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Fabry's disease in a female carrier with bilateral thalamic infarcts: a case report and a family study.

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An unusual case of a young woman, heterozygote for Fabry gene is reported, who presented bilateral thalamic infarcts due to occlusions of central nervous system vessels. Three other members of her family were studied. Fabry's disease (angiokeratoma corporis diffusum) is included among the rare causes of ischemic stroke in young adults.

UNITERMS: Fabry's disease, thalamic infarction, stroke in young adults.

CASE REPORT

Fabry's disease (angiokeratoma corporis diffusum) is an X-linked disorder of glycosphingolipid metabolism due to alpha-galactosidase-A deficiency. The enzymatic defect leads to storage of ceramides in body fluids and lysosomes of most visceral tissues, particularly of the vascular endothelium (12,17).

Clinical findings in homozygous males include pain and paresthesias in the limbs, angiokeratoma of skin and mucous membranes and corneal and lenticular opacities since early life. With increasing age, renal and cardiac involvement, as well as neurologic disease may become manifest (12). Although heterozygous females usually present the characteristic corneal dystrophy, they are generally asymptomatic or have an attenuated form of the disease (4,12). Rarely they can be as severely affected as homozygous males (4); central nervous system (CNS)

symptoms have been reported in only a few cases of heterozygous females (2,10,11,28,29).

We report the unusual case of a young woman heterozygote for Fabry gene, who presented with successive episodes of occlusions of CNS vessels, including bilateral thalamic infarcts. This is, to our knowledge, the first report of such an involvement in a female heterozygote for Fabry's disease. Additionally, her sister and her father, also affected, and her paternal grandmother, were studied.

REPORT OF CASES

Case 1- A 25-year-old white female presented with a throbbing headache for three days, followed by vertigo and bilateral eyelid ptosis. Her past medical history revealed that she had suffered from episodic pain in the limbs since childhood. At age 16, a heart murmur was detected and an echocardiogram disclosed a mitral valve prolapse. At age 22 she suffered sudden blindness in the left eye. An ophtalmologic examination at that time detected an occlusion of the central retinal artery associated with an edematous pale disc in that eye. After an extensive investigation her visual loss was believed to be secondary to an embolic event. In the following years she had many

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episodes of amaurosis fugax in the left eye. At age 23, she had sudden deafness in the right ear, which was attributed to an embolic cochlear infarct. These events were presumed to be secondary to her mitral valve prolapse.

On admission physical examination showed no abnormalities, except for auscultatory findings suggestive of mitral valve prolapse. She was alert and oriented. There was bilateral eyelid ptosis and marked changes in eye movements. The left eye was deviated downwards and slightly laterally and would not elevate above midline; adduction, depression and abduction were normal in this eye; the right eye could abduct normally and had about 50% of elevation; adduction and depression were completely absent. The left eye was blind and showed marked optic atrophy with diffuse narrowing of the retinal arteries. The right eye had normal vision and fundus examination. Pupils were equal in size and showed no light reaction in the left eye, but no efferent defect. The rest of neurologic examination was normal, except for deafness in the right ear.

The results of complete blood cell count, platelet count, serum glucose, cholesterol, triglycerides, prothrombin time, partial thromboplastin time, antinuclear antibody, rheumatoid factor, complement levels, erythrocyte sedimentation rate, serum protein electrophoresis and serologic tests for syphilis and toxoplasmosis were normal. A CT scan of the brain was normal and examination of the cerebrospinal fluid revealed 18 white cells/mm with 96% of lymphocytes, a protein content of 36 mg/dl, with normal pattern electrophoresis.

The patient was initially suspected to have a vasculitis, a embolic phenomena from mitral valve prolapse, or a demyelinating disease. In a thorough Ophthalmologic evaluation, however, typical whorl-like opacities in the cornea ("cornea vermicillata") were observed at slit-lamp examination and the diagnosis of Fabry's disease was established. There were no changes in the lens or conjunctival vessels. Dermatologic consultation showed no angiokeratoma in the skin or mucous membranes and thorough renal evaluation was normal.

Two months later, she presented throbbing headache for a few days, followed by an acute confusional state and behavioral disturbances, characterized by temporospatial disorientation and poor personal hygiene. Neuropsychological examination showed severe deficits in temporal orientation, immediate and recent memory, verbal fluency, mild anomia and inappropriate laughter. Mini-mental status examination score was 23/30. A repeated cerebrospinal fluid examination revealed 23 white cells/mm (100% mononuclear) and a protein content of 31mg/dl. A CT scan showed questionable thalamic hypodensities and a magnetic resonance imaging disclosed,

on T1 and T2 weight images, bilateral thalamic lesions with precise limits, compatible with infarcts. Peripheral nerve conduction and needle electromyography studies were normal. Electron microscopy examination of a sural nerve specimen revealed the typical pattern of concentric and lamellar inclusions with alternating light and dark staining bands in the lysosomal apparatus of perineurium cells, compatible with Fabry's disease. Painful episodes responded well to carbamazepine. One month later she had moderate improvement in her mental status but eyelid ptosis and eye movements abnormalities remained unchanged.

Case 2- Father of patient 1, a 52 years aged male was thoroughly investigated and findings were consistent with classic x-linked Fabry's disease. Physical examination showed typical angiokeratomas of the scrotum and penis, lymphoedema in both legs, and corneal and lenticular opacities characteristic of Fabry's disease. Other findings included cardiac involvement with concentric hypertrophy of the left ventricle, aortic regurgitation, mitral valve annulus thickening and atrial fibrillation, complete obstruction of the right renal artery with renal function impairment and bilateral aseptic necrosis of the femoral heads. There was also a past history of emergency laparotomy due to small intestine loop necrosis and emergency revascularization surgery for acute obstruction of the left femoral artery.

Neurologic examination showed marked behavioral abnormalities with periods of temporospatial disorientation, agitation, paranoid ideation and poor critics. No motor or sensory deficits were detected. A CT scan showed an old infarct in the right frontotemporal region. In an eight-month follow-up period, accentuation of his cognitive deficits and behavioral disturbances was observed. Peripheral nervous system findings consisted of episodic pain in the limbs. Nerve velocities and needle electromyography studies were normal. Electron microscopy examination of a sural nerve specimen showed electron-dense deposits in perineural and endothelial cells.

Case 3- Sister of patient 1, a 19-year-old female also suffered from excruciating pain in the limbs and unexplained fever episodes since age 7. A heart murmur was detected at age 10 and she received the diagnosis of rheumatic fever. Ocular examination revealed whorl-like opacities and posterior lenticular opacities (Fabry cataract) in both eyes. Skin examination showed no angiokeratomas and auscultatory findings were suggestive of mitral valve prolapse. Renal function studies and urinary sediment were normal.

Case 4- Paternal grandmother of patient 1, a 75-year-old female, had a history of hypertension and angina pectoris but no ocular or skin abnormalities of Fabry's

disease were observed.

COMMENTS

Neurologic involvement in Fabry's disease in male homozygotes is highly variable and include focal or multifocal disturbances of cerebral hemispheres, brainstem, cerebellum or diffuse encephalopathy, presenting with cognitive dysfunction, psychotic behavior and personality changes (8,12,14).

Major vessel thrombosis and multifocal small vessel occlusion due to ceramide storage in vessel endothelium may account for sudden-onset symptoms, whereas lipid storage in neurons may explain more insidiously developing symptoms (16,18). In case 2 combination of both mechanisms would more suitably explain neurologic findings.

CNS symptoms are extremely rare in female carriers of the disease. We could find only six previous reports of such condition (2,10,11,15,28,29). Findings included memory loss, stroke (10,15), presenile dementia (29), episodic vertigo, ataxia, dysarthria, long tract signs and bladder incontinence (2).

When a young woman without family history of Fabry's disease presents with neurologic illness, diagnosis can be extremely difficult. These patients may strikingly resemble those with multiple sclerosis, especially when neurologic symptoms have had several remissions and more than one area in the CNS has been affected (29). Coexistence of valvular heart disease, including mitral valve prolapse, a common feature of Fabry's disease in female carriers (23), can lead to a misdiagnosis of embolic vascular occlusion, as occurred in patient 1. A high index of suspicion is therefore necessary to establish the diagnosis in these circumstances. Useful hints are pain and paresthesias in the limbs occurring in conjunction with early onset cerebrovascular disease. Slit-lamp examination should be done for detection of the characteristic corneal opacities.

Case 1 presented with unique feature of the disease occurring in a heterozygote. Acute visual loss as result of central retinal artery occlusion has only rarely been described, even in homozygotes (24,25). We could find just one example of this feature in a female carrier (22). Hearing loss probably resulting from small vessel occlusion is another rare recognized complication of the disease (2). Only one affected female with this symptom has been described (2). Eye movements abnormalities indicate a lesion in the right upper portion of midbrain, involving right oculomotor nucleus, presumably due to occlusion of basilar artery branches.

However, the most unusual of neurologic involvement occurring in patient 2 was the sudden onset of severe cognitive dysfunction, especially of language and memory, heralded by a transient acute confusional state. These features can be ascribed to bilateral thalamic infarcts, combined with peduncular lesions (6).

Clinical syndromes associated with thalamic lesions include sensory and motor loss, ataxia, involuntary movements and cognitive dysfunction (5,7,9). In case 1 prominent features of thalamic infarcts were severe impairment of both immediate and recent memory, decreased verbal output, mild anomia, and inappropriate laughter.

Bilateral thalamic lesions may give rise to a global deterioration of higher mental functions that justify the term thalamic dementia, which is particularly marked by deficits of attention and memory, decreased spontaneous movements, perseveration and affective disturbances (9). Language disturbances as decreased verbal output and word-finding difficulties which were present in this patient can occur in thalamic lesions (5,13). Memory disturbances almost always accompany thalamic aphasia (19), as observed in this case. Left or right-sided lesions impair memory for verbal or non-verbal material, respectively (26,27). Disorientation for time and place has been associated with thalamic lesions, especially left-sided ones (1). Bilateral lesions in the thalami have been implicated in inappropriate laughter, although pathologic confirmation was lacking in such cases (20). Thalamic infarcts resulted from occlusion of small, penetrating branches of the thalamogeniculate pedicle.

This is, to our knowledge, the first description of thalamic infarcts occurring in a female carrier of Fabry's disease. Although cognitive dysfunction and behavioural abnormalities have long been recognized in Fabry's disease, the role of lacunar infarcts in neuropsychiatric manifestations of the disease has probably been underestimated. Non-invasive high resolution neuroimaging techniques, such as MRI, will probably allow a more precise clinico-anatomical correlation, thus providing useful information to elucidate the role of vascular occlusive disease in Fabry's dementia.

This family provides an additional example of the great variability of this illness, specially in female heterozygotes (21). While case 4, an obligate carrier of the Fabry gene, presents no clinical manifestation of the disease, her two grand-daughters (cases 1 and 3) present a variable clinical expression of the disease. These differences probably are correlated with variability of alpha-galactosidase A activity, but we have not these data.

Markedly variable expression of the disease can be expected for x-linked enzymatic deficiencies. It is diffi-

cult, however, to explain the high frequency of clinical involvement in heterozygotes by random x-chromosome inactivation only. Preferential x-inactivation has also been proposed to explain clinical expression of the disease in heterozygotes. Further clinical, biochemical and genetic studies are needed to a better insight into the mechanisms underlying the variability of expression of Fabry's disease in the heterozygous state.

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RESUMO

Relata-se o caso de uma jovem, heterozigota para doença de Fabry, que desenvolveu infartos talâmicos bilaterais por oclusão de vasos do sistema nervoso central. Três outros membros de sua família foram também avaliados. A doença de Fabry inclui-se entre as causas raras de acidente vascular cerebral em adultos jovens.