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Permalink

<https://escholarship.org/uc/item/3fx1x1pg>

Journal

Journal of Neurosurgery Pediatrics, 18(3)

ISSN

1933-0707

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Publication Date

2016-09-01

DOI

10.3171/2016.3.peds15694

Peer reviewed

## Indirect and direct revascularization of *ACTA2* cerebral arteriopathy: feasibility of the superficial temporal artery to anterior cerebral artery bypass with posterior auricular artery interposition graft: case report

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Mutations in the smooth muscle–specific isoform of alpha actin (*ACTA2*) cause smooth muscle dysfunction in arteries. This rare loss-of-function mutation may cause a diffuse occlusive cerebral arteriopathy, resulting in stroke. While *ACTA2* arteriopathy is often described as moyamoya-like, it has a distinct phenotype characterized by dilation of the proximal internal carotid artery (ICA) and occlusion of the terminal ICA and proximal middle cerebral artery. Intracranial arteries have an abnormally straight course, often with small aneurysms. There is limited experience with revascularization procedures for *ACTA2* arteriopathy, and the safety and efficacy of these procedures are unknown. In this paper the authors present a symptomatic 6-year-old patient with *ACTA2* cerebral arteriopathy who underwent both indirect revascularization and direct cerebrovascular bypass. Postoperatively, the patient suffered an ischemic infarct in a neighboring vascular territory. While direct cerebrovascular bypass is technically feasible, patients with *ACTA2* arteriopathy may be at increased risk for perioperative stroke compared with patients with moyamoya disease.

<http://thejns.org/doi/abs/10.3171/2016.3.PEDS15694>

**KEY WORDS** *ACTA2*; cerebral arteriopathy; indirect revascularization; cerebrovascular bypass; stroke; vascular disorders

**P**ATIENTS with mutation of the *ACTA2* gene (10q23.31) are predisposed to stenocclusive arterial disease throughout the vascular tree, including a diffuse cerebral arteriopathy.<sup>2,5–7</sup> This arteriopathy is frequently described as resembling moyamoya disease, although there are distinct clinical features in patients with *ACTA2* mutations.<sup>1</sup> Cerebral angiography reveals a characteristic dilation of the proximal internal carotid arteries (ICAs), occlusion of the terminal ICA and proximal middle cerebral arteries (MCAs), intracranial arteries with an abnormally straight course, and multiple small aneurysms.<sup>1</sup> Patients with *ACTA2* mutations lack the leptomeningeal collateral circulation that forms at the base of the brain in moyamoya disease.<sup>8</sup> While direct and indirect revascularization techniques are established forms of treatment for patients with moyamoya,<sup>3,10</sup> there are few reports of revascularization

procedures for patients with *ACTA2* arteriopathy. In their experience, Munot et al. observed a relatively high rate of postoperative ischemic stroke in children with *ACTA2* mutations who underwent revascularization surgery, suggesting these patients may be at high risk of perioperative stroke.<sup>8</sup> We report the 3-year follow-up of a patient with symptomatic *ACTA2* arteriopathy and the first case of direct cerebrovascular bypass, along with an indirect bypass in a different vascular territory.

### Case Report

#### Clinical Presentation and Imaging Studies

A 3-year-old girl with a history of congenital mydriasis, patent ductus arteriosus, and bladder dysfunction presented with an acute left-sided hemiparesis and was found to

**ABBREVIATIONS** ACA = anterior cerebral artery; AP = anteroposterior; ECA = external carotid artery; ICA = internal carotid artery; MAP = mean arterial pressure; MCA = middle cerebral artery; MIFA = middle internal frontal artery; PAA = posterior auricular artery; STA = superficial temporal artery.

**SUBMITTED** November 30, 2015. **ACCEPTED** March 2, 2016.

**INCLUDE WHEN CITING** Published online May 13, 2016; DOI: 10.3171/2016.3.PEDS15694.

have a right MCA ischemic infarct on MRI.<sup>1</sup> A cerebral angiogram at that time showed a diffuse cerebral arteriopathy involving the right MCA M<sub>1</sub> segment, with features consistent with an *ACTA2* arteriopathy (Amans et al. previously described the neuroradiological appearance of *ACTA2* arteriopathy using this patient's imaging;<sup>1</sup> Fig. 1). Genetic testing confirmed heterozygous Arg179His substitution. She subsequently underwent a revascularization procedure on the right side that consisted of a combined superficial temporal artery (STA) synangiosis and temporalis muscle onlay. She remained asymptomatic for several years, but at 6 years of age developed recurrent episodes of transient bilateral lower-extremity weakness. While MRI of her brain did not show evidence of acute infarction, a cerebral angiogram showed progression of the arteriopathy on both sides. The right anterior cerebral artery (ACA) disease had worsened to near occlusion. However, there was evidence of revascularization from the previous procedure primarily supplying the right MCA territory. In addition, there was additional collateral supply of the right hemisphere from an enlarged left middle meningeal dural artery (Fig. 2). She was prescribed midodrine hydrochloride and increased hydration, particularly at nighttime, but continued to experience transient lower-extremity weakness when awakening from sleep. The symptoms were attributed to transient ischemic attacks caused by reduced flow in the ACA territories. It was believed that a combined approach of both an indirect and direct revascularization of the ACA circulation would offer the best option to reduce the likelihood of permanent stroke.

#### Surgical Procedure

The patient was continued on midodrine hydrochloride and oral hydration as well as 81 mg of aspirin daily leading up to surgery. The day prior to surgery she was hydrated with 1.5-times her maintenance intravenous fluids. Her mean arterial pressure (MAP) was 77 mm Hg with a

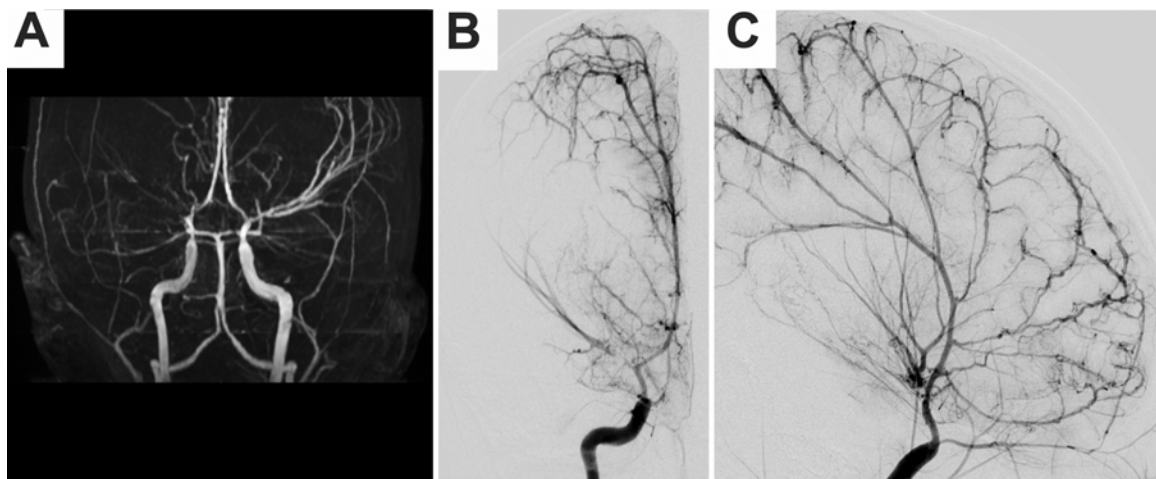
systolic blood pressure of 124 mm Hg immediately prior to induction of anesthesia.

The planned procedure was a left STA to ACA bypass using the left posterior auricular artery (PAA) as an interposition graft. Through a small bifrontal craniotomy and interhemispheric approach, an end-to-side anastomosis was created using the PAA to a branch of the ACA. Then, an end-to-end anastomosis was created from the STA to the interposition graft. Care was taken to preserve existing collaterals. After the direct bypass was performed, a second craniotomy was made for a temporalis muscle onlay over the left temporal lobe (Fig. 3). At the conclusion of the operation, patency of the bypass graft was confirmed with indocyanine green video angiography and Doppler ultrasonography.

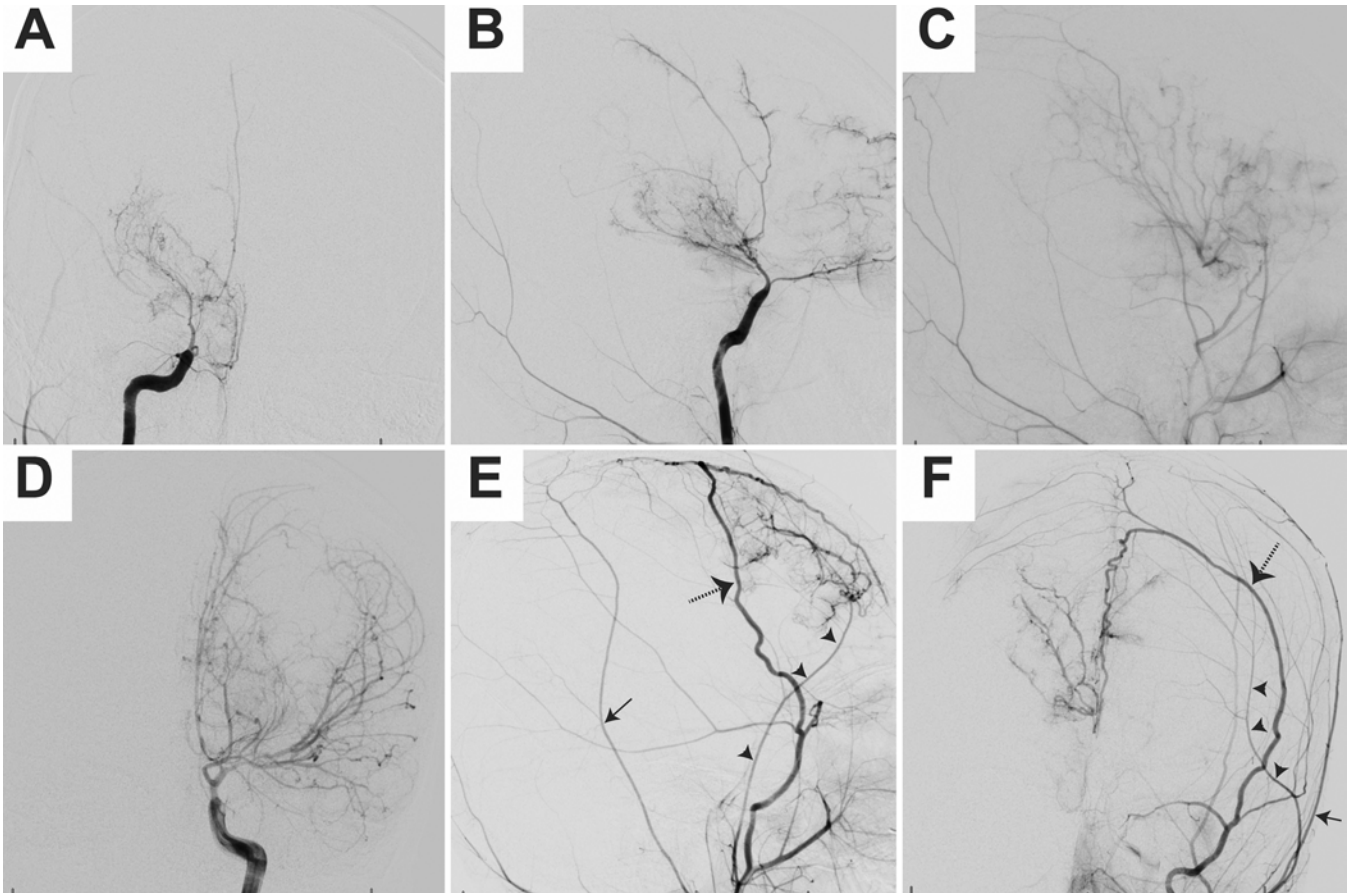
Throughout the surgery, her MAP was maintained between 70 and 80 mm Hg with a combination of vasopressors (dopamine 2–10 µg/kg/min and occasionally phenylephrine 5–20 mg/min) and intravenous fluids. Total anesthesia duration was approximately 10 hours, surgery duration was approximately 8 hours, and temporary artery occlusion duration was 46 minutes.

#### Postoperative Course

The patient was monitored in the intensive care unit and administered 81 mg of aspirin immediately following the operation. Midodrine hydrochloride and intravenous fluids were administered to maintain MAP > 65 mm Hg. Occasional fluid boluses were required to meet these blood pressure targets, but pharmacological vasopressors were not. On postoperative Day 3 she developed acute onset of right-sided hemiparesis and expressive aphasia. An MR image of the brain demonstrated a large acute ischemic infarction involving a portion of the left anterior ACA territory, the anterior superior division of the MCA, and the MCA-ACA watershed areas, as well as acute punctate infarcts in the left putamen and right caudate head.



**FIG. 1.** Imaging on initial presentation at 3 years of age. **A:** A 3D MR angiogram reconstruction demonstrating characteristic findings of *ACTA2* angiopathy with dilation of bilateral cavernous ICA segments, stenocclusive disease of bilateral carotid arteries (worse on the right), and straightening of the vascular tree. **B and C:** Anteroposterior (AP) and lateral projection angiograms of the right ICA demonstrating high-grade stenosis of the supraclinoid ICA and ACA A<sub>1</sub> segment, and occluded MCA M<sub>1</sub> segment. Only filling of the right ACA circulation is noted on the lateral projection (C).



**FIG. 2.** Cerebral angiography on follow-up at 6 years of age. **A and B:** AP and lateral projection angiograms of the right ICA demonstrating interval progression of occlusive disease with near occlusion of the supraclinoid ICA and A<sub>1</sub> segment. Minimal reconstitution of the right pericallosal artery is observed. **C:** Right external carotid artery (ECA) angiogram demonstrating excellent leptomeningeal collateralization from the indirect bypass, supplying the entire right MCA circulation. **D:** AP projection angiogram of the left ICA with severe stenosis involving the left supraclinoid ICA, left MCA, and ACA. There is interval progression in the left-sided circulation. **E and F:** Lateral and AP projection angiograms of the left ECA showing an enlarged left middle meningeal artery supplying falcine collaterals to the right ACA circulation (*dotted arrow*). The STA frontal branch (*arrowheads*) and PAA (*solid arrow*) are also identified.

A CT angiogram 2 months after surgery showed progressive attenuation of the distal ACA and MCA vasculature, consistent with worsening vasculopathy, but the direct bypass remained patent, indicating that the perioperative stroke was not related to thrombosis of the graft (Fig. 4). An angiogram was not performed postoperatively given the risks (Munot et al. reported a case of severe lower limb ischemia after femoral artery puncture<sup>8</sup>). With rehabilitation, her hemiparesis improved, but she has a persistent partial expressive dysphasia.

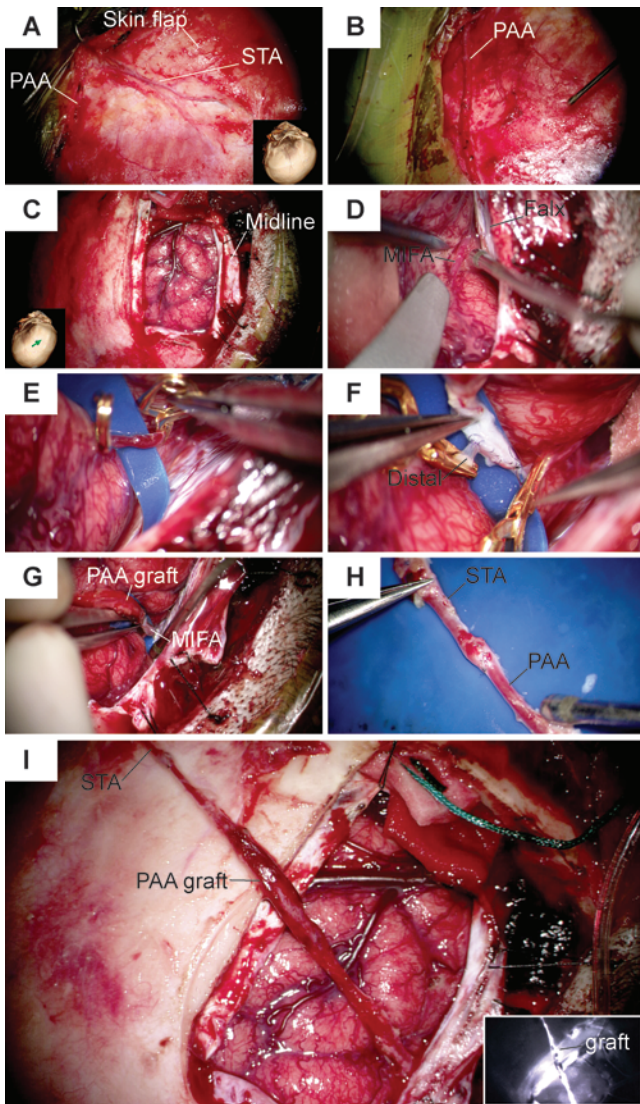
## Discussion

Mutations in the *ACTA2* gene cause smooth muscle dysfunction and an occlusive cerebral arteriopathy, often resulting in stroke in children. It is important to distinguish this arteriopathy from moyamoya disease, as patients with *ACTA2* mutations have other systemic manifestations, such as thoracic aortic aneurysms, that require evaluation and management. The cerebrovascular abnormalities

in *ACTA2* arteriopathy are also different from those seen in moyamoya disease. There is a characteristic fusiform dilation of the cavernous to clinoid segment of the supraclinoid ICA, with coexisting stenosis or occlusion. This focal ICA dilation, presumably due to focal weakness of the vessel wall, is not noted with moyamoya disease.<sup>7</sup> Genetically, the conditions do not appear to be related, based on the absence of nonsynonymous mutations in *ACTA2* in patients with nonfamilial moyamoya disease.<sup>4,9,11</sup>

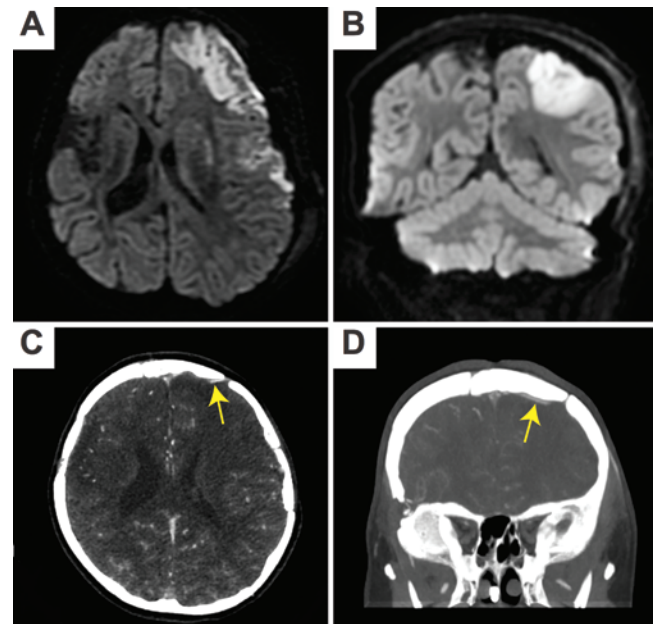
While revascularization is safe and effective in patients with moyamoya disease, the few reports describing revascularization surgery for patients with an *ACTA2* mutation consist of indirect bypass procedures. In a report of 3 patients who underwent indirect revascularization surgery, 2 had postoperative strokes. This report, along with our experience, suggests these patients may be at higher risk for perioperative ischemia.<sup>8</sup>

The patient presented first underwent indirect revascularization at 3 years of age. Because the patient did experience a good revascularization response to her initial



**FIG. 3.** Intraoperative photographs. **A and B:** Dissection of the STA and PAA. **C:** Bifrontal craniotomy. **D and E:** Middle internal frontal artery (MIFA) in the interhemispheric fissure. **F and G:** End-to-side anastomosis between the MIFA and the posterior auricular graft. **H:** End-to-end anastomosis between the PAA and STA. **I:** Patent STA-PAA-ACA bypass and indocyanine green videoangiography (*inset*).

indirect bypass procedure on the right side, an isolated indirect procedure on the left side was considered. However, because she was having reproducible and escalating signs of bilateral ACA oligemia, a direct bypass in addition to the indirect procedure was believed to be her best option for immediate restoration of blood flow. Additionally, indirect revascularization techniques are not as favorable at the vertex where there are fewer and less-vascular tissues available for onlay grafting (i.e., pericranium), as compared with the lateral convexity. Prior to her second revascularization surgery, it was unclear if her vasculature was amenable to direct bypass based on the small caliber and anticipated quality of the arterial tissue. *ACTA2* mutations result in intracranial vessels with extremely thin,



**FIG. 4.** Postoperative imaging. **A and B:** Axial and coronal diffusion-weighted imaging demonstrating an acute infarct in the left ACA territory and left ACA-MCA watershed zone. A few punctate infarcts are also observed in the left putamen. **C and D:** CT angiography demonstrating patency of the bypass graft (*arrows*).

fragile walls. This was evident when performing her bypass, although an interposition graft allowed for a tension-free anastomosis. This case is significant in demonstrating that direct extracranial-intracranial bypass can be performed in patients with *ACTA2* mutations. Arteries on the paramedian convexity were too small for direct bypass, but dissecting into the interhemispheric fissure identified a recipient artery with sufficient caliber, which increases the anastomotic depth and difficulty. ACA vessels were indeed fragile, but gentle bites with the needle and suture taken separately from the bites in normal scalp artery avoided tension on the needle, suture pullouts, and tears. The midline location of this bypass necessitated an interposition graft with the PAA, which is unusual. In most cases, the STA bifurcates and the second limb can be used as an interposition graft instead. Scalp arteries typically have a serpentine morphology that can be straightened to reach distant recipients, but the STA and PAA were linear in this patient and unable to elongate. The STA and PAA were otherwise entirely normal in their appearance and handling. These arteries are small and an interposition graft makes it long, but “fish-mouthing” their end-to-end anastomosis helps minimize resistance. The feasibility of this STA-PAA-ACA bypass demonstrates that direct bypasses can be used in *ACTA2* patients, perhaps more commonly with MCA recipients. Sylvian fissure dissection to larger recipients might make this bypass more difficult, but interposition grafts should not be necessary.

Although technically successful, her second revascularization procedure was complicated by an ischemic infarct involving the left anterior ACA, MCA territory, and border zone areas. Steps to prevent ischemia included the

following: Brainlab neuronavigation and Doppler ultrasonography to avoid transection of a large, native extracranial-to-intracranial carotid artery collateral on the scalp; electroencephalography burst suppression during temporary intracranial clamping; preoperative and early postoperative administration of aspirin; and maximizing cerebral perfusion with continuous blood pressure monitoring and avoidance of dehydration. While the patient did not have an optimal outcome, the technical feasibility of direct cerebrovascular bypass is demonstrated, and arguably the direct bypass prevented an even larger postoperative infarct involving the medial frontal lobe. While patients with *ACTA2* mutations appear to be at high risk for perioperative stroke, early consideration of direct or indirect bypass procedures, prior to the loss of cerebrovascular reserve capacity, may allow for a safer surgery.

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## Disclosures

Dr. Lawton has served as a consultant for Zeiss and has received royalties from Mizuho America.

## Author Contributions

Conception and design: Lawton, Rutledge. Drafting the article: Rutledge, Choudhri, Walcott, Benet. Critically revising the article: Lawton, Choudhri, Walcott, Benet, Fox, Gupta. Reviewed submitted version of manuscript: Lawton, Rutledge. Approved the final version of the manuscript on behalf of all authors: Lawton. Study supervision: Lawton.

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