Clinical Case Report

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Elevated serum lipoprotein(a) as a risk factor for combined intracranial and extracranial artery stenosis in a child with arterial ischemic stroke

A case report

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Abstract

Rationale: Stroke is an uncommon disease in childhood with an estimated incidence of 1 to 6 per 100,000 and stenoocclusive arteriopathy is the main risk factor of recurrent pediatric arterial ischemic stroke (AIS). Dyslipidemia may influence strongly before puberty and in late adolescence when plasma levels are naturally highest.

Patient concerns: An 11-year-old male presented with acute onset seizure, a drowsy mentality, and right hemiplegia.

Diagnoses: Magnetic resonance (MR) angiogram demonstrated occlusion of distal basilar artery and left vertebral arteries. Serum Lp(a) was significantly increased as 269 nmol/L (normal<75 nmol/L) only. Thus, he was diagnosed as pediatric AIS.

Interventions: He was started on aspirin (100 mg/day) for secondary stroke prevention and received nicotinic acid (2 g/day) as a Lp(a)-lowering agent.

Outcomes: Consciousness gradually improved and the patient regained a normal orientation after 2 weeks. The Lp(a) level was reduced to 48 nmol/L after nicotinic acid administration.

Lessons: High Lp(a) level may be considered in the risk profile assessment of pediatric AIS. Niacin and certain inhibitors of cholesteryl ester transfer protein can be considered to reduce Lp(a).

Abbreviations: AIS = arterial ischemic stroke, apo = apolipoprotein, LDL = low-density lipoprotein, Lp(a) = lipoprotein(a), MRI = magnetic resonance imaging.

Keywords: cranial artery stenosis, high lipoprotein(a), niacin, pediatric arterial ischemic stroke

1. Introduction

Pediatric arterial ischemic stroke (AIS) is an uncommon disease except in the perinatal period and incidences are ranged from 2.6 to 6.4 per year, reflecting a trend toward a higher incidence in previous studies.[1,2] The most frequent cause of pediatric AIS is the pathology of stenoocclusive arteriopathy, which is the main risk factor of recurrent pediatric AIS.[3] Dyslipidemia may influence strongly before puberty and in late adolescence when plasma levels are naturally highest. It may be a risk factor for stroke related with steno-occlusive arteriopathy, as well as an interaction with infectious or inflammatory state.[3] Elevated lipoprotein(a) [Lp(a)] plasma concentration has been identified as a positive association with AIS in infants and children.[4,5] Lp(a) is a cholesterol ester-rich plasma lipoprotein with a lipid composition similar to that of low-density lipoproteins (LDLs), and consists of 2 major proteins, apolipoprotein (apo) B and apo (a).[5] Lp(a) competes with plasminogen for binding sites on a specific endothelial cell receptor and may interfere with endogenous endothelial cell mediated fibrinolysis.[6] Besides, Lp(a) also binds and inactivates tissue factor pathway inhibitor.[5] This report describes a first Korean pediatric AIS caused by combined extra- and intracranial artery stenosis with a high Lp(a) as the only cerebrovascular risk factor.

2. Case presentation

All subjects provided written informed consent for clinical and molecular analyses and the study protocol was approved by the Institutional Review Board of the Catholic University of Korea. Consent for publication of this case report was obtained from the proband's parents. An 11-year-old male presented with acute onset seizure, a drowsy mentality, and right hemiplegia. Two days before admittance, the patient complained of

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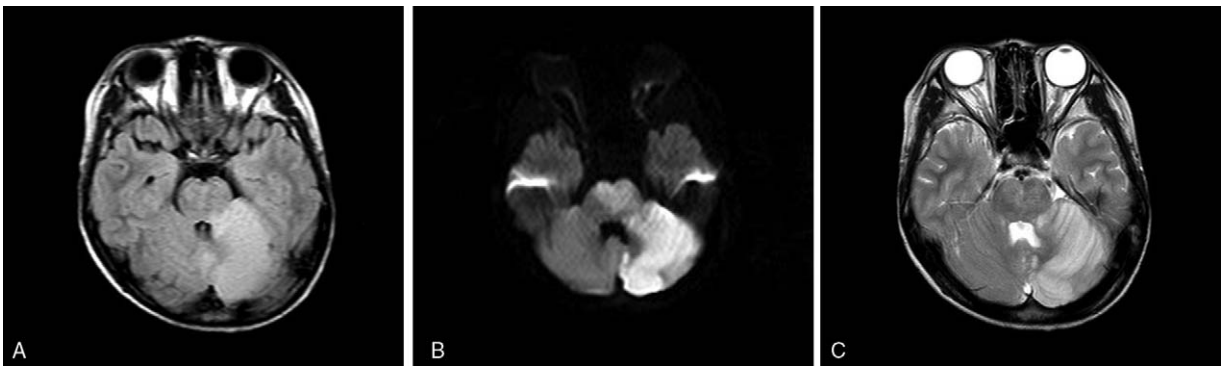

Figure 1. Brain magnetic resonance imaging (MRI) showed high signal intensity in the left cerebellar hemisphere, consistent with acute cerebellar infarction. (A) Flair, (B) diffusion, and (C) T2W1 imaging.

intermittent headache and dizziness. There was no history of head trauma, focal weakness, infection, toxin ingestion, dysesthesia, trauma, neck manipulation, or prodromal illness. Neurological examination showed a complete right hemiplegia with loss of muscle tone, increased tendon reflex, and positive Babinski sign. Deep pain sensation was normal. On admittance, a general physical examination was negative and his medical history was unremarkable. Brain computed tomography was normal, while brain magnetic resonance imaging (MRI) showed areas of high signal intensity on T2-weighted images, and of low signal intensity on T1-weighted images in the superior and medial aspects of the left cerebellar hemisphere and vermis at the territory of distal basilar artery (Fig. 1). Transfemoral angiography showed as distal basilar artery occlusion with partial stenosis in the left vertebral arteries (Fig. 2). Cervical spine radiographs indicated no cervical subluxation or cervical abnormalities. A thoracic and transesophageal echocardiogram failed to reveal a cardiac source of the emboli and structural or valvular abnormalities. Echocardiography and Holter monitoring revealed no arrhythmias. Target resequencing using the TruSight One Sequencing Panel (Illumina, Inc., San Diego, CA) was performed but showed no underlying genetic cause of the patient's condition. Laboratory studies including prothrombotic and lipid profiles were within normal limits; however, serum Lp(a) was significantly increased as 269 nmol/L (normal < 75 nmol/L). He was started on aspirin (100 mg daily) for secondary stroke prevention. Nicotinic acid (2 g/day) was used as a Lp(a)-lowering agent. Consciousness gradually improved and the patient regained a normal orientation after 2 weeks. The Lp(a) level was reduced to 48 nmol/L after nicotinic acid administration. One year after rehabilitation, he made a good recovery; he has mild hemiplegia but can walk without an aid.

3. Discussion

We reported a child with AIS who had a high Lp(a) but no other risk factor, and our data are in agreement with the hypothesis that Lp(a) actively promotes atheromatosis rather than lipohyalinosis and favors thrombosis on atheromatous plaques by reducing fibrinolysis. Extensive workup for underlying risk factors ruled out cardiac disorders, hematological disorders, and arteriopathies. With normal inflammatory markers and an absence of involvement of any other organ system, autoimmune diseases were less likely considered. Acute hemiparesis is the most frequent focal deficit, but the condition may be erroneously attributed to other causes, which can mimic stroke (e.g., headache, seizures or Todd paresis,

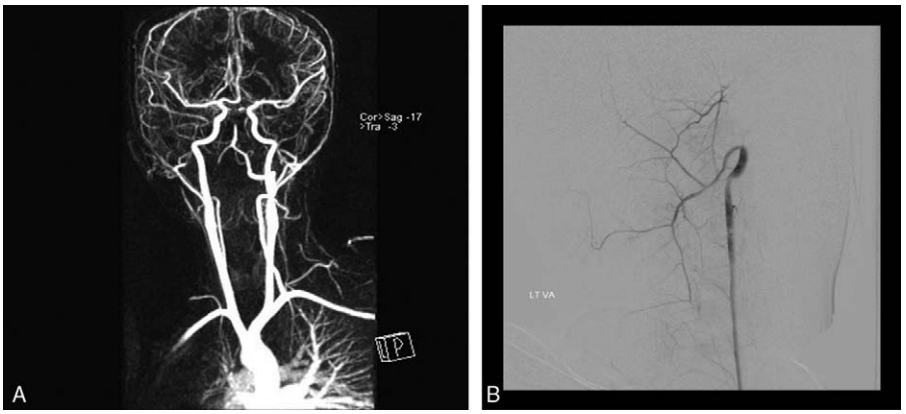

Figure 2. Magnetic resonance angiography (MRA) and cerebral angiogram findings. (A) Initial MRA showed occlusion of distal basilar artery and left vertebral arteries. (B) Cerebral angiogram of the left vertebral artery taken 5 days after admission showing irregularity and narrowing.

meningoencephalitis, or demyelination).[7] The potential causes of AIS in infants and children are multitudinous, and are frequently various in individual cases. The existence of certain prothrombotic states increases the risk of stroke recurrence in children and adolescents, including factor V Leiden, protein C deficiency, and elevated Lp(a) plasma concentrations.[8] Among them, Lp(a) may provide a link between the cholesterol transport system in the fibrinolytic system and plasma, and act as a modulator of the precise balance between fibrinolysis and blood coagulation.[9] Lp(a) interferes with clot lysis by competing with plasminogen binding to molecules and endothelial cells, which result in diminish plasminogen activation, plasmin generation, and delayed fibrinolysis. Lp (a) also binds to macrophages via a high-affinity receptor that advances in cell formation and the deposition of cholesterol in atherosclerotic plaques.

The apo(a) component of Lp(a) has 80% homology with plasminogen by character of shared repetitive kringle-4 domains. Thus, the apo(a) component is thought to act like in the pathogenesis of cardiovascular events. The International Pediatric Stroke Study described probable risk factors for pediatric AIS and elevated Lp(a) was observed as prothrombotic states in 21 out of 674 studied children.[5] The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommend evaluating Lp(a) levels as part of routine screening in infant or children with an hemorrhagic or ischemic stroke or with a parental history of atherosclerotic cardiovascular disease not clarified by classical risk factors.[5] In addition, several studies have revealed that Lp(a) levels are correlated with the burden of and extra- and intracranial carotid stenosis.[4,10,11]

Recent researches suggest that Lp(a)-lowering treatment may be beneficial to prevent recurrent AIS. Considerable modification of Lp(a) level has been difficult to achieve without pharmacological agents. Niacin, not selective for Lp(a), has long been considered a Lp(a)-lowering drug, but niacin in combination with other lipid-lowering drugs has produced controversial results.[11] Niacin and certain inhibitors of cholesteryl ester transfer protein can reduce Lp(a) by about 20% and 40%, respectively.[12] Large randomized trials of niacin and cholesteryl ester transfer protein inhibitors in the secondary prevention of coronary heart disease are required.[13] Pathologic research into the role of Lp(a) in the burden of cerebral atherosclerosis may be valuable.

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