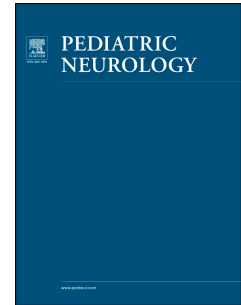


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Reversible Cerebral Vasoconstriction Syndrome: A novel mechanism for neurologic complications in Schimke Immuno-osseous Dysplasia

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Title: Reversible Cerebral Vasoconstriction Syndrome: A novel mechanism for neurologic complications in Schimke Immuno-osseous Dysplasia.

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Abstract

Background: Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disease secondary to biallelic SMARCAL1 mutations, characterized by short stature, nephropathy and immunodeficiency, presenting in early childhood. Approximately 50% of those affected have neurological complications including migraines, transient ischemic attacks, and strokes.

Case: We present a six-year-old SIOD patient without evidence of atherosclerotic disease with recurrent episodes of severe headache, fluctuating hemiparesis and aphasia. Magnetic resonance imaging/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 SIOD, as opposed to accelerated atherosclerosis alone. This new insight may provide a basis for novel preventative therapy in this rare disorder.

Key Words: stroke, pediatrics, Schimke immuno-osseous dysplasia, transient ischemic attack, reversible cerebral vasoconstriction syndrome

Introduction

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disease with an estimated prevalence of 1:1-3,000,000 live births¹, characterized by a triad of short stature, nephropathy, and immunodeficiency. SIOD is complicated by transient ischemic attacks (TIA) of uncertain pathophysiology, previously hypothesized to be secondary to accelerated atherosclerosis in combination with systemic hypertension¹⁻³. Kilic, proposed that SMARCAL1 mutations are associated with disruptions in immunologic homeostasis, leading to inflammation

and vascular reactivity⁴, as SMARCAL1, which is responsible for chromatin remodeling, is highly expressed in human and mouse neuro-progenitor cells and neurons⁵. We present a six-year-old boy with severe SIOD with progression from migraines to TIAs, infarcts, and seizures in whom imaging showed reversible cerebral vasoconstriction syndrome (RCVS).

Case

The patient presented at 21 months for failure to thrive and was subsequently diagnosed with focal segmental glomerular sclerosis progressing rapidly to end stage renal disease. The diagnosis of SIOD was made at 3.5 years with two pathogenic mutations in SMARCAL1 (c.2291G>A and c.1910T>C). At 5 years, the patient presented with right sided hemiplegia and dysarthria following a severe headache; blood pressure on arrival was at the 50% for age and habitus though later in admission became elevated. Limited magnetic resonance imaging and angiography (MRI and MRA) of the head and neck were normal; no perfusion imaging was performed. Electroencephalogram showed left temporo-parieto-occipital slowing, perhaps suggestive of left hemispheric dysfunction related to decreased perfusion. Echocardiogram and hypercoagulable work up were normal. Diagnosis on discharge was TIA and aspirin was started for secondary prevention. Daily valproic acid was also initiated for headache prophylaxis given intermittent mild headaches in the preceding year, however was tapered off shortly thereafter for behavioral side effects.

Six months later, the patient presented with left sided weakness, aphasia, and disabling headache in the setting of hypertension. MRI initially demonstrated multi-focal restricted diffusion in the right hemisphere along with corresponding diminished relative cerebral blood flow on arterial spin labeling (ASL) imaging; MRA showed peripheral branch narrowing of right anterior, middle, and posterior cerebral arteries (Figure 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 (Figure 2). Given the

potential for RCVS, verapamil was introduced to target vasospasm, in addition to his current aspirin. Over the next week, there was complete resolution of symptoms with improved perfusion imaging on discharge (Figure 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 elevated to 90-95% for age and habitus. His most recent presentation was the most severe, consisting of right hemiplegia, aphasia and hemi-clonic seizures, progressing to status epilepticus. On presentation, blood pressure was elevated and the patient was febrile. MRI showed multifocal bilateral non-confluent patchy restricted diffusion, predominantly posteriorly, left more than right, which progressed to the entire left hemisphere days later. MRA and ASL imaging could not be obtained due to the severity of illness. He was discharged to home hospice with persistent symptoms. Overall, these findings of reductions in cerebral blood flow with corresponding multifocal reversible branch vessel narrowing with headaches, fluctuating hemiparesis, and seizures suggest RCVS perhaps on a background of posterior reversible encephalopathy syndrome.

Discussion

SIOD was first described by Schimke in 1971,⁶ and later named by Spranger in 1991⁷. Virtually all individuals have short stature and progressive nephropathy with 75% displaying spondyloepiphyseal dysplasia and T-cell immunodeficiencies. Other features include growth failure, characteristic facies, hyperpigmented macules,^{8,9} and in 50% neurologic complications^{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 SMARCA1¹⁰.

The neurological complications were first described by Ehrich in 1995³. Despite subsequent advances, the neuro-pathophysiology 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 clinico-radiologic 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 months¹¹⁻¹⁴. RCVS may be complicated by subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, and hemorrhagic or ischemic infarcts¹¹. It is rare in children^{12,15-17} and has not been reported in SIOD.

Ehrich described three children with SIOD and TIAs with shifting areas of decreased perfusion on positron emission tomography; no MRI or vascular imaging was included³. Sigurdardottir described a teenager with step-wise developmental regression and worsening seizures, where MRI showed biparietal encephalomalacia and narrowing of middle cerebral artery branches¹⁸. Subsequent studies reported patients with narrowing and irregularity of intracranial vessels, suggestive of diffuse atherosclerosis and Moyamoya disease^{2,9,19}. In 2005, Kilic published a series, where 13 of 29 patients had severe, recurrent migraine-like headaches without mention of neurologic findings. Six had abnormal MRIs⁴. One of five children with abnormal angiography had reversible vascular stenosis during cerebral attacks⁴. Our case, with reversible perfusion deficits and vascular changes along with these prior observations, suggest that the severe migraine-like headaches, TIAs, and infarcts are 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.

Based on review of the literature and this experience, we recommend early MRI with vessel imaging and perfusion studies, prior to neurological symptoms, for all SIOD patients. Revascularization procedures have been performed in asymptomatic SIOD patients with silent infarcts and intracranial atherosclerosis²¹. Risk factor management of hyperlipidemia, hypertension, prophylactic anti-platelet/thrombotic medication is indicated^{5,19}. Given the possible etiology of RCVS, the use of calcium channel blockers may be beneficial though did not seem particularly helpful for our patient. In prior cases, the vasodilatory agents minoxidil and pentoxifyllin were temporarily effective in preventing attacks^{3,4}. More research is needed regarding the connection between RCVS and SIOD in order to discover new treatments and slow disease progression.

Conflicts of Interest: The authors declare no conflicts of interest.

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Figure 1

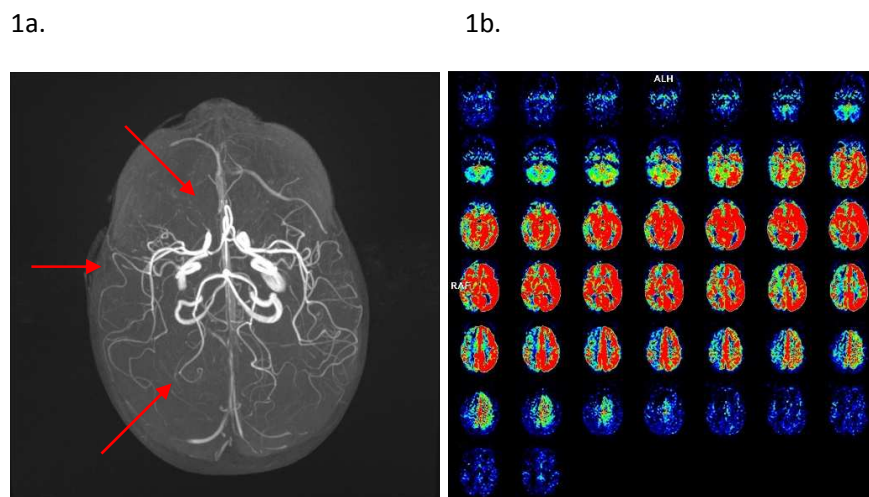


Figure 2



Figure 3

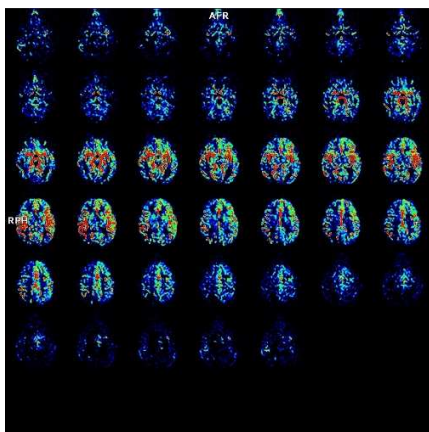


Figure 1: Magnetic resonance angiography and arterial spin labeling in a 6-year-old male with Schimke immuno-osseous dysplasia (SIOD). Images are from the day of presentation of his second lifetime attack, presenting with severe headache, left sided weakness and aphasia.

Figure 1a. Magnetic resonance angiography demonstrating pruning of the right middle cerebral artery branches (see arrows).

Figure 1b. Arterial spin labeling images with decreased relative cerebral blood flow in the right cerebral hemisphere.

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

Figure 3: Arterial spin labeling images with asymmetric blood flow, diminished on right, though improved from initial study from one week after Figure 1.