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Case report

Neurological Manifestation of Fabry Disease – A Case Report

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A B S T R A C T

Fabry disease is an X-linked recessive glycolipid storage disease. It is caused by deficiency of the lysosomal enzyme α-galactosidase A and leads to the accumulation of the enzyme substrate, globotriasylceramide (Gb3) in many tissues including endothelial cells, pericytes and smooth muscle cells of blood vessels, renal epithelial cells, cardiac myocytes and numerous neuronal cells. In this report, we present 20-year-old male patient with ischemic stroke in pons. The case had previously been misdiagnosed as polimyositis and vasculitis. Angiokeratomas, neuropathic pain and ischemic stroke in young age suggested a Fabry disease. The diagnosis was confirmed biochemically and genetically. All young adults with stroke, especially if they have additional symptoms like angiokeratomas, proteinuria, neuropathic pain in toes and fingers should be tested for Fabry disease.

Key words: *Fabry disease, x-linked, recessive, strike, genetic, Croatia*

Introduction

Fabry disease is an X-linked recessive glycolipid storage disease, caused by the deficiency of the lysosomal enzyme α-galactosidase A that leads to the accumulation of the enzyme substrate, globotriasylceramide (Gb3) in many tissues including endothelial cells, pericytes and smooth muscle cells of blood vessels, renal epithelial cells, cardiac myocytes and numerous neuronal cells[1]. Fabry disease usually presents in childhood with acroprasthesia (constant burning pain) especially in the toes and fingers, and with painful crises, during which there are extremely severe attacks of sharp pain. The disease usually causes death in adult life from renal, cardiac or cerebrovascular complications of vascular disease. Stroke is a major cause of mortality and morbidity in patients with Fabry diseases[2]. The most common cerebrovascular disorder in patients with FD is ischemic stroke involving infarctions in the vertebrobasilar territory[3,4]. The possible etiologies of ischemic stroke affecting essentially the posterior circulation are progressive stenosis of small vessels with Gb3 deposits, arterial remodeling, endothelial dysfunction, pro-thrombotic state, cerebral hypoperfusion consecutive to dysautonaumy and cardiac embolism[4]. Fabry disease may be misdiagnosed with different diseases including multiple sclerosis, vasculitis[5,6]. In this case report, we aimed to evaluate diagnostic difficulties and treatment modalities in a patient with FD who had an initially misdiagnosed of vasculitis.

Case Report

In February 2008 a 21-year-old male was referred to our hospital for neurological evaluation, two months after he had ischemic stroke of undetermined etiology. In childhood he had a frequent neuropathic pain in hands and legs, especially when he had fever or after exercise.

In 2005, he had diplopia and vertigo which spontaneously resolved in 15 days. Hyperintensive lesions, deep in white matter, predominantly frontaly left had been observed in cerebral magnetic resonance imaging (MRI) examination.

The case had been diagnosed as Raynaud syndroma. The entire time patient had neuropathic pains. In the mean time, because of constant pain, muscle biopsy had been done. According to result of muscle biopsy, diagnosis of neurogenic myopathy had been established.

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In 2007, he had right hemiparesis and dysarrthrya. MRI pointed out ischemic lesion in pons. Extensive cardiac, arterial and hematologic investigations did not identify the etiology of his stroke. Although all laboratory tests for vasculitis were negative, except high CRP which was 77, the diagnosis of vasculitis had been established. He had been treated with high dose of corticosteroids and anticoagulant therapy.

In February 2008 he had been hospitalized at Department of Neurology. His neurological examination revealed normal mental status, residual right hemiparesis and difficulty in tandem walk. He had multiple red-purple papules, symmetrically distributed on the lower back. Clinical, medical record and radiological findings suggested Fabry disease. The diagnosis was confirmed biochemically by the absence of α-galactosidase A enzime activity (0 nmol/L normal 4-22 nmol/L). No cardiac, kidney or ophthalmologic involvements were defined.

The genetic analysis was performed in Rostock and pointed out GLA mutation in the DNA-sample with deletion c.115_132delACGCCTACCATGGG. This mutation is so far not described in literature, but results in a frameshift that causes a different protein sequence.

Family tree includes mother, father, 4 sisters and 1 brother and 18 relatives had been tested for Fabry disease, but all were negative. The patient is under agalisidase beta to replace α-galactosidase A enzyme for 10 months with a dose of 1 mg/kg (totally 70 mg) once every 2 weeks. The patient still has pain in legs and palms, but with lower intensity than before.

Discussion

In this case report, we present a patient with FD who was misdiagnosed for many years. His first symptoms were neuropathic pains, but it was misdiagnosed and treated for Raynaud syndrome.

After some years, when the changes of white matter in brain were seen on MRI, poliomyositis was diagnosed. He was treated with corticosteroids. In the age of 20 years he had ischemic stroke in pons, but again he was misdiagnosed, this time with vasculitis. All parameters for vasculitis were negative, excepted high sedimentation rate.

He came to our hospital for second opinion. Clinical picture which include angiokeratomas, neuropathic pain and stroke in young adults suggested Fabry disease.

The diagnosis was confirmed biochemically and genetically. His complete family was tested biochemically and genetically but all were negative. So we can conclude that this patient has a new mutation of enzyme α-galactosidase A. Fabry disease may mimic various neurological diseases such as demyelinating disease, neuropathies, and stroke.

In the literature, some case reports about misdiagnose of FD with multiple sclerosis were reported.

Unfortunately, in this case, the FD was misdiagnosing with poliomyositis and vasculitis and the patients had been treating with corticosteroids. Fabry disease must be considered in all cases of unexplained stroke in young patients, especially in cases with the combination of infarction in the vertebrobasilar artery system and proteinuria[6-9]. Fabry disease usually presents in childhood with acroparasthesia (constant burning pain) especially in the toes and fingers, and with painful crises, during which there are extremely severe attacks of sharp pain.

All children with unexplained neuropathic pain in toes and fingers especially with additional signs have to be checked for α-galactosidase enzyme activity. There is no cure for Fabry disease. Treatment with recombinant alpha-Gal A is available and should be considered for eligible individuals. Two formulations of recombinant human alpha-Gal A have been developed, agalsidase alpha and agalsidase beta.

Although there is no clear evidence of the benefit of enzyme replacement therapy in patients with cerebrovascular events, several studies have shown that such treatment does have an effect on resting cerebral blood flow abnormalities[10].

Further studies are required to determine whether enzyme replacement treatment in Fabry disease will result in a reduction in clinical outcomes such as stroke, ischemic heart disease and end-stage renal disease.

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NERUOLOŠKE MANIFESTACIJE FABRYEVE BOLESTI – PRIKAZ SLUČAJA

S A Ž E T A K

Fabryeva bolest je X-vezani recesivni poremećaj nakupljanja glikolipida. Uzrokuje ju nedostatak lizosomskog enzima α-galaktozidaze A, koji dovodi do nakupljanja supstrata, globotriasilceramida (Gb3) u mnogim tkivima koja uključuju endotel, pericite i glatke mišiće krvnih žila, stanice bubrežnog epitela, srčani mišić i mnoge neurone. U ovom prikazu slučaja prikazan je muški pacijent starosti 20 godina, koji je primljen zbog ishemičnog moždanog udara u području ponsa. Prije ove epizode, pacijent je bio pogrešno dijagnosticiran kao polimiozitis i vaskulitis. Pojava angiokeratoma, neuropatske boli i ishemičnog moždanog udara kod mladog pacijenta ukazala je na Fabryevu bolest. Dijagnoza je potvrđena biokemijski i genetski. Svi mladi pacijenti s moždanim udarom, posebno ako imaju dodatne simptome poput angiokeratoma, proteinurije, neuropatske boli nožnih prstiju i prstiju ruke trebali bi biti testirani na Fabryevu bolest.