THE NEW ARMENIAN MEDICAL JOURNAL
Vol.14 (2020), No 3, p.66-72

CASCADE GENETIC SCREENING FOR DIAGNOSTICS OF PRECLINICAL FORMS OF FABRY DISEASE IN CHILDREN

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Received 20.02.2020; accepted for printing 14.07.2020

Abstract

The article is devoted to Fabry disease, which is a very rare disorder (orphan disease). Fabry disease is a multisystem enzymopathy, the second most common lysosomal disorder after Gaucher disease. Fabry disease is related to the lysosomal storage of the decomposition product of complex lipids, such as globotriaosylceramide (GL-3 and lyso GL-3) in the endothelial cells of the heart vessels, kidneys, brain and peripheral nervous system resulting ftom a decrease in the activity of alpha-galactosidase-A enzyme (α -GAL A). The example of a family case in the article reflects the necessary diagnostic algorithm for early verification of this disease. It is important to evaluate organs – systems, the control of the plasma globotriaosylsphingosine (Plasma Gb3) biomarker for the timely initiation of etiopathogenetic enzyme replacement therapy, which should be used in children with neuropathic pain and albuminuria (with a creatinine level in blood plasma > 3 mg/mmol), severe gastrointestinal tract lesions, abdominal pain and heart damage. Enzyme replacement therapy should also be used for the asymptomatic form of Fabry disease in boys from the age of 7. The article demonstrates the correlation of the therapy and prognosis of patients with etiotropic enzyme replacement therapy prescription.

Cascade genetic screening of children having at least one first-degree relative with Fabry disease is the simplest and most effective method for diagnosing the disease. It has been shown that Fabry disease is a rare disorder and a high index of professional medical competence is required for the initial diagnosis. Early detection of Fabry disease in clinical practice may be difficult due to the heterogeneity of the clinical manifestations of the disease and the similarity with other rheumatological diseases that are more common in children. Neuropathic pains in the extremities, acroparesthesia in combination with abdominal pain and connective tissue dysplasia in boys can serve as "Red Flags" for doctors, allowing to suspect Fabry disease. All children with Fabry disease, including those with preclinical forms of the disease, need constant control and regular clinical monitoring. The article demonstrates an examination of 24 members of one family, 12 of which with Fabry disease, and thus verifies the algorithm for diagnosing this disease.

Keywords: *Fabry disease, cascade genetic screening, lysosomal diseases, enzymopathy, children.*

Introduction

Fabry disease (FD) is a multisystem enzymopathy, the second most common lysosomal disorder after Gaucher disease [*Crivaro A et al., 2019*]. The disease is related to the lysosomal storage of the decomposition product of complex lipids, such as globotriaosylceramide (GL-3 and lyso GL-3) in the endothelial cells of the heart vessels, kidneys, brain and peripheral nervous system, resulting from a decrease in the activity of alpha-galactosidase-A -enzyme (α -GAL A). Unlike other storage diseases, manifested by severe developmental delay and clinical symptoms appearing at an early age, Fabry disease is often revealed after the age of 20, when patients visit cardiologists, nephrologists or neurolo-

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gists [*Suntjens E et al., 2017; Wilson H et al., 2017*]. Clinical expression in hemizygous men is detected in adolescence and youth. As for heterozygous women, it can vary from an asymptomatic course throughout life to manifestations as severe as in hemizygous men, thus justifying the necessity for cascade genetic screening [*Schiffmann R, 2015; Karovaikina E et al., 2019*]. Screening is performed for patients with chronic renal failure (CRF) receiving treatment with programmed hemodialysis, hypertrophic cardiomyopathy, and patients with early strokes [*Moiseev S, 2019 a; b*].

Due to the gradual accumulation of globotriaosylceramide from the prenatal age, the symptoms of the disease in children are less severe [*Politei J et al., 2018*]. Clinical manifestations of the disease can only appear as fever and abdominal pain of unknown origin, sometimes in combination with acroparasthesia. The most common symptoms of Fabry disease in children and adolescents are neuropathic pain, hyperhidrosis/anhydrosis, angiokeratomas, vortex keratopathy, and microalbuminuria [*Marchesoni C et al., 2018; Politei J et al., 2018; Germain D et al., 2019*]. Over time, the symptoms of renal failure increase, cardiac disorders and cerebrovascular pathology join [*Kuzenkova L et al., 2015; Germain D et al., 2019*].

Fabry disease is a rare disorder and a high index of professional medical competence is required for the initial diagnosis. Early detection of Fabry disease in clinical practice may be difficult due to the heterogeneity of the clinical manifestations of the disease and its similarity with other rheumatological diseases that are more common in children [*Moiseev S, 2019b; Vordenbäumen S et al., 2019*]. Classic manifestations of the disease, primarily myocardial hypertrophy and kidney damage, are not typical for children [*Garman S, Garboczi D, 2002; Wilson H et al., 2017*]. With the advent of enzyme and genetic screening, an earlier diagnosis and initiation of Fabry disease therapy in children has become possible [*Politei J et al., 2018; Germain D et al., 2019*].

Cascade (genetic) family screening (CGS) is a unique method for detecting the disease before the development of clinical symptoms with a family history of Fabry disease, which enables to undertake early initiation of targeted treatment with enzyme-replacing and enzyme-reducing drugs [*Ramaswami U et al., 2019; Spada M et al., 2019*]. Traditional CGS starts with the identification of an adult patient with Fabry disease who suffers from CRF, heart failure, or suffered an early stroke. When examining a proband, several diseased relatives are usually identified. CGS includes systematic testing of all 1st degree relatives (parents, brothers, sisters and children), followed by testing the 2nd and 3rd degree relatives, if the disease is detected in relatives of the 1st line.

Fabry disease is registered in the OMIM database (Online Mendelian Inheritance in Man; No 301500). Currently, about 800 mutations in the GLA gene have been identified, most of which are pathogenic, leading to a decrease in α-GAL synthesis and progressive accumulation of globotriosylceramide in the lysosomes, manifested by various types of FD course [*Germain D et al., 2020*]. GLA gene mutations are available in the UGMD international database. Most of the described mutations are single missense and nonsense mutations, although the so-called "major" mutations that are common in large families and populations are described as well [*Germain D et al., 2020*]. Most of them are unique for each family [*Zhou C et al., 2018; Cerón-Rodríguez M et al., 2019*]. Only in some cases there are clear geno-phenotypic correlations [*Germain D et al., 2020*]. Many researchers have shown the dependence of the disease onset age, the severity and the pathological process diffusion on the nature of mutations and the level of α-GAL and Lyso Gb3 (Tab. 1) [*Marchesoni C et al., 2018; Politei J et al., 2018; Zhou C et al., 2018; Moiseev S, 2019c*]. CGS allows us to establish interdependence between various mutation versions with a predominant prevalence of kidney or cardiovascular pathology in a patient [*Militaru S et al., 2019; Arora V et al., 2020; Hoss S et al., 2020*].

Clinical case

Three children (an 11-year-old girl, 6 and 7-year-old boys) with Fabry disease underwent examination (tab. 2). The onset of the disease in all children debuted with complaints of intermittent pain in the legs that occurred after physical activity.

The 11-year-old girl underwent examination (I). A child from the first pregnancy without complications; urgent, natural delivery; the perinatal history is not burdened;

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

TABLE 1

Publications about FD in children with presents of their own clinical cases with the 2017-2019

Articles				Age(years)	
Authors	Country	Year	N	Average	Range
Cerón-Rodríguez M.	Mexico	2019	7	6	3-12
Ramaswami U.	UK	2019	31	12	5-18
Semyachkina A.	Russia	2018	6	11	5-17
Zhou Cat.	China	2018	1	12	12
Marchesoni C.	Argentina	2018	44	15	7-21
Liern M.	Argentina	2018	31	12	
Ersoz MG.	Turkey	2018	1	11	11
Namazova-Baranova L,.	Russia	2017	110	10	2-18
Suntjens E.	Netherlands	2017	47	12	5-18
Wilson H.C.	USA	2017	26	10	<18

early psychomotor development according to age. At the age of 6 she underwent surgery for "acute abdomen" and suspicion of appendicitis. From the age of 9, the girl had fatigue, periodic pain in the legs, creeping, tingling and cold sensations in the distal extremities (mainly hands), frequent abdominal pain, sometimes with vomiting. Fabry disease was detected in maternal relatives and in the mother of the child. Therefore, the girl was also examined. Vortex keratopathy OU (cornea verticillata) was revealed. CGS revealed a heterozygous mutation of c. (1133G-> A) (p. [Cys 378Tyr]). The level of α-GAL is 4.0 *mmol/l* (the norm is over 1.2 *mmol/l*), Lyso Gb3 is 5.7 *ng/ml* (norm is 0-3.5 *ng/ml*). The girl's mother (IV), 29 years old, had burning pains in her hands and feet, periodic rises in temperature to subfebrile state, hypohidrosis, dizziness, and poor physical exercise tolerance, since adolescence. The examination revealed peripheral polyneuropathy, vortex keratopathy and microalbuminuria with preserved renal function. At the age of 25, the CGS revealed a heterozygous mutation of c. [1133G-> A] (p. [Cys 378Tyr]), elevated Lyso Gb3 level of 7.6 *ng/ml*, α-GAL level of *4.0 mmol/l*. The brother of the child's mother (V, proband) suffered from chronic renal failure from adolescence, received treatment with program hemodialysis and died at the age of 37 as a result of a progressing chronic heart failure. The CGS allowed to verify Fabry disease. The disease was diagnosed in the proband's mother (VIII) (65 years of age), siblins - three sisters (VI, IV) (45 and 29 years of age) and twins - brother (VIII) and sister (VII) (26 years of age). Probably, another brother (IX) who died in adolescence (at the age of 15) suffered from Fabry diseasee. He died of chronic renal failure and was diagnosed with "Fanconi syndrome", angiokeratomas, tubulointerstitial nephropathy, and limb deformity. Two brothers (X, XI) of the proband (42, 44 years of age) are healthy. All the siblings of the proband with a diagnosed Fabry disease had periodic episodes of subfebrile condition and dizziness, physical activity intolerance, acroparasthesia, neuropathic pains mainly in the hands, hypohidrosis, angiokeratomas and vortex keratopathy. Proband and all the FD siblings received enzyme replacement therapy with intravenous infusions of agalsidase-beta. The 7-year-old son of the praband's younger sister (VII) suffering from Fabry disease, a child from the first, normal pregnancy;

TABLE 2

Baseline characteristics of children with c.1133G->A/p.Cys 378Tyr variant

Patient	Age (y)	Sex	α-Gal A activity nl: >1.64 (*μmol/L/hr*)	Plasma Gb3 nl: <7.0 (*μg/ml*)	Genotype	Phenotype	Symptoms
1	11	girl	4.0	5.7	Heterozygous c[1133G->A] (p.[Cys 378Tyr])		Acr, a.p., c.v.
2	7	boy	3.7	95.4	Hemizygous c[1133G->A] (p.[Cys 378Tyr])	ctd	Acr
3	6	boy	2.4	69.2	Hemizygous c[1133G->A] (p.[Cys 378Tyr])	ctd	

NOTES: *ctd - connective tissue dysplasia, a.p. - abdominal pains, acr - acroparaesthesia, c.v. - cornea verticillata.*

natural, urgent delivery; early development according to age. From the age of 6, the boy had pains in the arms and legs, periodic pains in the abdomen. Connective tissue dysplasia was revealed. CGS detected a hemizygous mutation of c.[1133G-> A] (p. [Cys 378Tyr]), an elevated level of Lyso Gb3 of 95.4 *ng/ml*, and an α-GAL level of 3.7 *mmol/l*. Four daughters of the proband's elder sister(VI) suffering from Fabry disease underwent examination. According to the results, two children (XII, XIII) are healthy and two children (26 and 27 years of age) have FD (XIV, XV) with complaints of burning episodes in their hands. In addition, the two children of the patient XIV were examined. The daughter is healthy (XVI), but the son (XVII, 6 years old) has a hemizygous mutation, an elevated level of Lyso Gb3 of 69.2 *ng/ml*, an α-GAL level of 2.4 *mmol/l* without clinical manifestations of FD. The boy's perinatal history is not burdened; the child is from a first, normal pregnancy; natural, urgent delivery; early psycho-motor development was without pathology. The examination revealed signs of connective tissue dysplasia.

In total, 24 members of one family underwent CGS examination. Fabry disease was revealed in 12 of them. The proband's mother (64 years old), brothers and sister (aged 26-45), as well as the siblings' children (aged 7-22) and the grandson of the proband's sister (6 years old) underwent examination too. The DNA diagnostics revealed a change in the nucleotide sequence c.1133G> A, leading to the replacement of p.C378Y in 6 women in the heterozygous state and in 6 men in the hemizygous state, described in the international HGMD mutation database (CM 993664) (Fig.1).

Discussion

Fabry disease is a multi-organ disorder that has various phenotypic gene expression even in the same genealogy, from mild and blurred to marked and severe forms. In recent years, the diagnostics of Fabry disease has significantly improved. The application of fluorometric research of dry blood spots and mass spectrometry in FD risk groups, cascade family screening, genetic studies [*Politei J et al., 2018; Germain D et al., 2019*] allow to identify mutations leading to a significant damage to the cardiovascular system or kidneys [*Germain D et al., 2020*].

During the FD diagnostics in a proband, pathological alleles of the GLA gene can be detected in children of subsequent generations in the absence of significant gender differences.The diagnostics of the disease in children remains a challenge due to polymorphism and nonspecificity of the early manifestations of the disease [*Wilson H et al., 2017*].

Typical manifestations of the disease, in most cases, develop in adulthood, which is related to age-dependent penetration and variable expressiv-

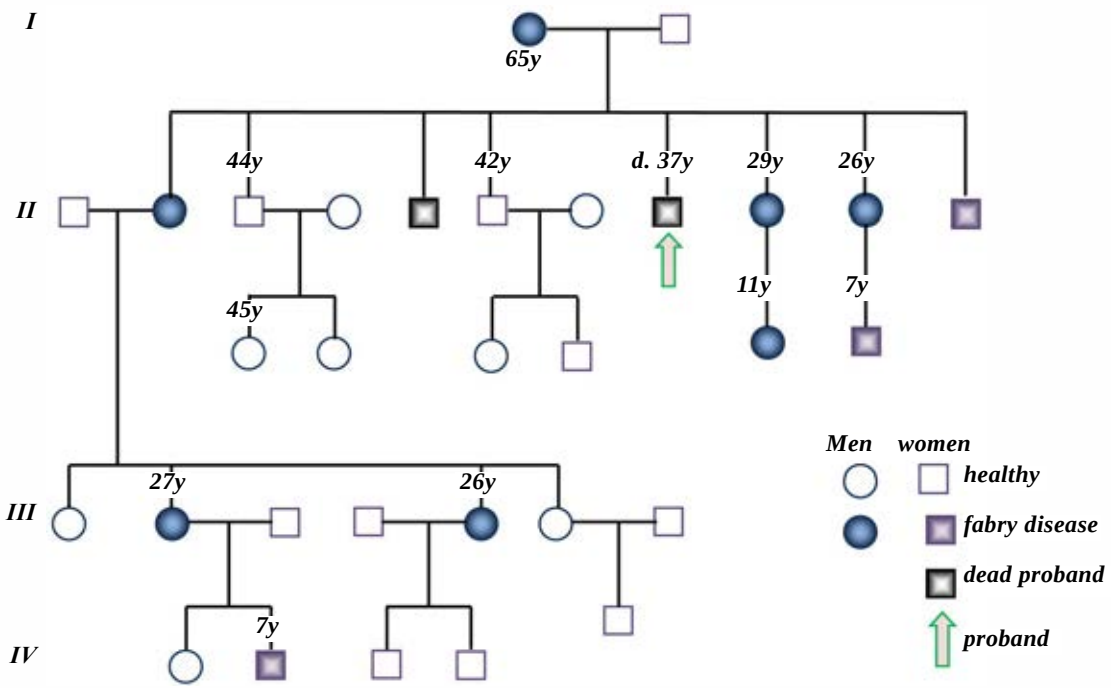

***Figure** . Cascade genetic screening.*

ity of the dominant gene. Due to the lack of specific symptoms of the disease, the diagnostics of index cases in children is rare. The main signs and symptoms of FD in childhood are pain in the limbs, fatigue, problems with the gastrointestinal tract, decreased or absent sweating accompanied by episodes of hyperthermia, intolerance to physical exertion and angiokeratoma [*Pensabene L et al., 2016; Wilson H et al., 2017*] Among the additional signs are: hearing loss, dizziness, albuminuria and stunted growth [*Germain D et al., 2019*]. Relatives, especially males, who died from heart, kidney failure or stroke before the age of 50 are aggravating factors for the development of Fabry disease. According to literature, the average age of neuropathic pain onset in boys is 7 years, whereas for girls it is 9 years [*Namazova-Baranova L et al., 2017; Semyachkina A et al., 2018*], which coincides with our data. Also, in the observed children, neuropathic pain was accompanied by abdominal pain, which is typical of the clinical manifestations of the disease in childhood (chronic pain in the extremities cannot be specific predicts of the disease, whereas the nature of the pain and comorbidity with other symptoms are important, most often in children with abdominal pains) [*Pensabene L et al., 2016; Namazova-Baranova L et al., 2017*]. It should be noted that connective tissue dysplasia was detected in the boys with FD. However, in literature it is described as a nonspecific symptom of this disease [*Semyachkina A et al., 2018*].

The proband and all its direct, blood relatives underwent partial analysis of the GLA gene by means of direct automatic sequencing, which revealed a change in the nucleotide sequence of c.1133G> A, leading to a replacement of p.C378Y, described in literature as a classic phenotype of Fabry disease. Angiokeratomas on the buttocks and hips, as well as functional disorders of the renal and cardiovascular systems occurring in adulthood were previously described as typical of FD patients with this pathogenic GLA mutation. However, the proband had heart failure in adolescence, whereas the proband's brother suffered from it in childhood and this pathology led to early disability and death of the patients at the age of 37 and 15 years, respectively. The combination of angiokeratoma, tubulointerstitial nephropathy and limb deformities detected in the proband's brother in childhood have not been described in literature as typical conditions for patients with this mutation.

Four generations of one family underwent CGS examination, which allowed to identify 3 children (2 boys and 1 girl) with early clinical manifestations of Fabry disease. Within the same family, the picture of the disease varies in severity and clinical manifestations in childhood, which may be important for determining the treatment tactics for children with FD if the disease has no clinical manifestations or has a mild form. Also, moderate and severe forms of the disease can be significantly delayed by early targeted therapy [*Kuzenkova L et al., 2015; Vordenbäumen S et al., 2019*].

The French expert group has presented clinical recommendation for the treatment and monitoring of children with FD. According to their suggestions, it is necessary to conduct clinical and laboratory monitoring of boys from the age of 5 every year, and girls from the age of 12-15 every 2-3 years in case of asymptomantic course. These steps should be taken urgently in case of a monosymptomatic course.

It is necessary to evaluate the cardiovascular, renal, nervous and gastrointestinal systems, conduct an assessment of vision, hearing, bone system disorders, as well as hold control over the plasma globotriosylsphingosine (Plasma Gb3) biomarker. Etiotropic enzyme replacement therapy (ERT) should be administered in children with neuropathic pain and albuminuria (with plasma creatinine levels of > 3 *mg/mmol*), severe gastrointestinal damage, abdominal pain, and heart damage. ERT should also be administered in cases of asymptomatic FD forms in boys from the age of 7. At the same time, symptomatic therapy of the clinical manifestations of the disease (NSAIDs and carbamazepine in severe acroparesthesia) should be conducted.

The prognosis of Fabry disease depends on the timely diagnostics and administration of etiotropic enzyme replacement therapy. Cascade genetic screening of children with at least one first-degree relative with Fabry disease is the simplest and most effective method for diagnosing the disease.

CONCLUSION

Cascade genetic family screening is the most optimal method for verifying the the phenotype of children with Fabry disease who have a family history of the disease.

Neuropathic pains in the limbs, acroparesthesia in combination with abdominal pain and connective tissue dysplasia in boys can serve as "red flags" for the doctor, thus allowing to suspect FD.

All children with Fabry disease, including those in preclinical forms, require constant control and regular clinical monitoring.

REFERENCES

1. *Arora V, Anand K, Chander I.* Genetic Testing in Pediatric Kidney Disease. Indian Journal of Pediatrics. Springer. 2020
2. *Cerón-Rodríguez M, Ramón-García G, Barajas-Colón E, Franco-Álvarez I, Salgado-Loza J.* Renal globotriaosylceramide deposits for Fabry disease linked to uncertain pathogenicity gene variant c.352C>T/p.Arg118Cys: A family study. Mol Genet Genomic Med. Wiley-Blackwell. 2019; 7(11): e981
3. *Crespo Liern ML, Collazo A, Valencia M, Fainboin A, Isse L, Costales-Collaguazo C.* Podocituria en pacientes pediátricos con enfermedad de Fabry. Nefrología. Elsevier BV. 2019; 39(2): 177-183
4. *Crivaro A, Juan Mucci, Constanza Bondar, Maximiliano Ormazabal, Romina Ceci., et al.* Efficacy of pentosan polysulfate in in vitro models of lysosomal storage disorders: Fabry and Gaucher Disease. PLoS One. Public Library of Science. 2019; 14(5)
5. *Garman SC, Garboczi DN.* Structural basis of Fabry disease. Mol Genet Metab. 2002; 77(1-2): 3-11
6. *Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P., et al.* Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet Blackwell Publishing Ltd. 2019; 96(2): 107-117
7. *Germain DP, Oliveira J, Bichet D, Yoo H, Hopkin R, Roberta M.* Use of a rare disease registry for establishing phenotypic classification of previously unassigned GLA variants: a consensus classification system by a multispecialty Fabry disease genotype–phenotype workgroup. J Med Genet. 2020. P. jmedgenet-2019-106467
8. *Hoss S, Habib M, Silver J, Care M, Chan R, Hanneman K.* Genetic Testing for Diagnosis of Hypertrophic Cardiomyopathy Mimics: Yield and Clinical Significance. Circ Genomic Precis Med. 2020
9. *Karovaikina E, Moiseev A, Bulanov N, Nosova N, Kuchieva A, Novikov P.* Screening, diagnosis and treatment of Fabry disease. Clin Pharmacol Ther. 2019; 28(3): 68-74
10. *Kuzenkova LM, Namazova-Baranova L, Podkletnova T, Gevorkyan A, Vashakmadze N, Savostyanov K.* Fabry Disease: Symptoms in Children and Teenagers. Curr. Pediatr. 2015; 14(3): 341
11. *Marchesoni C, Cisneros E, Pfister P, Yañez P, Reisin R.* Brain MRI findings in children and adolescents with Fabry disease. J Neurol Sci Elsevier B.V. 2018; 395: 131-134
12. *Militaru S, Adam R, Ismail G, Rusu E, Dulamea A, Jurcut R.* Demographic and Clinical Characteristics of the Full 2015-2018 Cohort of Romanian Fabry Disease Patients. Curr Heal Sci. J. 2019; 45(3): 272-277
13. *Moiseev S, Fomin V, Savostyanov K, Pushkov A, Moiseev A, Svistunov A.* The Prevalence and Clinical Features of Fabry Disease in Hemodialysis Patients: Russian Nationwide Fabry Dialysis Screening Program. Nephron. S. Karger AG. 2019a; 141(4): 249-255
14. *Moiseev S, Karovaikina E, Moiseev A, Bulanov N, Fomin V.* Strategies of Screening for Fabry Disease in Patients with Unexplained Left Ventricular Hypertrophy. Mayo Clinic Proceedings. Elsevier Ltd. 2019b; 94(8): 1644-1646
15. *Moiseev S, Karovaikina E, Novikov P, Ismailova D, Moiseev A, Bulanov N.* What rheumatologist should know about Fabry disease. Annals of the Rheumatic Diseases. BMJ Publishing Group. 2019c
16. *Namazova-Baranova LS, Baranov A, Pushkov A, Savostyanov K.* Fabry disease in children: a federal screening programme in Russia. Eur J Pediatr Springer Verlag, 2017; 176(10): 1385-1391
17. *Pensabene L, Sestito S, Nicoletti A, Graziano F, Strisciuglio P, Concolino D.* Gastrointestinal symptoms of patients with Fabry disease. Gastroenterol. Res. Pract. Hindawi Publishing Corporation. 2016; 2016: Article ID9712831
18. *Politei J, Albertón V, Amoreo O, Antongiovanni N, Arán M, Barán M.* Clinical parameters, LysoGb3, podocyturia, and kidney biopsy in children with Fabry disease: is a correlation possible? Pediatr Nephrol Springer Verlag. 2018; 33(11): 2095-2101
19. *Ramaswami U, Bichet D, Clarke L, Dostálová G, Fainboim A, Fellgiebel A.* Low-dose agalsidase beta treatment in male pediatric patients with Fabry disease: A 5-year randomized controlled trial Mol Genet Metab Academic Press Inc. 2019; 127(1): 86-94
20. *Schiffmann R.* Fabry disease. Handbook of Clinical Neurology. Elsevier B.V. 2015; 132: 231-248
21. *Semyachkina AN, Nikolaeva EA, Zakharova EYu, Kharabadze MN, Davydova YuI, Bochenkov SV.* [Fabry's disease in children: Analysis of personal observations, treatment possibilities] [Published in Russian]. Ross Vestn Perinatol i Pediatr National Academy of Pediatric Science and Innovation, 2018; 63(1): 71-77

22. *Spada M, Baron R, Elliott P, Falissard B, Hilz M, Monserrat L.* The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease – A systematic literature review by a European panel of experts. Molecular Genetics and Metabolism. Academic Press Inc. 2019; 126(3): 212-223

23. *Suntjens E, Dreschler W, Hess-Erga J, Skrunes R, Wijburg F, Linthorst G.* Hearing loss in children with Fabry disease. J Inherit Metab Dis Springer Netherlands. 2017; 40(5): 725-731

24. *Vordenbäumen S, Brinks R, Richter J, Albrecht K, Schneider M.* Response to What rheumatologist should know about Fabry disease by Moiseev et al. Annals of the Rheumatic Diseases. BMJ Publishing Group. 2019

25. *Wilson HC, Hopkin R, Madueme P, Czosek R, Bailey L, Taylor M.* Arrhythmia and Clinical Cardiac Findings in Children with Anderson-Fabry Disease. Am. J Cardiol Elsevier Inc. 2017; 120(2): 251-255

26. *Zhou C, Huang J, Cui G, Zeng H, Wang D, Zhou Q.* Identification of a novel loss-of-function mutation of the GLA gene in a Chinese Han family with Fabry disease. BMC Med Genet BioMed Central Ltd. 2018; 19(1)