

CROATIAN SOCIETY FOR NEUROVASCULAR DISORDERS OF CROATIAN
MEDICAL ASSOCIATION
CROATIAN SOCIETY OF NEUROIMMUNOLOGY AND NEUROGENETICS
CROATIAN SOCIETY OF NEUROLOGY OF CROATIAN MEDICAL
ASSOCIATION
CROATIAN SOCIETY OF NEPHROLOGY, DIALYSIS AND TRANSPLANTATION
OF CROATIAN MEDICAL ASSOCIATION
GUIDELINES FOR DIAGNOSIS, THERAPY AND FOLLOW
UP OF ANDERSON-FABRY DISEASE

Vanja Bašić Kes¹, Marijan Cesarik², Iris Zavoreo¹, Silva Soldo-Butković³, Petar Kes⁴, Nikolina Bašić-Jukić⁴, Sanjin Rački⁵, Marko Jakić⁶, Diana Delić-Brkljačić⁷, Zlatica Jukić⁸, Zlatko Trkanjec¹, Vesna Šerić¹, Vesna Vargek Solter¹, Ivan Bielen⁹, Silvio Bašić¹⁰ and Vida Demarin¹¹

¹Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb

²Department of Neurology, Požega General Hospital, Požega

³Department of Neurology, Osijek University Hospital Center, Osijek

⁴Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation, Zagreb University Hospital Center, Zagreb

⁵Department of Nephrology and Dialysis, Rijeka University Hospital Center, Rijeka

⁶Department of Dialysis, Osijek University Hospital Center, Osijek

⁷Department of Cardiology, Sestre milosrdnice University Hospital Center, Zagreb

⁸Department of Dermatology, Osijek University Hospital Center, Osijek

⁹Department of Neurology, Sveti Duh University Hospital, Zagreb

¹⁰Department of Neurology, Dubrava University Hospital, Zagreb

¹¹Aviva Medical Center, Zagreb, Croatia

SUMMARY – Fabry disease (Anderson-Fabry disease) is one of the most common lysosomal storage diseases (after Gaucher disease) caused by deficient activity of the α -galactosidase A (α -Gal A) enzyme, which leads to progressive accumulation of globotriaosylceramide in various cells, predominantly in endothelium and vascular smooth muscles, with multisystem clinical manifestations. Estimates of the incidence range from one *per* 40,000 to 60,000 in males, and 1:117,000 in the general population. Pain is usually the first symptom and is present in 60%-80% of affected children, as well as gastrointestinal disturbances, ophthalmologic abnormalities and hearing loss. Renal failure, hypertrophic cardiomyopathy, or stroke as the presenting symptom may also be found even as isolated symptoms of the disease. Life expectancy is reduced by approximately 20 years in males and 10-15 years in females, therefore enzyme replacement therapy should be introduced in patients of any age and either sex, who meet treatment criteria for Anderson-Fabry disease.

Key words: *Anderson-Fabry disease, diagnosis, treatment*

Pathophysiology

Fabry disease (Anderson-Fabry disease, AFD) is one of the most common lysosomal storage diseases (after Gaucher disease). In 1897, William Anderson was the first to describe clinical manifestations of Fabry disease as multiple telangiectasias in a 39-year-old patient, and in 1898 Johannes Fabry described “angiokeratoma corporis diffusum” and proteinuria in a 13-year-old boy. Fabry disease is an X-linked recessive lysosomal storage disorder caused by deficient activity of the α -galactosidase A (α -Gal A) enzyme, which leads to progressive accumulation of globotriaosylceramide in various cells, predominantly in endothelium

GAL gene mutation (X-linked disorder)



α -galactosidase enzyme deficiency



incapacity of glycosphingolipid catabolism



accumulation of globotriaosylceramide (Gb3) in endothelium and visceral organs



multisystem organ failure

Fig. 1. Genetic and molecular basis of Fabry disease.

and vascular smooth muscles, with multisystem clinical manifestations, including the nervous system (Fig. 1). The gene for α -galactosidase A is located on Xq22, and more than 585 mutations have been identified. Most of them are missense mutations, while other can clinically present as a monosymptomatic disease or oligosymptomatic disease (classical clinical picture). Due to X-linked recessive pattern of inheritance, Fabry disease predominantly affects males, but female carriers of the defective gene are also often affected (Figs. 2-4)^{1,2}.

According to Lyon hypothesis and consecutive mosaicism of the X chromosome in female patients, the

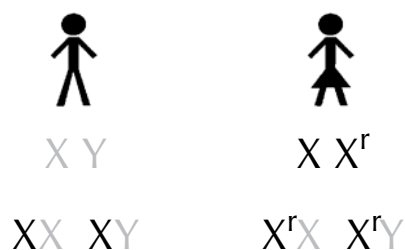


Fig. 2. Female X-linked recessive trait segregation.

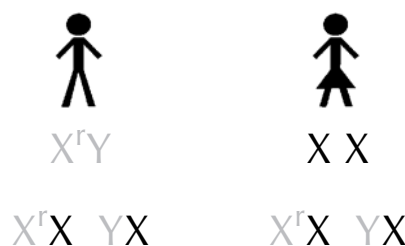


Fig. 3. Male X-linked recessive trait segregation.

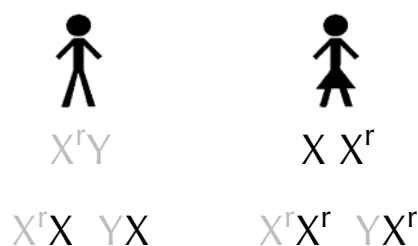


Fig. 4. Female and male X-linked recessive trait segregation.

heterogeneity of symptoms is even more pronounced (Fig. 5). The symptoms also tend to start later in life than in male patients, have slower progression and milder clinical manifestations (Table 1).

Estimates of the incidence range from one *per* 40,000 to 60,000 males; in the general population, it is estimated to be 1/117,000 in Australia³, 1/476,000 in The Netherlands⁴, and as high as 1/15,000 in Nova Scotia⁵.

Clinical Signs and Symptoms

Clinical signs and symptoms vary between males and females in number, severity and time of appearance, as described before. The symptoms usually ap-

Table 1. Onset of Fabry disease symptoms due to age in male patients; in female patients later onset and wide range of symptoms in clinical picture

| Childhood | Adolescence | Adulthood |
|--------------------------------|--------------------------------|--------------------------------|
| Acroparesthesias | Acroparesthesias | Acroparesthesias |
| Pain in limbs | Pain in limbs | Pain in limbs |
| Lenticular and corneal changes | Lenticular and corneal changes | Lenticular and corneal changes |
| Fever | Fever | Fever |
| Heat and cold intolerance | Heat and cold intolerance | Heat and cold intolerance |
| Psychosocial changes | Psychosocial changes | Psychosocial changes |
| | Proteinuria | Proteinuria |
| | Gastrointestinal symptoms | Gastrointestinal symptoms |
| | Angiokeratoma | Angiokeratoma |
| | Fatigue | Fatigue |
| | | Renal failure |
| | | Cardiac failure |
| | | Stroke |
| | | Hearing loss and tinnitus |

pear during childhood or adolescence⁶, and by middle age, life-threatening complications often develop in untreated patients. In the classic Fabry disease, they include renal, cardiac and cerebrovascular manifestations that lead to early death. These patients have either no or very small amounts of detectable enzyme activity, while milder variants have decreased enzyme activity. Patients present clinically with chronic neuropathic pain, gastrointestinal disturbances, angiokeratoma, progressive renal impairment, cardiomyopathy, and stroke. Recognition of Fabry disease is still difficult because of the heterogeneous presentation of the disorder. Due to the heterogeneity of symptoms, the diagnosis is often missed⁷; the results from Fabry Outcome Survey have shown that the mean time between the onset of symptoms and diagnosis was 12.4 years in females and 12.2 in males⁸. The so called 'cardiac variant'^{9,10}, 'renal variant'¹¹ or 'stroke variant'¹² may be one of the first and only symptoms of Fabry disease. Clinically, they present with late onset hypertrophic cardiomyopathy, isolated stroke or isolated end-stage renal disease (ESRD) as their initial manifestation.

Symptoms in childhood and adolescence may vary, usually they start between the age of 3 and 10 years, often a few years later in girls than in boys^{12,13}. In 60%-80% of affected children, pain is the first symptom. They may experience acute, unexplained episodes of

burning pain in the extremities, often accompanied or triggered by fever (episodic or Fabry crisis). Pain diminishes the quality of life, and may even lead to anxiety or depression. Chronic pain or discomfort in the extremities (acroparesthesia) is another form of painful sensation described. These symptoms are due to a dysfunctional condition of small nerve fibers¹⁴. Unexplained gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal discomfort and pain, loss of weight) are very common. The most visible early clinical sign is angiokeratoma, small raised, dark-red spots, which are typically found on the buttocks, groin, umbilicus and upper thighs. Ophthalmologic abnormalities, especially cornea verticillata and retinal vessel tortuosity, hearing impairment or dyhidrosis (hypohidrosis or anhidrosis) can be found. Inability to sweat leads to heat, cold, and exercise intolerance (Table 1). Early signs of cardiac and renal abnormalities may be present during adolescence (proteinuria, microalbuminuria, impaired concentration ability, impaired heart rate variability, arrhythmias, ECG abnormalities, mild valvular insufficiency)¹⁵.

Adults often present with worsening of childhood symptoms. Isolated end-stage renal failure, hypertrophic cardiomyopathy, or stroke as the presenting symptom may also be found. Hearing loss is common, often with rapid onset. More extensive angiok-

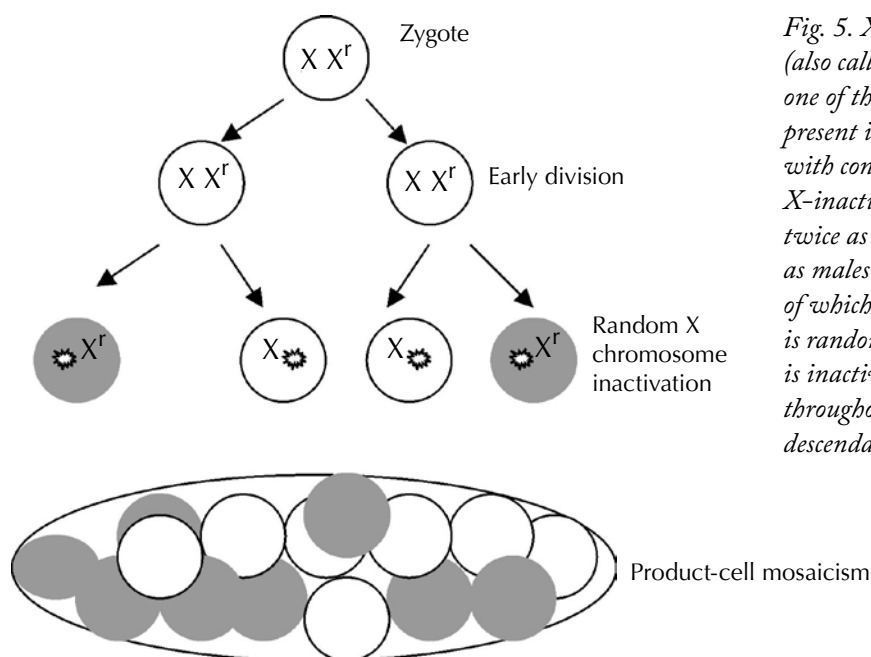


Fig. 5. X-inactivation (also called lyonization) is a process by which one of the two copies of the X chromosome present in female mammals is inactivated with consecutive mosaicism of the cells. X-inactivation prevents them from having twice as many X chromosome gene products as males – dosage compensation. The choice of which X chromosome will be inactivated is random, but once an X chromosome is inactivated it will remain inactive throughout the lifetime of the cell and its descendants in the organism.

Table 2. Differential diagnosis of Fabry disease according to leading symptoms

| | |
|---|---|
| Angiokeratoma | Petechiae of meningococcal meningitis (during Anderson-Fabry disease crisis) Hereditary hemorrhagic telangiectasias Fordyce disease, Schindler disease, fucosidosis and sialidosis (lysosomal storage diseases) Systemic lupus erythematosus |
| Pain (elevated erythrocyte sedimentation levels) | Rheumatoid arthritis Rheumatic fever Raynaud's disease „Growing pains“ |
| Neurologic symptoms | Multiple sclerosis and other demyelinating diseases Stroke (caused by conventional risk factors, vasculitis, thrombophilia) Different causes of polyneuropathy |
| Renal impairment | Before biopsy – more common causes of early onset end stage renal failure, e.g., glomerulonephritis, pyelonephritis, exposure to silica dust |
| Cardiac disease | Cardiomyopathy (hypertrophic and restrictive) Amyloidosis Congestive heart failure Coronary heart disease |
| Gastrointestinal | Appendicitis Irritable bowel syndrome Pancreatic insufficiency |

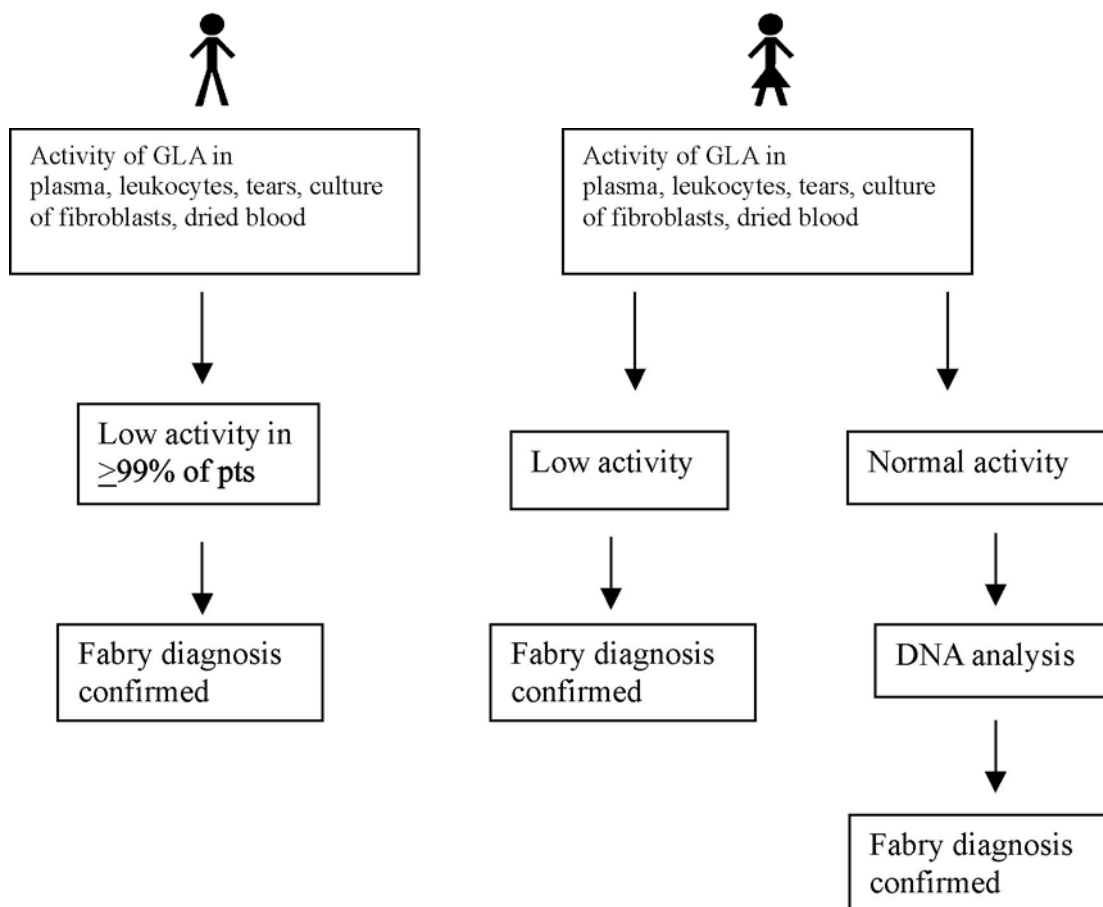


Fig. 6. In most female patients, DNA sequencing as the first step in Fabry diagnosis establishment is obligatory, while in male patients it should be done to confirm the number and type of the GLA gene mutation.

eratomas may be present or can cover only the genital area. Nephropathy is one of the major complications of Fabry disease and an important cause of death. Age at onset of end-stage renal failure is usually in the 30s and is not seen in childhood. Abnormalities include proteinuria, hematuria, nephrotic syndrome and chronic renal failure requiring dialysis and/or renal transplantation¹⁶. Common cardiac defects include left and right ventricular hypertrophy, enlarged left atrium, heart valve abnormalities, atrial arrhythmia and conduction disturbance, angina, shortness of breath, fatigue, and syncope. Cardiac involvement may be the only symptom in some hemizygous males¹⁰ and up to 4% of males with hypertrophic cardiomyopathy may have a 'cardiac' variant of AFD¹⁰. Nervous system involvement includes transient ischemic attack (TIA) or stroke¹⁷. It is estimated that 1%-2% of

stroke patients aged 18 to 55 years could have Fabry disease¹⁸. The mean age recorded for cerebrovascular events is around 5 years earlier in men than in women^{19,20}. Ischemic stroke is considerably more common than hemorrhagic stroke^{19,20}, and most are small vessel infarcts. Recent studies¹⁹ have shown that nearly half of Fabry patients (45.9%) experienced their first stroke before being diagnosed. In fact, the median time from stroke to diagnosis was 4.8 years. The prevalence of Fabry disease in young patients with cryptogenic stroke has been reported to be as high as 4.9% in men and 2.4% in women¹⁸. Other studies suggest that α -GAL A deficiency may play a role in up to 1% of young patients presenting with cerebrovascular disease²¹. Vertebrobasilar dolichoectasia has also been reported in Fabry patients^{17,22}. Hyperintensity in the pulvinar on T1 weighted images is a common find-

ing in Fabry disease, likely reflecting the presence of calcification. Recent findings suggest that the pulvinar sign is a highly specific sign, distinctively characteristic of Fabry disease^{21,22}. Disturbed concentration, dizziness, dementia, headaches, and learning difficulties also occur. The peripheral nervous system may also be affected, with disturbances of touch, pain and sensitivity to temperature⁸. Respiratory involvement, manifesting as dyspnea with exercise, chronic cough and wheezing, is frequent in both genders with Fabry disease (Table 1)^{23,24}.

Life expectancy is reduced in both male and female patients by approximately 20 years in males and 10-15 years in females. The Fabry Outcome Survey (FOS) data have shown that the principal cause of death in males is renal failure, followed by cardiac and cerebrovascular incidents. In female patients, the main causes of death were cardiac disorders⁸.

Diagnostic Testing for Fabry Disease

Differential diagnosis of Fabry disease depends on the leading signs and symptoms; some of the most common states are listed in Table 2. As mentioned above, early diagnosis of Fabry disease is difficult. Early symptoms in childhood are often subtle and nonspecific, and may be easily misinterpreted. The median age at diagnosis was about 28 years among 688 patients in FOS, which was about 16 years after the first symptoms had started⁸. Patients often have to visit several medical specialists before a correct diagnosis is made. Medical specialists caring for patients with renal and cardiac disease or stroke are most likely to make a diagnosis, which is highly important since enzyme replacement therapy can significantly improve

the quality of life and medical care. Also, correct diagnosis leads to family screening and identification of other relatives who are affected or are carriers of the disease, enabling genetic counseling and prenatal diagnostics (Fig. 6).

After establishment of Fabry disease as a working diagnosis, it is of great importance to evaluate the GLA activity in plasma or peripheral blood leukocytes (plasma and lysosomal GLA), the concentration of Gb3 in serum and urine, and genetic testing to identify the GLA gene mutations.

Biochemical or molecular prenatal diagnosis of Fabry disease can be performed by determination of α -gal A activity in direct and/or cultured chorionic villi at 10 weeks of gestation, or in cultured amniotic cells at about 14 weeks of gestation. Since the implementation of enzyme replacement therapy in the management of Fabry disease, prenatal diagnosis has become ethically and medically questionable.

Diagnostic work up for patient suspect of Fabry disease should include:

- General status, quality of life, school or work performance, depression, anxiety, drug use, somatic growth
- Complete physical examination
- Neurologic examination, questionnaires (Brief Pain Inventory)
- Complete laboratory work up (complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, ionogram, BUN; urinary protein/creatinine ratio, albumin/creatinine ratio, liver function test, glucose levels, thyroid hormones, creatine phosphokinase, lactate dehydrogenase)

Table 3. Fabry disease – evaluation of kidney involvement

| Organ system | Assessment | Recommendation |
|--------------|--|--|
| Kidney | Serum electrolytes, creatinine, BUN; 24-h urine or spot urine for total protein/creatinine, albumin/creatinine, sodium, creatinine | Baseline, every 3 months if CKD stage 1 or 2 and >1 g/day of proteinuria or CKD stage 4 |
| | | Every 6 months if CKD stage 3 |
| | | Every 12 months if CKD stage 1 or 2 and <1 g/day of proteinuria |

BUN = blood urea nitrogen; CKD = chronic kidney disease

- Alpha-galactosidase A activity, Gb3 levels in serum and urine, and genotype
- ECG, echocardiography 2-D with Doppler
- Holter monitoring
- Cardiac MRI
- Coronary angiography
- Brain MRI without contrast
- Magnetic resonance angiography
- Evaluation of the head and neck blood vessels by means of ultrasound (echo tracking, intima media thickness, measurement of vasoreactivity, Color Coded Flow imaging and Power Doppler)
- Comorbid stroke risk factors: cholesterol (total, LDL, HDL), triglycerides, Lp(a), total plasma homocysteine, testing for vasculitis and thrombophilia
- Abdominal ultrasound
- Renal biopsy in selected cases
- General ophthalmologic exam
- Spirometry
- Endoscopic evaluations of gastrointestinal system
- Audiometry, tympanometry, otoacoustic emissions Dermatologic examination and skin biopsy in selected cases Bone mineral density, 25(OH) vitamin D levels

Epidemiology and the Need of Screening

We do not recommend screening in the general population. (Ungraded statement)

We recommend obtaining informed consent from the patient before screening, using an information form drafted in collaboration with a clinical geneticist. (Ungraded statement)

We recommend screening for Fabry disease in male chronic kidney disease (CKD) patients below 50 years of age in whom a reliable renal diagnosis is absent. (Ungraded statement) (Table 3)

We suggest screening for Fabry disease in females with unexplained CKD, irrespective of age, with other unexplained symptoms potentially associated with Fabry disease. (Ungraded statement)

We recommend discussing with the patient the implications of diagnosing a genetic disease and the possible implications for the at risk relatives. (Level 1C)

Screening Methods

We recommend using enzyme activity measurement for α -Gal A as a primary tool in males, followed by confirmation with mutation analysis when positive. (Ungraded statement)

We suggest using mutation analysis as a primary tool for screening in females. (Ungraded statement)

Treatment guidelines

Enzyme replacement therapy

Enzyme replacement therapy (ERT) supplies the organs with recombinant enzyme and therefore reduces THE amount of Gb3 accumulation in tissues with consecutive multisystem damage. Treatment of Fabry disease with ERT is available since 2001, in THE form of two recombinant GLA preparations – agalsidase alfa (Replagal, Shire Human Genetic Therapies, Cambridge, MA, 0.2 mg/kg *per* infusion), and agalsidase beta (Fabrazyme, Genzyme Corporation, Cambridge, MA, 1 mg/kg *per* infusion)²⁵⁻²⁷.

ERT should be considered in patients of any age and either sex, who meet any of the set criteria.

Diagnostic work up should be performed as well as introduction of ERT at clinical hospital centers and then continued according to the place of living.

Renal

It is not recommended to start ERT in patients with proteinuria [protein-to-creatinine ratio >1 g/g (>0.1=gram/mol) creatinine] or eGFR <60 mL/min/1.73 m², except for non-renal indications. (1D)

We recommend that when ERT is deemed indicated, it should be started as part of a well-designed clinical trial, either observational or interventional. (Ungraded statement)

In a patient on hemodialysis, and when ERT is deemed indicated, we recommend administering the ERT during a hemodialysis session. (1A)

We recommend kidney transplantation as a valuable option in patients who are eligible for this intervention. (Ungraded statement)

After renal transplantation, we do not suggest ERT for renal indications, but it can be continued for non-renal indications. (Ungraded statement)

We recommend not considering female carriers for living donation, unless in exceptional cases. In these cas-

es, we recommend a kidney biopsy to evaluate the risk for the donor and recipient. (Ungraded statement)²⁹⁻⁴².

Cardiac

Any patient with Fabry disease and cardiac disease as defined in the criteria for cardiac diagnosis should be considered candidate for enzyme replacement, providing other causes of their cardiac findings have been excluded⁴⁰⁻⁴².

Neurological

Transient ischemic attacks documented by a neurologist or early onset central nervous system infarction, or unexplained, progressive white matter changes identifiable as microvascular changes on magnetic resonance imaging²⁵⁻²⁷.

Gastrointestinal

Severe gastrointestinal symptoms: intractable abdominal pain and diarrhea refractory to other therapies²⁵⁻²⁷.

Pain

Intractable neuropathic pain refractory to other therapies²⁵⁻²⁷.

Treatment of comorbidities

Specific attention should be paid to cerebrovascular and cardiovascular risk factors. Patients with Fabry disease carry a very high risk of vascular events, so the management of other vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, increased weight, smoking) should be aggressive²⁵⁻²⁷.

Symptomatic Treatment

Pain and painful episodes

Lifestyle modifications (in particular, avoidance of stimuli that precipitate Fabry pain, i.e. fatigue, lack of sleep) and certain prophylactic medications can be useful for symptom management. Diphenylhydantoin (Dilantin)¹⁵, carbamazepine (Tegretol)¹⁶ and gabapentin (Neurontin)¹⁷ have been found to be effective in some patients. Nonsteroidal anti-inflammatory drugs, serotonin reuptake inhibitors or tricyclic antidepressants may be used for intermittent pain. Chronic, debilitating pain is managed best by an expert in pain management.

Gastrointestinal symptoms

Pancrelipase or metoclopramide can improve gastrointestinal symptoms²³.

Psychosocial support

Fabry disease, especially with early onset in childhood and adolescence as well as later in life, causes many psychosocial problems, therefore it is of great importance to include psychiatrist in early treatment of Fabry patient.

Follow-up of Fabry disease

Clinical course will determine the frequency of tests and clinical evaluation. Detailed baseline and follow-up data of all patients with established Fabry disease should be transferred to a central registry. There should be obligatory baseline and subsequent yearly evaluation of asymptomatic Fabry disease patients, more frequently for symptomatic patients (every 3 months), by a multidisciplinary team, including kidney function and albuminuria, in all patients with established Fabry disease (cardiology, neurology and nephrology diagnostic work up)^{43,44}.

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONES

Within each recommendation, the strength of recommendation is indicated as Level 1 and Level 2, or Not Graded and the quality of the supporting evidence is shown as A,B,C or D.

| Grade | Implications | | |
|-----------------------------------|---|---|---|
| | Patients | Clinicians | Policy-makers |
| Level 1 (we recommend) | Most people in your situation would want the recommended course of action and only a small proportion would not | Most patients should receive the recommended course of action | The recommendation can be evaluated as a candidate for developing a policy or a performance measure. |
| Level 2 (we suggest) | The majority of people in your situation would want the recommended course of action but many would not | Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences. | The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined. |

* The additional category „Not graded“ was used typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendation regarding monitoring intervals, counseling, and referral to other clinical specialist. The ungraded recommendations are generally written as a simple declarative statement, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

| Grade | Quality of evidence | Meaning |
|----------|---------------------|---|
| A | High | We are confident that the true effect lies close to that of the estimate of the effect. |
| B | Moderate | The true effect is likely to be close to the estimate to the effect, but there is a possibility that it is substantially different. |
| C | Low | The true effect may be substantially different from the estimate to the effect. |
| D | Very low | The estimate of the effect is very uncertain, and often will be far from the truth. |

References

1. BRADY RO, GAL AE, BRADLEY RM, MARTENSON E, WARSHAW AL, LASTER L. Enzymatic defect in Fabry's disease. Ceramide trihexosidase deficiency. *N Engl J Med* 1967;276:1163-7.
2. PETERS FPJ, VERMEULEN A, KHO TL. Anderson-Fabry's disease: α -galactosidase deficiency. *Lancet* 2001;357:138-40.
3. MEIKLE PJ, HOPWOOD JJ, CLAGUE AE, CAREY WF. Prevalence of lysosomal storage disorders. *JAMA* 1999;281:249-54.
4. POORTHUIS BJ, WEVERS RA, KLEIJER WJ, *et al.* The frequency of lysosomal storage diseases in Netherlands. *Hum Genet* 1999;105:151-6.
5. WEST M, DYACK S, RIDDELL C, LeMOINE K, CAMFIELD C, CAMFIELD P. A Nova Scotia kindred with Fabry disease. *Acta Paediatr* 2002;91:439S:116.
6. RIES M, RAMASWAMI U, *et al.* The early clinical phenotype of Fabry disease: a study of 35 European children. *Eur J Paediatr* 2003;162:767-72.
7. MEHTA A, LEWIS S, LAVERY C. Treatment of lysosomal storage disorders. *BMJ* 2003;327:462-3.
8. MEHTA A, BECK M, SUNDER-PLOSSMANN G. Fabry disease: perspectives from 5 years of FOS. Oxford PharmaGenesis Ltd., England, 2006.
9. ELLEDER M, BRADOVA V, SMID F, BUDESINSKY M, HARZER K, KUSTERMANN-KUHN B, *et al.* Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. *Virch Arch Pathol Anat Histopathol* 1990;417:449-55.
10. NAKAO S, TAKENAKA T, MAEDA M, KODAMA C, TANAKA A, TAHARA M, *et al.* An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995;333:288-93.
11. NAKAO S, KODAMA C, TAKENAKA T, TANAKA A, YASUMOTO Y, YOSHIDA A, KANZAKI T, ENRIQUEZ AL, ENG CM, TANAKA H, TEI C, DESNICK RJ. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. *Kidney Int* 2003;64:801-7.
12. SALVIATI A, BURLINA AP, BORSINI W. Nervous system and Fabry disease, from symptoms to diagnosis: damage evaluation and follow-up in adult patients, enzyme replacement, and support therapy. *Neurol Sci* 2010;31:299-306.
13. GERMAIN DP. Fabry disease. *Orphanet J Rare Dis* 2010;5:30.
14. TSAKIRIS D, SIMPSON HKL, JONES EHP, *et al.* Rare diseases in renal replacement therapy in the ERA-EDTA Registry. *Nephrol Dial Transplant* 1996;11:4-20.
15. MITSIAS P, LEVINE SR. Cerebrovascular complications of Fabry's disease. *Ann Neurol* 1996;40:8-17.
16. ROLFS A, BOTTCHER T, ZSCHIESCHE M, MORRIS P, WINCHESTER B, BAUER P, *et al.* Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. *Lancet* 2005;366:1794-6.
17. SIMS K, POLITEIJ, BANIKAZEMI M, LEE P. Stroke in Fabry disease frequently occurs before diagnosing and in the absence of other clinical events: natural history data from the Fabry Registry. *Stroke* 2009;40:788-94.
18. SCHIFFMANN R, WARNOCK DG, BANIKAZEMI M, BULTAS J, LINTHORST GE, PACKMAN S, *et al.* Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant* 2009;24:2102-11.
19. BROUNS R, THIJS V, EYSKENS F, Van den BROECK M, BELACHEW S, Van BROECKHOVEN C, *et al.* Belgian Fabry Study: Prevalence of Fabry disease in a cohort of 1000 young patients with cerebrovascular disease. *Stroke* 2010;41:863-8.
20. PASSERO SG, CALCHETTI B, BARTALINI S. Intracranial bleeding in patients with vertebrobasilar dolichoectasia. *Stroke* 2005;36:1412-5.
21. MOORE DF, YE F, SCHIFFMANN R, BUTMAN JA. Increased signal intensity in the pulvinar on T1-weighted images: a pathognomonic MR imaging sign of Fabry disease. *AJNR Am J Neuroradiol* 2003;24:1096-101.
22. BURLINA AP, MANARA R, CAILLAUD C, LAISSY JP, SEVERINO M, KLEIN I, BURLINA A, LIDOVE O. The pulvinar sign: frequency and clinical correlations in Fabry disease. *J Neurol* 2008;255:738-44.
23. ROSENBERG DM, FERRANS VJ, FULMER JD, LINE BR, BARRANGER JA, BRADY RO, CRYSTAL RG. Chronic airflow obstruction in Fabry's disease. *Am J Med* 1980;68:898-905.
24. BROWN LK, MILLER A, BHUPTANI A, SLOANE MF, ZIMMERMAN MI, SCHILERO G, ENG CM, DESNICK RJ. Pulmonary involvement in Fabry disease. *Am J Respir Crit Care Med* 1997;155:1004-10.
25. MOTABAR O, SIDRANSKY E, GOLDIN E, ZHENG W. Fabry disease – current treatment and new drug development. *Curr Chem Genomics* 2010;4:50-6.
26. DEEGAN PB. Fabry disease, enzyme replacement therapy and the significance of antibody responses. *J Inher Metab Dis* 2012;35:227-43.
27. ELSTEIN D, ALTARESCU G, BECK M. Fabry Disease. Dordrecht-Heidelberg-London-New York: Springer, 2010.
28. ENG CM, GERMAIN DP, BANIKAZEMI M, *et al.* Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med* 2006;8: 539-48.
29. GERMAIN DP, WALDEK S, BANIKAZEMI M, *et al.* Sustained, longterm renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007;18:1547-57.

30. LINTHORST GE, BOUWMAN MG, WIJBURG FA, *et al.* Screening for Fabry disease in high-risk populations: a systematic review. *J Med Genet* 2010;47:217-22.
31. ORTIZ A, CIANCIARUSO B, CIZMARIK M, *et al.* End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry. *Nephrol Dial Transplant* 2010;25:769-75.
32. ORTIZ A, OLIVEIRA JP, WALDEK S, *et al.* Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. *Nephrol Dial Transplant* 2008;23:1600-7.
33. PASCHKE E, FAULER G, WINKLER H, *et al.* Urinary total globotriaosylceramide and isoforms to identify women with Fabry disease: a diagnostic test study. *Am J Kidney Dis* 2011;57:673-81.
34. SCHIFFMANN R, WARNOCK DG, BANIKAZEMI M, *et al.* Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant* 2009;24:2102-11.
35. SHAH T, GILL J, MALHOTRA N, *et al.* Kidney transplant outcomes in patients with Fabry disease. *Transplantation* 2009;87:280-5.
36. TERRY W, COCHAT P, FROISSART R, ORTIZ A, PIRSON Y, POPPE B, SERRA A, Van BIESEN W, VANHOLDER R, WANNER C. Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice. *Nephrol Dial Transplant* 2013;28:505-17.
37. WANNER C, OLIVEIRA JP, ORTIZ A, *et al.* Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry registry. *Clin J Am Soc Nephrol* 2010;5:2220-8.
38. WARNOCK DG, ORTIZ A, MAUER M, *et al.* Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. *Nephrol Dial Transplant* 2012;27:1042-9.
39. ZOCCALI C, ABRAMOWICZ D, CANNATA-ANDIA JB, *et al.* European best practice *quo vadis?* From European Best Practice Guidelines (EBPG) to European Renal Best Practice (ERBP). *Nephrol Dial Transplant* 2008;23:2162-6.
40. SACHDEV B, TAKENAKA T, TERAGUCHI H, TEI C, LEE P, McKENNA WJ, ELLIOTT PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002;105:1407-11.
41. NAKAO S, TAKENAKA T, MAEDA M, KODAMA C, TANAKA A, TAHARA M, YOSHIDA A, KURIYAMA M, HAYASHIBE H, SAKURABA H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995;333:288-93.
42. MONSERRAT L, GIMENO-BLANES JR, MARIN F, HERMIDA-PIRIETO M, GARCIA-HONRUBIA A, PEREZ I, FERNANDEZ X, de NICOLAS R, de la MORENA G, PAYA E, YAGUE J, EGIDO J. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2007;50:2399-403.
43. BAŠIĆ KES V, CESARIK M, ZAVOREO I, MADŽAR Z, DEMARIN V. Anderson-Fabry disease: developments in diagnosis and treatment. *Acta Clin Croat* 2012; 51:411-417
44. DEMARIN V, BAŠIĆ KES V, BITUNJAC M, IVANKOVIĆ M. Neurological Manifestation of Fabry Disease – A Case Report. *Coll. Antropol.* 2009; 33(2): 177-179.

Sažetak

SMJERNICE ZA DIJAGNOSTICIRANJE, TERAPIJU I PRAĆENJE ANDERSON-FABRYJEVE BOLESTI

V. Bašić Kes, M. Cesarik, I. Zavoreo, S. Soldo-Butković, P. Kes, N. Bašić-Jukić, S. Rački, M. Jakić, D. Delić-Brkljačić, Z. Jukić, Z. Trkanjec, V. Šerić, V. Vargek Solter, I. Bielen, S. Bašić i V. Demarin

Fabryjeva bolest (Anderson-Fabryjeva bolest) je jedna od najčešćih lizosomskih bolesti nakupljanja (nakon Gaucherove bolesti) uzrokovana smanjenom aktivnošću enzima α -galaktosidaze A (α -Gal A) uz posljedično nakupljanje globotriaosilceramida u različitim stanicama, ponajprije u endotelnim i vaskularnim glatkim mišićnim stanicama uz posljedične multisistemske manifestacije. Pojavnost bolesti u muškaraca je 1:40.000-60.000, dok je u općoj populaciji oko 1:117.000. Bol je najčešće prvi simptom bolesti u 60%-80% djece, kao i simptomi probavnog sustava, oftalmološki simptomi, gubitak sluha. Smanjenje bubrežne funkcije, hipertrofična miokardiopatija ili moždani udar mogu se iskazati kao izolirani simptomi bolesti. Očekivani životni vijek se skraćuje u bolesnika s Fabryjevom bolešću i to u muškaraca za oko 20 godina, a u žena za 10-15 godina, stoga je uvođenje enzimske nadomjesne terapije nužno u svih bolesnika bez obzira na dob i spol koji zadovoljavaju kriterije za terapiju ove bolesti.

Cljučne riječi: *Anderson-Fabryjeva bolest, dijagnoza, terapija*