

Clinical Manifestations of Anderson-Fabry's Disease in Pediatrics

Sandra Matiz Mejía^{1*} and Carlos Acosta Ordoñez²

¹*Pediatric Cardiologist - El Bosque University, Bogota, Colombia*

²*Pediatrician, University Foundation San Martín, Bogota, Colombia*

***Corresponding Author:** Sandra Matiz Mejía, Pediatric Cardiologist - El Bosque University, Bogota, Colombia.

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Summary

Anderson-Fabry Disease (EAF) represents a diagnostic challenge today, considering that its initial clinical manifestations are non-specific and that in isolation do not lead to a particular diagnosis.

The identification and timely identification of signs and symptoms presented by patients in the pediatric age will allow a rapid diagnosis of the disease and therefore an early start of Enzyme Replacement Therapy (TRE), which has shown improvement in clinical manifestations of the EAF.

The aim of this article is to record the different signs and symptoms of FAS according to the pediatric age groups, to recognize early the clinical picture of the disease, provide important diagnostic tools to the Pediatrician and thus initiate the ERT in a timely manner.

Abstract

The initial clinical manifestations of the Anderson Fabry Disease are unspecific and analyzing them independently doesn't leave to a specific diagnosis. This is why at this time, this disease represents a diagnostic challenge.

A prompt identification and determination of signs and symptoms in the pediatric patients will lead to an opportune disease diagnosis and an early enzymatic replacement therapy (ERT) with a better patient clinical evolution.

This study pretends to register different AFD signs and symptoms at different pediatric stages, getting to know the clinical evolution of those patients and giving the pediatricians, important diagnostic tools to begin the TRE as soon as possible.

Keywords: *Fabry Disease; Diagnosis; Treatment*

Anderson-Fabry Disease (EAF) is a rare X-linked hereditary metabolic disorder caused by an absence or deficiency of lysosomal alpha-galactosidase A (a-Gal A) hydrolase activity, resulting in progressive intracellular accumulation of (Gb3), in various organs and tissues including kidney, heart and blood vessels [1-3].

EAF belongs to the group of lysosomal storage disorders, which represent at least 40 to 50 inherited diseases, which are genetically distinct but biochemically related [1,4]. Each disorder is caused by an inborn error of metabolism, due to a monogenetic defect, resulting in the deficiency of lysosomal enzymes. EAF is pan-ethnic, but due to the unusual nature of its presentation, determining the exact frequency of the disease is difficult [1,5].

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Epidemiology

The epidemiological characteristics of FAS are difficult to determine due to under diagnosis and delay in recognition of the clinical manifestations of the disease. Likewise, the lack of the same clinical presentation in men and women, the under diagnosis in women is more marked, since the manifestations are usually less severe.

The incidence in the general population of FAS is 1: 117,000 to 1: 476,000 live births [6], which can be as high as 1: 40,000 to 1: 60,000 in men [7-8] and in some reports Specifically identified the deficiency and mutations of a-Gal A, is up to 1: 3,100 men born alive [9].

In Colombia to date there are no epidemiological studies or population burden of the EAF, however it is known that according to data updated to May 2015, there are 65 patients with a diagnosis of EAF according to the Colombian Association of Patients with Lysosomal Deposit Diseases (ACOPEL).

History

EAF was first described in 1898 as "Angiokeratoma Corporis Diffusum" by dermatologists William Anderson and Johannes Fabry, with an independent case report in Germany and the United Kingdom [10,11]. The term angiokeratoma was first used by Wyndham Cottle in 1878 and later described by Vittorio Mibelli in 1989 [12].

Anderson and Fabry described their first cases in 1897, Anderson's patient was a 39-year-old painter who developed an erythema on the anterior face of the knees from age 11, which spread rapidly to a maximum extent at age 17. At age 15, he noticed a small neuroma in his right hip and minor varicose veins in his legs, and at age 18 he had an episode of minor digestive bleeding with no further complaints of health.

Anderson described the lesions as generalized multi-capillary angiectasia that tended to be sub-epidermal prominences, some with verrucous thickening of the epidermis. Angiectasis varied in small sizes, with papular structures and covered the surface of the skin except the face, palms and plants, being more numerous and prominent in the scrotum [10].

Only a few months earlier, Fabry describes a 13-year-old male patient who, at age 9, had skin eruptions on the posterior aspect of the left knee, which later spread to the trunk and limbs. At 12 years of age, the patient presented dilated capillaries on the posterior aspect of the right knee and reported that afterwards he had lost weight and had worsened his physical condition.

During the physical examination, Fabry described a patient with mucocutaneous pallor, facial edema with predominance of palpebral and labial predominance, signs of pulmonary consolidation in the left hemithorax, and multiple non-painful palpable nodes in the neck and inguinal region. Blood and urine tests were not altered. On the skin, it showed grouped eruptions of small size, the largest were blue-black papules and dilated capillaries arranged in small groups at the labial commissures.

After this initial evaluation of Fabry, the patient presented an episode of hemoptysis and epistaxis, with no further manifestations.

The biopsy revealed hypertrophy of the corneal stratum, elongated papillae, enlargement of capillary clusters, surrounded by lymphocytes and plasma cells. The hair follicles and sweat glands were normal. Additionally, it described partial vegetations of the intima and thrombosis of the capillaries [11].

While Anderson called his observations "angiokeratoma corporis diffusum", without commenting on its etiology, Fabry suggested that the pathology could be a form of nevus angiokeratoma corporis naeviforme or developmental defect [10,11].

Clinical Manifestations

EAF is characterized by presenting a series of multi-systemic manifestations, which begin with dysfunction at the cellular level, followed by an alteration of the organic function, leading to structural damage that develops over a period of years or decades.

The lysosomal accumulation of Gb3 begins in utero and the cellular inclusions of Gb3 have been detected in fetuses, in the kidney, cardiomyocytes, hepatocytes and the cornea. The spiral cornea was detected at 22 weeks of gestation in a male fetus. Prenatal and neonatal studies of EAF histopathology have confirmed that pathological Gb3 accumulation occurs in the placenta, fetal tissues, and fetal placenta regions of affected males [13].

Despite the evidence of Gb3 accumulation at birth, the natural history of the disease is very heterogeneous and signs and symptoms may take years to manifest, but this deposition process may lead to early symptoms in childhood.

There is a wide range of variability in the presentation of the disease, in terms of age of onset, clinical characteristics and clinical course. Currently, the EAF is divided into the "Classic" and the "Non-Classical" or Atypical. More than 600 variants of the GLA gene have been described and the prevalence of the classical "EAF" phenotype in male patients with mutations in the GLA gene is 0.12% or 1/1000 sieved individuals [5]. The first clinical symptoms usually appear in childhood, between the ages of 3 and 10 years and children are often affected earlier and more severely than girls. The most common clinical features in the "Classic" form in hemizygous males with no a-Gal A residual activity are burn-like pain, hypohidrosis, transient ischemic attack, cerebrovascular attack, angiokeratoma, proteinuria and cardiomyopathy, demonstrating severity in Disease in males. Intermediate variants have been described, with patients without cardiac signs of EAF in childhood, who present with hypertrophic cardiomyopathy and arrhythmias at 40 years of age and subsequently progress to end-stage renal failure [5,13,14].

Dermatological Manifestations

Angiokeratoma

Angiokeratoma is the visible clinical feature that is found earlier in the course of the disease. It consists of vascular lesions and dilations, some arranged in reddish-purple clusters and typically involving the periumbilical and inguino-scrotal regions, buttocks and thighs, but also appear in areas exposed to trauma, such as elbows, waist, Extensor surfaces of the limbs, back and in mucosal areas such as the mouth. Histologically, skin lesions are small superficial angiomas caused by the accumulated damage of the vascular endothelial cells of the skin, by the deposition of Gb3 in the lysosomes of the endothelial, perithelial and smooth muscle cells, with dilation of the vessels in the dermis that They increase in number and size with age and can occur individually or in groups.

Angiokeratomas are frequently found in patients older than 5 years of age. In affected patients, changes in injuries in general are not correlated with the severity of the disease [13]. The recognition and follow-up of this disease characteristic can improve the quality of life of the patient, and may also reduce the misdiagnosis by physicians who are not familiar with this dermatological finding which is predominantly benign [1,13,17].

Hipohidrosis

The absence of sweating (anhidrosis) or a decrease in the ability to sweat (hypohidrosis) with decreased skin impedance are a significant problem for patients with EAF and may cause heat and exercise intolerance.

Skin biopsies in these patients have not revealed a decrease in nerve fiber density or innervation of sweat glands, but have demonstrated storage of lamellar intracytoplasmic inclusions of lipids in the sweat glands, particularly in myoepithelial cells and Small vessels

around the eccrine glands. The staining of the dermal nerve endings has also not shown a decrease in the neural proteins of the sweat glands [5]. This, together with the rapid clinical response to enzymatic infusion, suggests a dysfunction of the sweat glands due to accumulation of glycolipids (Gb3) and not due to dysfunction of the autonomic system [1,5].

Peripheral Neuropathy

Pain

Early neuronal damage mainly involves small nerve fibers from the somatic and autonomic systems, with onset of earlier-related symptoms in children than in girls. Pain is experienced in 60 - 80% of children affected in the classic way and is one of the first symptoms of EAF [1]. There are reports in the literature of children between 2 and 4 years old with acroparesthesia / neuropathic pain. There are also reports of pain crises in children aged 2.5 years to 4 years of age [15,16].

Two types of pain have been described: episodic crises (Fabry crisis), whose estimated prevalence among men aged 5 to 15 years with the classic phenotype is 90% [17] and are characterized by arthritic pain type burning Originates in the extremities and radiates to the inner face of the extremities and other parts of the body and may be precipitated by fever, exercise, stress, fatigue and sudden changes in temperature. Chronic pain, on the other hand, is characterized by burning, shooting pain and dysesthesia and paresthesias in the hands and feet (acroparesthesia).

A study of the natural history of Fabry's disease revealed a decrease in pain in (11%) of patients during aging [18]. With increasing age and therefore with increasing disease burden, nerve fiber damage can become so extensive that its function is completely lost and the pain can diminish or disappear.

There is evidence of a significant decrease in quality of life as a result of pain in patients with EAF.

Other possible causes of pain that should be ruled out, such as rheumatoid arthritis, rheumatic fever, Raynaud's disease, systemic lupus erythematosus (SLE) and "growing pains" should be considered.

Ophthalmological Manifestations

Córnea Verticillata

Corneal verticillata (corneal verticillata), easy to identify by a basic examination with a slit lamp, are the most common and early ocular signs and occur in almost all hemizygous males. It should be noted, however, that treatment with amiodarone or chloroquine can produce similar ophthalmic signs. The prevalence of cornea verticillata ranges from 71.9% to 88% for men and from 76% to 94.1% for women [19]. Neither corneal dystrophy nor retinal or conjunctival lesions impair visual acuity; However, acute loss of vision caused by unilateral occlusion of the central retinal artery has been reported [5].

Crystalline and Retina

The lens may have anterior, capsular or sub-capsular (whitish and granular) cataracts, as well as the so-called Fabry cataract, consisting of fine granular deposits irradiated from the posterior pole along the capsule [17].

The marked tortuosity of conjunctival and retinal vessels is observed in patients with EAF and information has been reported suggesting that the presence of these vascular tortuosities of the retina may be related to the severity of the disease in children [13].

Hearing Manifestations

Hypoacusia, Tinnitus and Vertigo

Auditory and vestibular abnormalities are frequent alterations observed in EAF, giving rise to a series of symptoms, such as hearing loss, intermittent tinnitus and vertigo. The high incidence of both progressive hearing loss and sudden deafness in male patients affected with the classic form of EAF has been demonstrated. About 54.5% of individuals report auditory disorders and in about 33% of those who do not report them, luminal tonal audiometry shows an additive loss in the range of high frequencies [17]. A correlation was found between neuropathic and vascular damage with hearing loss in male patients in whom the residual activity of a-Gal A appears to have a protective effect against hearing loss [5,20]. Progressive vestibular loss was found in 80% of males and 77% of females when evaluated with the head impulse test [1,21]. Functional tests support the hypothesis that auditory and vestibular dysfunction results from pathology at the level of hair cells in the labyrinth [5].

Cardiovascular Manifestations

The deposition of Gb-3 in the heart leads to an increase in ventricular wall thickness, diastolic dysfunction, mitral valve prolapse, atrio-ventricular conduction defects, rhythm disorders, especially ST-segment tachyarrhythmias and electrocardiographic alterations, and The T wave, whereas in the cardiac variant of the disease, the main manifestation is hypertrophic cardiomyopathy [17,22,23].

Heart Commitment

Cardiac involvement reported in 40-60% of patients with EAF includes left ventricular hypertrophy, arrhythmias, angina, dyspnoea and myocardial ischemia [24-26]. Arrhythmias and heart rate variability are derived from sinus node involvement, conduction system, and imbalance between sympathetic and parasympathetic tone. Diastolic dysfunction and left ventricular hypertrophy, which is usually non-obstructive, are important features and men are often more severely affected than women. With age, progressive myocardial fibrosis develops producing interstitial fibrosis [27,28]. Substitution fibrosis almost always begins in the posterolateral wall of the myocardium. In end-stage patients, transmural fibrosis gradually reduces cardiac function to the stage of congestive heart failure [23,29,30]. Malignant arrhythmias are responsible for a number of cardiac deaths in patients with EAF [26,30,31].

Vascular Commitment

Vasculopathy in EAF is associated with abnormalities in the functional control of blood vessels secondary to endothelial dysfunction and a prothrombotic state [32]. An increase in arterial remodeling and intimal and medial thickening were demonstrated in patients with EAF. Lymphedema has been associated with structural and functional changes in the lymphatic micro vessels of the skin [33]. In reports from the literature, left ventricular hypertrophy and thickening of the intima of the common carotid artery occurred concomitantly and in the absence of focal atherosclerotic plaques, suggesting common pathogenesis [34]. Electron microscopy examination of endomyocardial biopsies revealed lysosomal deposition in cardiomyocytes [35]. Coronary microvascular function is abnormal and myocardial perfusion is significantly reduced. Myocardial ischemia and infarction may be the result of compromised coronary vascular function [36,37].

Electrocardiographic Changes

Electrocardiographic changes in patients with EAF are frequent and include voltage criteria and changes in repolarization related to left ventricular hypertrophy and ventricular remodeling, ST segment depression and T wave inversion [38]. Other abnormalities include a short PR interval (< 0.12 ms), due to short P wave, QRS complex widening and QT interval increase, paroxysmal supraventricular tachycardia, AV node blockages, branch blocks and arrhythmias [25,26,29]. The 24-hour ECG-Holter is therefore useful and recommended at the beginning and during the follow-up of enzyme replacement therapy. The cardiac manifestations observed in patients with classical EAF are also observed in patients with the cardiac variant of EAF [39].

Renal Manifestations

Chronic Renal Failure

In patients with classically affected EAF, renal lesions result from the deposition of Gb-3 in the glomerular endothelium, interstitial and mesangial cells, podocytes and also in the epithelium of the loop of Henle and the distal tubules [40,41]. Renal failure often begins with microalbuminuria and proteinuria in the second to third decade of life and the gradual deterioration of renal function and the development of azotemia generally occurs in the third to fifth decades of life [42]. At this stage, fibrosis, sclerosis, and tubular atrophy dominate the disease activity in anticipation of end-stage renal disease that usually occurs in the fourth to fifth decade of life. It is the leading cause of death in male patients with EAF, which in most cases is secondary to uremia, unless chronic hemodialysis or renal transplantation is performed. Najafian, *et al.* [43] reported on the Gb-3 deposit in renal biopsies of 4-year-old children with Gb-3 inclusions in all glomerular cell types. Reports of clinical renal involvement in the pediatric population with EAF are limited, but may include microalbuminuria, proteinuria, and decreased GFR. Among reported cases of patients younger than 5 years of age, there is a reported case of clinical renal involvement in a 4-year-old child with an estimated GFR of 56 ml / min / 1.73 m² (18.46). Because of the rare decrease in GFR or significant proteinuria in young children, its presence should rule out other causes and perform diagnostic tests, including renal biopsy. However, it should be noted that renal damage occurs before there is clinical evidence of proteinuria. Evaluation of renal function should be performed in all patients with serum creatinine, estimated GFR, urinary protein excretion, and urinary sodium. In the early stages of renal compromise, quantitative estimates of GFR are necessary. Urinary protein excretion is strongly associated with progression of renal disease [44,45].

Gastrointestinal Manifestations

Diarrhea, Vomit and Abdominal Pain

Gastrointestinal symptoms in children with EAF usually present as abdominal pain (often after eating), abdominal bloating, alternating episodes of diarrhea and constipation, nausea and vomiting which is a major cause of anorexia [46]. These symptoms are probably related to gastrointestinal dysmotility caused by autonomic dysfunction [47], and may be secondary to the deposition of Gb-3 in the autonomic ganglia of the intestine and mesenteric blood vessels [48]. Irritable bowel syndrome with diarrhea is a differential diagnosis [46].

Cefalea, Vertigo, Acv

Some of the most devastating neurological injuries of EAF are caused by damage to the cerebrovascular level, as a result of multifocal alteration of small blood vessels. Cerebrovascular compromise can lead to a wide variety of signs and symptoms, ranging from mild to severe, including headache, dizziness or dizziness, transient ischemic attacks, cerebrovascular attack and, to a lesser extent, vascular dementia [49]. Stroke may be the first manifestation of the disease. The prevalence of stroke in ADF was estimated at 6.9% in males and 4.3% in females, much higher than in the general population [50]. There is increasing evidence that EAF is an underlying cause of a number of idiopathic stroke. The progressive deposition of Gb-3 occurs in the endothelial cells and smooth muscle cells of the vessels, leading to progressive stenosis as well as dilation of the small arterial vessels [51].

Vascular ectasia occurs more frequently in the posterior circulation and it has been shown that increased diameter of the basilar artery is a sensitive indicator of EAF. Some patients may also have aseptic meningitis. Some imaging modalities such as MRI can show hyperintensity in T1 at the pulvinar level (a sign of pulvinar), which is a very specific and characteristic sign of EAF [52].

Conclusion

Anderson-Fabry Disease (EAF) is caused by an absence or deficiency of alpha-galactosidase A (a-Gal A), resulting in a progressive accumulation of glycosphingolipids, with X-linked inheritance making male patients more affected, although there may be women with similar clinical involvement. Its two varieties of clinical presentation depend on the residual activity of the enzyme a-Gal A, despite the

evidence its natural history of the disease is very heterogeneous and the signs and symptoms may take years to manifest, however this deposit process can lead to early symptoms in childhood. Among its more conclusive clinical manifestations is the angiokeratoma, although not exclusive of this disease, is a sign that leads to diagnostic suspicion, however the most frequent manifestations are neuropathic pain and acroparesthesias, which are presented in an important percentage of patients with EAF and present at an early age. The main cause of mortality in these patients is chronic renal failure, therefore proteinuria, used as an early marker of renal damage, is of great importance for diagnosis and to avoid late complications. Cardiovascular compromise, usually in the form of symmetric ventricular hypertrophy, represents a high burden of morbidity. The identification of signs and symptoms in pediatric patients may allow early initiation of Enzymatic Replacement Therapy (TRE), which has shown improvement in clinical manifestations and patients' quality of life, with a better response the earlier is performed, as it prevents the progressive deterioration of vital organs.

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