A review of Fabrys disease- pathophysiology, clinical presentation and treatments

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Abstract

Fabrys disease is a lysosomal storage disorder, caused due to mutation in the GLA gene in X-chromosome encoding for alpha galactosidase A enzyme. It’s a pan ethnic disorder with multisystem involvement. The reported prevalence of Fabrys is less but new-born screening shows higher values, indicating it is largely underestimated.

It is inherited as X-linked dominant form. The hemizygous males manifests greater severity of symptoms and heterozygous females presents asymptomatic to severe symptoms. Pathophysiological changes occur due to insufficient breakdown of globotriosylceramide in lysosomes. Hence its accumulation causes dysfunction of cells, tissues and organ systems.

The classic type 1 of Fabrys disease shows symptoms in childhood and late-onset type 2 shows later in life at around 30-40 years of age. The early symptoms are neuropathic pain, diarrhea, corneal verticellata, hypohydrosis, intolerance to heat and exercise followed by renal, cardiac and cerebrovascular involvement. The life expectancy and quality of life in Fabrys disease is considerably lesser than that of general population.

Rigorous new-born screening, detection in family members, early diagnosis and enzyme replacement and supportive management is important for slowing the progression of disease and decreases the morbidity and mortality, thus improving the overall well-being. There a is a need for awareness and education of physicians and patients about the disease with more research encouraged to develop newer and more efficient therapies for its management.

Keywords: Fabrys disease; Pathophysiology; diagnosis; Treatment

1. Introduction

Fabrys disease is a genetic lysosomal storage disorder. It is inherited in X linked dominant pattern. The mutation is present in GLA gene on X chromosome resulting in alpha galactosidase A enzyme deficiency or its complete absence. It shows increased severity in males as they have only one X chromosome and that too has defective GLA gene. Females may show variable severity since they have two X chromosomes hence ranging from asymptomatic to severe. For every patient diagnosed five family members may have this disease. If males are affected all daughters are affected. If female is affected there is 50% chance of transmitting the disease in both boy and girl child.

The basic abnormality is a genetic mutation causing either deficiency or absence of enzyme alpha galactosidase A. This enzyme is responsible for breakdown of globotriosyl ceramide (GL3 or Gb3) to lactosyl ceramide and galactose in lysosomes in the interior of a cell.
As a result, the substrate Globotriosyl ceramide (Gb3 or GL3) accumulates in lysosomes and produce cellular dysfunction. Impaired cellular functions are reflected in different organs leading to multisystem abnormality.

Fabrys disease is a pan ethnic disorder. Its prevalence has been estimated to be 1:40,000 to 1:117,000 [1]. Classic Fabry disease mutations are seen in approximately 1:22,000 to 1:40,000 males and atypical presentations are associated with about 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females. Saudi Aramco medical services organization collected 25 years data of Saudi infants born from 1983-2008 which showed an incidence rate of Fabrys disease of 5 in 100000 live births [2]. The prevalence of Fabrys disease in hemodialysis patients in Kingdom of Saudi Arabia was 4.8 per 1000 patients [3]. The new born screening in Spain shows GLA mutations in 0.1% males which included 0.013% with classical type of Fabrys disease [4]. Spada et al study on Italian newborns shows 1 in ~3,100, with an 11:1 ratio of patients with the later-onset: classic phenotypes [5]. The Japanese study showed a frequency of 0.013% of GLA variant mutation including 0.008% pathogenic variants [6].

2. Inheritance

Fabrys disease is a genetic lysosomal storage disorder. It is inherited in X linked dominant pattern. The mutation is present in GLA gene on X chromosome resulting in alpha galactosidase A enzyme deficiency or its complete absence. It shows increased severity in males as they have only one X chromosome with defective GLA gene. Hemizygous males have increased severity of symptoms at an earlier age. Females may be heterozygous and show variable severity from asymptomatic to severe [7].

For every patient diagnosed, five of his or her family members may have this disease. If males are affected all daughters are affected. If female is affected there is 50% chance of transmitting the disease to both boy and girl child.

Fabrys disease presented in two forms depending on the absence or deficiency of alpha galactosidase hence differing in severity and clinical presentation as shown below-

Type 1 - The classic Fabrys disease: there is no GAL enzyme activity. Symptoms are evident in childhood. Early symptoms include pain associated with acroparesthesias, hypohidrosis, angiokeratomas, corneal verticillate and gastrointestinal problems

Type 2 - Late onset Fabrys disease: This type is more common than the classical form and has enzyme activity more than 1%. Onset of symptoms start around 30-50 years of age. They have been further divided into three types according to organ system involved most and its presentation.

Cardiac variant: Show cardiovascular symptoms like left ventricular hypertrophy, rhythm abnormalities or cardiomyopathy. Symptoms start by 60-80 years [8]

Renal variant: Show renal symptoms which include symptoms of kidney insufficiency like decreased GFR proteinuria, chronic renal disease and end stage renal disease. Patients usually present earlier than cardiac variant.

Cerebrovascular variant: Presenting with strokes and transient ischemic attacks.

3. Pathophysiology

Deficiency of alpha galactosidase leads to accumulation of Gb3 that is globotriosylceramide in lysosomes of cells. Inclusion bodies appearing as myelin figures or zebra bodies can be seen by microscopy [9]. Increased intracellular Gb3has been found in endothelial cells, cardiac, renal, skin and nervous system producing inflammation and fibrosis [10, 11]. The increased release of inflammatory mediators such as prostaglandins and cytokines triggered by Gb3 accumulation can produce detrimental changes in cellular functions [10] and even increase reactive oxygen species. The major pathophysiological cause of functional decline in various organs is vasculopathy and neuropathy. Accumulation of Gb3 in endothelial cells produces sclerosis and smooth muscle hypertrophy [13]. This decreased vascular compliance coupled with increased inflammatory markers is the major cause of pathologic changes with Fabrys disease. The vasculopathy lead to damage to somatic and autonomic nerves, intestine, heart kidneys, brain and even endocrine glands. Measurement of Gb3 levels was positively correlated with clinical severity.
4. Clinical presentation

Maximum number of patients present with neuropathic pain followed by gastrointestinal symptoms and skin manifestation with symptoms starting in childhood [14]. Cardiac renal and cerebrovascular abnormalities are frequently seen in later stages of life. The resultant decline in function produces greatly lowered quality of life along symptoms of pain, anhydrosis with inability to tolerate heat and exercise and gastrointestinal abnormalities like diarrhea. The incidence of symptoms of depression hypochondriasis and hysteria in these people is higher than general population [15] taking its toll on the emotional and mental health effecting the general wellbeing and social life.

4.1. Neuropathic pain and Acroparaesthesia

Pain is mainly observed as burning, numbness, throbbing, electric shock like, stabbing or pins and needles sensation. It is initially observed as numbness and burning in hands and feet. This is the main presenting complaints in hemizygous males and occurs at younger age. Severe abdominal pain can also be observed. Pain can be triggered by hot, cold, fever, alcohol, stress or even exercise [16] and can lead to pain crisis. Microangiopathic changes in vaso nervosum have been implicated for neuropathic pain [17]. Neuropathic pain and decreased sweating reduce the quality of life tremendously.

4.2. Ophthalmic manifestation

Whorled or spoked corneal verticellata are one of the early manifestations of Fabrys disease. This is observed by using a slit lamp. Lens may show presence of opacities and tortuous vessels in conjunctiva and retina. About 90% of affected individuals show corneal verticillate, 60% have conjunctival vascular changes, 55% has tortuous vessels and 50% show cataracts [18]. The Gb3 deposition may damage the endothelial cells and weaken the vessels to blood pressure changes producing tortuosity [19]. Vision is usually not affected but if visual loss occurs, it may be due to retinal artery occlusion.

4.3. Gastrointestinal symptoms

More than 50%-70% of Fabrys patients have gastrointestinal (GI) symptoms [20, 21]. The GI symptoms are seen in both males and females. They are one of the early manifestations of disease and frequently misdiagnosed. The symptoms are of diarrhoea with urgency which many times might cause incontinence. These changes can be attributed to neuropathic changes leading to dysmotility of intestine.

4.4. Skin

Angiokeratomas: Small red to black elevations are seen over the skin which do not blanch on pressure. These are dilated blood vessels and are called as angiokeratomas. They are mostly distributed in lower abdomen, around umbilicus and thighs. Sometimes it might be noticed on lips also. Accumulation of Gb3 in cutaneous endothelial cells makes the blood vessels dilated and incompetent. Angiokeratoma start from age 5 in children and are found in 83% of adult males and 80% in adult females [22]. Other skin manifestation include reynauds phenomenon, sparse facial hair and lower limb lymphoedema [23, 24].

4.5. Decreased sweating (Hypohydrosis)

Hypohydrosis is also an earlier sign of the disease. It manifested in childhood itself in hemizygous Fabrys disease. It is 3.7 times more common in male than females [25]. It can be due to decreased sweat gland innervation [26]. Hypohydrosis and anhydrosis may cause problems like fever, exercise and heat intolerance [27]. This can be associated with decreased secretion of salivary glands and lacrimal glands.

Hyperhydrosis: Rarely, in few patients of Fabrys, hyperhydrosis is also observed which may be attributed to peripheral neuropathy.

4.6. Lymphoedema

It occurs due to accumulation of glycolipids in lymphatic vessels and microangiopathy [28]

4.7. Renal abnormality

Decreased GFR, proteinuria, increased serum creatine with progression to end stage renal failure is observed in Fabrys disease. The involvement of kidney in Fabrys starts early in life with progression to ESRD by the age of 55 years [29] requiring dialysis and renal transplant. Accumulation of Gb3 in cells of epithelium interstitial endothelial and glomerular cells of kidneys can be seen in microscopy as large whorled bubble like inclusion bodies [30] causing...
interstitial fibrosis and glomerular sclerosis with decline in renal function [31]. The accumulation of Gb3 in kidneys cells leads to structural changes and increases permeability causing loss of proteins in urine.

4.8. Cardiovascular presentation in Fabrys disease

Around 75% of deaths are associated to cardiovascular complication, involving sudden cardiac arrest and some due to rhythm abnormalities such as atrial and ventricular fibrillation [32], left ventricular hypertrophy, rhythm changes arterial intimal thickness and angina are some of the presentation of Fabrys cardiac involvement.

4.9. Cerebrovascular involvement

Fabrys disease shows vasculopathy with impairment of blood flow, blood vessel wall and blood components [33]. Neurological manifestations include hemiparesis, vertigo or dizziness, diplopia, dysarthria, nystagmus, nausea and vomiting, headaches, hemiataxia and dysmetria, cerebellar gait ataxia and cerebral haemorrhage [34]. Approximately 24-48% of Fabrys patients suffer from stroke with symptoms according to the area involved [35]. Many times MRI-Brain shows several white matter lesions too giving a misdiagnosis of multiple sclerosis. The mean age at first stroke for males was less than 30 years and females was less than 45 years [36].

4.10. Hearing loss and tinnitus

Germain et al described hearing loss in 54.5% of male patients with Fabrys disease ranging from progressive hearing loss to sudden deafness. 27% complained of tinnitus [37].

4.11. Endocrine glands

Fabrys disease individuals show hypofunctioning of many endocrine glands such as subclinical hypothyroidism with elevation of serum TSH, adrenal involvement with decreased serum cortisol with increase in its regulatory hormone ACTH and gonadal dysfunction with menses abnormalities and miscarriages in women and asthenozoospermia, oligozoospermia in in men [38].

Bone mineral densities: decreased bone mineral densities are observed in 50% of patients with Fabrys disease with increased osteocalcin blood levels. [39]

5. Diagnosis

Early diagnosis is highly recommended for better management of disease and slows down its progression. Early diagnosis plays an important role in decreasing morbidity and mortality.

5.1. Enzyme essay

Tests for alpha galactosidase in blood sample. The blood sample is either collected in fluid form or dried blood spot. Deficient alpha Galactosidase A enzyme activity in plasma, isolated white blood cells or cultured cells is diagnostic for Fabrys Disease in males. Females who are heterozygous may show the presence of enzyme activity and therefore this test is not reliable for diagnosis.

Estimation of Gb3 levels in blood: Increased Gb3 in blood is diagnostic for Fabrys disease and also helps in checking the severity. Globotriaosylsphingosine (lyso-Gb3) levels act as a marker for severity of disease. The increase in lyso-Gb3 is greater in hemizygous males than heterozygous females and may explain the decrease in severity in females. But Schiffman et al found that the levels of lyso-Gb3 was useful in understanding the progression of renal and cardiac disease [40].

5.2. Genetic testing

Testing for gene mutations in GLA gene is diagnostic for Fabrys disease. Genetic testing is especially important in females as enzyme activity may be normal and presence of Fabrys can be detected by genetic testing only. They are about 370 mutations discovered so far related with this disease. Mutations include deletion, frameshift, nonsense, missense and splice variants. It is beneficial to know the type of mutation so as to be able to look for similar mutation in family members. Confirmation of hemizygous GLA pathogenic variant by molecular genetic testing confirms the diagnosis in a male proband and heterozygous GLA pathogenic variant in females.
Kidney or heart biopsy: A biopsy of renal or cardiac tissue shows presence of Gb3 inclusion bodies in cellular lysosomes. Skin sample can also be used for detecting Gb3.

6. Treatment

6.1. Treatment:

i. Enzyme replacement therapy: Agalsidase alpha (Replagal® ) and agalsidase beta (Fabrazyme®) are two enzyme preparations available in market for treatment of Fabrys disease. Agalsidase alpha as 0.2mg/kg or Agalsidase beta in a dose of 1 mg/kg body weight by infusion every two weeks is given. Initiating enzyme therapy early in disease stage can help decrease Gb3 accumulation in cells and reduce progression of organ damage, vasculopathy and inflammation. Study by Ortiz et al revealed that enzyme therapy slows the reduction in estimated GFR per year than untreated patients [41]. It can significantly produce clearance of Gb3 in cells [42] and also prove to be helpful in reducing the progression of left ventricular hypertrophy [43] with better outcomes if started at an early age and before the onset of renal and cardiac symptoms.

ii. Chaperon therapy: Chaperones are proteins which help in protein folding, thereby stabilizing them helps them to take correct form. Chaperones have been able to correct most of the mutations associated with Fabrys disease and therefore can correct enzyme's functional impairment. It can decrease the average number of Gb3 inclusion bodies in lysosomes. Galafold (migalastat) is the chaperone used in clinical practice. It is found to increase alpha galactosidase A activity with decreased in lyso-Gb3 levels and have been helpful in reducing left ventricular mass [44].

6.2. Supportive treatment

i. Neuropathic pain: Patient education to avoid triggers for pain should be done. NSAIDs are not used as they do not have much benefit and are also not good for renal function. Antiepileptics and antidepressant drugs are used against the neuropathic pain, for example: carbamezapine, gabapentin levetiracetam, phenytoin. Carbamazepine was found to show the most relief compared to other drugs [44]. But their adverse effects such as decreased focusing and fatigue are observed.

ii. Diarrhea: Advice the patients to eat a healthy diet in small frequent meals spread throughout the day. Enzyme replacement therapy is found to reduce GI symptoms [45]. Carbamazepine and gabapentin are helpful for abdominal pain. Nausea if present can be reduced using metoclopramide or ondansetron. Lomotil, proton pump inhibitors, H2 blockers and probiotics are helpful for diarrhea, gastric inflammation and bacterial overgrowth [45].

iii. Hypertension: hypertension might be present due to kidney affection and left ventricular hypertrophy. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are ideally given as they are also protective to kidneys.

Renal dysfunction may ultimately need dialysis and renal transplantation.

iv. Cardiac abnormalities: cardiac abnormalities may advance to heart failure. Hypotension is most often seen in these patients. They may require heart transplantation.

6.3. New treatment options still in experimental stage:

The newer techniques for treatment of Fabrys disease which are in developmental stage are given below [46]

i. Enzyme replacement therapy with PRX 102 which is a copy alpha galactosidase enzyme produced and modified in plant cells.

ii. Gene therapy-by introduction of normal genetic material for production of the deficient enzyme.

iii. Substrate reduction therapy for blocking the formation of substrate Gb3 and therefore decreasing its concentration and accumulation in cells.

iv. Apabetalone a selective bromodomain and extra-terminal (BET) inhibitor for regulation of disease-causing genes.

7. Prognosis

Life expectancy for individuals with Fabrys disease is considerably lesser with 58 years for males and 75 years for females compared to 75 and 80 years for general population in United States. The leading cause of death was found to be cardiovascular (50% of cases), cerebrovascular (12.5%) and renal (10.7%) disease [47].
8. Conclusion

Fabry's disease, though a rare disease, is associated with increased morbidity and mortality with decreased quality of life. The multisystem involvement including cardiac, renal and cerebrovascular disorder makes the individuals life quite miserable and debilitating unable to perform the normal day to day activities. More physician and patient education should be done to detect the cases early and initiate a suitable management therapy. Further, more research should be encouraged to uncover treatment therapies for improvement of well-being and reduction of debility of these people.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declares there is no conflict of interest.

References

[1] Germain DP. Fabry disease. Orphanet J Rare Dis. 2010; 5: 30.
[2] Moammar H, Cherian G, Mathew R, Al-Sannaa N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med. 2010; 30(4): 271-277.
[3] Alhemyadi SA, Elawad M, Fourtounas K, et al. Screening for Fabry disease among 619 hemodialysis patients in Saudi Arabia. Saudi Medical Journal. Aug 2020; 41(8): 813-818.
[4] Colon C, Ortolano S, Melcon-Crespo C, Alvarez JV, Lopez-Suarez OE, Couce ML, Fernández-Lorenzo JR. Newborn screening for Fabry disease in the north-west of Spain. Eur J Pediatr. Aug 2017; 176(8): 1075-1081.
[5] Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick R. High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening*. The American Journal of Human Genetics. 2006; 79(1): 31-40.
[6] Sawada T, Kido J, Yoshida S, Sugawara K, Momosaki K, Inoue T, Tajima G, Sawada H, Mastumoto S, Endo F, Hirose S, Nakamura K. Newborn screening for Fabry disease in the western region of Japan. Molecular genetics and metabolism reports. 2020; 22: 100562.
[7] Ries M, Ramaswami U, Parini R, Lindblad B, Whybra C, Willers I, Gal A, Beck M Eur J Pediatr. Nov 2003; 162(11): 767-72.
[8] Mehta A, Hughes DA. Fabry Disease. [Updated 2017 Jan 5]. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle. 5 Aug 2002; 1993-2021.
[9] Bernades T, Foresto R, Kirsztajn G. Fabry disease: genetics, pathology, and treatment. Revista da Associação Médica Brasileira. 2020; 66(suppl 1): s10-s16.
[10] Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Pinto A, Licata G. Anderson-Fabry disease: a multiorgan disease. Curr Pharm Des. 2013; 19(33): 5974-5996.
[11] S Baig, R Vijapurapu, F Alharbi, S Nordin, R Kozor, J Moon, B Bembali, T Geberhiwot, R P Steeds, Diagnosis and treatment of the cardiovascular consequences of Fabry disease, QJM: An International Journal of Medicine. January 2019; 112(1): 3–9.
[12] Rozenfeld P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Molecular Genetics and Metabolism. 2017; 122(3): 19-27.
[13] Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE. Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab. 2010; 99(2): 99-108.
[14] Hopkin R, Bissler J, Banikazemi M. et al. Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry. Pediatr Res. 2008; 64: 550–555.
[15] Crosbie TW, Packman W, Packman S. Psychological aspects of patients with Fabry disease. J. Inherit. Metab. Dis. 2009; 32: 745-753.

[16] 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.

[17] Luciano CA, Russell JW, Banerjee TK, Quirk JM, Scott LJ, Dambrosia JM et al. Physiological characterization of neuropathy in Fabry's disease. Muscle Nerve. 2002; 26: 622–9.

[18] Kuzman T, Juri J, Mrsić M, Jeren-Strujić B, Mandić Z, Šličić J. Fabryjeva bolest i promjene na ocima [Ocular findings in Fabry's disease]. Acta Med Croatica. 2006; 60(2): 163-166.

[19] Libert J, Toussaint D. Tortuosities of retinal and conjunctival vessels in lysosomal storage diseases. Birth Defects Orig Artic Ser. 1982; 18: 347–58.

[20] Hoffmann B, Schwarz M, Mehta A, Keshav S, Fabry Outcome Survey European Investigators. Clin Gastroenterol Hepatol. Dec 2007; 5(12): 1447-53.

[21] Eng CM, Fletcher J, Wilcox WR, Waldek S, Scott CR, Sillence DO, Breunig F, Charrow J, Germain DP, Nicholls K, Banikazemi M. In: Mehta A, Beck M, Sunder Ginsberg L. editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 20, Issue FI2.

[22] Shanat Baig, Nicky C Edward, Dipak Kotecha, Boyang Liu, Sabrina Nordin, Rebecca Kozor, James C Moon, Tarekgn Geberhiwot, Richard P Steeds, Ventricular arrhythmia and sudden cardiac death in Fabry disease: a systematic review of risk factors in clinical practice, EP Europace, Volume 20, Issue F12. September 2018; f153–f161.

[23] Schillmann R, Moore DF. Neurological manifestations of Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 21.

[24] Mitros P, Levine SR. Cerebrovascular complications of Fabry's disease. Ann Neurol. 1996; 40: 8–17.

[25] Buechner S, Moretti M, Burlina AP, Cei G, Manara R, Ricci R, et al. Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. J Neurol Neurosurg Psychiatry. 2008; 79: 1249–1254.

[26] Ginsberg L. Chapter 23. Nervous system manifestations of Fabry disease: data from FOS – the Fabry Outcome Survey, Mehta A, Beck M, Sunder-Plassmann G, In: Fabry Disease: Perspectives From 5 Years of FOS. Oxford: Oxford PharmaGenesis. 2006.
Germain DP, Avan P, Chassaing A, Bonfils P. Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients. BMC Med. Genet. 2002; 3: 10.

Faggiano A, Pisani A, Milone F, et al. Endocrine dysfunction in patients with Fabry disease. J Clin Endocrinol Metab. 2006; 91(11): 4319-4325.

Mersebach H, Johansson JO, Rasmussen Å. et al. Osteopenia: a common aspect of Fabry disease. Predictors of bone mineral density. Genet Med. 2007; 9: 812–818.

Schiffmann R, Ries M, Blankenship D, Nicholls K, Mehta A, Clarke JTR, Steiner RD, Beck M, Barshop BA, Rhead W, West M, Martin R, Amato D, Nair N, Huertas P. Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. Genet. Med. 2013; 15: 983-989.

Ortiz A, Kanters S, Hamed A, DasMahapatra P, Poggio E, Maski M et al. Agalsidase beta treatment slows estimated glomerular filtration rate loss in classic Fabry disease patients: results from an individual patient data meta-analysis. Clinical Kidney Journal. 2020.

C Tøndel, L Bostad, KK Larsen, et al. Agalsidase benefits renal histology in young patients with Fabry disease. J. Am. Soc. Nephrol. 2003; 24: 137-148.

F Weidemann, M Niemann, S Störk, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J. Intern. Med. 2013; 274: 331-341.

Müntze J, Gensler D, Maniuc O, et al. Oral Chaperone Therapy Migalastat for Treating Fabry Disease: Enzymatic Response and Serum Biomarker Changes After 1 Year. Clin Pharmacol Ther. 2019; 105(5): 1224-1233. Riccio E, Zanfardino M, Ferreri L. et al. Switch from enzyme replacement therapy to oral chaperone migalastat for treating fabry disease: real-life data. Eur J Hum Genet. 2020; 28: 1662–1668.

Zar-Kessler C, Karaa A, Sims KB, Clarke V, Kuo B. Understanding the gastrointestinal manifestations of Fabry disease: promoting prompt diagnosis. Therap Adv Gastroenterol. 2016; 9(4): 626-634.

Walker M. Experimental Treatments for Fabry Disease [Internet]. Fabry Disease News. 2021.

Waldek S, Patel M, Banikzemi M. et al. Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. Genet Med. 2009; 11; 790–796.