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Clinical Observations

Reversible Cerebral Vasoconstriction Syndrome: A Novel Mechanism for Neurological Complications in Schimke Immuno-osseous Dysplasia

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ABSTRACT

Background: Schimke immuno-osseous dysplasia is a rare autosomal recessive disease resulting from biallelic SMARCAL1 mutations. It presents in early childhood and is characterized by short stature, nephropathy, and immunodeficiency. Approximately 50% of those affected have neurological complications including migraines, transient ischemic attacks, and strokes.
Methods: We present a six-year-old boy with Schimke immuno-osseous dysplasia without evidence of atherosclerosis with recurrent episodes of severe headache, fluctuating hemiparesis, and aphasia.
Results: Magnetic resonance imaging and angiography were normal during the initial episode; multiple areas of reversible restricted diffusion with decreased perfusion and arterial stenosis were seen with subsequent attacks.
Conclusions: This constellation of symptoms and imaging findings is suggestive of reversible cerebral vasoconstriction syndrome, which we propose as a mechanism for the transient ischemic attacks and infarcts seen in some patients with Schimke immuno-osseous dysplasia, as opposed to accelerated atherosclerosis alone. This new insight may provide a basis for novel preventative therapy in this rare disorder.

Introduction

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disease with an estimated prevalence of 1:1-3,000,000 live births.[1] It is characterized by a triad of short stature, nephropathy, and immunodeficiency. SIOD is complicated by transient ischemic attacks (TIAs) of uncertain pathophysiology, previously hypothesized to be secondary to accelerated atherosclerosis in combination with systemic hypertension.[1-3] Kilic et al. proposed that SMARCAL1 mutations are associated with disruptions in immunologic homeostasis, leading to inflammation and vascular reactivity,[4] as SMARCAL1, which is responsible for chromatin remodeling and is highly expressed in human and mouse neuroprogenitor cells and neurons.[5] We present a 6-year-old boy with severe SIOD with progression from migraines to TIAs, infarcts, and seizures in whom imaging showed reversible cerebral vasoconstriction syndrome (RCVS).

Patient Description

This boy presented at 21 months with failure to thrive. He was subsequently diagnosed with focal segmental glomerular sclerosis which progressed rapidly to end-stage renal disease. The diagnosis of SIOD was made at 3.5 years with the demonstration of two pathogenic mutations in SMARCAL1 (c.2291G>A and c.1910T>C). At age five years, he presented with right-sided hemiplegia and dysarthria after a severe headache; blood pressure on arrival was at the 50% for age and habitus, although later on admission it was

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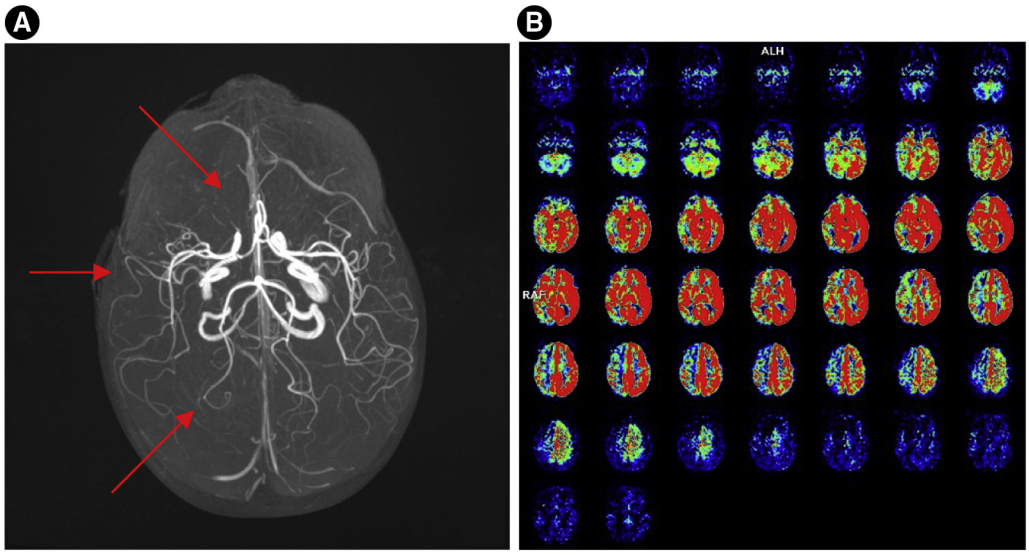

FIGURE 1. Magnetic resonance angiography and arterial spin labeling in a six-year-old boy with Schimke immuno-osseous dysplasia. Images are from the day of presentation of his second lifetime attack, presenting with severe headache, left-sided weakness, and aphasia. (A) Magnetic resonance angiography demonstrating pruning of the right middle cerebral artery branches (see arrows). (B) Arterial spin labeling images with decreased relative cerebral blood flow in the right cerebral hemisphere. The color version of this figure is available in the online edition.

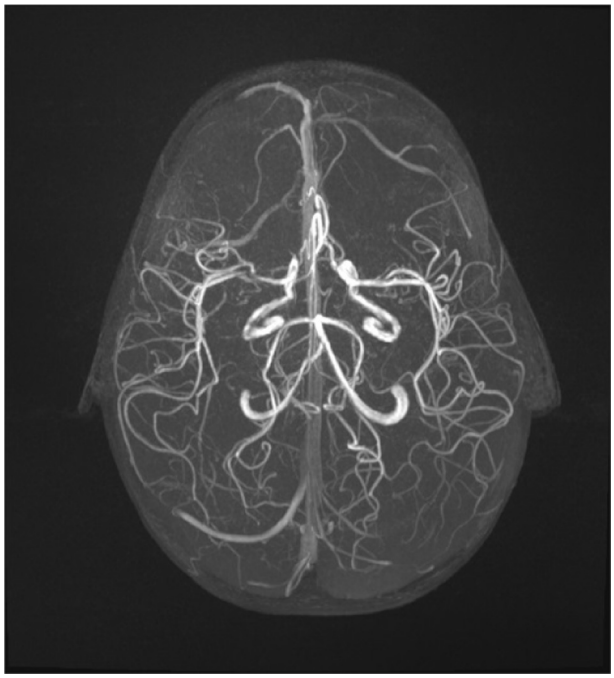

FIGURE 2. Magnetic resonance angiography. Images are from the day following those shown in Fig 1, demonstrating increased caliber for the right hemispheric arteries with a new focal narrowing of the right middle cerebral artery bifurcation.

increased. Limited magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head and neck were normal; no perfusion imaging was performed. Electroencephalography showed left temporoparietooccipital slowing, perhaps suggestive of left hemispheric dysfunction related to decreased perfusion. His echocardiogram and hypercoagulable evaluation were normal. Diagnosis on discharge was TIA, and aspirin was started for secondary prevention. Daily valproic acid was also initiated for headache prophylaxis given his intermittent mild headaches in the preceding year; however, it was soon tapered because of behavioral side effects.

Six months later, he presented with left-sided weakness, aphasia, and disabling headache in the setting of hypertension. MRI initially demonstrated multifocal restricted diffusion in the right hemisphere along with corresponding diminished relative cerebral blood flow on arterial spin labeling imaging; MRA showed peripheral branch narrowing of right anterior, middle, and posterior cerebral arteries (Fig 1A,B). Imaging the next day demonstrated increased areas of restricted diffusion within the right hemisphere but improved visualization of distal middle cerebral and posterior cerebral branches (Fig 2). Given the potential for RCVS, verapamil was introduced to target vasospasm, and his aspirin was continued. Over the next week, there was complete resolution of symptoms with improved perfusion imaging on discharge (Fig 3).

In the following months, he presented with increasing frequency of severe headaches and alternating hemiplegia. With milder episodes of less severe weakness and more rapid return to baseline, imaging did not show diffusion changes, and only subtle vasoconstriction correlating to the side of hemiplegia. Blood pressures were moderately increased to 90% to 95% for age and habitus. His most recent presentation was the most severe, consisting of right hemiplegia, aphasia, and hemiclonic seizures, progressing to status epilepticus. On presentation, blood pressure was increased and the patient was febrile. MRI showed multifocal bilateral nonconfluent patchy restricted diffusion, predominantly posteriorly, left more than right, which progressed to the entire left hemisphere days later. MRA and arterial spin labeling imaging could not be obtained because of the severity of illness. He was discharged to hospice with persistent symptoms. Togther the occurrence of reduced cerebral blood flow, multifocal reversible branch vessel narrowing, headaches, fluctuating hemiparesis and seizures suggests RCVS perhaps on a background of posterior reversible encephalopathy syndrome.

Discussion

SIOD was first described by Schimke et al.[6] and later named by Spranger et al.[7] Virtually all individuals have short stature and progressive nephropathy and 75% experience spondyloepiphyseal

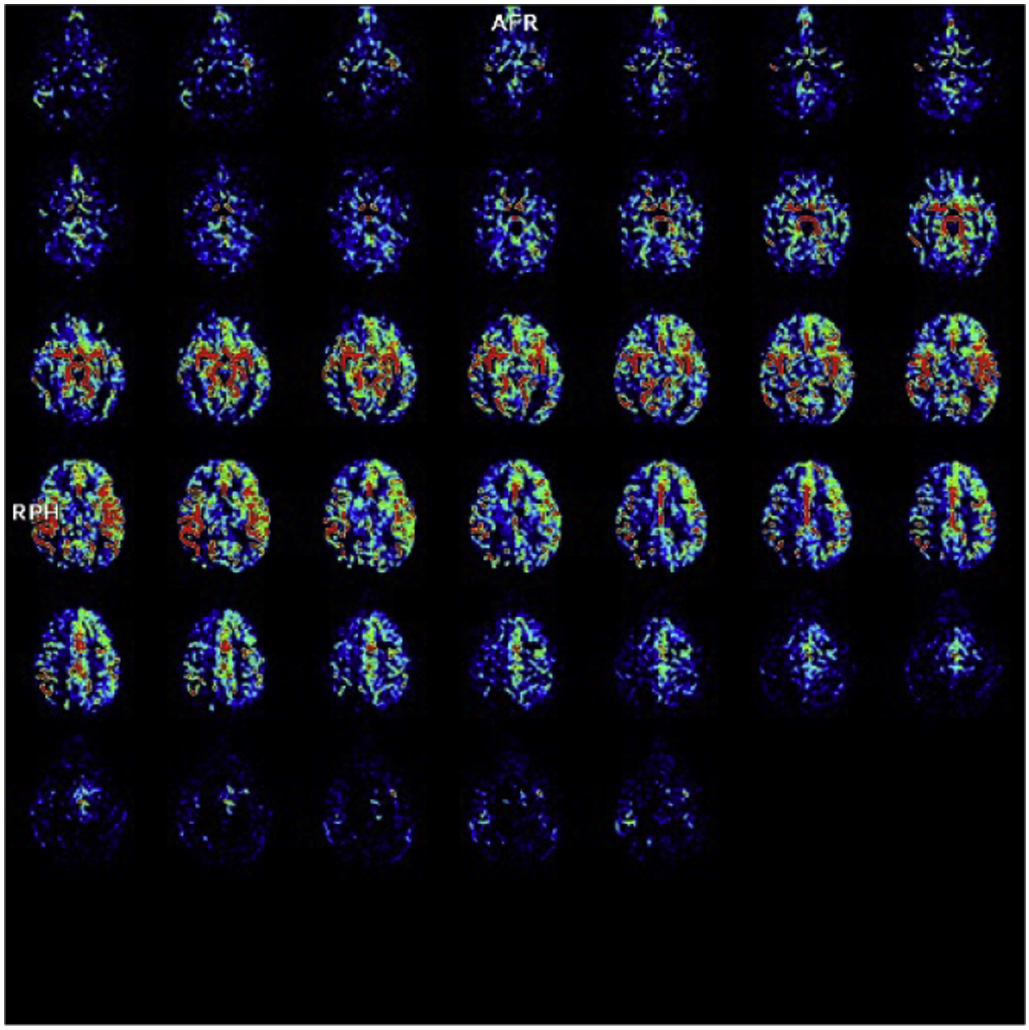

FIGURE 3. Arterial spin labeling images with asymmetric blood flow, diminished on right, although improved from initial study from on week after Fig 1. The color version of this figure is available in the online edition.

dysplasia and T-cell immunodeficiency. Other features include growth failure, characteristic facies, hyperpigmented macules,[8,9] and neurological complications (in 50%).[1,3,4] Presentation ranges from early onset with death within four to eight years from diagnosis to the later-onset form with individuals surviving to adulthood with renal transplantation.[1,9] The diagnosis is confirmed by genetic testing, demonstrating biallelic pathogenic mutations in SMARCAL1.[10]

The neurological complications were first described by Ehrich et al.[3] Despite subsequent advances, the neuropathophysiology is still poorly understood. We suggest RCVS as a contributing factor in this syndrome, given the severe recurrent headaches and alternating hemiplegia with MRI showing corresponding areas of patchy reversible restricted diffusion, diminished perfusion, and reversible arteriopathy in our patient. RCVS is a clinicoradiologic syndrome characterized by "thunderclap" headaches with or without neurological symptoms, in the setting of diffuse segmental constriction of cerebral arteries, which typically resolves within 3 months.[11-14] RCVS may be complicated by subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, and hemorrhagic or ischemic infarcts.[11] It is rare in children[12,15-17] and has not been reported in SIOD.

Ehrich et al. described about three children with SIOD and TIAs with shifting areas of decreased perfusion on positron emission tomography; no MRI or vascular imaging was included.[3] Sigurdardottir et al.[18] described a teenager with stepwise developmental regression and worsening seizures; this patient's MRI showed biparietal encephalomalacia and narrowing of middle cerebral artery branches. Subsequent studies reported patients with narrowing and irregularity of intracranial vessels, suggestive of diffuse atherosclerosis or moyamoya disease.[2,9,19] In 2005, Kilic et al. published a series in which 13 of 29 patients had severe, recurrent migraine-like headaches without mention of neurological findings. Six had abnormal MRIs.[4] One of five children with abnormal angiography had reversible vascular stenosis during cerebral attacks.[4] Our patient with reversible perfusion deficits and vascular changes, along with these prior observations, suggests that the severe migraine-like headaches, TIAs, and infarcts could be more of a spectrum rather than two distinct phenomena in SIOD patients. We posit that RCVS may act as a bridge between the two, either independently or in conjunction with atherosclerosis.

On the basis of the review of the literature and this experience, we recommend early MRI with vessel imaging and perfusion studies, before neurological symptoms, for all SIOD

patients. Revascularization procedures have been performed in asymptomatic SIOD patients with silent infarcts and intracranial atherosclerosis.[20] Risk factor management of hyperlipidemia, hypertension, and prophylactic anti-thrombotic medication is indicated.[5,19] Given the possible etiology of RCVS, the use of calcium channel blockers may be beneficial, although it did not seem particularly helpful for our patient. In prior patients, the vasodilatory agents minoxidil and pentoxyphilline were temporarily effective in preventing attacks.[3,4] More research is needed regarding the connection between RCVS and SIOD to discover new treatments and slow disease progression.

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