

Fabry Disease

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ABSTRACT

Fabry disease is a rare genetic disease involving a deficiency of an enzyme. A decrease in the enzyme activity leads to a selective suffering of specific anatomic and functional structures resulting in heteromorphic clinical signs that increase the difficulty of early diagnosis.

Knowing and identifying the clinical signs suggestive for this disease makes it easier to initiate the methods needed for confirming this diagnosis.

The introduction of enzyme replacement therapy from the onset, slows down the complications of the disease, improves the quality of life and reduces the emotional and mental burden caused by the clinical symptoms.

The patient presented in the reported case received clinical explorations according to the data presented in the literature, confirming the diagnosis of Fabry disease, thus enabling to start the therapy as soon as possible and including the patient in the National Program for Fabry disease.

Following enzyme replacement therapy, the clinical symptoms and the quality of life were improved.

The emotional, mental and physical impact of this disease can be greatly reduced by knowing the clinical signs that allows for the diagnosis and early initiation of the treatment.

Keywords: Fabry disease, diagnosis, treatment

INTRODUCTION

Fabry disease, known as corporis diffuse humangiokeratoma, is a recessive lysosomal disease, X-linked caused by the deficiency of the enzyme α -galactosidase A (1,2). Due to this enzymatic deficiency, there is a progressive lysosomal accumulation of glycosphingolipids (globotriaosylceramide-Gb3), located mainly endothelial and in the vascular smooth muscle, causing a progressive multisystemic damage of the cornea, skin, kidneys, central and peripheral nervous system (amygdaloid nuclei, hypothalamus, substantia nigra, reticular system, nuclei of the brainstem, spinal cord and sympathetic dorsal root ganglia) and heart, through inflammation and fibrosis (2). Globally, the prevalence of Fabry disease is estimated to be between 0.85 and 2.5 cases per 100,000 inhabitants (1).

The onset of symptomatology occurs during childhood, with the occurrence of complications at

the age of young adult in the absence of replacement treatment (2).

Clinical manifestations consist of cutaneous angiokeratomas, neuropathic limb pain in the extremities, acroparaesthesiae, heat intolerance, anhidrosis, premature cerebrovascular complications, renal insufficiency and hypertrophic cardiomyopathy due to progressive vasculopathy and small fibers neuropathy, which in turn are caused by the accumulation of glycosphingolipids in the endothelial cells (2,3).

In the disease progression, a degree of motor dysfunction is validated, involving the gait, the speed of execution of the fine movements and their precision, in correlation with the severity of the disease (3). Motor involvement may be due to small fiber neuropathy, lesions of the neurons in the brainstem or cerebrovascular damage (3).

On a MRI evaluation, T2 sequence shows hyperintense lesions, located periventricular, in the

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Article History:

Received: 27 November 2018

Accepted: 8 December 2018

white matter of the frontal and parietal lobes, which can also be seen in the case of asymptomatic patients (4). In the T1 sequence the hyperintensity change located at the pulvinar level is considered a hallmark of Fabry disease (4). The disease specific MRI changes regress if the treatment is initiated early (4).

Diagnosis is confirmed by determining the activity of α -Gal A in leukocytes, plasma or fibroblasts and secondary growth of Gb3 in plasma and in urine accompanied by the confirmation of the genetic mutation of GLA gene (5).

Fabry disease is a multisystemic disease that requires enzymatic substitution from the moment of diagnosis confirmation, to stop disease advancement and to improve lifestyle conditions (5). Early administration prevents irreversible damage to the cardiac and renal system, reduces neuropathic pain, improves heat intolerance and acroparesthesia (5).

The limits of substitution therapy are related to the reduction of the frequency of the cerebrovascular events, since the enzyme compounds can not cross the blood brain barrier and cerebral endothelial damage precedes the administration of the therapy (5). Symptomatic pain treatment involves the administration of anti-epileptic medication such as Phenytoin, Carbamazepine, Oxcarbazepine, Gabapentin with the mention of avoiding NSAID medication that can worsen the renal dysfunction (5). Prophylactic measures address situations that can exacerbate the occurrence of neuropathic pain such as high temperature exposure, intense physical activity, stress, smoking. Antiplatelet therapy is needed to prevent cerebrovascular events (5).

CASE REPORT

The current illness began at the age of 12 (1994) with sudden burning pain, located at the upper and lower limb extremities, extended down to the fingers tips, with a high-intensity lasting around 30 minutes, accompanied by fever and fatigue, improved with local cold bandages. The first episode of pain was followed within weeks by the appearance of cutaneous angiokeratomas in both lumbar regions. Following a pediatric examination, the pain was explained as a normal growing pain. The dermatological examination did not offer a clinical interpretation for the cutaneous lesions at that time.

During the following years, the patient presented approximately 4 painful nocturnal episodes each year, in the extremities, with increased intensity, lasting 20-30 de minutes, with partial improvement under the administration of Metamizol, associated with acroparaesthesiae. On day time the painful episodes were similar to the nocturnal ones, but they were triggered by heat exposure, physical activity or stress.

At the age of 21 (2003) the patient went under a dermatological reevaluation due to the appearance of numerous pigmented nevi and the extension of cutaneous angiokeratomas at the level of labial mucosa, joints and on the medial surface of the thighs. After the assessment of the renal function, cardiac activity and ophthalmic examination, which were within normal limits, a cutaneous biopsy of a left lumbar angiokeratoma was performed. The biopsy result (vessels with angioectatic appearance in the superior dermis) raised suspicion of Fabry disease. Despite this result no treatment or diagnosis procedure was initiated. On his own initiative, following a documentation on his pathology, the patient began a self-administration of Carbamazepine 200 mg, therapy that helped relieving the pain.

At the age of 28, the general examination also highlighted a mild tremor affecting the hands and the routine biological tests emphasised proteinuria.

In August 2017, at the age of 36, the patient went to emergency room from the territory where he lived, presenting a diffuse occipital pressure sensation. The biological tests showed hypercholesterolemia and proteinuria. Cardiac and neurological evaluation did not show pathological change. The patient received anxiolytic treatment with Coaxil 12,5 mg and Magnesium. At the end of the same day, due to the persistence of occipital pressure symptoms and vertigo, the patient went again to the emergency medical service of the Neurology Clinic in Cluj-Napoca where he received treatment for vertigo and anxiety, without neurological changes. In the next day the patient presented a sensation of difficulty in controlling the left leg and facial paresthesia, therefore he went again to the emergency room from the territory where he lived. He was hospitalized and treated with Milgamma and Alprazolam. The symptoms improved under treatment.

Two days after he was hospitalized, he was transferred to the Neurology Clinic in Cluj-Na-

poca. At admission, the general examination revealed diffuse angiokeratomas and multiple pigmented nevi. The neurological exam revealed a slight bilateral constitutional ptosis, tinnitus in the left ear for 2 years, brisk reflexes, left acroparesthesia, facial paresthesia and anxiety.



FIGURE 1. Labial mucosa angiokeratomas



FIGURE 2. Lumbar angiokeratomas

During hospitalization, the patient received a biological re-evaluation that revealed hypercholesterolemia and proteinuria, *Borrelia burgdorferi* antibodies test ruling out Lyme disease. He also underwent a Doppler ultrasonography of carotid and vertebral arteries, with no particular changes. Following a psychological examination, the patient was diagnosed with a mild depression, moderate anxiety and emotional instability.

The cerebral MRI investigation revealed multiple hyperintense lesions, neighbouring the occipital horns of the lateral ventricles, with millimetric size, with tendency to confluence-nonspecific, possible microischemic lesions. Similar lesions were noticed in the semioval centers area. On the SWAN sequence, symmetrical thalamic hypointense le-

sions were found in the pulvinar area. These lesions also had a hyperintensity correspondent on T1 sequence. The previously described MRI changes raised suspicion of Fabry disease.

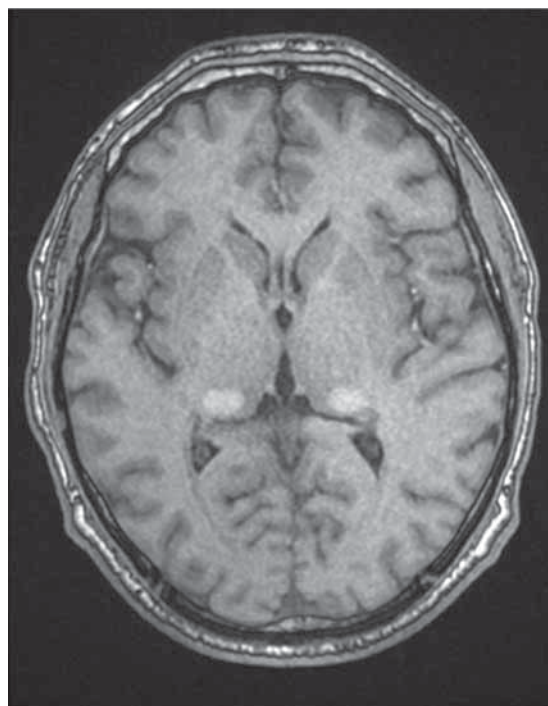


FIGURE 3. Axial T1-FSPGR 3D–Pulvinar hyperintensity

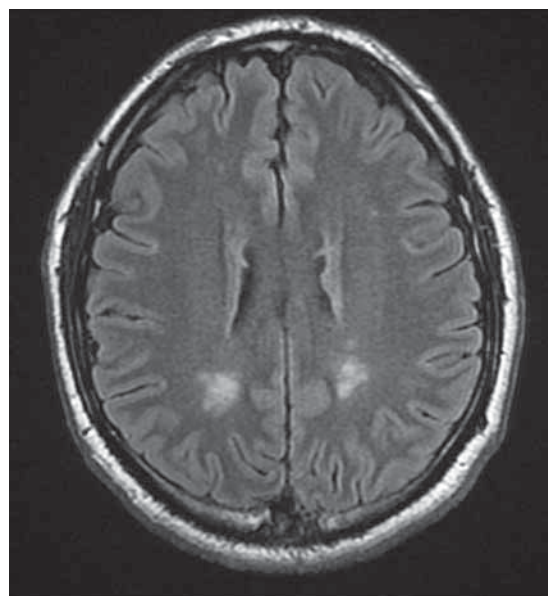


FIGURE 4. Axial FLAIR–Hyperintensities neighbouring the occipital horns of lateral ventricles

Following investigations, suspicion of Fabry disease was raised, reason why it was decided to determine the activity of the alpha-galactosidase enzyme and the genetic testing, who confirmed the mutation of GLA gene and an enzymatic lysosomal

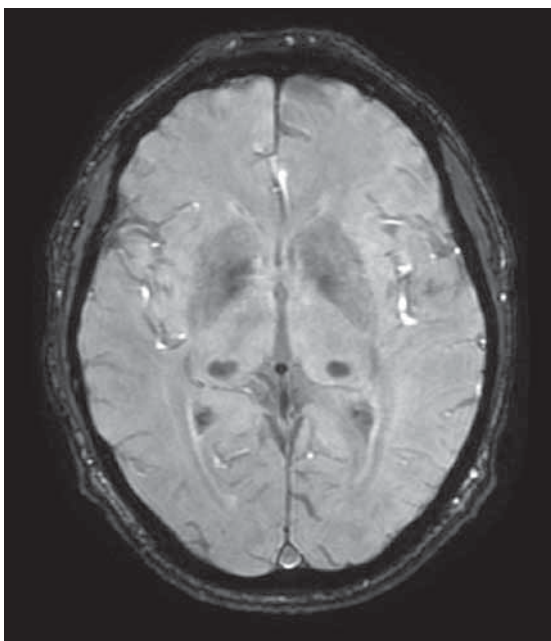


FIGURE 5. Axial SWAN-Pulvinar hypointensity

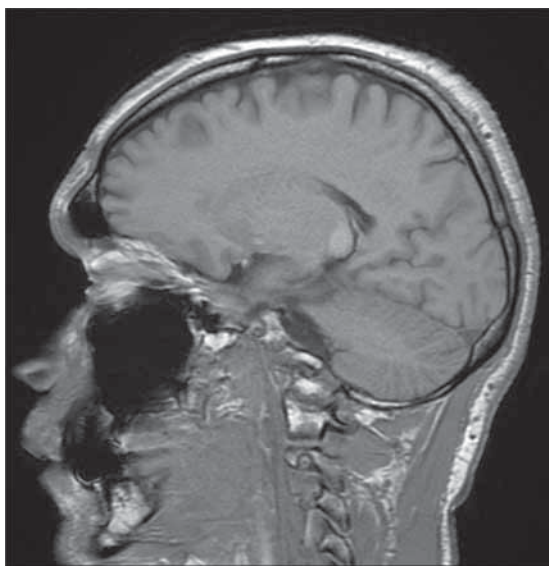


FIGURE 6. Sagittal T1–pulvinar hyperintensity

activity of 0,0 $\mu\text{mol/l/h}$ with confirmation of diagnosis of Fabry disease.

It was decided to include the patient in the National Program for the Fabry disease and the initiation of enzyme replacement therapy. Until the present the patient followed two cures with Fabryzyme, monthly (2x35 mg) with no adverse events from the infusion course with improvement of pain symptoms. Prophylactically it was associated anti-platelet drugs as Aspirin 75 mg.

CONCLUSIONS

Knowing the clinical signs of Fabry disease and the diagnostic confirmation protocol, allows for early diagnosis of this condition with the possibility of initiating therapy as close as possible to the onset, thus improving the quality of life and preventing the occurrence of irreversible organic changes.

Persistent neuropathic pain in children, associated with skin changes should be carefully investigated taking into account the possibility of a neurological pathology to be the cause of the symptomatology.

The emotional, mental and physical impact of this illness can be greatly reduced by a high-standard medical approach.

Conflict of interest: none declared

Financial support: none declared

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