the pathophysiology of hypertrophic cardiomyopathy with diastolic dysfunction without features of LV and atrial dilation with features of elevated filling pressure. The following are also characteristic: granular, thickened myocardium, mainly in the LV inferior and posterior wall, normal LV systolic function with impaired diastolic compliance. Myocardial changes are accompanied by thickening of the heart valves.

— **Assessment of longitudinal strain** is an essential component of a correctly performed echocardiogram in patients with suspected FD. This technique allows the assessment of both left and right ventricular myocardium, as well as multidimensional atrial function. The speckle-tracking echocardiography (STE) technique makes it possible to assess global longitudinal strain (GLS) and segmental strain. In addition, this technique allows the determination of transverse and circular strain and strain rate. Several studies have shown that GLS function deteriorates significantly as the disease progresses [55–57].

— **Three-dimensional (3D) echocardiography** allows for increased precision in the assessment of cardiac morphology and function in selected cases. The use of this technique is an important adjunct to standard measurements, especially in the context of assessing the volume and systolic function of cardiac chambers, as well as assessing the significance of valvular defects, in exceptional cases of stress testing. The 3D examination, particularly the transesophageal examination, is of value in terms of qualification for valvular surgery, both cardiac and percutaneous.
— **Echocardiography with contrast agent administration** is helpful in identifying intracardiac thrombi or insufficient acoustic window.

Echocardiography is a useful method of monitoring patients and should be performed whenever there is a clinical indication and as a form of monitoring every 6–12 months, regardless of clinical status.

Cardiac magnetic resonance (CMR) makes it possible to assess the development of inflammation and fibrosis in response to globotriaosylceramide accumulation. This examination provides a comprehensive assessment of cardiac anatomy, segmental and global ventricular function and tissue characteristics for both early differential diagnosis and disease staging [58]. Detection and quantification of myocardial fibrosis using late gadolinium enhancement (LGE) and T1 mapping are key diagnostic and prognostic features in patients with FD (Figure 3).

T1 mapping is a well-established and reproducible CMR technique for characterising myocardial tissue, including assessment of the longitudinal relaxation time of myocardial tissue without contrast agent administration. A characteristic feature is the low level of native T1 mapping at an earlier stage of glycosphingolipid storage in myocytes without endocardial involvement. These changes occur before the development of significant hypertrophy and fibrosis of the muscle. In the later stage of the disease, such a picture occurs in up to approximately 50% of FD patients [58].

Nordin et al. [59] proposed a three-phase model of myocardial involvement in FD:

— storage beginning in childhood with progressively lower T1 mapping, still without the myocardial hypertrophy and fibrosis seen in LGE;
— inflammation and/or hypertrophy, with low T1 levels, beginning with myocardial hypertrophy (mainly in males) and T2 mapping indicating inflammation in the baso-infero-lateral segment associated with LGE fibrosis;

— fibrosis and/or impaired contractility with increased T1 values (pseudonormalisation) and fibrosis present in the LGE, with wall thinning in the baso-infero-lateral segments of the left ventricle.

Typical of FD is intramural myocardial fibrosis in the baso-infero-lateral and antero-lateral segments. Less commonly, LGE fibrosis has also been described in the basal antero-septal and apical segments in patients with asymmetric septal hypertrophy and apical hypertrophy. This type of fibrosis in the central part of the myocardium is presumed to be due to increased stress at the interface between the fibrous mitral ring and the left ventricular midwall. There is growing evidence that a zone of fibrosis may develop before left ventricular hypertrophy, especially in women. These patients are a group at particular risk of ventricular arrhythmias and sudden cardiac death. Some investigators suggest considering implantation of a cardioverter-defibrillator for primary prevention in FD patients with significant fibrosis identified on CMR using LGE and with ventricular arrhythmias. These recommendations are currently not included in the guidelines and a specific sudden cardiac death risk calculator for FD patients has not been established. According to expert recommendations, in the absence of contraindications, CMR should be considered in all adult patients (class IIa recommendations). CMR is also useful for monitoring adult patients with FD — consideration should be given to repeating it every 5 years to assess fibrosis progression and left ventricular function based on disease severity (class IIb recommendations) [60–64].

Radioisotope studies (single-photon emission computed tomography (SPECT) and positron emission tomography [PET]) allow assessment of coronary perfusion. Numerous studies in FD patients have demonstrated abnormal perfusion without lesions in the epicardial coronary arteries, suggesting microvascular dysfunction. No perfusion or coronary flow reserve improvement was observed after 12 months of specific treatment.

The combination of PET and CMR (a hybrid study) allows us to assess the role of inflammation in the diagnosis of FD [63]. The first paper on a small group (13 patients) undergoing PET/CMR was published in 2015. The authors observed focal 18F-fluorodeoxyglucose (18F-FDG) tracer uptake in all patients with T1 abnormalities and fibrosis on CMR using LGE. Elevated troponin levels were also found in this group of patients [62]. Later studies documented inflammation in early FD based on PET (increased focal 18F-FDG uptake) and CMR (increased signal intensity on T2 images) [63]. Abnormal glucose metabolism on PET with 18F-FDG correlates with echocardiographic parameters of hypertrophy. However, the studies do not explain the mechanisms of preferential fibrosis of the basal inferolateral wall of the left ventricle [61].

Experimental studies have used 123I metaiodobenzylguanidine (MIBG) scintigraphy to determine whether cardiac sympathetic innervation may be dysfunctional in FD patients. Ponsiglione et al. [64] demonstrated reduced MIBG uptake in the inferolateral wall compared with the septum and anterolateral walls in patients with fibrosis and thinning of the inferolateral wall. Additionally, they proposed three patterns of 123I-MIBG uptake and fibrosis of the inferolateral wall:

— normal MIBG uptake without fibrosis,
— reduced MIBG uptake without fibrosis,
— reduced MIBG uptake with locally corresponding fibrosis.

The findings suggest that sympathetic nerve damage may precede myocardial fibrosis in this area. Imaging studies using 123I-MIBG, which is a norepinephrine analogue, may play a unique role in assessing the risk of developing ventricular arrhythmias and sudden cardiac death by assessing myocardial denervation [62–64].

CLINICAL PICTURE AND NEPHROLOGICAL DIAGNOSIS

Patients with FD are at high risk of developing chronic kidney disease (CKD). The prevalence of FD in dialysis patients has been estimated at 0.21% for men and 0.15% for women, indicating a much higher incidence than in the general population [5]. A complex pathogenesis characterises renal involvement in FD. Glycosphingolipid globotriaosylceramide (Gb3) deposition due to low α-GAL A enzyme activity leads to hypertrophy of endothelial cells, particularly podocytes, resulting in cellular damage, podocyturia and effacement of foot processes [66]. Smooth muscle cell proliferation, release of inflammatory and profibrotic mediators, increased oxidative stress, vasoconstriction, and ischaemia of renal structures lead to glomerular hardening, thickening of capillary walls, tubular atrophy, interstitial pulmonary fibrosis, and arteriosclerosis [67, 68]. The symptoms associated with glomerular damage are similar to those observed in diabetic nephropathy, with hyperfiltration in the early stages, albuminuria, proteinuria and a subsequent gradual decrease in glomerular filtration rate (GFR) [5].

The clinical picture is not typical of FD but is associated with glomerular damage. Two clinical presentations of FD have been described: the classic type 1 phenotype and the non-classic or late-onset type 2 phenotype. In the classic type, patients up to 16 usually present with albuminuria; those between 17 and 30 have proteinuria exceeding 1 g/24 hours, while those over 30 develop features of CKD. As a result, untreated men with the classic phenotype, in particular, usually develop end-stage renal disease (ESRD) between the fourth and fifth decades

of life [69, 70]. The late-onset phenotype is characterised mainly by cardiac damage, but may also include features of kidney damage, typically in the chronic cardiorenal syndrome type 2 [71].

It is worth remembering that perihilar cysts are more common in FD compared to other nephropathies, regardless of age, gender and stage of CKD [72].

FD-specific biomarkers and bio-indicators:

— lyso-Gb3 — is an established bio-indicator for confirming the diagnosis of FD, especially in the population of women in whom α-GAL A activity is often normal. The Lyso-Gb3 concentration is also considered a prognostic factor for FD complications, such as end-stage renal disease, atrial fibrillation or cerebrovascular events, and its determination also plays an important role in monitoring the effectiveness of FD treatment [67–75];

— Gb3 — there are elevated levels of Gb3 secreted from renal tubule cells and urinary tract epithelial cells in the urine of FD patients. This bio-indicator may have a diagnostic function in FD screening tests. Urinary Gb3 concentration varies depending on the genotype, gender and implemented causal treatment [74].

Renal non-specific bio-indicators:

— proteinuria (albuminuria) — when it comes to identifying the initial stage of nephropathy in the course of FD, the sensitivity of the test is low. In some patients with FD, proteinuria may not appear even at an advanced stage of chronic kidney disease [74]. Despite the outlined limitations, assessment of proteinuria and albuminuria in patients with FD should be performed as soon as suspicion is raised, followed by regular monitoring to control renal function and the effectiveness of causal and supportive treatment;

— estimated glomerular filtration rate (eGFR) — remains the primary method of assessing renal function in CKD, including in patients with FD nephropathy. The diagnosis of early GFR decline in patients with FD and CKD is made difficult due to the inaccuracy of GFR estimates based on serum creatinine levels. Overestimation of the actual GFR may be particularly important in male patients with FD. Moreover, it should be remembered that in some patients hyperfiltration and an increase in GFR values may be the first symptom of kidney disease with FD. It is important to note that the absence of changes in GFR values does not indicate the absence of renal damage in FD [70];

— podocyturia — in patients with FD may occur even before the onset of clinically apparent proteinuria [67, 68]. A direct correlation between podocyturia and proteinuria and an inverse correlation between podocyturia and eGFR has been demonstrated in male patients with FD, suggesting that there is a significant correlation between podocyturia

and the severity of Fabry nephropathy. The loss of glomerular podocytes is thought to be irreversible and the alleviation or stopping of the progress of podocyturia may be a reasonable indicator of the efficacy of treatment of kidney damage. However, various limitations to the treatment of podocyturia as an early marker of Fabry nephropathy have been reported, the most important of which is that the various techniques used to assess podocyturia have not yet been standardised to the point that they can be followed in clinical practice [74–79].

Renal biopsy — histopathological evaluation of the renal biopsy is still the primary method for the diagnosis of many nephropathies, including FD nephropathy. The information obtained from renal biopsy allows the diagnosis of FD even in patients without proteinuria and in patients with preserved renal filtration function. Gb3 deposits have been noticed in many types of fetal kidney cells as early as in the 1st week of pregnancy.

Progressive accumulation of Gb3 in podocytes is age-dependent and occurs between the early renal damage period and the onset of albuminuria [67, 69, 75].

Electron microscopy reveals layered membrane structures that look like the so-called *zebra bodies* in enlarged podocyte lysosomes. Lipid deposits are found mainly in endothelial cells, but less frequently in other cell types. Globotriaosylceramide (Gb3) was shown to be the main component of the stored material.

The diagnosis of FD-associated nephropathy is difficult and should be differentiated from: glomerulopathies associated with podocyte pathology (podocytopathies), distal tubular acidosis, Fanconi syndrome, cardio-renal syndrome, renal uremia and perihilar cysts [75–77].

Symptomatic, nephroprotective treatment of FD patients with renal involvement must be combined with specific (causal) treatment. In the general management of patients, the recommendations based on the involvement of other organs should be taken into account. In the case of FD nephropathy, guidelines for the treatment of CKD should be followed [78]. There is currently no strong evidence for the renal-protective effect of drugs from the angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) groups and flosins, routinely used for nephroprotection, but given their proven beneficial renal and cardiovascular effects in CKD patients, their administration may be considered in individual cases of FD [79]. Qualification for the initiation of renal replacement therapy in people with FD should be in accordance with the principles applicable to the population of patients in stage 5 of CKD, following the Kidney Disease: Improving Global Outcomes (KDIGO) [13]. The choice of type of dialysis (hemodialysis, peritoneal dialysis) depends on the individual patient’s preference.

The results of kidney transplantation in terms of graft and patient survival are similar to those obtained after kidney transplantation for other reasons. However, in FD patients, long-term graft survival may be adversely affected by cardiovascular involvement. Recurrence of FD nephropathy after renal transplantation (confirmed by histological examination) has been observed, with no impact on long-term graft survival [79].

CLINICAL PICTURE AND NEUROLOGICAL DIAGNOSIS

Patients diagnosed with FD are at high risk of developing and intensification of neurological symptoms. These include symptoms of peripheral nerve damage and signs of vascular brain damage [80, 81].

Symptoms of peripheral nerve damage

The first neurological symptoms may appear as early as childhood or adolescence and these are the so-called acroparesthesias, i.e. chronic pain, usually in the hand and/or foot area, described by patients as burning, tingling, breaking or a feeling of constant discomfort [82]. These symptoms usually occur with varying intensity throughout the day. Such chronic pain conditions may be accompanied by the so-called Fabry crises, i.e. attacks of very strong, tearing, breaking, burning pain, initially felt in the hands and feet, and then radiating to other parts of the body. The crises are very exhausting and can last from a few minutes to several days and are usually caused by a cold, heat, physical or emotional stress, comorbidities or alcohol consumption. During that period, decreased sweating, reduced saliva and tear production, impaired bowel motility, orthostatic disturbances and dizziness may occur [83]. This is the result of fine fibre neuropathy, which in FD is due to damage to A-delta fibres.

Neuropathic pain associated with FD occurs in 77% of men and 70% of women [84]. It is believed that hearing loss — found in as many as 41% of men and 23.3% of women, tinnitus — found in 38% of men and 25% of women, and frequent dizziness are the result of narrowing of the vessels of the cochlea and vestibule of the ear, globotriaosylceramide deposits in the spiral ganglion of the cochlea and vestibular structures and ischemic neuropathy of the auditory nerve. Hearing impairment appears already in early childhood [84].

It should be noted that autonomic functions are usually preserved in FD. Rarely, autonomic disorders occur in the form of: heart rate variability, orthostatic pressure drops and sexual disorders. These symptoms, if they occur, are usually a consequence of organ damage due to globotriaosylceramide deposits in the cells [84].

Vascular brain damage

The first symptoms of vascular brain damage in FD patients are noticeable later than symptoms of peripheral nerve damage. The risk of these symptoms increases with age, and they appear already in early adulthood [84–89].

The neurological symptoms observed in transient ischemic attack (TIA) or ischaemic stroke are typical of the disease; there are no TCI- or stroke-specific symptoms characteristic of FD alone [85]. The following mechanisms are considered in the pathomechanism of TIA/ischaemic stroke in the course of FD: overproduction of free radicals, endothelial dysfunction, prothrombotic state [87] and cardiac arrhythmias [8].

Stroke in FD accounts for 5% of all cryptogenic strokes [87]. TIA/ischemic stroke occurs in approximately 25% of men and 21.5% of women [84, 85].

It is worth remembering that magnetic resonance imaging of the brain can reveal typical, but non-specific, changes in the form of multiple ischaemic foci, microhemorrhages (11%-30%), white matter lesions, arteriopathy of vertebral and basilar arteries and the so-called *pulvinar sign* [80]. Thrombosis of veins and venous sinuses as well as arterial dissection is also described [88]. White matter lesions occur in approximately 80% of FD patients. Their localisation is not specific to the disease. Interestingly, long-term enzyme replacement therapy can result in stabilisation or even regression of such lesions [87]. Arteriopathy of the vertebral and basilar arteries, characteristic of FD, consists in their elongation, high tortuosity and the occurrence of focal aneurysmal dilatations of the arteries [87]. The so-called pulvinar sign is a hyperintense lesion seen in the thalamus on T1-weighted non-contrast MRI sequence or CT. Initially, it was thought to be a symptom typical of FD. However, it turned out to be present in only 3% of patients and it is now considered that such a lesion — due to its rarity and lack of specificity — is not FD-specific [80, 87]. The progressive nature of cerebrovascular lesions leads, over time, to cognitive and dementia disorders and psychiatric symptoms in the form of depression, anxiety, panic attacks or adaptive disorders [87].

Management of neurological disorders

Every FD patient should be monitored for signs of peripheral nervous system damage and vascular brain damage.

Once a year, medical examinations should be performed for neuropathic symptoms:

— history of typical FD pain symptoms,

— assessment of pain intensity, heat and cold intolerance using standard scales,

— vibration sensory threshold (preferably quantitatively) and assessment of the autonomic system function, including changes in blood pressure in response to standing upright,
— confirmation of fine fibre neuropathy by skin biopsy (once) [87],
— monitoring of hearing impairment according to individual patient needs.

Considering the assessment of vascular changes in the brain, it is recommended to:

— perform the first MRI in men at the age of 21 and in women at the age of 30,
— monitor MRI brain images every 3 years, unless there is a clinical need and the examination should be performed earlier. In patients with contraindications to MRI, brain imaging with CT should be performed.

The treatment of neuropathic pain, in addition to specific treatment, should include:

— first step: anticonvulsants, for example carbamazepine, gabapentin and pregabalin,
— then: serotonin and noradrenaline reuptake inhibitors, for example duloxetine [83, 86],
— other medications listed in current recommendations for the treatment of neuropathic pain — it is important to avoid pain triggers through lifestyle modification, for example, avoiding extreme temperatures, staying hydrated, using air conditioning, cooling waistcoats, face mists/sprays [83, 86].

Secondary prophylaxis of ischaemic stroke in FD should follow the recommendations for stroke [7]. No data on primary prophylaxis in FD are available [87].

CLINICAL PICTURE AND RHEUMATOLOGICAL DIAGNOSIS

In childhood, the first clinical signs are mainly musculoskeletal pain complaints, which increase with the duration of the disease (chapter: Fabry disease in children). Unfortunately, the symptoms are non-specific, which can often steer the diagnosis down the wrong path and be a diagnostic trap. This is why it is estimated that only 35% of patients with FD are correctly diagnosed. Among musculoskeletal symptoms in children and adolescents, burning pain in the limbs and numbness in the hands and feet (acroparaesthesias) predominate, and all age groups experience paroxysmal pain in the hands, feet, wrist and ankle joints.

It is worth noting that musculoskeletal symptoms depend on the duration and severity of the disease. In the early stages of FD, atypical musculoskeletal symptoms predominate. These are mainly limb pain, acroparaesthesias, polyneuropathies and sweating disorders (“FD rheumatological red flags”). In the later stages of the disease, the pain becomes chronic and generalised, and there is significant musculoskeletal impairment and multi-organ failure. The diagnosis of congenital metabolic disorder (FD, Gaucher’s disease, and mucopolysaccharidosis type I, II, VI) as causes of musculoskeletal complaints allows the implementation of appropriate

pharmacological intervention. The survey results of 360 rheumatologists and paediatricians showed a low level of knowledge about this disease [88–92].

Rheumatological symptoms of FD:

— acroparaesthesias (burning pain aggravated by heat, sun exposure, exertion, fever),
— small fibre neuropathy,
— dysautonomia,
— chronic joint pain,
— metabolic arthritis,
— deformation of the interphalangeal joints (drum flail fingers and toes),
— Charcot like arthropathy,
— gout,
— osteopenia, early-onset osteoporosis,
— osteoporotic fractures,
— carpal tunnel syndrome,
— avascular necrosis and amputations (rare),
— hypohidrosis/anhidrosis.

A diagnostic clue for rheumatologists is the coexistence of joint pain and burning pain in the limbs — acroparaesthesia — resulting from metabolic polyneuropathy, which often manifests as numbness, tingling and stinging in the fingers and toes [93, 94].

The causes of polyneuropathy in FD are complex and include:

— diabetes,
— vitamin B1, B6 and B12 deficiencies,
— systemic vasculitis,
— monoclonal gammopathy,
— Guillain–Barré syndrome.

FD pain is neuropathic and is the most common symptom during developmental age (up to 3 years). Patients describe its bimodal nature. The first type is a severe, burning episodic pain that starts in the limbs and spreads throughout the body, lasting for several hours or days, not disappearing after pain medication, referred to as Fabry’s crisis. The second type of pain is constant and chronic, with burning, stabbing and paraesthesias. This type presents in about 80% of FD patients in adulthood and most women (heterozygotes) in their first two decades of life. Exposure to heat, stress, exertion, or fever can trigger and provoke pain [94]. It is often accompanied by abnormal sweat secretion and limb slimming. Pain and hypohidrosis are more common than excessive sweating. This results in intolerance to heat and exercise (symptom

triggers) and often leads to patients missing school sports or being unable to participate in sports and recreation activities. The pain is probably related to the predominance of damage to small, unmyelinated fibres [95]. This clinical picture, together with complaints of joint pain, is very suggestive and may prove helpful in establishing the diagnosis, especially as most patients do not have joint effusion or synovitis, and ultrasound and electromyography findings are usually normal.

True arthritis is also very rarely observed in the course of FD, which always requires differentiation between infectious and autoinflammatory causes [96–102]. Other conditions requiring differentiation from rheumatological lesions in FD may include systemic sclerosis, frostbite, erythromelalgia and growing pains in the limbs.

Rheumatologic misdiagnoses of patients with FD [100–102] include the following:

— arthritis,
— systemic vasculitis (IgA vasculitis, Behçet's disease, granulomatosis with polyangiitis),
— systemic lupus erythematosus (SLE),
— sarcoidosis,
— Sjögren's syndrome,
— Rendu–Osler–Weber disease,
— rheumatic fever,
— antiphospholipid syndrome (APS),
— fever of unknown origin (FUO),
— Mediterranean fever.

Rarer rheumatological manifestations of FD include:

— polyarticular complaints resembling chronic arthritis or systemic autoimmune diseases [89, 93],
— mono- or oligoarticular arthritis mimicking inflammatory and/or degenerative arthropathy and/or neuropathic arthropathy. Patients with ulcerative acropachy and lymphoedema without comorbid diabetes, amyloidosis, renal failure, leprosy or syphilis have also been described in the course of FD [103–104]. The authors suggested that ulcerative acropachy may be associated with changes in small nonmyelinated fibres:
— Charcot foot — the destruction of the osteoarticular system of the foot as a result of neuropathic, microcirculatory and metabolic abnormalities similar to those in the diabetic foot,
— gout in the course of chronic kidney disease due to FD,
— sterile necrosis of the femoral head,

— cardiomyopathy in combination with skeletal myopathy [104],
— osteoporosis and osteopenia — comprehensive assessment is not routinely performed in patients with FD. The risk of osteoporosis in FD patients is associated with, among other things, the use of analgesics, immunosuppressants, and antiepileptic drugs, multimorbidity and low vitamin D levels, and delayed sexual maturation accompanied by gastrointestinal and endocrine disorders [105–112]. Literature data indicate that a very high proportion of FD patients are found to have osteopenia (50–88%) or osteoporosis [110–113].

Laboratory diagnosis of FD patients is based on specific and non-specific biochemical markers, imaging studies and histological evaluation of biopsy specimens [112–116].
FD-specific biomarkers/bio-indicators in patients with rheumatological manifestations of FD are the same as for the involvement of other systems.

Currently, no calcium–phosphate metabolism markers or bone turnover markers are recommended for diagnosing and monitoring musculoskeletal involvement in patients with FD.

Symptomatic treatment of the rheumatological complications of FD should be combined with specific treatment. In addition to this treatment, symptomatic treatment is recommended to relieve pain and symptoms of osteoporosis, osteopenia and polyneuropathy (Table 4). Due to the potential for variability in the clinical picture, constant and systematic monitoring of FD musculoskeletal symptoms is necessary.

CLINICAL PICTURE AND DERMATOLOGICAL DIAGNOSIS

Skin lesions are characteristic and prominent symptoms of FD. The typical FD skin lesions are shown in Table 5.

The most common FD skin lesions are diffuse angiokeratomas representing capillary malformations [117–120]. They present in approximately 65% of men and 35% of women. They usually adevelop between the ages of 5 and 10, and their number and size increase with age [117–121]. Clinically, they manifest as small, ranging from the size of a pinhead to 5 mm in diameter, flat, blotchy or slightly raised red to purplish-blue papules above the skin level, with slight surface keratosis, particularly evident in larger lesions. Angiokeratomas may be diffuse or occur in clusters. The most typical location is the region from the navel to the knees, involving the skin of the hips, buttocks and thighs [117–121]. The bilateral, symmetrical distribution of the lesions is characteristic. In men, the common location is the penile and scrotal skin. Because of the characteristic distribution of angiokeratomas in patients with FD, it is sometimes referred to as the swimming trunk pattern. Angiokeratomas may also develop on the

oral mucosa and the conjunctiva. FD angiokeratomas require differential diagnosis with angiokeratoma of Fordyce, angiokeratoma of Mibelli, angiokeratoma circumscriptum naeviformis, acral pseudolymphomatous angiokeratoma of children (APACHE), penile angiokeratomas (PEAKERs) or idiopathic angiokeratoma [117].

The second most common FD skin lesion is dilated small blood vessels, i.e. telangiectasias. They develop on the face, neck or other sun-exposed skin areas. They also appear on the vermilion border and the oral mucosa [117–120].

Sweating disorders — the most common is reduced sweating (hypohidrosis), diagnosed in more than 50% of men and almost 30% of women. Complete absence of sweating (anhidrosis) affects 25% of men and almost 5% of women. Much less frequently, increased sweating (hyperhidrosis) may occur, affecting 6% of men and more than 12% of women. Sweating disorders and neuropathic pain alter temperature sensation [117, 118, 120].

Bushy eyebrows represent the numerous facial dysmorphic features termed the Fabry face [120].

The skin manifestations of FD also include cutaneous pain, particularly in the distal parts of the hands and feet. This pain is often paroxysmal and described by patients as burning.

Dermoscopy and histological examination of skin biopsy specimens can be used in doubtful cases. Dermoscopy reveals red to blue and black vascular areas with clear borders [120]. Histopathological examination reveals vascular proliferations in the dermis, erythrocyte-filled vascular spaces and acanthotic or orthokeratotic epidermis. GL3 deposits are found in the endothelial cells of the dermis vessels [117, 120].

Diagnostic algorithm — summary

The diagnosis of FD and the multi-organ complications associated with its development should always include comprehensive investigations of all potentially involved organs. The proposed set of basic laboratory and imaging investigations in patients with FD (Tables 6 and 7) should be considered preliminary, personalised and possibly expanded depending on the clinical picture and the function of the affected organs.

GENETIC DIAGNOSIS

The molecular basis of FD is a defect in the *GLA* gene (OMIM 300644) located on the long arms of the X chromosome (Xq21.3-q22), which encodes the lysosomal enzyme α-Gal A. The coding part of the gene consists of 1,290 base pairs (bp), is divided into seven exons ranging in size from 92 to 291 bp and encodes a protein composed of 429 amino acids.

The diagnosis of FD is based on determining an enzyme deficiency and identifying a pathogenic variant in the GLA gene. To date, more than 750 sequence variants within the GLA gene have been described, including ones that truncate the protein (nonsense and frameshift mutations), lead to its misfolding (alternative splicing variation), alter its structure (structural missense variation) or affect its function (functional missense variation).

Some mutations described so far are associated with specific populations/ethnic groups. In 1991, the founder effect for the p.Ala143Pro variant was described in Nova Scotia (an Atlantic province of Canada); later, the c.640-801G>A variant, a non-classic (late-onset) phenotype with a dominant cardiac presentation, was shown to be relatively popular in Taiwanese, Japanese or Chinese populations.

The genetic diagnosis of FD is based on the sequencing of the entire GLA gene, i.e. all its exons together with flanking intron regions. The classic Sanger sequencing technique, which was initially used, has been superseded by next-generation sequencing (NGS) for about a decade. The GLA gene testing can be either targeted or based on gene panels involved in the pathogenesis of hereditary cardiomyopathies, nephropathies or other symptoms presenting in the patient. Although more costly, panel testing is usually preferred, as it allows for a simultaneous differential diagnosis of many different (ultra-)rare conditions that may cause the disease. In some cases, FD is detected incidentally as a result of an extended genetic diagnosis of a patient with a non-specific phenotype.

Recently, exome sequencing (ES), also known as whole exome sequencing (WES), with subsequent bioinformatics analysis of a selected set of genes (gene panel) or all genes, has become increasingly common. However, it is important to recognise that although NGS is currently the gold standard for diagnosing inherited diseases, it still has numerous limitations. Standard protocols cannot detect complex gene rearrangements, multiple copy number variations and changes within regulatory DNA elements (promoters, introns, enhancers, silencers, etc.). Therefore, it is important that the laboratory performing the testing is familiar with the specific molecular alterations of the gene in question and has the skills to interpret the results correctly. Interpretation of pathogenicity variants should be carried out following the latest guidelines (e.g. criteria of the American College of Medical Genetics/Association of Molecular Pathologists (ACMG/AMP), ACGS Best Practice Guidelines for Variant Classification and national recommendations of scientific societies).

In Poland, the Quality Certificate of the Polish Society of Human Genetics is the measure of the quality and correctness of the results. Despite adherence to these recommendations and quality control, not all genetic tests give a clear answer. Approximately

5%–10% of results are estimated to be inconclusive. Due to the method's limitations, a pathogenic variant may not be detected, or variants of unknown significance (VUS) may be found. In this case, a functional assay is conclusive — measuring the enzyme activity *in vivo* (for hemizygous males) or *in vitro* for variants present in females — the latter, unfortunately, is only possible through scientific collaboration. An in-depth analysis of the structure-to-function relationship of the effect of a specific mutation on enzyme activity is not only relevant for assessing the prognosis of the patient but also helps to determine the response to treatment with selected chaperones.

As mentioned above, NGS makes it possible to detect FD even in people in the asymptomatic phase. The GLA gene is the so-called useful gene listed in the list of actionable genes published by the American College of Medical Genetics and Genomics (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/). According to these recommendations, anyone with an indication for exome testing (e.g. for other health reasons: cancer, neurological disease or autism spectrum disorders) can agree to extend their test to include analysis of genes on this list.

TREATMENT

The decision to start specific therapy should be made by a specialist, in consultation with the patient and their family, in a centre conducting diagnosis and treatment of FD. In Poland, treatment cost reimbursement is possible under a therapeutic programme (Fabry disease treatment — ICD 10: E.75.2) [121]. The decision to treat is a two-step process. The physician sends an application containing the results of necessary laboratory tests, imaging and consultations. The final decision on eligibility for treatment is made by the Coordination Team for Ultra-rare Diseases appointed by the President of the National Health Fund. The effectiveness of the treatment is verified every 6 months, based on the assessment of the clinical condition and the effectiveness of the therapy.

Currently, targeted treatment under the National Health Fund therapeutic programme for patients meeting the eligibility criteria involves the selection of:

— **enzyme replacement therapy (ERT)** — recombinant forms of human alpha-galactosidase (agalsidase α and agalsidase β) or

— **migalastat** — an oral chaperone protein (chaperone therapy) that facilitates the transport of α-Gal A into lysosomes. The drug can only be used in people with a mutation defined as "sensitive" to treatment (https://galafoldhcp.com/check-amenability).

Enzyme replacement therapy involves intravenous administration of recombinant α-GAL A enzyme, which is deficient or inactive in FD patients. Infusions of the drug, usually every two weeks, can alleviate symptoms and improve patients' quality of life, as well as reduce the risk of renal, cardiac and cerebral complications [122]. The overall efficacy of agalsidase α and agalsidase β has not been directly compared in long-term randomised trials [123]. A CFDI study and a Cochrane meta-analysis (based on a systematic review of the literature) showed comparable efficacy of agalsidase α and agalsidase β at doses administered according to the SmPC. Similar conclusions are presented in international guidelines, which emphasise the lack of advantage in terms of the effectiveness of any of the therapeutic options. It is recommended to administer agalsidase α at a dose of 0.2 mg/kg body weight every 2 weeks, by intravenous infusion over 40 minutes, or agalsidase β at a dose of 1.0 mg/kg body weight every 2 weeks, by intravenous infusion at a rate of no more than 15 mg/hr during the first infusion. If well tolerated, the infusion rate can be gradually increased during subsequent administrations of the drug [124–130].

Migalastat is an oral pharmacological chaperone registered for use in patients at the age of 16 and over with a “drug-sensitive” mutation. The safety and efficacy of migalastat has been confirmed in both a blinded randomised trial [131] and the phase III FACETS and ATTRACT studies (comparison with ERT), which showed a reduction in left ventricular mass and stabilisation of renal function and plasma lyso-Gb3 levels [132, 133]. Similar results were confirmed in later publications, both in patients who started their first migalastat therapy and in patients who had previously received ERT and changed therapy to migalastat [134, 135].

There is no evidence on the optimal age at which it is best to start the treatment, so there are no uniform guidelines or conditions as to when to start infusions, and guidelines vary from country to country. Indications for initiating treatment include the patient's clinical condition and observation of signs or symptoms related to FD, as well as records of indications.

Detailed criteria for initiating FD treatment are the subject of separate studies [122, 136] — examples of organ indications are shown in Table 8.

Many experts, including the authors of this paper, tend to favour simplified indications for the treatment of FD:

— in men with classic FD when there are early clinical signs of renal, cardiac or cerebral involvement, no earlier than at the age of 8 (for migalastat >16 years of age) and/or even if there are no symptoms or signs of organ damage and the mutation found is described as pathogenic,

— in women and men with non-classical FD when there are early clinical signs of renal involvement (e.g. hyperfiltration, tubular dysfunction, albuminuria), heart or brain involvement,
— in women with non-classical FD, when there are early clinical symptoms of FD [2],
— agalsidase α, as stated in the SmPC, can be used in children (Poland has experience with the use of the drug in children from the age of 6).

A patient with FD is at risk of developing chronic kidney disease. Initially, albuminuria or an abnormal glomerular filtration rate (GFR <60 ml/min/1,73 m^2 or >130 ml/min/1,73 m^2)]. A condition considered an early marker of nephropathy in FD is glomerular hyperfiltration, defined as a GFR greater than 130 ml/min, adjusted for age (>40 years: -1 ml/min/1.73 m^2/year) [137]. In a randomised clinical trial in a paediatric population, arteriolopathy and segmental glomerulosclerosis with obliteration of the glomerulus were found in all patients with normal GFR and no albuminuria (uACR <30 mg/g) in those who underwent renal biopsy. This observation suggests treatment even without a diagnostic biopsy, with an automatic diagnosis of chronic kidney disease, in all men with a confirmed pathogenic mutation.

Cardiac changes with the phenotype of hypertrophic cardiomyopathy and/or arrhythmia and/or conduction disorders, as well as stroke are classic indications for treatment [2, 17, 122, 137]. In the absence of renal, cardiac, nervous system, vascular or gastrointestinal changes, pain alone that reduces the quality of life may be a sufficient reason to initiate ERT.

Overall, the available evidence suggests that ERT slows the progression of renal disease and results in a reduction in the features of cardiac hypertrophy, especially when initiated before the onset of fibrosis. It has also been found that ERT treatment does not reduce the incidence of stroke [138]. Enzymatic replacement therapies are among the therapies with well-established evidence of efficacy and safety, are well-documented and have the longest current track record (more than 20 years) in actual clinical practice.

Enzyme replacement therapy may also be considered in patients with severe renal failure (migalastat is contraindicated in such patients), dialysis patients, renal transplant patients or those with cognitive impairment [122].

Clinically significant FD kidney disease does not recur in the transplanted kidney, although some recipients may develop Gb3 deposition in endothelial cells that does not compromise graft function.

Contraindications to specific treatment in FD are few and depend on the assessment of the individual patient's condition [121]. Some guidelines list the following contraindications [136]:

— severe multi-organ failure or other comorbidities leading to a life expectancy of less than 1 year,
— advanced-stage renal, cardiac or brain disease that does not respond to specific therapy,
— cognitive function decline due to any cause or lack of improvement after 1 year of treatment when the only indication for therapy is neuropathic pain,
— non-compliance with medical instructions or irregular attendance at appointments,
— allergy to the components of the preparations or the occurrence of severe allergic reactions during infusion without the possibility of switching to another drug,
— patients with severe chronic renal failure with GFR of 30 ml/min/1.73 m^2 should not receive migalastat.

Additionally, a situation may arise that requires termination of specific therapy. In the drug programme for agalsidase α or agalsidase β or migalastat, such cases are:

— hypersensitivity to an active ingredient or to any of the excipients,
— serious adverse events,
— initiation of therapy with chloroquine, amiodarone, monobenzone or gentamicin — applies to treatment with agalsidase α or agalsidase β,
— pregnancy or lactation,
— significant disease progression despite treatment,
— lack of cooperation of the patient during the programme implementation [120].

Immunogenicity — formation of agalsidase antibodies

Enzyme replacement therapy with recombinant α-GAL A can lead to the formation of neutralising anti-drug antibodies (ADA), which limit the efficacy of treatment in patients with FD. In line with the conclusions of van der Veen's work from 2020, a statistically significant increase in the risk of developing antibodies occurred in men, especially in the case of nonsense mutations ($P = 0.05$), high baseline lyso-Gb3 concentrations ($P < 0.01$) and the use of agalsidase β as initial therapy ($P = 0.006$) [137].

Clinical trials have shown the formation of ADAs against recombinant agalsidase α in 24% of patients (17% after 12 months) and agalsidase β in more than 50% of patients [136–148], mostly IgG with peak concentrations around 3 months after first administration. In one of the studies, 3 patients were withdrawn after confirming the presence of immunoglobulin E in serum (IgE) or positive skin tests [149]. However, all of them successfully resumed therapy later on, and none developed anaphylaxis.

The presence of neutralising antibodies reduces the efficacy of ERT [150]. Exogenous α-GAL A forms complexes with antibodies in the bloodstream, which reduces the response to ERT. In the study by Lenders et al. inhibition was not dependent on the initially used compound (agalsidase α or agalsidase β). Additionally, agalsidase inhibition was associated with more FD symptoms, including increased bowel dysfunction, fatigue and neuropathic pain. Higher doses of ERT may eliminate neutralising antibodies [150]. At the same time, dose escalation may result in a heterogeneous, unpredictable ADA response [151]. Regardless of the increase in ADA concentrations, Gb3 concentrations decreased and cardiac and renal parameters remained stable after the enzyme dose escalation.

The analysis of the information contained in the summary of product characteristics shows that agalsidase β is more likely to trigger an immune response than agalsidase α. Cross-reactivity between antibodies against agalsidase α and agalsidase β has also been demonstrated. Neutralising ADAs may not only inhibit the activity of infused α-GAL A, but can also inhibit the endothelial uptake of α-GAL A. It has been proven that internalised α-GAL A/ADA complexes may not dissociate, which emphasises the need to find new ways to reduce PPA to increase the effectiveness of therapy in patients affected by the disease [152].

An alternative to dose escalation (to neutralise ADA) to overcome the problem of enzyme inhibition may be conversion to another molecule (from agalsidase α to agalsidase β or vice versa) [151]. The problem of the lack of standardised international standards for the determination of antibodies when assessing the immunogenicity of different ERT preparations remains unresolved.

Interestingly, immunosuppression applied after renal transplantation was associated with lower antibody concentrations and reduced ERT inhibition in a group of men with FD after renal or heart transplantation [153]. Further prospective studies are undoubtedly necessary to assess the long-term impact of immunosuppression on the effects of ERT treatment and to determine whether people with high antibody concentrations will require different dosage regimens.

Infusion-related reactions

The incidence of infusion-related reactions (IRR), defined as any related adverse events occurring after the initiation of the infusion and up to 2 hours after the end of the infusion. In clinical trials, infusion-related reactions (at least 1 reported event) occurred in 13.7% of patients treated with agalsidase α and in 67% of patients receiving agalsidase β. The most commonly observed symptoms of IRR were hypersensitivity, pruritus, nausea, dizziness, chills and

myalgia. Treatment of IRR depends on the severity of the reaction and includes reduction of the infusion rate, administration of antihistamines, antipyretics and/or corticosteroids. Premedication with antihistamines and/or corticosteroids may prevent further reactions in cases where symptomatic treatment was necessary.

Rationale for clinical practice:

- Male patients with poor clinical response (or worsening condition) to ERT infusions should be tested for agalsidase inhibition by anti-agalsidase antibodies.
- It is recommended to review the summary of product characteristics for:

  Replagal

  https://ec.europa.eu/health/documents/community-register/2016/20161006136213/anx_136213_pl.pdf

  Fabrazyme

  https://ec.europa.eu/health/documents/community-egister/2021/20210617151811/anx_151811_pl.pdf)

New therapies

In May 2023, *the European Medicines Agency* (EMA) approved another form of the drug for use in the European Union for the treatment of FD as part of enzyme replacement therapy — *pegunigalsidase α* [19]. The drug was designed to provide a prolonged plasma half-life and potentially reduce the incidence of anti-drug antibodies (against recombinant agalsidase) [140, 141]. Pegunigalsidase α showed no less effectiveness than agalsidase β in terms of the rate of loss of renal function — change in eGFR over 2 years. It has also been shown to have favourable tolerability and lower immunogenicity compared to other ERTs [141]. Several further clinical trials of new molecules are currently underway (Table 9) [142–146].

Moss α-GAL is a genetically derived form of α-GAL, currently in phase II and III of clinical trials. The source of the enzyme is a genetically modified moss — *Physcomitrella patens*. Hennerman et al. in a phase I study showed that moss α-GAL is safe and leads to prolonged reduction of Gb3 [146]. The enzyme enters cells differently from agalsidase α and agalsidase β — not through mannose-6-phosphate receptor-mediated endocytosis but directly through the mannose receptor, which is present on macrophages, endothelial cells and in the kidney.

Lucearstat and venglustat inhibit glucosylceramide synthase and reduce Gb3 production (inhibition of substrate synthesis) [142–146]. In phase II of the clinical trial with venglustat,

there were no biochemical or histological features of Fabry disease progression within 3 years of the follow-up observation [146–154]. Currently, a phase III clinical trial of venglustat is being conducted by PERIDOT, in which the main endpoint is the severity of abdominal pain and neuropathic pain [146].

Gene therapy has the potential for a long-term cure for FD and tissue-targeted treatment. New data from early-phase experimental and clinical trials are promising, but further studies are needed to establish clinical efficacy and safety. It is hypothesised that the delivered gene for α-GAL will be highly expressed in target cells, which will secrete it and transport it to lysosomes via mannose-6-phosphate receptors. Successful gene therapy requires efficient transcription, mRNA stabilisation and inhibition of replication of the vector virus (e.g. lentivirus). Several techniques are being tested, e.g., using stem/progenitor cells and cDNA integration (with the use of lentivirus or adenovirus) or lipid nanoparticles with mRNA encoding the human α-GAL enzyme [144].

NURSING CARE AND ORGANISATION OF FD CARE IN POLAND

Nursing care for FD patients requires securing the patients during the administration of enzyme replacement therapy at regular 2-week intervals. The patients require efficient preparation for infusion and supervision of the administration with possible support in case of possible complications. Caring for FD patients can also take place in the home environment. An important role in the care of the patient at home is played by the community and family nurse who helps the patient in everyday activities that are particularly difficult for them, reduces or eliminates pain by participating in pharmacotherapy and the use of non-pharmacological methods of pain relief, teaches the patient and their family how to cope with care activities and provides psychological support to the patient and family.

In Poland, a programme for the treatment of FD patients has been implemented since 2018 (no. B.104). Currently, more than 135 adult patients and 11 children are treated in 30 centres (Table 10). The Polish Forum for Fabry Disease has been operating since 2023, which brings together more than 40 experts from many fields of medicine.

Article information

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MKos received honoraria for participation in advisory boards of Takeda. MKr, MKu received honoraria for educational lectures and participation in advisory boards from: Sanofi, Takeda Amicus Theapeutics. BLZ received honoraria for lectures and participation in advisory boards of: Takeda, AstraZeneca, Novartis. MN received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda, Amicus Therapeutics, AstraZeneca, Swixx Pharma.
KMS received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda, Amicus Therapeutics, Chiesi. KP, ŁP received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda, Amicus Therapeutics. KR, DR, RS, ZŻ, MB received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda. SS received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda, Amicus Therapeutics, Novartis. MKom received honoraria for lectures and participation in advisory boards of: Sanofi, Takeda, Amicus. Other authors declared no conflict of interest.

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REFERENCES

1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010; 5: 30, doi: 10.1186/1750-1172-5-30, indexed in Pubmed: 21092187.
2. Nowicki M, Bazan-Socha S, Błażejewska-Hyzorek B, et al. Enzyme replacement therapy in Fabry disease in Poland: A position statement. Pol Arch Intern Med. 2020; 130(1): 91–97, doi: 10.20452/pamw.15117, indexed in Pubmed: 31868861.
3. Cairns T, Müntze J, Gernert J, et al. Hot topics in Fabry disease. Postgrad Med J. 2018; 94(1118): 709–713, doi: 10.1136/postgradmedj-2018-136056, indexed in Pubmed: 30559317.
4. Toyooka K. Fabry disease. Curr Opin Neurol. 2011; 24(5): 463–468, doi: 10.1097/WCO.0b013e32834a9433, indexed in Pubmed: 21825987.
5. Coelho-Ribeiro B, Silva HG, Sampaio-Marques B, et al. Inflammation and exosomes in Fabry disease pathogenesis. Cells. 2024; 13(8): 654, doi: 10.3390/cells13080654, indexed in Pubmed: 38667269.

6. Rozenfeld P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Mol Genet Metab. 2017; 122(3): 19–27, doi: 10.1016/j.ymgme.2017.09.004, indexed in Pubmed: 28947349.
7. Marques ARA, Saftig P. Lysosomal storage disorders — challenges, concepts and avenues for therapy: Beyond rare diseases. J Cell Sci. 2019; 132(2): jcs221739, doi: 10.1242/jcs.221739, indexed in Pubmed: 30651381.
8. Bartolotta C, Filogamo M, Colomba P, et al. Fp907 history of Anderson-Fabry disease. Nephrol Dial Transplant. 2015; 30(Suppl 3): iii379, doi: 10.1093/ndt/gfv186.08.
9. Duro G, Zizzo C, Cammarata G, et al. Mutations in the GLA gene and lysogb3: is it really Anderson-Fabry disease? IJMS. 2018; 19(12): 3726, doi: 10.3390/ijms19123726.
10. Michaud M, Mauhin W, Belmatoug N, et al. When and how to diagnose Fabry disease in clinical pratice. Am J Med Sci. 2020; 360(6): 641–649, doi: 10.1016/j.amjms.2020.07.011, indexed in Pubmed: 32723516.
11. Germain DP, Fouilhoux A, Decramer S, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet. 2019; 96(2): 107–117, doi: 10.1111/cge.13546, indexed in Pubmed: 30941742.
12. Ries M, Moore DF, Robinson CJ, et al. Quantitative dysmorphology assessment in Fabry disease. Genet Med. 2006; 8(2): 96–101, doi: 10.1097/01.gim.0000200950.25118.dd, indexed in Pubmed: 16481892.
13. Ramaswami U, Whybra C, Parini R, et al. Clinical manifestations of Fabry disease in children: Data from the Fabry Outcome Survey. Acta Paediatr. 2006; 95(1): 86–92, doi: 10.1080/08035250500275022, indexed in Pubmed: 16498740.
14. Hopkin RJ, Bissler J, Banikazemi M, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatr Res. 2008; 64(5): 550–555, doi: 10.1203/PDR.0b013e318183f132, indexed in Pubmed: 18596579.
15. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008; 372(9647): 1427–1435, doi: 10.1016/S0140-6736(08)61589-5, indexed in Pubmed: 18940466.
16. Marchesoni C, Cisneros E, Pfister P, et al. Brain MRI findings in children and adolescents with Fabry disease. J Neurol Sci. 2018; 395: 131–134, doi: 10.1016/j.jns.2018.10.009, indexed in Pubmed: 30316069.
17. Cabrera-Salazar MA, O'Rourke E, Charria-Ortiz G, et al. Radiological evidence of early cerebral microvascular disease in young children with Fabry disease. J Pediatr. 2005; 147(1): 102–105, doi: 10.1016/j.jpeds.2005.03.004, indexed in Pubmed: 16027705.

18. Caputo F, Lungaro L, Galdi A, et al. Gastrointestinal involvement in Anderson-Fabry disease: A narrative review. Int J Environ Res Public Health. 2021; 18(6): 3320, doi: 10.3390/ijerph18063320, indexed in Pubmed: 33807115.
19. Hilz MJ, Arbustini E, Dagna L, et al. Non-specific gastrointestinal features: Could it be Fabry disease? Dig Liver Dis. 2018; 50(5): 429–437, doi: 10.1016/j.dld.2018.02.011, indexed in Pubmed: 29602572.
20. Kalkum G, Pitz S, Karabul N, et al. Paediatric Fabry disease: Prognostic significance of ocular changes for disease severity. BMC Ophthalmol. 2016; 16(1): 202, doi: 10.1186/s12886-016-0374-2, indexed in Pubmed: 27852300.
21. Davey PG. Fabry disease: A survey of visual and ocular symptoms. Clin Ophthalmol. 2014; 8: 1555–1560, doi: 10.2147/OPTH.S66748, indexed in Pubmed: 25170250.
22. Luna P, Boggio P, Larralde M. Dermatologic aspects of Fabry disease. J Inborn Errors Metabol Screen. 2016; 4: 232640981666135, doi: 10.1177/2326409816661353.
23. Chan B, Adam DN. A review of Fabry disease. Skin Therapy Lett. 2018; 23(2): 4–6, indexed in Pubmed: 29562089.
24. Silva CA, Moura-Neto JA, Dos Reis MA, et al. Renal manifestations of Fabry disease: A narrative review. Can J Kidney Health Dis. 2021; 8: 2054358120985627, doi: 10.1177/2054358120985627, indexed in Pubmed: 33786192.
25. Germain DP, Arad M, Burlina A, et al. The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease – A systematic literature review by a European panel of experts. Mol Genet Metab. 2019; 126(3): 224–235, doi: 10.1016/j.ymgme.2018.09.007, indexed in Pubmed: 30413388.
26. Echevarria L, Benistan K, Toussaint A, et al. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016; 89(1): 44–54, doi: 10.1111/cge.12613, indexed in Pubmed: 25974833.
27. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. Mol Genet Metab. 2008; 93(2): 112–128, doi: 10.1016/j.ymgme.2007.09.013, indexed in Pubmed: 18037317.
28. Germain DP, Altarescu G, Barriales-Villa R, et al. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. Mol Genet Metab. 2022; 137(1-2): 49–61, doi: 10.1016/j.ymgme.2022.07.010, indexed in Pubmed: 35926321.

29. Germain DP, Levade T, Hachulla E, et al. Challenging the traditional approach for interpreting genetic variants: Lessons from Fabry disease. Clin Genet. 2022; 101(4): 390–402, doi: 10.1111/cge.14102, indexed in Pubmed: 34927718.
30. Wanner C, Arad M, Baron R, et al. European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab. 2018; 124(3): 189–203, doi: 10.1016/j.ymgme.2018.06.004, indexed in Pubmed: 30017653.
31. Whybra C, Miebach E, Mengel E, et al. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genet Med. 2009; 11(6): 441–449, doi: 10.1097/GIM.0b013e3181a23bec, indexed in Pubmed: 19346951.
32. Viggiano E, Politano L. X chromosome inactivation in carriers of Fabry disease: Review and meta-analysis. Int J Mol Sci. 2021; 22(14): 7663, doi: 10.3390/ijms22147663, indexed in Pubmed: 34299283.
33. Gibas AL, Klatt R, Johnson J, et al. Disease rarity, carrier status, and gender: A triple disadvantage for women with Fabry disease. J Genet Couns. 2008; 17(6): 528–537, doi: 10.1007/s10897-008-9179-7, indexed in Pubmed: 18931895.
34. Gragnaniello V, Burlina AP, Commone A, et al. Newborn screening for Fabry disease: Current status of knowledge. Int J Neonatal Screen. 2023; 9(2): 31, doi: 10.3390/ijns9020031, indexed in Pubmed: 37367212.
35. Laney DA, Clarke V, Foley A, et al. The impact of Fabry disease on reproductive fitness. JIMD Rep. 2017; 37: 85–97, doi: 10.1007/8904_2017_17, indexed in Pubmed: 28324326.
36. Ries M, Gal A. Genotype–phenotype correlation in Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G. ed. Fabry Disease: Perspectives from 5 Years of FOS. Oxford PharmaGenesis, Oxford, UK 2006.
37. Koca S, Tümer L, Okur İ, et al. High incidence of co-existing factors significantly modifying the phenotype in patients with Fabry disease. Gene. 2019; 687: 280–288, doi: 10.1016/j.gene.2018.11.054, indexed in Pubmed: 30468909.
38. Germain DP, Benistan K, Angelova L. X-linked inheritance and its implication in the diagnosis and management of female patients in Fabry disease. Rev Med Intern. 2010; 31(Suppl 2): S209–S213, doi: 10.1016/S0248-8663(10)70013-8, indexed in Pubmed: 21211665.
39. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med

Genet. 2001; 38(11): 769–775, doi: 10.1136/jmg.38.11.769, indexed in Pubmed: 11732485.

40. Wang RY, Lelis A, Mirocha J, et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007; 9(1): 34–45, doi: 10.1097/gim.0b013e31802d8321, indexed in Pubmed: 17224688.
41. Niemann M, Herrmann S, Hu K, et al. Differences in Fabry cardiomyopathy between female and male patients: Consequences for diagnostic assessment. JACC Cardiovasc Imaging. 2011; 4(6): 592–601, doi: 10.1016/j.jcmg.2011.01.020, indexed in Pubmed: 21679893.
42. Fukushima M, Tsuchiyama Y, Nakato T, et al. A female heterozygous patient with Fabry's disease with renal accumulation of trihexosylceramide detected with a monoclonal antibody. Am J Kidney Dis. 1995; 26(6): 952–955, doi: 10.1016/0272-6386(95)90061-6, indexed in Pubmed: 7503071.
43. Lidove O, Barbey F, Niu DM, et al. Fabry in the older patient: Clinical consequences and possibilities for treatment. Mol Genet Metab. 2016; 118(4): 319–325, doi: 10.1016/j.ymgme.2016.05.009, indexed in Pubmed: 27221354.
44. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet. 2001; 38(11): 750–760, doi: 10.1136/jmg.38.11.750, indexed in Pubmed: 11694547.
45. Linhart A, Lubanda JC, Palecek T, et al. Cardiac manifestations in Fabry disease. J Inherit Metab Dis. 2001; 24(Suppl 2): 75–83, doi: 10.1023/a:1012428009627, indexed in Pubmed: 11758683.
46. Linhart A, Magage S, Palecek T, et al. Cardiac involvement in Fabry disease. Acta Paediatr Suppl. 2002; 91(439): 15–20, doi: 10.1111/j.1651-2227.2002.tb03104.x, indexed in Pubmed: 12572837.
47. Wilcox WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004; 75(1): 65–74, doi: 10.1086/422366, indexed in Pubmed: 15154115.
48. Beck M, Ricci R, Widmer U, et al. Fabry disease: Overall effects of agalsidase alfa treatment. Eur J Clin Invest. 2004; 34(12): 838–844, doi: 10.1111/j.1365-2362.2004.01424.x, indexed in Pubmed: 15606727.
49. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018; 123(4): 416–427, doi: 10.1016/j.ymgme.2018.02.014, indexed in Pubmed: 29530533.

50. Ortiz A, Abiose A, Bichet DG, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: Data from the Fabry Registry. J Med Genet. 2016; 53(7): 495–502, doi: 10.1136/jmedgenet-2015-103486, indexed in Pubmed: 26993266.
51. Linhart A, Germain DP, Olivotto I, et al. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail. 2020; 22(7): 1076–1096, doi: 10.1002/ejhf.1960, indexed in Pubmed: 32640076.
52. Jastrzębski M, Petkow-Dimitrow P. Electrocardiogram in Fabry's disease [article in Polish]. Kardiol Pol. 2008; 66: 688–692.
53. Sheth KJ, Thomas JP. Electrocardiograms in Fabry's disease. J Electrocardiol. 1982; 15(2): 153–156, doi: 10.1016/s0022-0736(82)80010-1, indexed in Pubmed: 6461709.
54. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004; 34(3): 236–242, doi: 10.1111/j.1365-2362.2004.01309.x, indexed in Pubmed: 15025684.
55. Azevedo O, Cordeiro F, Gago MF, et al. Fabry disease and the heart: A comprehensive review. Int J Mol Sci. 2021; 22(9): 4434, doi: 10.3390/ijms22094434, indexed in Pubmed: 33922740.
56. Spinelli L, Giugliano G, Imbriaco M, et al. Left ventricular radial strain impairment precedes hypertrophy in Anderson-Fabry disease. Int J Cardiovasc Imaging. 2020; 36(8): 1465–1476, doi: 10.1007/s10554-020-01847-z, indexed in Pubmed: 32306159.
57. Shanks M, Thompson RB, Paterson ID, et al. Systolic and diastolic function assessment in fabry disease patients using speckle-tracking imaging and comparison with conventional echocardiographic measurements. J Am Soc Echocardiogr. 2013; 26(12): 1407–1414, doi: 10.1016/j.echo.2013.09.005, indexed in Pubmed: 24125876.
58. Perry R, Shah R, Saiedi M, et al. The role of cardiac imaging in the diagnosis and management of Anderson-Fabry disease. JACC Cardiovasc Imaging. 2019; 12(7 Pt 1): 1230–1242, doi: 10.1016/j.jcmg.2018.11.039, indexed in Pubmed: 31272606.
59. Nordin S, Kozor R, Vijapurapu R, et al. Myocardial storage, inflammation, and cardiac phenotype in Fabry disease after one year of enzyme replacement therapy. Circ Cardiovasc Imaging. 2019; 12(12): e009430, doi: 10.1161/CIRCIMAGING.119.009430, indexed in Pubmed: 31826677.
60. Lanzillo C, Fedele E, Martino A, et al. Cardiac magnetic resonance in Fabry disease. Eur Heart J Suppl. 2023; 25(Suppl C): C200–C204, doi: 10.1093/eurheartjsupp/suad045, indexed in Pubmed: 37125302.

61. Tower-Rader A, Jaber WA. Multimodality imaging assessment of Fabry disease. Circ Cardiovasc Imaging. 2019; 12(11): e009013, doi: 10.1161/CIRCIMAGING.119.009013, indexed in Pubmed: 31718277.
62. Nappi C, Ponsiglione A, Pisani A, et al. Role of serial cardiac F-FDG PET-MRI in Anderson-Fabry disease: A pilot study. Insights Imaging. 2021; 12(1): 124, doi: 10.1186/s13244-021-01067-6, indexed in Pubmed: 34487259.
63. Linhart A, Germain DP, Olivotto I, et al. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail. 2020; 22(7): 1076–1096, doi: 10.1002/ejhf.1960, indexed in Pubmed: 32640076.
64. Ponsiglione A, De Giorgi M, Ascione R, et al. Advanced CMR Techniques in Anderson-Fabry Disease: State of the Art. Diagnostics (Basel). 2023; 13(15): 2598, doi: 10.3390/diagnostics13152598, indexed in Pubmed: 37568960.
65. Doheny D, Srinivasan R, Pagant S, et al. Fabry disease: Prevalence of affected males and heterozygotes with pathogenic mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. J Med Genet. 2018; 55(4): 261–268, doi: 10.1136/jmedgenet-2017-105080, indexed in Pubmed: 29330335.
66. Najafian B, Tøndel C, Svarstad E, et al. Accumulation of globotriaosylceramide in podocytes in fabry nephropathy is associated with progressive podocyte loss. J Am Soc Nephrol. 2020; 31(4): 865–875, doi: 10.1681/ASN.2019050497, indexed in Pubmed: 32127409.
67. Rozenfeld PA, de Los Angeles Bolla M, Quieto P, et al. Pathogenesis of Fabry nephropathy: The pathways leading to fibrosis. Mol Genet Metab. 2020; 129(2): 132–141, doi: 10.1016/j.ymgme.2019.10.010, indexed in Pubmed: 31718986.
68. Del Pino M, Andrés A, Bernabéu AÁ, et al. Fabry nephropathy: An evidence-based narrative review. Kidney Blood Press Res. 2018; 43(2): 406–421, doi: 10.1159/000488121, indexed in Pubmed: 29558749.
69. Riccio E, Sabbatini M, Bruzzese D, et al. Glomerular hyperfiltration: An early marker of nephropathy in Fabry disease. Nephron. 2019; 141(1): 10–17, doi: 10.1159/000493469, indexed in Pubmed: 30466100.
70. Schiffmann R, Hughes DA, Linthorst GE, et al. Screening, diagnosis, and management of patients with Fabry disease: Conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017; 91(2): 284–293, doi: 10.1016/j.kint.2016.10.004, indexed in Pubmed: 27998644.

71. Capuano I, Buonanno P, Riccio E, et al. Parapelvic cysts: An imaging marker of kidney disease potentially leading to the diagnosis of treatable rare genetic disorders? A narrative review of the literature. J Nephrol. 2022; 35(8): 2035–2046, doi: 10.1007/s40620-022-01375-0, indexed in Pubmed: 35749008.
72. Nowak A, Beuschlein F, Sivasubramaniam V, et al. Lyso-Gb3 associates with adverse long-term outcome in patients with Fabry disease. J Med Genet. 2022; 59(3): 287–293, doi: 10.1136/jmedgenet-2020-107338, indexed in Pubmed: 33495303.
73. Simonetta I, Tuttolomondo A, Daidone M, et al. Biomarkers in Anderson-Fabry disease. Int J Mol Sci. 2020; 21(21): 8080, doi: 10.3390/ijms21218080, indexed in Pubmed: 33138098.
74. Rodríguez ALM, Abraham MVS, Vázquez MYV, et al. Histopathological findings in renal biopsies in Anderson–Fabry disease. Case series. Rev Med Hosp Gen Mex. 2018; 81(4): 243–247, doi: 10.1016/j.hgmx.2016.08.010.
75. Johar L, Lee G, Martin-Rios A, et al. Polycystic kidney disease complicates renal pathology in a family with Fabry disease. Mol Genet Metab Rep. 2022; 33: 100934, doi: 10.1016/j.ymgmr.2022.100934, indexed in Pubmed: 36406818.
76. Król N, Trąd S, Milian-Ciesielska K, et al. Fabry disease related nephropathy – case family report and literature review. Eur J Clin Exp Med. 2022; 20(4): 482–487, doi: 10.15584/ejcem.2022.4.15.
77. Levin A, Stevens PE, Bilous RW, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kid Inter Suppl. 2013; 3(1): 1–150, doi: 10.1038/kisup.2012.73.
78. Stompór T, Adamczak M, Kurnatowska I, et al. Pharmacological nephroprotection in non-diabetic chronic kidney disease-clinical practice position statement of the Polish Society of Nephrology. J Clin Med. 2023; 12(16): 5184, doi: 10.3390/jcm12165184, indexed in Pubmed: 37629226.
79. Ersözlü S, Desnick RJ, Huynh-Do U, et al. Long-term outcomes of kidney transplantation in Fabry disease. Transplantation. 2018; 102(11): 1924–1933, doi: 10.1097/TP.0000000000002252, indexed in Pubmed: 29688992.
80. Cocozza S, Russo C, Pontillo G, et al. Neuroimaging in Fabry disease: Current knowledge and future directions. Insights Imaging. 2018; 9(6): 1077–1088, doi: 10.1007/s13244-018-0664-8, indexed in Pubmed: 30390274.

81. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010; 5: 1–49, doi: 10.1186/1750-1172-5-30.
82. Lenders M, Brand E. Fabry disease: The current treatment landscape. Drugs. 2021; 81(6): 635–645, doi: 10.1007/s40265-021-01486-1, indexed in Pubmed: 33721270.
83. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet. 2001; 38(11): 750–760, doi: 10.1136/jmg.38.11.750, indexed in Pubmed: 11694547.
84. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001; 38(11): 769–775, doi: 10.1136/jmg.38.11.769, indexed in Pubmed: 11732485.
85. Mehat A, Hughes DA. Fabry disease 2002. In: Adam MP, Mirzaa GM, Pagon RA. ed. GeneReviews. University of Washington, Seattle (WA) 1993–2023.
86. Mishra V, Banerjee A, Gandhi AB, et al. Stroke and Fabry disease: A review of literature. Cureus. 2020; 12(12): e12083, doi: 10.7759/cureus.12083, indexed in Pubmed: 33489501.
87. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018; 123(4): 416–427, doi: 10.1016/j.ymgme.2018.02.014, indexed in Pubmed: 29530533.
88. Moiseev S, Karovaikina E, Novikov P. What rheumatologist should know about FD? Ann Rheum Dis. 2020; 79: 6.
89. Lidove O, Zeller V, Chicheportiche V, et al. Musculoskeletal manifestations of Fabry disease: A retrospective study. Joint Bone Spine. 2016; 83(4): 421–426, doi: 10.1016/j.jbspin.2015.11.001, indexed in Pubmed: 26697993.
90. Paim-Marques L, Cavalcante AV, Verçosa I, et al. Frequency of Fabry disease in a juvenile idiopathic arthritis cohort. Pediatr Rheumatol Online J. 2021; 19(1): 91, doi: 10.1186/s12969-021-00563-9, indexed in Pubmed: 34118938.
91. Hopkin RJ, Bissler J, Banikazemi M, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatr Res. 2008; 64(5): 550–555, doi: 10.1203/PDR.0b013e318183f132, indexed in Pubmed: 18596579.
92. Politei J, Remondino G, Heguilen R, et al. When arthralgia is not arthritis. Eur J Rheumatol. 2016; 3(4): 182–184, doi: 10.5152/eurjrheum.2016.15073, indexed in Pubmed: 28149664.

93. Slouma M, Ben Dhia S, Cheour E, et al. Acroparesthesias: An overview. Curr Rheumatol Rev. 2024; 20(2): 115–126, doi: 10.2174/0115733971254976230927113202, indexed in Pubmed: 37921132.
94. Johnson SA, Shouman K, Shelly S, et al. Small fiber neuropathy incidence, prevalence, longitudinal impairments, and disability. Neurology. 2021; 97(22): e2236–e2247, doi: 10.1212/WNL.0000000000012894, indexed in Pubmed: 34706972.
95. Conigliaro P, De Martino E, Giuseppe I, et al. Severe lupus nephritis: An unexpected association with Fabry disease. Lupus. 2020; 29(8): 1004–1005, doi: 10.1177/0961203320928396, indexed in Pubmed: 32493151.
96. Yanfang W, Juanjuan H, Shengli Z, et al. Fabry disease misdiagnosing as polymyalgia rheumatica. Medicine (Baltimore). 2023; 102(44): e34630, doi: 10.1097/md.0000000000034630, indexed in Pubmed: 37933054.
97. Sen R, Borghoff K, Foster KW, et al. Hydroxychloroquine and Fabry disease: Three case reports examining an unexpected pathologic link and a review of the literature. Case Rep Rheumatol. 2022; 2022: 2930103, doi: 10.1155/2022/2930103, indexed in Pubmed: 35860433.
98. Luo Yi, Wu Di, Shen M. Recurrent fever of unknown origin: An overlooked symptom of Fabry disease. Mol Genet Genomic Med. 2020; 8(10): e1454, doi: 10.1002/mgg3.1454, indexed in Pubmed: 32797665.
99. Cimaz R, Guillaume S, Hilz MJ, et al. Awareness of Fabry disease among rheumatologists--current status and perspectives. Clin Rheumatol. 2011; 30(4): 467–475, doi: 10.1007/s10067-010-1445-z, indexed in Pubmed: 20393867.
100. Thévenot C. Joint involvement in patients with Fabry’s disease. A review of two cases. Sem Hop Paris. 1992.
101. Lidove O, Barbey F, Niu DM, et al. Fabry in the older patient: Clinical consequences and possibilities for treatment. Mol Genet Metab. 2016; 118(4): 319–325, doi: 10.1016/j.ymgme.2016.05.009, indexed in Pubmed: 27221354.
102. Chevrant-Breton J, Laudren A, Mazéas D, et al. Fabry's disease, lymphedema and ulcero-mutilating acropathy - a case [article in French]. Ann Dermatol Venereol. 1981; 108(11): 899–902, indexed in Pubmed: 6798913.
103. Sacre K, Lidove O, Giroux Leprieur B, et al. Bone and joint involvement in Fabry disease. Scand J Rheumatol. 2010; 39(2): 171–174, doi: 10.3109/03009740903270631, indexed in Pubmed: 20001766.

104. Germain DP, Benistan K, Boutouyrie P, et al. Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease. Clin Genet. 2005; 68(1): 93–95, doi: 10.1111/j.1399-0004.2005.00457.x, indexed in Pubmed: 15952993.
105. Mersebach H, Johansson JO, Rasmussen AK, et al. Osteopenia: A common aspect of Fabry disease. Predictors of bone mineral density. Genet Med. 2007; 9(12): 812–818, doi: 10.1097/gim.0b013e31815cb197, indexed in Pubmed: 18091430.
106. Horiuchi H, Saito N, Kobayashi S, et al. Avascular necrosis of the femoral head in a patient with Fabry's disease: identification of ceramide trihexoside in the bone by delayed-extraction matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. Arthritis Rheum. 2002; 46(7): 1922–1925, doi: 10.1002/art.10391, indexed in Pubmed: 12124877.
107. Germain DP, Benistan K, Boutouyrie P, et al. Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease. Clin Genet. 2005; 68(1): 93–95, doi: 10.1111/j.1399-0004.2005.00457.x, indexed in Pubmed: 15952993.
108. Mersebach H, Johansson JO, Rasmussen AK, et al. Osteopenia: a common aspect of Fabry disease. Predictors of bone mineral density. Genet Med. 2007; 9(12): 812–818, doi: 10.1097/gim.0b013e31815cb197, indexed in Pubmed: 18091430.
109. Talbot A, Ghali JR, Nicholls K. Antiepileptic medications increase osteoporosis risk in male fabry patients: bone mineral density in an Australian cohort. JIMD Rep. 2014; 17: 29–36, doi: 10.1007/8904_2014_328, indexed in Pubmed: 25062758.
110. Beerhorst K, Tan IY, De Krom M, et al. Antiepileptic drugs and high prevalence of low bone mineral density in a group of inpatients with chronic epilepsy. Acta Neurol Scand. 2013; 128(4): 273–280, doi: 10.1111/ane.12118, indexed in Pubmed: 23461582.
111. Chimenti C, Padua L, Pazzaglia C, et al. Cardiac and skeletal myopathy in Fabry disease: A clinicopathologic correlative study. Hum Pathol. 2012; 43(9): 1444–1452, doi: 10.1016/j.humpath.2011.09.020, indexed in Pubmed: 22406371.
112. Kramer J, Glaser F, Hasselblatt MA. Spinal ischemic lesion in a 24-year-old patients with FD. Front Immunol. 2020; 11: 595514, doi: 10.3389/fimmu.2020.595514, indexed in Pubmed: 33381118.
113. Lenders M, Brand E. FAbry STabilization indEX (FASTEX): Clinical evaluation of disease progression in Fabry patients. Mol Genet Metab. 2020; 129(2): 142–149, doi: 10.1016/j.ymgme.2019.12.010, indexed in Pubmed: 31879214.

114. Paim-Marques L, Oliveira Rde, Appenzeller S. Multidisciplinary Management of Fabry Disease: Current Perspectives. J Mulidisc Healthc. 2022; 15: 485–495, doi: 10.2147/jmdh.s290580, indexed in Pubmed: 35300178.
115. Burina A, Brand E, Hughes D. An expert Consensus on the recommendations for the use of biomarkers in FD. Mol Genet Metab. 2023; 139.
116. Lenders M, Brand E. Fabry disease: the current treatment landscape. Drugs. 2021; 81(6): 635–645, doi: 10.1007/s40265-021-01486-1, indexed in Pubmed: 33721270.
117. Chan B, Adam DN. A Review of Fabry Disease. Skin Therapy Lett. 2018; 23(2): 4–6, indexed in Pubmed: 29562089.
118. Orteu CH, Jansen T, Lidove O, et al. FOS Investigators. Fabry disease and the skin: data from FOS, the Fabry outcome survey. Br J Dermatol. 2007; 157(2): 331–337, doi: 10.1111/j.1365-2133.2007.08002.x, indexed in Pubmed: 17573884.
119. Zampetti A, Orteu CH, Antuzzi D, et al. Angiokeratoma: decision-making aid for the diagnosis of Fabry disease. Br J Dermatol. 2012; 166(4): 712–720, doi: 10.1111/j.1365-2133.2012.10742.x, indexed in Pubmed: 22452439.
120. Mehta A, Hughes AD, Adam EP. GeneReviews® [Internet]. Seattle (WA). University of Washington, Seattle 1993.
121. Obwieszczenie Ministra Zdrowia z dnia 30 sierpnia 2023 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 września 2023 r. Załącznik B.104. https://www.gov.pl/web/zdrowie/obwieszczenie-ministra-zdrowia-z-dnia-30-sierpnia-2023-r-w-sprawie-wykazu-refundowanych-lekow-srodkow-spozywczych-specjalnego-przeznaczenia-zywieniowego-oraz-wyrobow-medycznych-na-1-wrzesnia-2023-r (September 22, 2023).
122. Biegstraaten M, Arngrímsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015; 10: 36, doi: 10.1186/s13023-015-0253-6, indexed in Pubmed: 25885911.
123. El Dib R, Gomaa H, Carvalho RP, et al. Enzyme replacement therapy for Anderson-Fabry disease. Cochrane Database Syst Rev. 2016; 7(7): CD006663, doi: 10.1002/14651858.CD006663.pub4, indexed in Pubmed: 27454104.
124. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. J Med Genet.

2018; 55(5): 351–358, doi: 10.1136/jmedgenet-2017-104863, indexed in Pubmed: 29437868.

125. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015; 52(5): 353–358, doi: 10.1136/jmedgenet-2014-102797, indexed in Pubmed: 25795794.

126. Skrunes R, Tøndel C, Leh S, et al. Long-Term dose-dependent agalsidase effects on kidney histology in Fabry disease. Clin J Am Soc Nephrol. 2017; 12(9): 1470–1479, doi: 10.2215/CJN.01820217, indexed in Pubmed: 28625968.

127. Sirrs et al., J Inherit Metab Dis. 2018; 41 (Suppl 1): S188. El Dib, Cochrane Database Syst Rev. 2016; 7 (7): CD006663.

128. Weidemann F, Krämer J, Duning T, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch. J Am Soc Nephrol. 2014; 25(4): 837–849, doi: 10.1681/ASN.2013060585, indexed in Pubmed: 24556354.

129. Lenders M, Canaan-Kühl S, Krämer J, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction and switch-2-year follow-up. J Am Soc Nephrol. 2016; 27(3): 952–962, doi: 10.1681/ASN.2015030337, indexed in Pubmed: 26185201.

130. El Dib R, Gomaa H, Ortiz A, et al. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. PLoS One. 2017; 12(3): e0173358, doi: 10.1371/journal.pone.0173358, indexed in Pubmed: 28296917.

131. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N Engl J Med. 2016; 375(6): 545–555, doi: 10.1056/NEJMoa1510198, indexed in Pubmed: 27509102.

132. Hughes DA, Nicholls K, Sunder-Plassmann G, et al. Safety of switching to Migalastat from enzyme replacement therapy in Fabry disease: Experience from the Phase 3 ATTRACT study. Am J Med Genet A. 2019; 179(6): 1069–1073, doi: 10.1002/ajmg.a.61105, indexed in Pubmed: 30920142.

133. Schiffmann R, Bichet DG, Jovanovic A, et al. Migalastat improves diarrhea in patients with Fabry disease: clinical-biomarker correlations from the phase 3 FACETS trial. Orphanet J Rare Dis. 2018; 13(1): 68, doi: 10.1186/s13023-018-0813-7, indexed in Pubmed: 29703262.

134. Lenders M, Nordbeck P, Kurschat C, et al. Treatment of Fabry disease management with migalastat-outcome from a prospective 24 months observational multicenter study (FAMOUS). Eur Heart J Cardiovasc Pharmacother. 2022; 8(3): 272–281, doi: 10.1093/ehjcvp/pvab025, indexed in Pubmed: 35512362.
135. Perretta F, Jaurretche S. Fabry disease: Switch from enzyme replacement therapy to oral chaperone migalastat: what do we know today? Healthcare (Basel). 2023; 11(4): 449, doi: 10.3390/healthcare11040449, indexed in Pubmed: 36832983.
136. Nowicki M, Bazan-Socha S, Błażejewska-Hyzorek B, et al. Enzyme replacement therapy in Fabry disease in Poland: A position statement. Pol Arch Intern Med. 2020; 130(1): 91–97, doi: 10.20452/pamw.15117, indexed in Pubmed: 31868861.
137. van der Veen SJ, Vlietstra WJ, van Dussen L, et al. Predicting the development of anti-drug antibodies against recombinant alpha-galactosidase a in male patients with classical Fabry disease. Int J Mol Sci. 2020; 21(16): 5784, doi: 10.3390/ijms21165784, indexed in Pubmed: 32806627.
138. El Dib R, Gomaa H, Ortiz A, et al. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. PLoS One. 2017; 12(3): e0173358, doi: 10.1371/journal.pone.0173358, indexed in Pubmed: 28296917.
139. Schiffmann R, Goker-Alpan O, Holida M, et al. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year phase 1/2 clinical trial. J Inherit Metab Dis. 2019; 42(3): 534–544, doi: 10.1002/jimd.12080, indexed in Pubmed: 30834538.
140. Wallace E, Goker-Alpan W, Holida B, et al. First results of a head-to-head trial of pegunigalsidase alfa vs. agalsidase beta in Fabry disease: 2 year results of the phase 3 randomized, double-blind, BALANCE study. Mol Gen Metab . 2023; 138(2): 107351, doi: 10.1016/j.ymgme.2022.107351.
141. Deegan PB, Goker-Alpan O, Geberhiwot T, et al. Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open-label phase 2 study and its extension study. Mol Genet Metab. 2023; 138(2): 106963, doi: 10.1016/j.ymgme.2022.11.002, indexed in Pubmed: 36481125.
142. Guérard N, Oder D, Nordbeck P, et al. Lucerastat, an iminosugar for substrate reduction therapy: Tolerability, pharmacodynamics, and pharmacokinetics in patients

with fabry disease on enzyme replacement. Clin Pharmacol Ther. 2018; 103(4): 703–711, doi: 10.1002/cpt.790, indexed in Pubmed: 28699267.

143. Umer M, Kalra DK. Treatment of Fabry disease: Established and emerging therapies. Pharmaceuticals (Basel). 2023; 16(2): 320, doi: 10.3390/ph16020320, indexed in Pubmed: 37259462.

144. A study to evaluate the effect of venglustat tablets on left ventricular mass index in male and female adult participants with Fabry disease (CARAT). https://clinicaltrials.gov/study/NCT05280548 (accessed: September 20, 2023).

145. Hennermann JB, Arash-Kaps L, Fekete G, et al. Pharmacokinetics, pharmacodynamics, and safety of moss-aGalactosidase A in patients with Fabry disease. J Inherit Metab Dis. 2019; 42(3): 527–533, doi: 10.1002/jimd.12052, indexed in Pubmed: 30746723.

146. Linthorst GE, Hollak CEM, Donker-Koopman WE, et al. Enzyme therapy for Fabry disease: neutralizing antibodies toward agalsidase alpha and beta. Kidney Int. 2004; 66(4): 1589–1595, doi: 10.1111/j.1523-1755.2004.00924.x, indexed in Pubmed: 15458455.

147. Nakano S, Tsukimura T, Togawa T, et al. Rapid immunochromatographic detection of serum anti-α-galactosidase A antibodies in Fabry patients after enzyme replacement therapy. PLoS One. 2015; 10(6): e0128351, doi: 10.1371/journal.pone.0128351, indexed in Pubmed: 26083343.

148. Wilcox WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004; 75(1): 65–74, doi: 10.1086/422366, indexed in Pubmed: 15154115.

149. Lenders M, Stypmann J, Duning T, et al. Serum-mediated inhibition of enzyme replacement therapy in Fabry disease. J Am Soc Nephrol. 2016; 27(1): 256–264, doi: 10.1681/ASN.2014121226, indexed in Pubmed: 25933799.

150. Lenders M, Brand E. Assessment and impact of dose escalation on anti-drug antibodies in Fabry disease. Front Immunol. 2022; 13: 1024963, doi: 10.3389/fimmu.2022.1024963, indexed in Pubmed: 36569886.

151. Stappers F, Scharnetzki D, Schmitz B, et al. Neutralising anti-drug antibodies in Fabry disease can inhibit endothelial enzyme uptake and activity. J Inherit Metab Dis. 2020; 43(2): 334–347, doi: 10.1002/jimd.12176, indexed in Pubmed: 31587315.

152. Lenders M, Oder D, Nowak A, et al. Impact of immunosuppressive therapy on therapy-neutralizing antibodies in transplanted patients with Fabry disease. J Intern Med. 2017; 282(3): 241–253, doi: 10.1111/joim.12647, indexed in Pubmed: 28682471.
153. Doheny D, Srinivasan R, Pagant S, et al. Fabry disease: Prevalence of affected males and heterozygotes with pathogenic mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. J Med Genet. 2018; 55(4): 261–268, doi: 10.1136/jmedgenet-2017-105080, indexed in Pubmed: 29330335.
154. Najafian B, Tøndel C, Svarstad E, et al. Accumulation of globotriaosylceramide in podocytes in Fabry nephropathy is associated with progressive podocyte loss. J Am Soc Nephrol. 2020; 31(4): 865–875, doi: 10.1681/ASN.2019050497, indexed in Pubmed: 32127409.

Table 1. Most common symptoms of Fabry disease in children and adolescents

Symptoms	**Prevalence**	**Average age**
Pain (dysaesthesia, acroparesthesias, "Fabry crises", pain crises in the hands and feet, muscle and joint pain, "whole body" pain)	50%–70%	7–9 years of age (may appear as early as 2–4 years of age)
Sweating disorders (hypohidrosis or anhidrosis, less commonly hyperhidrosis)	25%–60%	5–10 years of age (may appear as early as 2–4 years of age)
Vortex keratopathy (*cornea verticillata*) Other ocular symptoms include: cataracts, corneal and lens opacities, tortuous conjunctival and retinal vessels	50%–70%	8 years of age (vortex keratopathy can appear as early as infancy)
Gastroenterological problems (nausea, vomiting, non-specific abdominal pain, diarrhoea, constipation)	20%–50%	1–18 years of age
Heat/cold intolerance **Exercise intolerance** **Paroxysmal fevers**	40%–25% (heat intolerance is more common)	5–15 years of age

Otological problems (hearing loss up to and including deafness, tinnitus, dizziness)	20% (hearing loss) 30%–40% (tinnitus) 20%–40% (dizziness)	10–15 year of life (hearing loss already at 2–4 years of age in boys)
Angiokeratoma (other skin symptoms are telangiectasias)	15%–40%	7–15 years of age
Renal problems (albuminuria, proteinuria, hyperfiltration, isosthenuria)	10%–20%	13–16 years of age
Cardiovascular problems (arrhythmias and conduction disorders, valvular defects)	15%–25% (valvular defects) 5%–10% (conduction disorders) 2%–7% (arrhythmias)	10–15 years of age

Table 2. Factors determining the inclusion of enzyme replacement therapy (ERT) for patients with Fabry disease (FD) aged over 50 years, which should be considered before starting the treatment

Potential indications for the inclusion of ERT	**Potential contraindications to the inclusion of ERT**
Potential limiting effect on left ventricular hypertrophy/potential antiarrhythmic effect of ERT	Lack of randomized trials in older population
Counteracting the *de novo* appearance of left ventricular hypertrophy and fibrosis	Difficulty in distinguishing between FD-specific symptoms and symptoms associated with ageing

Improving the quality of life of patients	Symptomatic treatment of heart failure and/or renal failure — necessary to include treatment independently of ERT

Table 3. Cardiological diagnostic algorithm for Fabry disease (red flags)

Clinical picture, family history	Symptoms (non-specific): dyspnoea, cardiac arrhythmias, reduced physical performance, dizziness, and headaches Family history: left ventricular hypertrophy, especially if there is no evidence of disease transmission, extra-cardiac symptoms typical of Fabry disease
Electrocardiography	Shortened PQ interval — early stages of the disease, bradycardia, chronotropic incompetence, atrioventricular blocks, repolarisation abnormalities in the inferior-lateral leads (deep negative T waves)
Echocardiography	Left ventricular hypertrophy with preserved systolic function, reduced global longitudinal strain, mild to moderate dilatation of the ascending aorta, thickening of the mitral and aortic valves with mild to moderate regurgitation, papillary muscle hypertrophy
Cardiac magnetic resonance	Late gadolinium enhancement within the inferior and posterolateral wall, low native T1 mapping, low extracellular volume value

Table 4. Strategies for symptomatic management of Fabry disease with a focus on the musculoskeletal system [29]

- Avoidance of factors that trigger or exacerbate neuropathy: heat, cold, stress, exercise, fever, alcohol
- Anti-inflammatory and antipyretic drugs — rarely effective
- Carbamazepine, pregabalin and gabapentin — first-line treatment
- Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine) — first-line treatment

- Lidocaine, capsaicin, tramadol — second-line treatment
- Opioids (cannabinoids) — third-line treatment
- Methadone, lamotrigine and botulinum toxin — fourth-line treatment

Table 5. Fabry disease skin lesions

- Diffuse angiokeratoma (*angiokeratoma corporis diffusum)*
- Telangiectasia
- Sweating disorders (anhidrosis, hypohidrosis, less commonly hyperhidrosis)
- Bushy eyebrows
- Cutaneous pain in the distal parts of the limbs

Table 6. Laboratory tests in patients with Fabry disease

Specific • Plasma lyso-Gb3 concentration • Anti-alpha-galactosidase antibody titres[a] • Genetic testing
General • CBC with smear evaluation, Fe, electrolytes (K, Na, Mg), CRP, hsCRP, hCG[b], TSH • Liver tests: AST, ALT, total bilirubin, GGTP, INR • Glucose (HbA1c), lipid profile
Cardiovascular • NT-proBNP[a], CK[a], CK-MB[a], troponin[a]
Renal • Urinalysis, proteinuria, albuminuria, podocyturia[a] • Creatinine, eGFR, urea

[a]In selected cases, taking into account the clinical picture. [b]In women

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGTP, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; hCG, human chorionic gonadotropin; hsCRP, high-sensitivity C-reactive protein; INR, international normalised ratio;

lyso-Gb3, globotriaosylsphingosine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid stimulating hormone

Table 7. Imaging studies in patients with Fabry disease

Cardiac • Electrocardiography (ECG), monitoring (Holter monitor, ABPM) • Echocardiography, carotid ultrasound • Peripheral vascular ultrasound[a] • Cardiopulmonary exercise testing, stress echocardiography* • Coronary computed tomography angiography and/or coronary angiography[a] • Cardiac magnetic resonance imaging (evaluation of myocardial fibrosis), radioisotope studies[a]
Urinary tract (kidneys) • Abdominal ultrasound • Computed tomography[a] • Renal biopsy*
Musculoskeletal system • Ultrasonography • Computed tomography[a] • Magnetic resonance imaging[a] • Biopsy[a]
Nervous system • Ultrasound of the carotid and vertebral and intracranial vessels • Computed tomography • Magnetic resonance imaging
Dermatological • Dermoscopy • Biopsy[a]

[a]In selected cases, taking into account the clinical picture

Table 8. Organ indications for initiating treatment according to expert consensus [136]

Renal (≥1 primary or ≥2 additional criteria met)

Primary criteria:

- Nephropathy in FD with reduced glomerular filtration rate[a]
- Persistent proteinuria ≥500 mg/d/1.73 m^2 after exclusion of other causes
- High-risk pathological changes in kidney biopsy (glomerular hyalinisation, tubular atrophy, fibrosis or vascular sclerosis) — men only

Additional criteria:

- Hyperfiltration
- Isolated proteinuria of 300 mg/d/1.73 m^2 or more advanced than expected for age and sex, persisting for ≥1 year after exclusion of other causes
- Renal tubular dysfunction
- Hypertension persisting for ≥1 year
- High-risk pathological changes in kidney biopsy (glomerular hyalinisation, tubular atrophy, fibrosis or vascular sclerosis) — women only

Cardiac (≥2 of the criteria met)

- Left ventricular wall thickness >12 mm in men and >11 mm in women
- Left ventricular mass index based on two-dimensional echocardiography >20% of expected value for age
- Left ventricular mass increase of ≥5 g/m^2/year (based on 3 measurements in ≥1 year)
- Left ventricular diastolic failure based on 2D echocardiography and Doppler echocardiography (grade 2 or 3 according to American Society of Echocardiography guidelines) and/or abnormalities in acoustic marker tracing
- Loss of left ventricular circumferential strain gradient from base to the apex of the heart
- Left atrial enlargement on two-dimensional echocardiography: parasternal long axis view >40 mm, left atrial volume index >34 ml/m^2
- Arrhythmias and conduction abnormalities: atrioventricular block, shortened PR interval, left bundle branch block, ventricular or atrial tachyarrhythmia, sinus bradycardia (not related to chronotropic negative drugs and not due to other causes)
- Moderate or severe aortic or mitral regurgitation
- Late contrast enhancement of the left ventricular muscle on magnetic resonance imaging

• NT-proBNP concentration above the upper limit of reference values for age and sex or troponin concentration in a high sensitivity test (a proxy for fibrosis) exceeding >2 times the upper limit of normal
Neurological (≥1 criterion met)
• History of stroke or transient cerebral ischemic attack • Severe and drug-resistant neuropathic pain • Sudden unilateral hearing loss after exclusion of other possible causes • Acute ischemic optic neuropathy after exclusion of other possible causes
Gastrointestinal symptoms
• Significant gastrointestinal symptoms that do not respond to other treatments for ≥6 months or are associated with growth retardation or significant deterioration in the quality of life

Abbreviations: FD, Fabry disease; NT-proBNP, N-terminal pro B-type natriuretic peptide

Table 9. New therapies in clinical trials [142–156]

Drug name	**Mechanism of action**	**Route of administration**	**Physiological effect**
Moss α-GAL	α-GAL from moss	Intravenous	Reduced accumulation of globotriaosylceramide (Gb3)
Lucerastat	Inhibits the enzyme glucosylceramide synthase	Oral	Reduced accumulation of glycosphingolipids, including glucosylceramide (GL-1) globotriaosylceramide (Gb3)
Venglustat	Inhibits the enzyme glucosylceramide synthase	Oral	Reduced accumulation of glycosphingolipids, including glucosylceramide (GL-1) globotriaosylceramide (Gb3)

Table 10. List of centres providing treatment under the drug programme in Poland (data from June 29, 2024)

LUBIN, Miedziowe Health Center, Department of Internal Medicine and Diabetology
OLEŚNICA, District Hospital Complex, Department of Internal Medicine
WAŁBRZYCH, Dr Alfred Sokolowski Specialist Hospital, Department of Nephrology
WROCŁAW, Jan Mikulicz-Radecki University Clinical Hospital, Clinical Department of Nephrology
TORUŃ, Ludwik Rydygier Voivodeship Polyclinical Hospital, Clinical Department of Nephrology, Diabetology and Internal Medicine
LUBLIN, Independent Public Clinical Hospital No. 4, Clinical Department of Neurology; Clinical Department of Nephrology, Transplantology and Internal Medicine
ŁÓDŹ, Polish Mother's Health Centre Institute, Department of Developmental Neurology and Epileptology
PABIANICE, Pabianice Medical Centre Sp. z o.o., 1st Internal Medicine Department; Children's Department
ŁÓDŹ, Independent Public Health Care Center, Central Teaching Hospital of the Medical University of Łódź, Department of Electroradiology; Department of Nephrology, Hypertensiology and Kidney Transplantology
KRAKÓW, St John Paul II Specialist Hospital, Clinical Department of Cardiovascular Diseases with Cardiac Intensive Care Unit
KRAKÓW, Ludwik Rydygier Specialist Hospital in Kraków Sp. z o.o., Department of Neurology and Brain Strokes with a Stroke Division
KRAKÓW, University Children's Hospital of Cracow, Department of Pediatrics, Rheumatology and Rare Diseases
WARSZAWA, Children's Memorial Health Institute in Warsaw, Department of Pediatrics, Nutrition and Metabolic Diseases
WARSZAWA, Institute of Psychiatry and Neurology, 1st Department of Neurology
SIEDLCE, St John Paul II Voivodeship Hospital of the Mazowieckie Voivodeship in Siedlce Sp. Z o.o., Department of Neurology with a Stroke Division
WARSZAWA, Cardinal Stefan Wyszyński Institute of Cardiology — National Research Institute, Department of Coronary Artery Disease
WARSZAWA, University Clinical Centre of the Medical University of Warsaw, Clinical Department of Nephrology, Dialysis Therapy and Internal Medicine
RZESZÓW, St Jadwiga the Queen Voivodeship Clinical Hospital No. 2 in Rzeszów, Department of Internal Medicine, Nephrology and Endocrinology with Nuclear Medicine Laboratory; Department of Child Neurology

KROSNO, St John Paul II Voivodeship Hospital of the Podkarpackie Voivodeship in Krosno, Department of Internal Medicine and Metabolic Diseases
BIAŁYSTOK, University Clinical Hospital in Białystok, Nephrology Outpatient Clinic; 2nd Department of Nephrology, Hypertensiology and Internal Medicine with Dialysis Center
GDAŃSK, Copernicus Healthcare Entity Sp z o.o., Department of Neurology
GDAŃSK, University Clinical Center, Department of Renal Diseases and Hypertension in Children and Adolescents; Department of Developmental Neurology
GDAŃSK, University Clinical Center, Department of Nutrition, Transplantology and Internal Medicine; Department of Adult Neurology
KATOWICE, Prof. Leszek Giec Upper-Silesian Medical Center of the Medical University of Silesia, 1st Department of Cardiology
KIELCE, Voivodeship Polyclinical Hospital in Kielce, Clinical Department of Nephrology and Kidney Transplantology
OLSZTYN, Voivodeship Specialist Hospital in Olsztyn, Department of Neurology
POZNAŃ, University Clinical Hospital in Poznań, Nephrology Outpatient Clinic; Clinical Department of Nephrology, Transplantology and Internal Medicine
KOŁOBRZEG, Regional Hospital in Kołobrzeg, Department of Neurology with a Stroke Division
SZCZECIN, Prof. Tadeusz Sokołowski University Clinical Hospital No. 1 of the Pomeranian Medical University in Szczecin, Department of Endocrinology, Metabolic Diseases and Internal Medicine

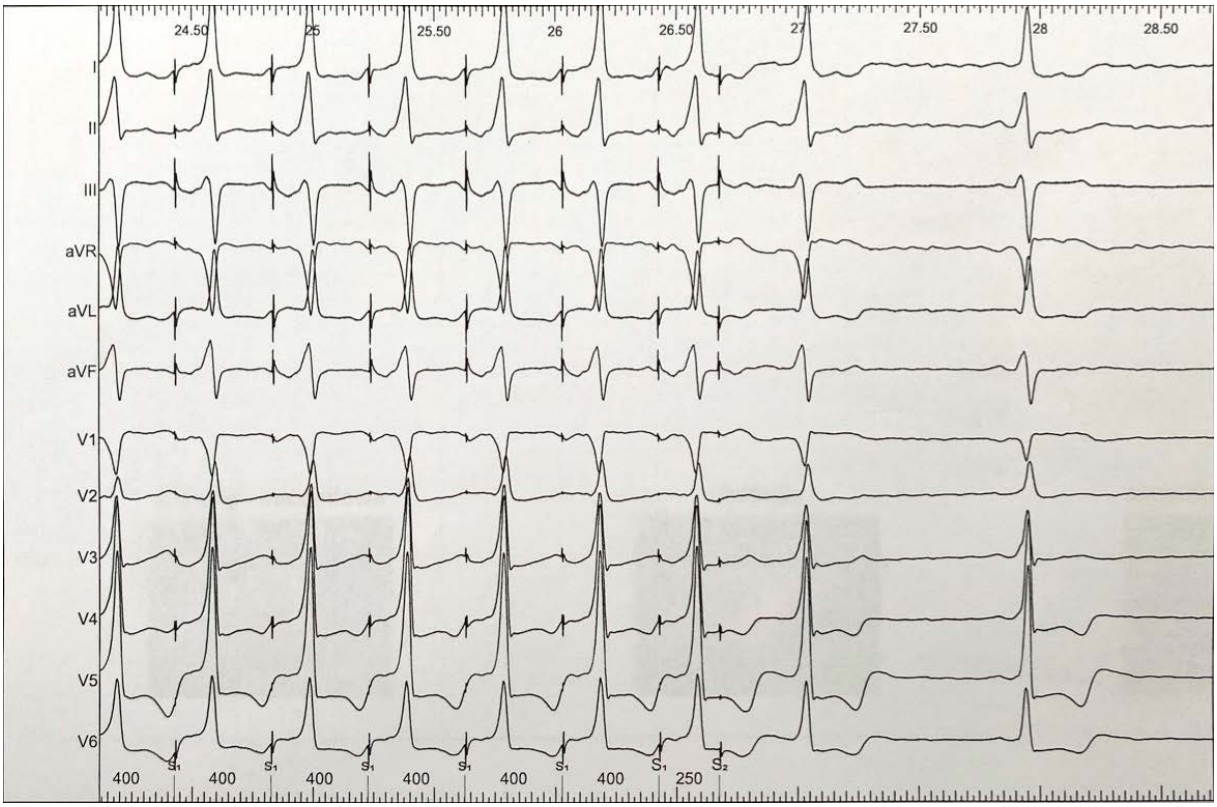
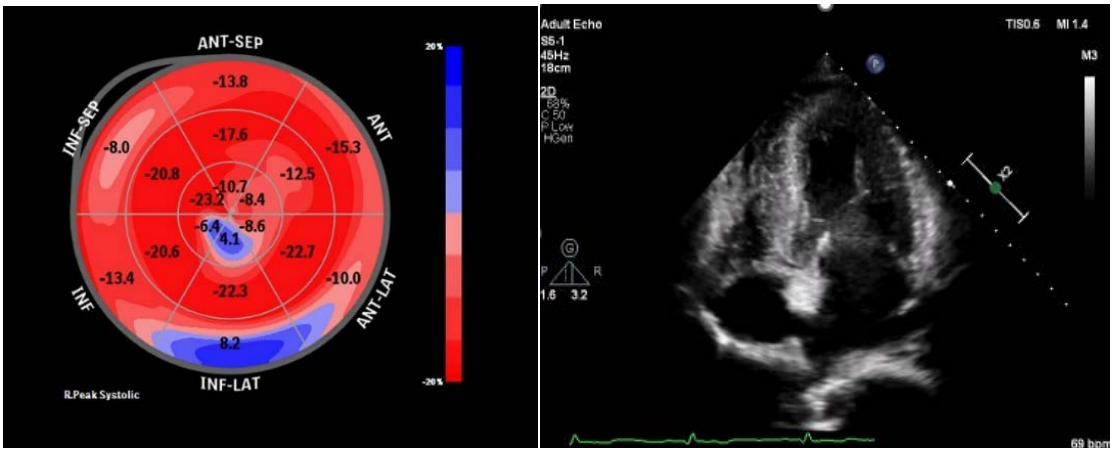


Figure 1. Electrocardiographic image of a 43-year-old man with Fabry disease during electrophysiological examination. The shortened PR interval and deformed (by hypertrophy) QRS may suggest typical pre-excitation (conduction by an accessory pathway with Kent bundle physiology), but coupled pacing reveals conduction with decrement, typical of physiological pathways



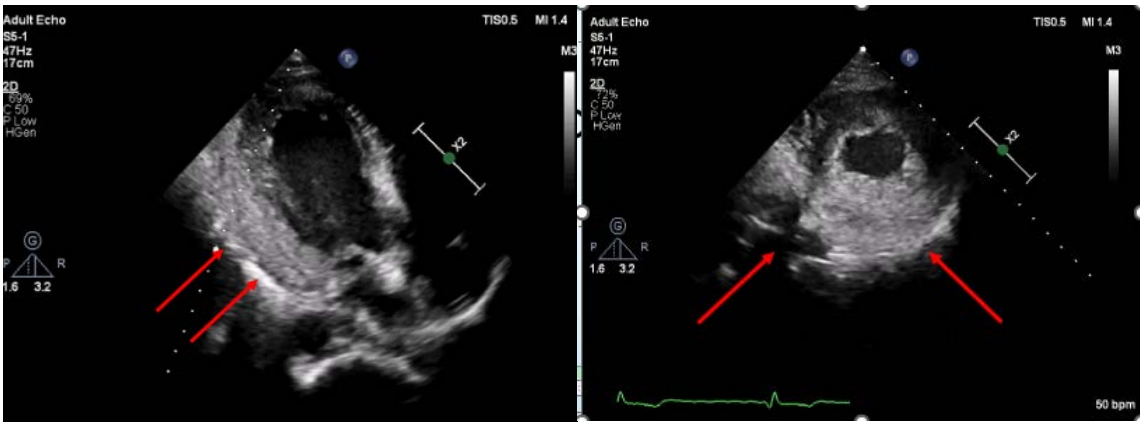


Figure 2. Echocardiographic changes in Fabry disease progression with myocardial involvement. **A.** Speckle-tracking echocardiography, reduced basal segment shortening function on the left ventricular inferior wall, preserved apical segment shortening function. **B.** Apical four-chamber view, visible atrial enlargement, concentric thickening and granular echostructure of the left ventricular muscle. **C.** Modified apical two-chamber view — marked hypertrophy of the left ventricular inferior wall can be seen **D.** Transverse apical view — marked hypertrophy of the apical segments of the inferior wall can be seen

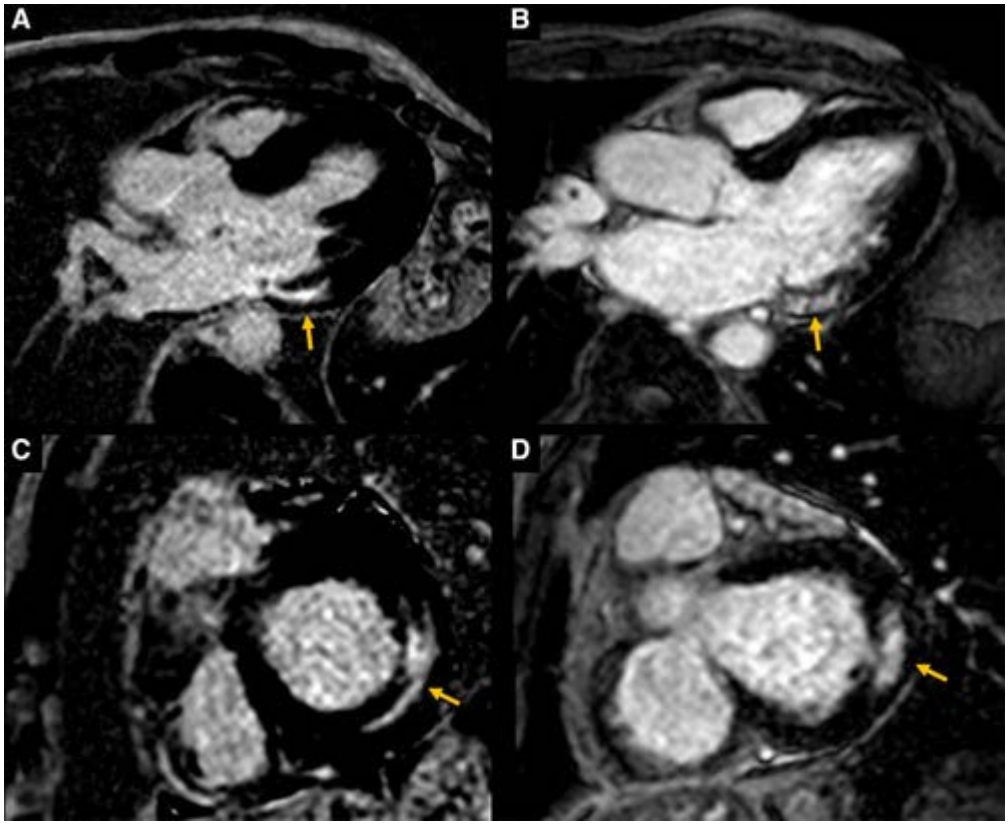


Figure 3. Cardiac magnetic resonance using late gadolinium enhancement in a patient with Fabry disease. Fibrosis of inferolateral wall segments to anterolateral wall segments (arrows)

in two patients; the first with increased myocardial thickness (**A** and **B**), and the second with wall thickness at the upper limit of the norm