Case report

Interatrial septal aneurysm and genetic prothrombotic disorders: possible interaction in the pathogenesis of pediatric stroke

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Stroke in children is a rare condition and has a multifactorial etiology. The association between ischemic stroke in young adults and some minor cardiac abnormalities such as atrial septal aneurysm with or without interatrial shunting has recently been reported: however, the pathogenetic mechanism still remains unclear. Genetic and acquired prothrombotic disorders are also risk factors for cerebral ischemic events in children.

We report a case of ischemic stroke in a 10-year-old female child who was heterozygous for the prothrombin G20210A variant and who presented with an atrial septal aneurysm associated with an interatrial shunt. We hypothesize that these risk factors play a synergic role but their relative importance and whether alone they can determine cerebral embolism remain to be determined.

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Introduction

Ischemic stroke is a very rare event in childhood: the annual incidence is 0.063-0.12 cases per 10 000 children[1]; cardiac diseases are the most common causes[2]. These include complex congenital heart diseases (i.e. tetralogy of Fallot, transposition of the great arteries, atrioventricular septal defects) with an intracardiac shunt permitting paradoxical embolism, or acquired disorders such as bacterial endocarditis, cardiomyopathies, rheumatic heart disease and cardiac tumors[3]. In the last years, the possible association between ischemic stroke in young adults and some cardiac abnormalities such as patent foramen ovale, atrial septal defects and atrial septal aneurysm has been reported[4-6]. It is still unclear how these cardiac malformations can cause cerebral ischemic events: the most likely mechanisms are paradoxical embolism through an interatrial communication and/or thrombus formation within the atrial septal aneurysm[7]. Recent studies have shown that genetic or acquired prothrombotic disorders may constitute risk factors for ischemic stroke in childhood[8]. These conditions include congenital plasminogen defects, acquired hypofibrinolysis, coagulation factor disorders (antithrombin III, protein C, protein S and protein C cofactor II deficiencies; the factor V G1691A gene mutation, and the presence of the prothrombin G20210A variant)[9], and circulating antiphospholipid antibodies[9,10].

We report a case of stroke in a female child presenting with a congenital coagulation defect (she was heterozygous for the prothrombin G20210 variant) the role of which in the pathogenesis of pediatric stroke is still unclear. This genetic variant was associated with the presence of an interatrial septal aneurysm and of an interatrial shunt.

Case report

Last July, a 10-year-old female child with a sudden onset of a speech disorder and paresis of the right upper limb was admitted to the Pediatric Division of our hospital. At the time of admission, neurological evaluation revealed aphasia, right hemiparesis, deficit of the seventh right cranial nerve and right homonymous hemianopsia. Laboratory tests (hematologic and blood chemical analyses, prothrombin time, activated partial thromboplastin time and fibrinogen values) were normal. A computed tomography scan of the brain revealed no hemorrhage. Mag-

netic resonance imaging study, performed to assess cerebral damage, showed, in T2-weighted images, an increased-intensity signal in the left sylvian cortex, attributable to a recent ischemic lesion (Fig. 1). Transcranial and extracranial Doppler ultrasonography revealed a possible obstruction of the intracranial left internal carotid segment, starting from the carotid siphon and extending to the proximal segment of the middle cerebral artery.

Angio-magnetic resonance scanning revealed a signal interrupted in the distal portion of the horizontal segment of the middle cerebral artery, before the subdivision of the sylvian vessels (Fig. 2). Electroencephalography (recorded with the patient awake) showed slow waves in the left centrotemporal region. Following initial evaluation, an antiplatelet therapeutic regimen was begun (aspirin 5 mg/kg/day).

Hemiparesis rapidly resolved within a few hours and the speech deficit and that of the seventh cranial nerve within the first 30 hours of symptom onset. Moreover, during the first 48 hours the patient had several episodes of vomiting. She was thus submitted to further evaluation: blood coagulation screening showed that the patient was heterozygous for the prothrombin G20210A gene variant; cardiological examination did not reveal any signs of heart disease and her electrocardiogram was normal. Transthoracic echocardiography revealed the presence of an atrial septal aneurysm (Fig. 3) associated with a small-sized interatrial defect with mild degree left-to-right shunting.

The patient was subsequently discharged with complete neurological recovery and on antiplatelet therapy (aspirin 150 mg/day) that she has taken for 6 months.

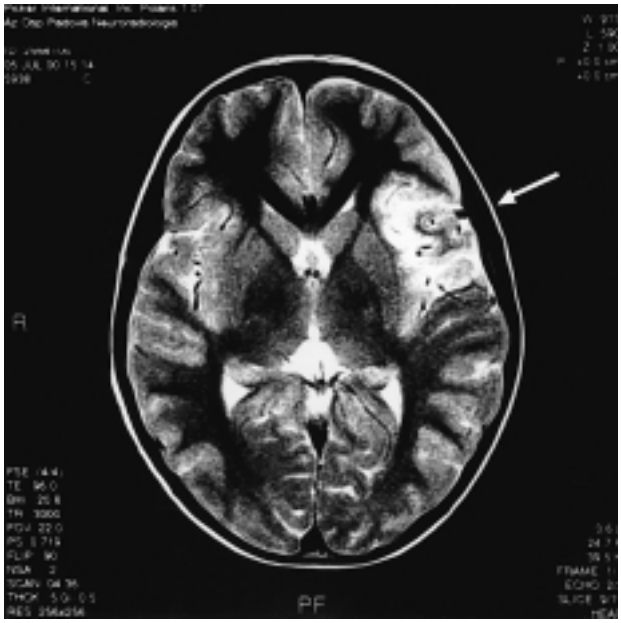

Figure 1. *Magnetic resonance image of the brain showing* (arrow) *T2-weighted increased-intensity signal in the left sylvian cortex attributed to a recent ischemic lesion.*

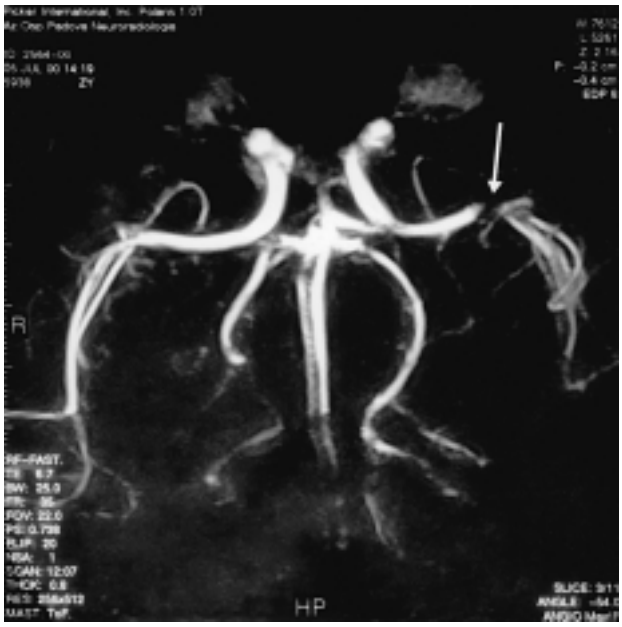

Figure 2. *Angio-magnetic resonance image of the brain showing signal interruption in the distal portion of the horizontal segment of the middle cerebral artery* (arrow)*, before the branching of the sylvian vessels.*

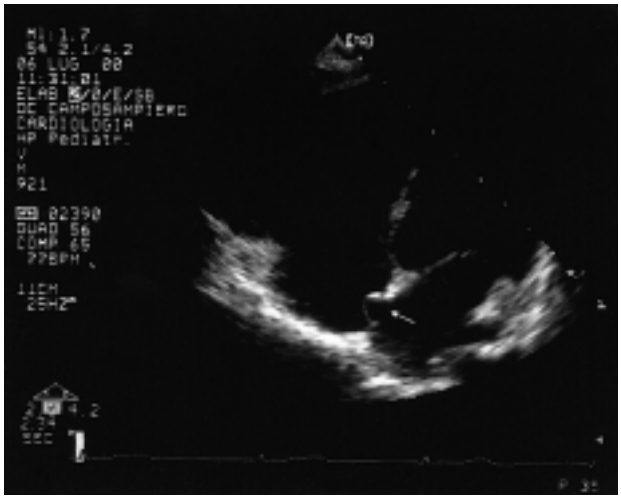

Figure 3. *Two-dimensional echocardiographic image (modified apical 4-chamber view) showing a small atrial septal aneurysm* (arrow).

Twenty days later the patient underwent cardiac catheterization that showed a 2.1 pulmonary/systemic flow ratio (Qp/Qs); the right ventricular pressures were 20/3 mmHg and the pulmonary artery pressures were 20/10/12 mmHg. Then, using the Amplatzer 18 mm device the atrial septal defect was closed and the aneurysm flattened. Subsequently a transthoracic echocardiography demonstrated adequate device positioning and no residual shunt (Fig. 4). At follow-up, neuropediatric evaluation and electroencephalography were normal. At 3 months of follow-up, magnetic resonance imaging and angio-magnetic resonance were repeated and revealed that the increased-intensity area had regressed and that the lumen of the left middle

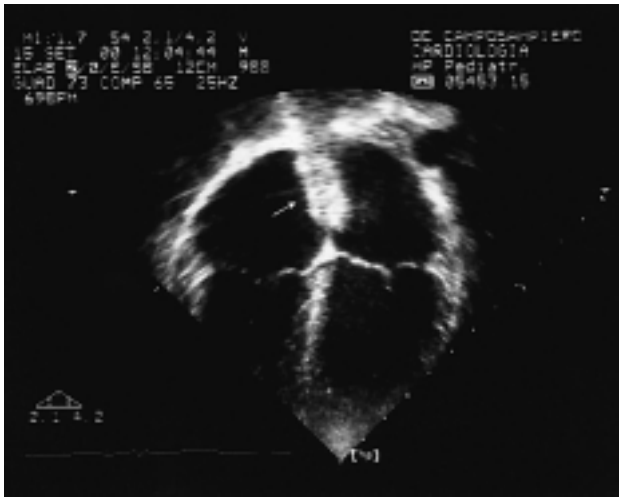

Figure 4. *Echocardiographic study performed after percutaneous closure of the interatrial defect (reversed apical 4-chamber view) showing good Amplatzer device positioning* (arrow).

cerebral artery was normal. The child's parents underwent cardiological evaluation and transthoracic echocardiography that did not reveal any cardiac abnormalities. Blood coagulation screening revealed that her mother, who did not present with any symptoms, was heterozygous for the prothrombin G20210A variant. At 1-year of follow-up the patient was well. There was no neurological deficit nor any recurrence of ischemia; transthoracic echocardiography was repeated and confirmed that the device was well positioned and that no thrombus had formed.

Discussion

Among the causes of stroke in children, some complex congenital and acquired heart diseases such as bacterial endocarditis or rheumatic heart disease are the most common underlying conditions and occur in 25% of cases of pediatric stroke. In the last years, the association between cryptogenetic stroke and some minor cardiac abnormalities has been reported. One of these is atrial septal aneurysm alone or, more frequently, in association with mitral valve prolapse, interatrial defects and/or patent foramen ovale[11]. How atrial septal aneurysm can cause ischemic stroke remains to be determined: possible mechanisms include paradoxical embolism when coexisting with an interatrial shunt or thrombus formation within the aneurysmal sac[12,13]. Moreover, it is still unclear if alone, these malformations may cause an embolic stroke or if they require the presence of other predisposing conditions such as a trombophilic status, trauma, infections or nutritional deficiencies.

On the other hand, it has been observed that genetic and acquired prothrombotic disorders also constitute risk factors for stroke in at least 30% of cases which occur during childhood[10]; however, the role of the prothrombin G20210A variant, carried by our patient, remains controversial: the majority of studies do not reveal that it is associated with pediatric ischemic stroke[9,14-16]. Only one report has shown that this genetic mutation may play a role in pediatric stroke[17]. In our case, it seems reasonable to postulate that this cardiac abnormality associated with a congenital trombophilic status may be causally related to the episode of cerebral embolism.

The risk of ischemic recurrence may have devastating outcomes in childhood[18]; so we thought that besides prescribing antiplatelet therapy, it would be appropriate to submit the patient to percutaneous closure of the interatrial defect and to flattening of the aneurysm, in spite of the absence of studies about the long-term outcomes of such procedures in pediatric populations[19].

In conclusion, our case suggests a possible multifactorial etiology of ischemic stroke in childhood. An atrial septal aneurysm associated with a congenital prothrombotic disorder may play a role in determining pediatric stroke. Large epidemiological studies investigating this association further are necessary.

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