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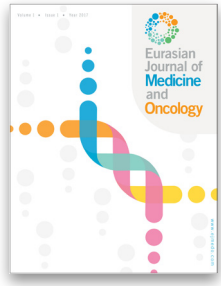

Case Report

Acute Stroke in a Patient with Mucopolysaccharidosis Type I with Increased Carotid Intima-Media Thickness

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Abstract

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive disease caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase. Cardiovascular involvement in MPS I includes deposition of glycosaminoglycans (GAGs) in the myocardium, cardiac valves, great vessels, and coronary arteries. Although the vascular effects of GAG accumulation are well known, the clinical effects of the histopathological changes are poorly understood. Because most studies on the vascular effects of GAG accumulation are performed postmortem or with invasive techniques such as angiography, recent studies have focused on endothelial function in patients with MPS I and noninvasive techniques that may help detect vascular dysfunction. Presently described is the case of a patient with MPS type I with acute stroke and proven endothelial dysfunction.

Keywords: Cardiovascular system, carotid intima-media thickness, mucopolysaccharidosis type I, stroke, vasculopathy

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Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive disease caused by the deficiency of the lysosomal enzyme α-L-iduronidase,which is involved in the degradation of sulfated glycosaminoglycans (GAGs). Its deficiency results in intracellular and pericellular accumulations of GAGs heparan sulfate and dermatan sulfate, resulting in the clinical features of these disorders, including dysostosis multiplex and coarsening of skin and facial features, as well as the dysfunction of central nervous system (CNS), respiratory system, and cardiovascular system. Severe MPS I (Hurler syndrome) results in profound CNS, respiratory, and cardiac involvement from the relentless accumulation of GAGs with death occurring within the first decade of life.[1, 2]

We present the case of a patient with MPS type I with acute stroke and radiological evidence of endothelial dysfunction.

Case Report

A 3-year-old girl with MPS I was admitted because of left hemiplegia. She was diagnosed with MPS I and was being followed up since 6 months of age in our clinic and had been receiving enzyme replacement therapy (ERT) since then.

Upon admission, she was afebrile and normotensive. Physical examination revealed right-sided central facial paralysis, hemiplegia and increased deep tendon reflexes, along with typical features of MPS I. Laboratory studies including complete blood count, C-reactive protein, erythrocyte sedimentation rate, prothrombin time, activated prothrombin time, bleeding time, lipid profile, plasma homocysteine, fasting blood sugar, anticardiolipin (antiphospholipid) antibody, lipoprotein A, plasma fibrinogen, factor V Leiden (FVL), antithrombin III, protein S, protein C, enzyme-linked immunosorbent assay, antinuclear antibody, Cytoplasmic

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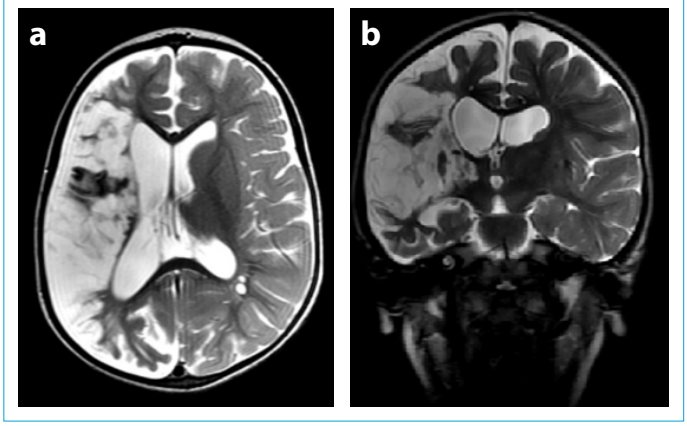

Figure 1 (a, b). T2 weighted cranial MRI findings consistent with extensive encephalomalacia of right cerebral hemispheric parenchyma after a period of stroke.

antineutrophil cytoplasmic antibodies (C-ANCA), Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA), and prothrombin showed normal results.

Brain magnetic resonance imaging (MRI) with diffusion-weighted imaging revealed an area of restricted diffusion in the right temporoparietal lobe, which appeared faintly hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences (Figs. 1a-b). Magnetic resonance angiography (MRA) demonstrated focal loss of flow-related enhancement within a branch of the right middle cerebral artery (MCA)(Figs. 1a-b, 2).

Low-molecular-weight heparin (LMWH) therapy was initiated beause of acute right MCA stroke.

Transthoracic echocardiography revealed moderate mitral and aortic valve regurgitation with no evidence of vegetations or thrombi. Carotid intima–media thickness (cIMT) was measured as 0.5 mm.

Genetic analysis for G20210A, MTHFR, and FVL was performed. The results of these investigations were significant only for heterozygous mutations of FVLand MTHFR A1298C.

The patient was discharged on the seventh day of admission with LMWH therapy. She is currently undergoing physiotherapy with no change in her neurological condition.

Discussion

Cardiac and vascular involvement is one of the major features of various MPSs.[1-3] Autopsies of patients with MPS I have revealed arterial narrowing to be caused by the development of "Hurler plaque" within the intima and inner portion of the media of large- and medium-sized arteries, particularly within the heart and other important vessels of the body.[2] With the help of hematopoietic stem cell transplantation (HSCT) and the availability of recombinant ERT, the natural history of Hurler syndrome has improved. The

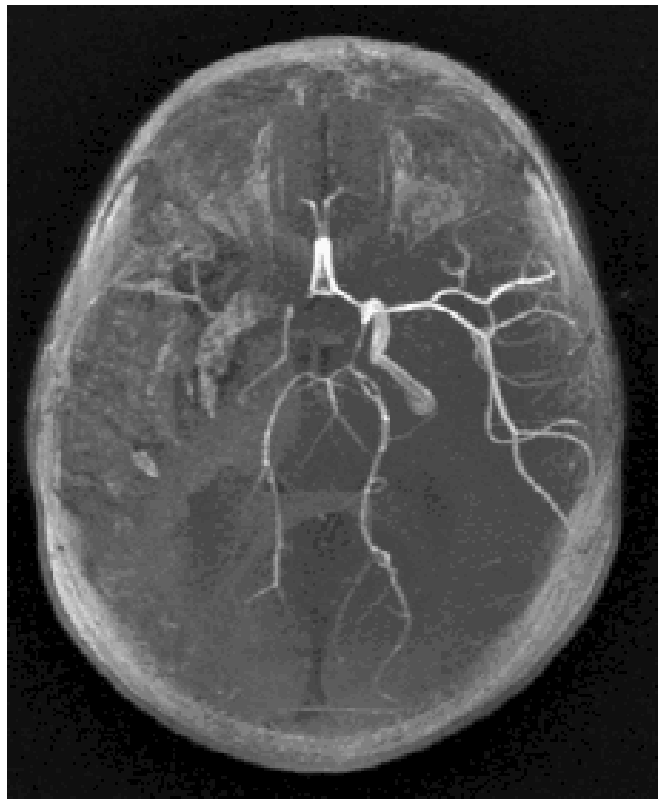

Figure 2. MRA findings consistent with right MCA occlusion.

cardiac effects of HSCT and ERT include preservation of ventricular function and resolution of ventricular hypertrophy.[2, 6]

cIMTcorrelates well with carotid histology, has been repeatedly validated as a predictive risk factor for myocardial infarction and cerebrovascular accident, and is also used as an end-point in interventional studies.[3] Because the devastating effects of the accumulation of GAGs in vessels have mostly been revealed by invasive techniques such as angiography or autopsies, researchers have recently focused on to the idea of determining a noninvasive marker to determine vasculopathy in patients with MPS I. A pilot study on this issue was conducted by Wang et al.[3] in 2011. cIMT of our patient was 0.5 mm, which was high compared to the reference values found in literate.[7]

Acute ischemic attacks in patients with MPS I have been rarely reported in the literature. The first reported case was that of a 21-year-old Korean man with MPS II[4] with a previous history of endocarditis. The second case was that of a 41-year-old woman with Scheie syndrome diagnosed after cerebral infarction. The authors suggested the embolism of a cardiac thrombus to the cerebral arteries to be the most likely cause of ischemia.[5] In neither of these cases apparent evidence of vasculopathy was detected by invasive or noninvasive methods. A third case was presented by Aydın

et al.,[6] which was that of a 3-year-old girl with MPS IIIB with recurrent subdural hematoma attacks and cranial MRA showing signs of occlusion in the posterior elements of the circle of Willis. In this case, dural biopsy showed inflammatory cells along the vascular wall; other etiological factors of vasculitis were not present; therefore, the authors suggested acute ischemic attack to be directly related with MPS.

Many conditions associated with GAG accumulation may contribute as a risk factor for stroke in patients with MPS. Valvular thickening and fibrosis may lead to cardiac thrombi, and intimal thickening of the aorta and coronary arteries may also occur in the cerebral vasculature.[1, 2] Severe hydrocephalus may compress cerebral arteries and cause brain infarction. In our patient, the second-degree mitral regurgitation may also have contributed to acute stroke.

The heterozygous A1298C mutation of MTHFR is known to be widespread among populations and mostly unrelated to ischemic stroke in children.[8] Although the heterozygous mutations of FVL are a risk factor for acute ischemic events, previous studies on the role of FVL in stroke have reported controversial findings.[9] A number of studies have proposed FVL as a predisposing factor for ischemic stroke only when it is accompanied by classical risk factors of stroke.[10] The heterozygous FVL mutation may have led to acute stroke in our patient on the basis of vasculopathy due to GAG accumulation, which may have triggered the event. Although stroke is not one of the expected complications of MPSs, the infiltration of vessels in CNS may predispose patients to ischemic attacks.

The evaluation of patients for vasculopathy may play an important role in determining patients at risk for vascular diseases in CVS and CNS. In addition, vascular involvement should be taken into consideration in patients with MPS with ischemic attacksto determine duration of treatment with LMWH, if needed. It is necessary to be aware of the risk of cerebral infarction in patients with MPS.

Disclosures

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Conflict of Interest: None declared.

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