pediatric stroke

Case Report

Acute Ischemic Stroke in an Infant Secondary to *ABCC6*-related Generalized Arterial Calcification of Infancy

Rachelle Herring, M.D.[a], Allyson Schenk, M.P.H.[b], Jo Tilley, D.N.P, C.P.N.P [a,e], Joel Steelman, M.D.[c], Ariel Brautbar, M.D.[d], Marcela Torres, M.D.[e]

a. Neurology Department, Cook Children's Medical Center
1500 Cooper St, Fort Worth, TX, 76104, USA

b. Research Data Science and Analytics, Cook Children's Medical Center
901 7th Avenue, Fort Worth, TX 76104, USA

c. Endocrinology Department, Cook Children's Medical Center
1500 Cooper St, Fort Worth, TX, 76104, USA

d. Department of Genetics, Joe DiMaggio Children's Hospital
1005 N 35th Ave., Hollywood, FL, 33021, USA

e. Hematology Department, Cook Children's Medical Center
1500 Cooper St, Fort Worth, TX, 76104, USA

Corresponding Author: Rachelle Herring, M.D.
Mailing Address: 1500 Cooper St, Fort Worth, TX, 76104, USA
Work Phone: 682-885-2500
Email: Rachelle.Herring@cookchildrens.org

pediatric stroke

Case Report

Abstract
Generalized arterial calcification of infancy (GACI) is a rare autosomal-recessive disorder caused by mutations in *ENPP1*, a gene involved in the generation of pyrophosphate. Mutations in *ABCC6* have also been reported. Arterial calcification and stenosis are characteristic of GACI, and often result in heart failure by six months of age. We describe a unique case of arterial ischemic stroke caused by *ABCC6*-associated GACI due to calcification of the cerebral arteries.

Introduction
Generalized arterial calcification of infancy (GACI) is a rare autosomal-recessive disorder characterized by calcification and stenosis of large- and medium-sized arteries throughout the body. GACI is most commonly caused by mutations in *ENPP1*, and more recently has been associated with *ABCC6* mutations.[1] Disrupted function of either gene is thought to interrupt production of inorganic pyrophosphate (PPi), a key inhibitor of hydroxyapatite crystal deposition, leading to vascular calcification, vessel intimal proliferation, and ectopic calcifications.[2] While the cerebral arteries are generally spared, their involvement can result in ischemic stroke.[3-4] This is the first case report describing a patient with acute arterial ischemic stroke secondary to *ABCC6*-associated GACI.

Case Report
A previously healthy 2-month-old female born full-term without complications, presented to the emergency department with hemi-clonic seizures. Magnetic resonance imaging (MRI) of the brain and neck revealed multifocal infarcts in the right middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) territories (Figure 1). Computed tomography (CT) showed calcification of the cavernous internal carotid arteries (ICAs), left vertebral artery, and common femoral arteries (Figure 2). Ultrasonography (US) confirmed arterial calcifications extending into the bilateral upper extremities (BUE), bilateral lower extremities (BLE), and renal arteries (Figure 3). Echocardiogram was normal.

Stroke etiologic workup to include infectious, inflammatory, and endocrinologic etiologies included a complete metabolic panel, phosphorus, vitamin D, parathyroid hormone, thyroid-stimulating hormone levels, erythrocyte sedimentation rate, and C-reactive protein, all of which were normal. Cerebrospinal fluid profile was unremarkable with negative herpes simplex virus polymerase chain reaction. Respiratory pathogen panel was positive for coronavirus (non-SARS CoV-2). Acetylsalicylic acid and oxcarbazepine were started for secondary stroke and seizure prevention, respectively.

A genetic disorder was suspected given the distinct calcification noted on her radiological imaging. Targeted genetic testing of the proband revealed compound heterozygous variants in the *ABCC6* gene:

c.742C>T (p.Leu248Phe) and c.2294G>T (p.Arg765Leu). Parental testing confirmed trans configuration, consistent with GACI. Following genetic confirmation, she was started on Sodium thiosulfate (STS), a calcium chelating agent shown to reverse calcification in other disorders. Intravenous STS (12.5 g/m^2) was initially given 3 days/week for the first 2 weeks and subsequently increased to 5 days/week.

Serial imaging assessments were performed throughout her treatment (Table 1). The timing of follow up imaging was based on conversations between the multidisciplinary team and the patient's family to allow time for changes to develop while balancing the risks of repeat radiation and/or sedation. Brain MRIs and CTs confirmed there was no new stroke or change in the intracranial calcifications. US showed decrease/resolution of calcifications in other arterial beds. STS treatment was used for 15 months, but ultimately discontinued due to recurrent central line infections, improvement in arterial calcification burden on US imaging, and continued absence of cardiac involvement. Periodic surveillance imaging is planned at a 6-12 month frequency while continuing clinical monitoring, and repeat treatment with STS or bisphosphonate could be considered if clinically indicated. The patient has continued prophylactic acetylsalicylic acid.

Discussion

GACI is genetically related to the disorder pseudoxanthoma elasticum (PXE). While both disorders are caused by mutations in *ABCC6* and *ENPP1*, PXE presents after 5 years old with distinct eye and skin findings along with arterial narrowing, frequently involving the cerebrovascular arteries, thereby increasing risk of stroke. [5] Literature regarding stroke in *ABCC6*-associated GACI is sparse. In our review, we found only one study reporting stroke in 4 ABCC6-deficient patients. However, the study did not describe stroke type or how many of these cases were isolated GACI versus PXE or a combination of both phenotypes. Patients with ABCC6 and ENPP1-deficiencies had similar rates of cerebral arterial involvement, but stroke was more frequent in ABCC6 deficiency. [4]

Patients with GACI often suffer cardiac-related mortality by six months of age, highlighting the importance of early diagnosis. The serious nature and often fatal outcome in GACI strongly favors attempting treatment in diagnosed infants. While data remains limited regarding treatment, bisphosphonates and STS have been postulated to slow or even reverse arterial calcification. [3] STS was administered in our patient due to unavailability of oral bisphosphonates and reported efficacy in a case of *ABCC6*-associated GACI. [6]

At 2 years of age, she is the second case of GACI with successful reduction in systemic arterial calcification while receiving STS. Although reversal was not seen in the intracranial arterial calcifications, they remained stable even after STS was discontinued and no additional strokes have occurred. New

coronary artery calcifications were detected on chest CT after STS was discontinued, but it is unclear if these were missed by prior echocardiograms. Cardiac function as assessed by echocardiography remains normal.

Neurologists should be aware of this rare cause of stroke. Any evidence of pediatric arterial calcifications necessitates prompt investigation into other organ involvement, consideration of genetic testing, and the potential for therapeutic intervention.

References

[1] Li Q, Brodsky JL, Conlin LK, et al. Mutations in the ABCC6 gene as a cause of generalized arterial calcification of infancy: Genotypic overlap with pseudoxanthoma elasticum. *Journal of investigative dermatology.* 2014;134(3):658-665. doi:10.1038/jid.2013.370.

[2] Jansen RS, Küçükosmanoglu A, de Haas M, et al. ABCC6 prevents ectopic mineralization seen in pseudoxanthoma elasticum by inducing cellular nucleotide release. *Proceedings of the National Academy of Sciences - PNAS.* 2013;110(50):20206-20211. doi:10.1073/pnas.1319582110.

[3] Boyce AM, Gafni RI, Ferreira CR., et al. Generalized arterial calcification of infancy: New insights, controversies, and approach to management. *Current osteoporosis reports.* 2020;18(3):232-241. doi:10.1007/s11914-020-00577-4.

[4] Ferreira CR, Kintzinger K, Hackbarth ME, et al. Ectopic Calcification and Hypophosphatemic Rickets: Natural History of ENPP1 and ABCC6 Deficiencies. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*. November 2021; 36(11):2193-2202. doi: 10.1002/jbmr.4418.

[5] Uitto J, Jiang Q, Váradi A, Bercovitch LG, Terry SF. Pseudoxanthoma elasticum: diagnostic features, classification and treatment options. *Expert opinion on orphan drugs.* 2014;2(6):567-577. doi:10.1517/21678707.2014.908702.

[6] Donuru A, Kandula V, Oliver E, Saul D. Generalized arterial calcification of infancy. *Radiology: Cardiothoracic Imaging.* 2020 Aug; 2(4):e190226. doi: 10.1148/ryct.2020190226.