ANDERSON-FABRY DISEASE: DEVELOPMENTS IN DIAGNOSIS AND TREATMENT

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SUMMARY – Fabry disease (Anderson-Fabry disease) is an X-linked recessive lysosomal storage disorder resulting from deficient activity of lysosomal hydrolase, α-galactosidase A (α-Gal A), which leads to progressive accumulation of globotriaosylceramide (Gb3) in various cells, predominantly endothelial and vascular smooth muscle cells, with clinical manifestations affecting major organs including the central nervous system. The incidence has been estimated to 1 *per* 40,000-60,000 males and 1 *per* 117,000 in the general population. Symptoms usually occur during childhood or adolescence, occasionally in middle age (according to the level of the enzyme activity). Life-threatening complications often develop in untreated patients. In classic Fabry disease, they include cutaneous, renal, cardiac and cerebrovascular manifestations that lead to premature death. Early recognition of symptoms, enzyme activity levels, concentration of Gb3 levels in the blood, urine and skin biopsies, as well as genetic testing (GLA gene) enable establishment of early diagnosis and therapeutic intervention with enzyme replacement therapy. Early therapy initiation prior to significant disease manifestations or complications may improve patient outcome.

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

Introduction

Fabry disease (Anderson-Fabry disease) is an X-linked recessive lysosomal storage disorder resulting from deficient activity of lysosomal hydrolase, α-galactosidase A (α-Gal A)[1], which leads to progressive accumulation of globotriaosylceramide (Gb3) in various cells, predominantly endothelial and vascular smooth muscle cells, with clinical manifestations affecting major organs including the central nervous system[2].

The incidence of Fabry disease has been estimated to 1 *per* 40,000-60,000 males and 1 *per* 117,000 in the general population[3], with wide variations, e.g., *per* 476,000 in The Netherlands[4] and as high as 1 *per* 15,000 in Nova Scotia[5].

Symptoms usually occur in childhood or adolescence[6], and occasionally in middle age, and life-threatening complications often develop in untreated patients. In classic Fabry disease, they include cutaneous, renal, cardiac and cerebrovascular manifestations that lead to premature 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. The diagnosis is often missed[7]. Results of the Fabry Outcome Survey (FOS) have shown that the mean time between the onset of symptoms and diagnosis was 12.4 years in females and 12.2 years

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in males[8]. The "cardiac variant"[9,10] and "renal variant"[11] subclassifications have been introduced for patients with predominant or exclusive cardiac or renal involvement because patients may present with late onset hypertrophic cardiomyopathy or isolated end stage renal disease (ESRD) as their initial manifestation[11,12]. Epidemiological studies have reported the condition in 0.2% to 1.2% of patients with ESRD[11,12] and in 1% to 6.3% of patients with unexplained hypertrophic cardiomyopathy[10,13,14].

The gene for α-Gal A is located on Xq22, and more than 585 mutations have been identified[15]. Most of them are missense mutations. Fabry disease predominantly affects males, but female carriers of the defective gene are also often affected. In female patients, the heterogeneity of symptoms is even more pronounced. In females, the symptoms also tend to start later in life than in male patients, have slower progression and milder clinical manifestations (in correlation with activity levels of the enzyme as end product of the mutated gene).

Early recognition of symptoms, enzyme activity levels, concentration of GB3 levels in the blood, urine and skin biopsies, as well as genetic testing (GLA gene) enable establishment of early diagnosis and therapeutic intervention with enzyme replacement therapy (ERT). Early initiation of therapy, i.e. prior to significant disease manifestations or complications, may result in improved outcomes for patients.

Clinical Picture

Childhood and adolescence

Symptoms in childhood and adolescence vary, but they are usually subtle and start between the age of 3 and 10 years, generally a few years later in girls than in boys[16,17]. Pain is usually the first symptom and is present in 60%-80% of affected children. They may experience acute, unexplained episodes of burning pain in the extremities, often accompanied or triggered by fever (episodic or Fabry crises). 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 caliber nervous fibers[18]. 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. Ophthalmological abnormalities, especially cornea verticillata and retinal vessel tortuosity, hearing impairment or dyshidrosis (hypohidrosis or anhidrosis) can be found. Inability to sweat leads to heat, cold, and exercise intolerance. 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)[19].

Adulthood

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 angiokeratomas 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 transplantation[20]. 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, syncope. Cardiac involvement may be the only symptom in some hemizygous males[10] and up to 4% of males with hypertrophic cardiomyopathy may have a 'cardiac' variant of Anderson-Fabry disease[13]. Nervous system involvement includes transient ischemic attack (TIA) or stroke[21]. It is estimated that 1%-2% of stroke patients aged 18 to 55 years may have Fabry disease[22]. The mean age recorded for cerebrovascular events is around 5 years earlier in men than in women[24,25]. Ischemic stroke is considerably more common than hemorrhagic stroke[23,24], and most are small vessel infarcts. Recent studies have shown that nearly half of Fabry patients (45.9%) experienced their first stroke before being diagnosed[23]. In fact, the median time from stroke to diagnosis was around 4.8 years.

Table 1. Main symptoms of Fabry disease in childhood

Pain	Rheumatoid arthritis, rheumatic fever, arthritis, Raynaud's disease, „growing pain", systemic lupus erythematosus, psychogenic
Angiokeratoma	Petechiae of meningococcal meningitis, hemorrhagic telangiectasia
Gastrointestinal symptoms	Irritable bowel syndrome, celiac disease, food intoxication, dyspepsia, gastroesophageal reflux, parasites
Cornea verticillata	Amiodarone or chloroquine treatment

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 women[22]. Other studies suggest that α-Gal A deficiency may play a role in up to 1% of young patients presenting with cerebrovascular disease[25]. Vertebrobasilar dolichoectasia has also been reported in Fabry patients[21,26]. Hyperintensity in the pulvinar on T1 weighted images is a common finding in Fabry disease, likely reflecting the presence of calcification[27]. Recent findings suggest that the pulvinar sign is a highly specific sign, distinctively characteristic of Fabry disease[27,28]. Disturbed concentration, dizziness, dementia, headaches, and learning difficulties also occur. The peripheral nervous system may also be affected, with disturbances of touch, pain and temperature sensitivity[8,29]. Respiratory involvement, manifesting as dyspnea with exercise, chronic cough and wheezing, is frequent in both sexes with Fabry disease[30,31].

Life expectancy is reduced in both male and female patients by apxproximately 20 years in males and 10-15 years in females. The FOS data have shown that the principal cause of death in males is renal failure, followed by cardiac and cerebrovascular causes. In female patients, the main causes of death were cardiac disorders and cancer[8].

Criteria for Testing for Fabry Disease

Early diagnosis of Fabry disease is difficult. Early symptoms in childhood are often subtle and nonspecific, and can be easily misinterpreted, as confirmed by data from the FOS registry: in 688 patients, median age at diagnosis was about 28 years, which is about 16 years after the first symptom onset[8]. 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 the 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 that are potentially at risk of this disorder. The opinion of a geneticist should be sought, which provides an opportunity to offer genetic counseling and timely therapeutic intervention.

Differential diagnosis of Fabry disease is wide; the main symptoms that should raise suspicion of this diagnosis in childhood are listed in Table 1. History or progression of symptoms in adult age can warn the clinician of Fabry disease, especially if the patient presents with stroke, renal or cardiac impairment. Also other possible causes of these symptoms should be excluded on differential diagnostic work-up (Table 2).

Diagnostic testing for Fabry disease

If clinical examination raises suspicion of Fabry disease, appropriate biochemical and/or genetic confirmation is needed (Table 3). Laboratory diagnosis of Fabry disease includes demonstration of markedly

Table 2. Other conditions leading to stroke and vascular encephalopathy

Juvenile cryptogenic ischemic stroke
Juvenile ischemic stroke associated with other acquired risk factors
Juvenile stroke in monogenic diseases (e.g., CADASIL, homocystinuria)
Central nervous system and systemic vasculitis
Multifocal/lacunar leukoencephalopathy of unspecified etiology
Amyloidosis
Demyelinating diseases (CSF examination)
Mitochondrial diseases (e.g., MELAS)

Table 3. Work-up algorithm for evaluation of patients suspect of Fabry disease

General status, quality of life, school or work performance, depression, anxiety, drug use, somatic growth Complete physical examination Genetic counseling Alpha-galactosidase A activity and genotype
Serum creatinine, ionogram, blood urea nitrogen; urinary protein/creatinine ratio, albumin/creatinine ratio Urinary Gb3 (optional)
ECG, echocardiography 2-D with Doppler Holter monitoring Cardiac MRI Coronary angiography
Audiometry, tympanometry, otoacoustic emissions
Neurologic examination, questionnaires (Brief Pain Inventory) Brain MRI without contrast Magnetic resonance angiography Comorbid stroke risk factors: cholesterol (total, LDL, HDL), triglycerides, Lpa, total plasma homocysteine
General ophthalmologic examination
Spirometry
Endoscopic evaluations
Bone mineral density, 25(OH) vitamin D levels

deficient or absent enzyme activity in plasma or peripheral blood leukocytes. Confirmation of the diagnosis of Fabry disease in women is more difficult, so molecular testing for identification of mutations in the GLA gene is performed.

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 pregnancy or in cultured amniotic cells at about 14 weeks of pregnancy. Since the implementation of enzyme replacement therapy in the management of Fabry disease, prenatal diagnosis has become ethically and medically questionable.

Treatment Guidelines

Enzyme replacement therapy

Enzyme replacement therapy supplies the organs with recombinant enzyme. It has been available for the treatment of Fabry disease since 2001. The two recombinant GLA preparations available for enzyme replacement therapy are 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)[31]. The guidelines for ERT are evolving, the experience with this form of therapy is limited and its long-term beneficial effect is still unclear. Enzyme replacement therapy should be considered in patients of any age and either sex who meet any of the following criteria.

Renal function

Declining renal function (baseline age adjusted creatinine clearance is less than 80 mL/min) or persistent 10% decline of renal function is an indication for ERT. Proteinuria alone is not considered an indication for ERT at present. Advanced renal disease: dialysis and/or transplantation often prolong life but do not alter the course of disease in other organ systems[23].

Cardiac

Any patient with Fabry disease and cardiac diagnosis (hypertrophic cardiomyopathy) should be considered a candidate for ERTif other causes of cardiac findings have been excluded. These patients often require care by a cardiologist for progressive heart disease, recognizing that some patients may even require heart transplantation.

Neurologic

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 imaging.

Specific attention should be paid to cerebrovascular and cardiovascular risk factors. Patients with Fabry disease carry a very high risk of vascular events, so management of other vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, increased weight, smoking) should be aggressive[18]. Hypertension should be promptly and effectively treated in order to minimize renal, cardiovascular, and cerebrovascular disease. An angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB, in patients intolerant of ACE inhibitors) should be considered in the treatment of hypertension associated with Fabry disease. There is currently no evidence that the use of ACE inhibitors in the context of Fabry disease will significantly benefit the proteinuria or impact renal function. Prophylaxis of vascular events with acetylsalicylic acid (ASA) should be considered for all patients provided they do not have contraindications for ASA use. A failure of ASA prophylaxis may be an indication for additional antithrombotic agents. In addition, patients with Fabry disease should not smoke and thus smoking cessation counseling should be offered.

Gastrointestinal

Severe gastrointestinal symptoms: intractable abdominal pain and diarrhea refractory to other therapies. Abdominal complaints (e.g., pain, diarrhea): pancrelipase or metoclopramide can improve gastrointestinal symptoms[32].

Pain

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)[19], carbamazepine (Tegretol)[20], and gabapentin (Neurontin)[21] have been found to be effective in some patients. Nonsteriodal 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.

Medical Follow-up of Fabry Disease

Clinical course (with or without enzyme replacement therapy) will determine the frequency of tests and clinical evaluation. Annual evaluations are recommended for asymptomatic individuals, for early detection of central nervous system involvement, kidney function and cardiac impairment. Symptomatic carriers should be followed annually and asymptomatic females at least every two years, with particular emphasis on cardiovascular and cerebrovascular complications of the disease.

Further Perspectives

A number of clinical studies have been undertaken for better understanding and treatment of cerebrovascular complications of Fabry disease.

SIFAP1 (Stroke In young Fabry Patients) examines the prevalence of underlying Fabry disease in an unselected group of about 5000 young stroke patients. Patients can decide whether their blood should be further analyzed with respect to stroke and Fabry. Consequently, one of the biggest and best defined BioBanks (containing DNA, clinical data, MRI data) has been established. This will enable scientists to conduct further studies on the cause of stroke with information from a well defined sample pool[33].

SIFAP2 has started evaluating the relapse rate of acute cerebrovascular events with clinical relevance in patients with different prophylactic therapeutic approaches. Patients with proven Fabry disease will be included in SIFAP2 for a minimum follow-up of 36 months. No influence on therapy of patients is exerted; according to the usual recommendations of specialized associations, all patients receive optimal therapy. Finally, the renewed occurrence of acute cerebrovascular events in patients with different standard therapy will be examined. This therapy is not prescribed, but corresponds to the local routine of participating centers[34].

FASEP (Fabry and Stroke Epidemiological Protocol): Risk Factors In Ischemic Stroke Patients With Fabry Disease is an ongoing study with the aim to evaluate how many strokes in young patients (age 18-55) were caused by Fabry disease and what risk factors (conventional risk factors such as diabetes, overweight, high blood pressure, etc.) might be able to predict this disease[34].

SWITCH (The Efficacy and Safety of Switch Between Agalsidase Beta to Agalsidase Alfa for Enzyme Replacement in Patients With Anderson-Fabry Disease). An extended shortage of Fabrazyme that began in June 2009 has necessitated a large number of patients to switch from Fabrazyme to Replagal. This offers the possibility to study the clinical status and adverse events in patients switched from Fabrazyme to Replagal on a large-scale basis. In addition, as a result of the increasing Fabrazyme shortage, many of these patients received a reduced dosage of Fabrazyme for an extended period before switching to treatment with Replagal[35].

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Sažetak

ANDERSON-FABRYJEVA BOLEST: NOVOSTI U DIJAGNOSTICI I LIJEČENJU

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Fabrijeva (Anderson-Fabryjeva) bolest je X-vezana recesivna lizosomna bolest nakupljanja koja je posljedica smanjene aktivnosti lizosomske hidrolaze-α-galaktosidaze A (α-gal A), što dovodi do progresivnog nakupljanja globotriaosilceramida (Gb3) u različitim stanicama, u prvom redu endotelnim i glatko-mišićnim stanicama vaskularnih struktura s posljedičnim oštećenjem glavnih organa, uključujući i središnji živčani sustav. Incidencija ove bolesti je 1 na 40.000-60.000 u muškaraca te 1 na 117.000 u općoj populaciji. Prvi simptomi se javljaju već u djetinjstvu ili adolescenciji, a mogu se javiti i u srednjoj dobi (ovisno o razini aktivnosti enzima). Teže komplikacije bolesti javljaju se u bolesnika koji su neprepoznati i kod kojih nije primijenjena enzimska nadomjesna terapija: kožne, bubrežne, srčane i cerebrovaskularne komplikacije koje mogu dovesti do iznenadne smrti. Rano prepoznavanje simptoma bolesti, mjerenje enzimske aktivnosti, koncentracije Gb3 u krvi, mokraći te bioptatu kože, kao i genetska ispitivanja (gen GLA) omogućavaju ranu dijagnozu i uvođenje rane enzimske nadomjesne terapije. Rano uvođenje enzimske nadomjesne terapije prije pojave značajnijih simptoma i komplikacija bolesti može znatno poboljšati ishod liječenja.

Ključne riječi: *Anderson-Fabryjeva bolest, dijagnostika, terapija*