CHOJNACKA, Natalia, CYMER, Radosław, JURASZ, Karolina, PODGÓRSKA, Dominika, RZESKA, Ewa, SANECKI, Miłosz, TOMCZYK, Karolina and KLARYCKI, Jakub. When should we think about Fabry disease? Journal of Education, Health and Sport. 2024;54:21-31. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.54.002
https://apcz.umk.pl/JEHS/article/view/47811
https://zenodo.org/records/10533705

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 04.01.2024. Revised: 17.01.2024. Accepted: 17.01.2024. Published: 19.01.2024.

When should we think about Fabry disease?

Natalia Chojnacka

Dr. Karol Jonscher Hospital in Lodz
ul. Milionowa 14, 93-113 Łódź
https://orcid.org/0009-0000-6454-5032

Radosław Cymer
Lower-Silesian Center of Oncology, Pulmonary and Hematology in Wroclaw
pl. L. Hirszfelda 12, 53-413 Wrocław
https://orcid.org/0009-0007-7165-2806

Karolina Jurasz
Ludwik Rydygier Memorial Hospital in Cracow
Osiedle Złotej Jesieni 1, 31-826 Kraków
https://orcid.org/0009-0004-4818-3261

Dominika Podgórska

St. Jadwiga Queen Clinical Regional Hospital No. 2 in Rzeszow
Lwowska 60, Rzeszów 35-301
https://orcid.org/0009-0005-0023-9630

Ewa Rzeska

District Hospital in Pultusk Gajda-Med Sp. z o.o.
Ul. Teofila Kwiatkowskiego 19, 06-102 Pułtusk
https://orcid.org/0009-0000-4141-2819

Miłosz Sanecki

St. Jadwiga Queen Clinical Regional Hospital No. 2 in Rzeszow
Lwowska 60, Rzeszów 35-301
https://orcid.org/0009-0009-2453-8482

Karolina Tomczyk

District Hospital in Stalowa Wola
Staszica 4, Stalowa Wola 37-450
https://orcid.org/0009-0008-6295-1166

Jakub Klarycki

District Hospital in Stalowa Wola
Staszica 4, Stalowa Wola 37-450
https://orcid.org/0009-0001-4168-0001

Abstract

According to the European Union definition, a rare disease is a disease that occurs with a frequency of less than 5 per 10,000. Rare diseases pose a major diagnostic problem for physicians. Due to the often uncharacteristic symptoms and rarity of the disease, it can take a long time before a correct diagnosis and treatment is made. Fabry disease is classified as a rare disease. It is an X-linked hereditary syndrome caused by alpha-galactosidase A deficiency. This leads to accumulation of glycosphingolipids in tissues and dysfunction of many organs. The clinical picture is variable and dependent on residual alpha-galactosidase A activity. The classic form of the disease occurs most often in males due to the presence of only one X chromosome. When alpha-galactosidase A activity is partially preserved, a non-classical form develops, which is more commonly seen in the female sex. The most common clinical manifestations reported by patients are angiokeratoma, anhidrosis, diarrhoea or left ventricular hypertrophy. To diagnose Fabry disease, alpha-galactosidase A activity can be measured in whole blood - dry blood drop test (DBS), plasma or leukocytes. Fabry disease can be treated effectively, but treatment must last for life. The treatments reimbursed in Poland are agalsidase alfa and beta preparations and migalastat.

Keywords: Rare diseases, Fabry disease, alpha-galactosidase A

Introduction

Rare diseases are a real challenge for clinicians and diagnosticians. They are faced with the problem of making accurate diagnoses. This results in a lengthy diagnostic process. This delays the initiation of correct treatment and results in the progression of irreversible organ damage (1). Fabry disease (FD) is one of the representatives of rare diseases and is the second most common lysosomal storage disease (2) . It is an X-chromosome-associated hereditary disorder caused by mutations in the alpha-galactosidase A (GLA) gene. α-Gal A is a homodimeric glycoprotein (3) that is encoded by the GLA gene. It is located on the long arm of the X chromosome (4,5) . This genetic alteration leads to abnormal lysosomal storage caused by reduced enzymatic activity of α-galactosidase A (α-Gal A). This leads to the accumulation of lysosomal globotriaosylceramide (Gb3) and globotriaosylphosphingosine (lyso-Gb3) in cells of various tissues (6,7). It leads to dysfunction in various organs. The most rapidly noticeable changes are in the cardiovascular system, kidneys and also the peripheral and central nervous system. The estimated incidence of FD ranges from approximately 1 in 37,000-117,000 live births. Initially, the disease was thought to affect only men, however, over the years it has been discovered that women can also be affected. The onset of the disease occurs later in them, the course in most cases is milder and the phenotypes are more variable (8) . In its expression, FD may be different in different patients. In heterozygous women, random inactivation of the X chromosome causes some cells to exclude the defective allele and in some cases may exclude the normal allele. This leads to a range of symptoms, from asymptomatic to a severe, classic form of the disease. In men with the classic form, due to only one X chromosome, symptoms will appear earlier and in most cases are more severe. Genetic testing is required to diagnose FD. At the moment, FD is one of the few genetic diseases that we can effectively treat, but this treatment lasts for life (2).

Symptoms

The symptoms of the disease are progressive in nature. For many years, the disease may not produce any symptoms (2) . Diagnosis is sometimes troublesome because of the lack of pathognomonic symptoms and the wide variety of the disease (9) . Physicians' lack of awareness and understanding of Fabry disease causes them to diagnose other more common diseases, which include growth pain, Raynaud's syndrome, rheumatic pain, fibromyalgia or primary erythomelalgia (10). For this reason, the disease is sometimes diagnosed quite late (2). Studies (11) have shown that in Europe and the United States, it takes up to 16 years from the onset of the first symptoms to a correct diagnosis of the disease. On the other hand, studies

(12) conducted in China also confirmed the long diagnostic time, which was up to 15 years there. With the publication of the Fabry Outcome Survey (FOS), the awareness of doctors about FD has increased over time, contributing to a shorter time to diagnosis for patients (8). In men, this time is noticeably shorter than in women (2).

Fabry disease can be divided according to the characteristics of symptoms and enzyme activity into a classic and late onset phenotype. Patients may show symptoms ranging from the severe classical phenotype found particularly in men to even the asymptomatic phenotype found more frequently in women (13). In the male gender, symptoms appear more frequently and earlier than in the female population (2) . More than a thousand mutations have been described that can result in different clinical phenotypes and disease course.The common effect for all these mutations is the accumulation in plasma and lysosomes of various glycosphingolipid substrates (14) . Glycosphingolipids deposited in organs cause a range of clinical symptoms and lead to progressive failure of the organs involved (15) . With age, symptoms worsen, leading to severe multi-organ damage and associated complications (10). Accumulation of Gb3 leads to the formation of lysosomal deposits in various organs and cells, called myelin figures and zebra bodies. This leads to cell death. Progressive fibrosis and irreversible organ damage lead to a shortened life expectancy for patients (16). Fabry disease affects multiple organs and is characterised by progressive neurological, cardiac, renal, ocular and dermatological symptoms (16).

The accumulation of Gb3 in small nerve fibres is responsible for the first symptoms appearing in early childhood. Pain is one of them. It occurs in various forms. Chronic pain, is manifested by paresthesias, a burning sensation in the limbs. Paroxysmal pain, on the other hand, is a burning pain that occurs in distal parts of the body. The pain is exacerbated in stressful situations, with physical exertion or infection (17).

Typical gastrointestinal symptoms encountered are postprandial crampy pain, diarrhoea, nausea, flatulence or vomiting. These occur particularly in patients with the classical phenotype. Treatment includes symptomatic treatment specific to the individual symptoms (18,19) and primary treatment of FD (20).

Poor nutrient absorption in patients with FD can result in poor weight gain and even malnutrition (20).

The disease is also manifested by impaired perspiration, which is particularly noticeable in the summer. It can present in a systemic form or as localised hypohidrosis. Hypohidrosis is the

reduced ability to sweat, while anhidrosis is the complete absence of it. It is caused by the deposition of substrate metabolising enzymes in the skin. This results in impaired sweat gland secretion and atrophy, as well as ischaemic damage due to constriction of the blood vessels supplying the sweat glands (21). Patients report a history of intolerance to high temperatures (17) due to damage to nociceptive receptors as a result of excessive lysoGb3 (16) and reduced exercise tolerance (17). Particularly in childhood, angiokeratoma-like skin lesions are seen in patients. These are clusters of reddish-purple vascular lesions with a maculopapular structure. They are located on the upper part of the thighs, the groin area, the navel or the buttocks. They range in size from spots to a few millimetres. They enlarge with age. (4) Patients have an increased incidence of otolaryngological disorders such as tinnitus and dizziness (17). Hearing loss is more common in patients with Fabry disease. A study (22) analysed hearing sensitivity in affected adults. The results showed more severe hearing loss in male patients with the classical form of the disease compared to those with the non-classical form and the female sex. The study also showed that despite the correct inclusion of ERT therapy, hearing loss did not improve. This is due to the deposition of Gb3 in the arteries, which leads to cerebrovascular changes that manifest as headaches and dizziness and even strokes (17).

The majority of patients with the classic form of the disease present with corneal keratopathy. It can be demonstrated by slit-lamp examination. It should be noted, however, that the occurrence of keratopathy of the cornea may be associated with the patient's use of various medications, such as amiodarone and many others (5).

The most common renal symptoms include proteinuria, hypertension and chronic kidney disease (14). The first renal symptoms are microalbuminuria and proteinuria, while the most common renal symptoms include hypertension, proteinuria and chronic kidney disease (17). A characteristic feature reported in patients is a higher incidence of renal cysts mainly peripelvic. The pathogenesis of these is unknown. The effect of Gb3 accumulation in epithelial cells results in 'mulberry' or 'Maltese cross' cells, which are visible on urinalysis (14). In classic Fabry disease, renal involvement begins early, already during intrauterine life. This results in the presence of irreversible lesions in the glomeruli, interstitial tubules and renal vasculature on biopsy, which are visible in patients even before the onset of clinical symptoms (17). However, it is important to note that renal symptoms are not pathognomonic features of FD; they may also be present in other renal diseases (14).

The accumulation of Gb3 in myocytes, the endothelium of coronary vessels, is a major factor in the pathological changes observed in the hearts of patients with FD. This leads to left

ventricular hypertrophy (LVH), conduction abnormalities, valve thickening or heart failure (23). The first test to assess the presence of cardiomyopathy is transthoracic echocardiography. Typical signs of FD are concentric LVH and prominent papillary muscle. When we suspect cardiac involvement as early as possible in a patient with FD, we perform cardiac MRI, echocardiography and 24-hour Holter ECG to assess cardiac structure and function (24) . Electrocardiographic (ECG) signs include atrioventricular (AV) node conduction disturbances. A shortened PR interval (<0.12ms), enlargement of the QRS complex or prolongation of the QTc interval are possible. The most common manifestations of FD on the ECG are features of LV hypertrophy with deep negative T-waves. Glycosphingolipid storage also affects the cardiac conduction system, leading to a shortened PQ interval (17).

Fabry disease also leads to a disruption of patients' social life. The clinical concerns present in patients are factors leading to a poorer quality of life (QoL). This leads to a higher incidence of psychiatric disorders such as depression in this group of patients and the need to start appropriate treatment under the care of psychiatrists. This problem affects both men and women (25) . Depending on the type of studies conducted and the population studied in different countries, the prevalence of depression in patients with FD is reported to be 38-65% (25,26) . Studies have shown that FD patients have a noticeably lower quality-adjusted life years (QALYs) value than patients with other chronic diseases. It is suspected that this is due, among other things, to the fact that patients are aware of their irreversibly progressive disease. By analysing the studies, it can be concluded that multispecialty care is necessary in patients with FD. Due to the range of symptoms from different organs and the associated higher incidence of depression, patients should be under the care of multiple specialists (25).

Diagnosis

FD can be suspected, among other things, in patients with a positive family history or based on the presence of typical clinical symptoms (18). Initiation of the diagnosis consists of taking a detailed history, in particular of family history of FD. This is followed by physical examination, biochemical examination, genetic examination, diagnostic imaging and specialist consultations. Initial investigations include assessment of the level of LysoGb3 present in plasma or urine, which may later be useful in monitoring the patient's disease course (14) . A dry blood spot test (DBS-dried blood spot) is used for diagnosis, which in patients shows a reduction in the activity of the lysosomal enzyme alpha-galactosidase A. Genetic testing to confirm the diagnosis is mandatory for men and women (24) . Testing of alpha-Gal A activity is diagnostic only for males. It is important to confirm the pathological

GLA mutation so that the disease phenotype can be established (5). In women, on the other hand, it is necessary to demonstrate a pathogenic mutation in the GLA gene by molecular genetic testing, as it is possible to have AGAL activity in the reference range in women with Fabry disease. In patients with residual alpha-GAL A activity, clinical symptoms are milder and onset is later (27). In unclear diagnostic cases, biopsies of the involved organs may be helpful. In the biopsy material, multilobular myelin bodies ('zebra bodies' or 'paper roll phenomenon'), which are pathognomonic for the disease, can be detected under the electron microscope (18). Enzymatic activity can be assessed in plasma, leukocytes or dried blood spots (DBS) (5). Studies show that a significant group of patients still remains undiagnosed. In order to improve the detection of the disease, a newborn screening programme (NBS) is being carried out in some countries (28) NBS programmes are based on enzymatic tests that assess α-Gal A activity. This allows identification and monitoring of individuals with Fabry disease mutations from an early age (5). Studies show that NBS appears to be the best way to detect FD at an early stage of the disease before the first symptoms appear (27). Prenatal diagnosis can be made by measuring AGAL activity in chorionic villi or cultured amniotic cells. In the case of a mutation known to run in the family found by molecular genetics methods (18).

When a patient is diagnosed with Fabry disease, screening diagnosis of family members at risk is recommended. One study reviewing patient pedigrees showed that approximately five family members were detected with Fabry disease. Such family members are usually detected at the asymptomatic stage of the disease with excellent treatment outcomes (5).

Treatment

Patient care should aim to achieve various goals such as reducing pain, preventing or delaying the progression of symptoms, improving quality of life and extending life expectancy (5,6). Therapies used to treat FD aim to reduce intracellular accumulation of Gb3 by replacing the deficient endogenous AGAL. This leads to improved transport and increases enzymatic activity in lysosomes reducing disease progression (18).

Since 2001 (23), Fabry disease can be treated with recombinant enzyme replacement therapy (ERT) administered intravenously. This includes agalsidase alfa (0.2 mg/kg body weight) produced in a human cell line and agalsidase beta (1 mg/kg body weight) produced in Chinese hamster ovary cells. Drug infusions are given every 2 weeks (18). Patients require treatment for the rest of their lives (8). ERT has shown good efficacy regarding the inhibition of disease

progression. Studies have shown an improvement in health particularly when treatment was started at a young age (29). However, therapeutic benefit has not been demonstrated in the end-stage of the disease or when antibody formation has occurred. This is due to the inability of enzyme therapy to reverse clinical symptoms (30). The Fabry Outcome Survey (FOS) showed that ERT attenuates the progression of renal disease and cardiomyopathy. Prompt treatment reduces the risk of cardiovascular and renal events (8). However, enzyme replacement therapy has several disadvantages including that it requires intravenous administration. Another is the formation of inhibitory antibodies in some patients (31).

Since 2016, migalastat, a small-molecule chaperone protein, has been approved as the first oral FD therapy. It is administered at a dose of 123mg every other day on an empty stomach. It is an alpha-galactosidase analogue (18). The action of migalastat is to stabilise the enzyme produced by the body. This leads to the breakdown of GL3 accumulated in cells (32). It is not recommended for use in patients with mutations causing complex enzymatic changes (31), so it can be used to treat some patients with a susceptible GLA mutation (18). The advantage of migalastat is that it allows enzyme levels to remain constant and stable, whereas ERT leads to fluctuating enzymatic activity (32). It is not recommended in dialysis patients and those with severe renal failure (eGFR<30ml/min/1.73m2) (33) In comparison with ERT, it crosses the blood-brain barrier (30).

One of the first studies (31) evaluating enzymatic activity in FD treatment showed a significant increase in alpha-Gal A activity and reduced levels of lyso-Gb3. Significant reductions in cardiac hypertrophy and serum creatinine levels were seen in patients treated with one year of migalastat. Simultaneous ERT therapy with migalastat is not allowed in the treatment of FD (33). The best treatment effects are seen in early diagnosed patients before irreversible organ damage occurs (20).

Disclosures

Author's cotribution:
Conceptualization - Radosław Cymer, Dominika Podgórska, Karolina Jurasz
Formal analysis - Jakub Klarycki, Natalia Chojnacka, Dominika Podgórska
Investigation - Miłosz Sanecki, Natalia Chojnacka, Karolina Tomczyk
Writing - rough preparation - Karolina Jurasz, Radosław Cymer, Karolina Tomczyk
Writing - review and editing - Karolina Jurasz, Miłosz Sanecki, Ewa Rzeska
Visualization - Ewa Rzeska, Jakub Klarycki, Dominika Podgórska

All authors have read and agreed with the published version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

Funding statement: No external funding was received to perform this review.

Statement of institutional review committee: not applicable.

Statement of informed consent: not applicable.

Statement of data availability: not applicable.

Bibliography

1. Germain DP, Moiseev S, Suárez-Obando F, Al Ismaili F, Al Khawaja H, Altarescu G, et al. The benefits and challenges of family genetic testing in rare genetic diseases—lessons from Fabry disease. Molecular Genetics & Genomic Medicine. 2021 April; 9.

2. Guo W, Xie Y, Ji P, Li S, Cai G, Chen X. The evolution of the initial manifestations and renal involvement of chinese patients with classical and late-onset Fabry disease at different sexes and ages. BMC Nephrology. 2023 April; 24.

3. Tuttolomondo A, Simonetta I, Riolo R, Todaro F, Di Chiara T, Miceli S, et al. Pathogenesis and Molecular Mechanisms of Anderson–Fabry Disease and Possible New Molecular Addressed Therapeutic Strategies. International Journal of Molecular Sciences. 2021 September; 22: p. 10088.

4. Michaud M, Mauhin W, Belmatoug N, Bedreddine N, Garnotel R, Catros F, et al. Maladie de Fabry : quand y penser ? La Revue de Médecine Interne. 2021; 42: p. 110-119.

5. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Molecular Genetics and Metabolism. 2018; 123: p. 416-427.

6. Wanner C, Arad M, Baron R, Burlina A, Elliott PM, Feldt-Rasmussen U, et al. European expert consensus statement on therapeutic goals in Fabry disease. Molecular Genetics and Metabolism. 2018 July; 124: p. 189–203.

7. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney International. 2017 February; 91: p. 284–293.

8. Beck M, Ramaswami U, Hernberg-Ståhl E, Hughes DA, Kampmann C, Mehta AB, et al. Twenty years of the Fabry Outcome Survey (FOS): insights, achievements, and lessons learned from a

global patient registry. Orphanet Journal of Rare Diseases. 2022 June; 17.

9. Slouma M, Ben Dhia S, Cheour E, Gharsallah I. Acroparesthesias: An Overview. Current Rheumatology Reviews. 2023 October;: p. 115–126.

10. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clinical Genetics. 2019 June; 96: p. 107–117.

11. Rosa Neto NS, Bento JCdB, Pereira RMR. Higher rate of rheumatic manifestations and delay in diagnosis in Brazilian Fabry disease patients. Advances in Rheumatology. 2020 January; 60.

12. Chen X, Qiu W, Ye J, Han L, Gu X, Zhang H. Demographic characteristics and distribution of lysosomal storage disorder subtypes in Eastern China. Journal of Human Genetics. 2016 January; 61: p. 345–349.

13. Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. Journal of the American Society of Nephrology. 2016 December; 28: p. 1631–1641.

14. Esposito P, Caputo C, Repetto M, Somaschini A, Pietro B, Colomba P, et al. Diagnosing Fabry nephropathy: the challenge of multiple kidney disease. BMC Nephrology. 2023 November; 24.

15. Schiffmann R, Fuller M, Clarke LA, Aerts JMFG. Is it Fabry disease? Genetics in Medicine. 2016 December; 18: p. 1181–1185.

16. MILITARU S, R. ADAM. Demographic and Clinical Characteristics of the Full 2015-2018 Cohort of Romanian Fabry Disease Patients. Current Health Sciences Journal. 2019;: p. 272-277.

17. Ilie-Robert D, Ştefan-George F. Fabry disease – current data and therapeutic approaches. Romanian Journal of Morphology and Embryology. 2021 October; 62: p. 5–11.

18. Lenders M, Brand E. Fabry Disease: The Current Treatment Landscape. Drugs. 2021 March; 81: p. 635–645.

19. Morand O, Johnson J, Walter J, Atkinson L, Kline G, Frey A, et al. Symptoms and Quality of Life in Patients with Fabry Disease: Results from an International Patient Survey. Advances in Therapy. 2019 August; 36: p. 2866–2880.

20. Hilz MJ, Arbustini E, Dagna L, Gasbarrini A, Goizet C, Lacombe D, et al. Non-specific gastrointestinal features: Could it be Fabry disease? Digestive and Liver Disease. 2018; 50: p. 429-437.

21. Wataya-Kaneda M. Genetic Disorders with Dyshidrosis: Ectodermal Dysplasia, Incontinentia Pigmenti, Fabry Disease, and Congenital Insensitivity to Pain with Anhidrosis. In Current Problems in Dermatology.: S. Karger AG; 2016. p. 42–49.

22. Suntjens E, Dreschler WA, Hess-Erga J, Skrunes R, Wijburg FA, Linthorst GE, et al. Hearing loss in children with Fabry disease. Journal of Inherited Metabolic Disease. 2017 May; 40: p. 725–731.

23. Lee CL, Lin SP, Niu DM, Lin HY. Fabry Disease and the Effectiveness of Enzyme Replacement Therapy (ERT) in Left Ventricular Hypertrophy (LVH) Improvement: A Review and Meta-Analysis. International Journal of Medical Sciences. 2022; 19: p. 126–131.

24. Irfan Vardarli KH, Weidemann F. Diagnosis and Screening of Patients with Fabry Disease. Therapeutics and Clinical Risk Management. 2020; 16: p. 551-558.

25. Polistena B, Rigante D, Sicignano LL, Verrecchia E, Manna R, d'Angela D, et al. Survey about the Quality of Life of Italian Patients with Fabry Disease. Diseases. 2021 October; 9: p. 72.

26. Körver S, Geurtsen GJ, Hollak CEM, van Schaik IN, Longo MGF, Lima MR, et al. Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain. Orphanet Journal of Rare Diseases. 2020 January; 15.

27. Sawada T, Kido J, Yoshida S, Sugawara K, Momosaki K, Inoue T, et al. Newborn screening for Fabry disease in the western region of Japan. Molecular Genetics and Metabolism Reports. 2020 March; 22: p. 100562.

28. Nakamura K, Mukai S, Takezawa Y, Natori Y, Miyazaki A, Ide Y, et al. Clinical utility of urinary mulberry bodies/cells testing in the diagnosis of Fabry disease. Molecular Genetics and Metabolism Reports. 2023 September; 36: p. 100983.

29. Lenders M, Brand E. Effects of Enzyme Replacement Therapy and Antidrug Antibodies in Patients with Fabry Disease. Journal of the American Society of Nephrology. 2018 August; 29: p. 2265–2278.

30. Li X, Ren X, Zhang Y, Ding L, Huo M, Li Q. Fabry disease: Mechanism and therapeutics strategies. Frontiers in Pharmacology. 2022 October; 13.

31. Müntze J, Gensler D, Maniuc O, Liu D, Cairns T, Oder D, et al. Oral Chaperone Therapy Migalastat for Treating Fabry Disease: Enzymatic Response and Serum Biomarker Changes After 1 Year. Clinical Pharmacology & Therapeutics. 2019 January; 105: p. 1224–1233.

32. McCafferty EH, Scott LJ. Migalastat: A Review in Fabry Disease. Drugs. 2019 March; 79: p. 543–554.

33. Perretta F, Jaurretche S. Fabry Disease: Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat: What Do We Know Today? Healthcare. 2023; 11.