Moyamoya Syndrome Associated with Alagille Syndrome: Outcome after Surgical Revascularization

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Vasculopathy is well-described in Alagille syndrome (ALGS); however, few data exist regarding neurosurgical interventions. We report 5 children with ALGS with moyamoya who underwent revascularization surgery. Postsurgical complications included 1 stroke and 1 death from thalamic hemorrhage. Global function improved in survivors. Revascularization is reasonably safe in patients with ALGS and may improve neurologic outcomes. *(J Pediatr 2015;166:470-3).*

Moyamoya is a chronic occlusive vasculopathy characterized by progressive stenosis of the basal intracranial vessels resulting in the formation of arterial collaterals that form a cloud-like blush on angiography.[1] The natural history of untreated disease can be progressive cerebral ischemia, stroke, neurologic disability, and sometimes death.[2-6] Surgical revascularization results in cessation of ischemic symptoms, prevention of further ischemic injury, and contributes to an excellent long-term prognosis.[7,8]

Alagille syndrome (ALGS) is a multisystem disorder associated with characteristic facies, liver, cardiac, ocular, skeletal, renal, and vascular anomalies, resulting from *JAGGED1* (*JAG1*) mutations.[9] The prevalence is 1 in 30 000. Vascular anomalies (of any type) and stroke are identified in almost 10% and 14% of individuals with ALGS, respectively.[10,11] In an ALGS cohort who underwent prospective magnetic resonance imaging (MRI)/magnetic resonance angiography, cerebrovascular pathology was identified in 35%, including 23% who were asymptomatic.[12] The cerebral vasculopathies in ALGS include treatable lesions, namely moyamoya syndrome and cerebral aneurysms.[10-17]

Moyamoya arteriopathy in ALGS has not been treated routinely because of a lack of data regarding natural history, interventions, or treatment outcomes. We sought to describe the outcomes of surgical revascularization in patients with ALGS with moyamoya.

Methods

We retrospectively reviewed a consecutive series of pediatric patients who underwent cerebral revascularization from 1985 to 2011 at Boston Children's Hospital. A survey was undertaken of seven North American pediatric centers to identify additional patients. All patients with ALGS included met classic clinical criteria or carried a *JAG1* mutation. Institutional review board approval was obtained for chart review. Patients were graded with a modified Rankin scale (mRS) score (standard scale rating global function) from 1 to 5, for normal function to profound disability.

ALGS	Alagille syndrome
CSF	Cerebrospinal fluid
EDAS	Encephaloduroarteriosynangiosis
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale

Results

Five patients with ALGS with moyamoya underwent surgical revascularization (**Table**). All patients presented with cerebral ischemia; 4 presented with transient ischemic attacks that were anterior circulation events composed of hemiparesis, speech arrest, or sensory loss (4/5), and 2 of these went on to develop arterial ischemic stroke. One patient presented initially with arterial ischemic stroke that resulted in hemiparesis. At the time of surgery, 2 patients had persistent neurologic deficits. Seizure activity at stroke onset was present in one patient and headache present in one patient.

Cortical fluid-attenuated inversion recovery change, which is a characteristic feature in moyamoya arteriopathy, was noted on all of the 5 preoperative MRIs, with all hemispheres affected. Infarcts were noted in 3 patients; they involved the middle cerebral artery (MCA) territory in 2 patients and the cortical watershed zone in 1 patient. Preoperative digital subtraction angiography was available for 4 patients. The angiographic characteristics of moyamoya arteriopathy in ALGS were indistinguishable from larger series describing idiopathic moyamoya (**Figure**).

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Table. Clinical and radiographic summary of 5 patients with ALGS and associated moyamoya syndrome

Patient no.	Age at presentation, y	Sex	Clinical presentation	Suzuki grade at presentation	Surgical treatment	Complications	Clinical outcome	mRS score*
1	1.7	F	Episodes of numbness and weakness or right side; right hemiparesis	I/II	Bilateral pial synangiosis	Seizure	Neurologically intact	0
2	4	M	Left hemiparesis, loss of vision, aphasia; seizure	II/III	Bilateral pial synangiosis	None	Neurologically intact	0
3	3	M	Episode of left hemiparesis	II	Bilateral pial synangiosis	CSF leak	Neurologically intact	0
4	2	M	Episodes of right hemiparesis	N/A	Bilateral pial synangiosis	Stroke in PCA territories	Visual field deficit, mild left hand weakness	1
5	2	F	Right hemiparesis; headaches	V	Left EDAS	None	Fatal left thalamic hemorrhage	6

ADL, activities of daily living; *F*, female; *M*, male; *PCA*, posterior cerebral artery; *N/A*, not available.
*0 = no symptoms, 1 = minor symptoms not affecting lifestyle, 2 = minor handicap but independent in ADL, 3 = requiring some help with ADL, 4 = requiring substantial help with ADL, 5 = totally dependent.

All patients underwent an indirect cerebral revascularization procedure. One patient, treated at Denver Children's Hospital, underwent unilateral encephaloduroarteriosynangiosis (EDAS).[18,19] The remaining 4 patients underwent bilateral pial synangiosis, a modification of EDAS, at Boston Children's Hospital.[20,21] This procedure involves dissecting a branch of the superficial temporal artery from the scalp and suturing the vessel to the pial surface of the brain after craniotomy. The bone is replaced and the vessel is left in contact with the brain. Subsequent ingrowth of blood vessels from this donor vessel and the dural margins occurs over several months and leads to collateral blood flow to ischemic brain tissue. One patient underwent a single bilateral operation, and 3 of the patients had staged procedures over an approximate 1-month interval. All patients also received aspirin daily.

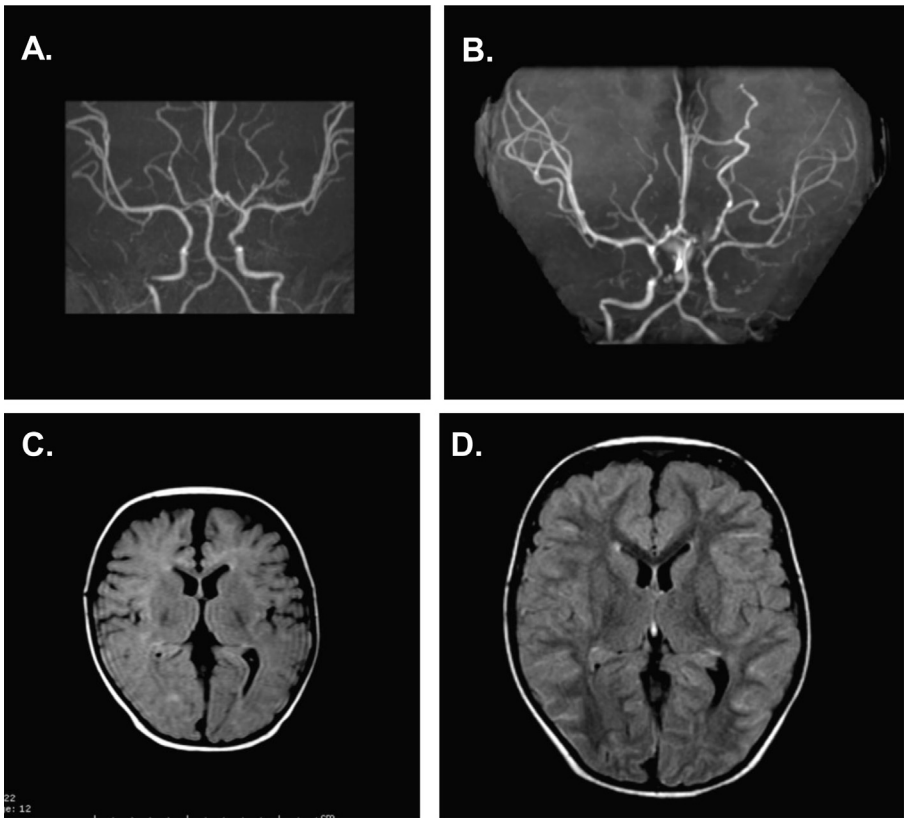

Figure. **A** and **B,** Magnetic resonance angiography and **C** and **D,** axial fluid-attenuated inversion recovery sequences from MRI of a child with ALGS during a 2-year period. **A** and **C,** Time zero; **B** and **D,** 2 years later. Note the progression in arteriopathy between **A** and **B** and the increased fluid-attenuated inversion recovery sulcal hyperintensity ("ivy sign," indicative of slowed cerebral blood flow) between **C** and **D**.