CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Metabolic Stroke as a Clinical Manifestation of Zhu-Tokita-Takenouchi-Kim Syndrome

A Case Series

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Abstract

Objective

This study reports 2 unrelated individuals with Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome who presented with a metabolic stroke, which has not been commonly reported as a clinical manifestation of this syndrome.

Methods

Two female children were identified after presenting to our institution with a metabolic stroke and carried a diagnosis of ZTTK syndrome because of their clinical characteristics and previous genetic testing demonstrating pathogenic variants in *SON*.

Results

Both individuals presented with acute-onset left hemiplegia. They underwent workup, and corresponding metabolic stroke was identified on brain MRI. Both individuals recovered with good functional outcome. One individual was treated with L-arginine, ubiquinol, and levocarnitine. The other individual recovered without any intervention.

Discussion

ZTTK syndrome is a rare condition caused by pathogenic variants in *SON*. This syndrome is characterized by global developmental delay, short stature, facial dysmorphisms, seizures, hypotonia, and brain abnormalities. A metabolic stroke has not been reported as a common manifestation. *SON* has been reported to play a role in mitochondrial function. This can explain why metabolic stroke can be seen in individuals with ZTTK syndrome. It is important to recognize that metabolic stroke can be a clinical manifestation of ZTTK syndrome because it carries clinical and therapeutic implications.

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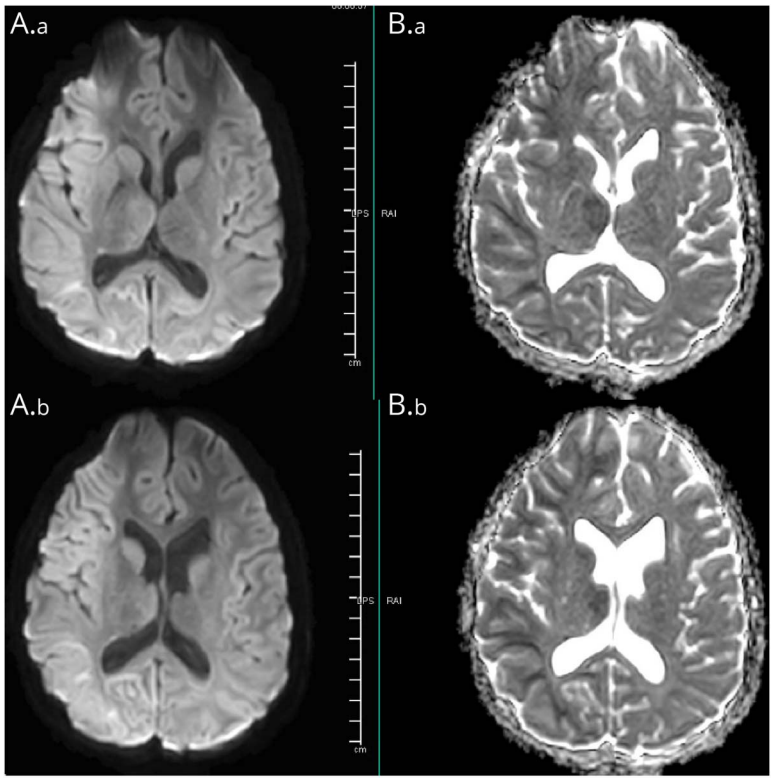
Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is a rare condition caused by a loss-of-function alteration in *SON* (SON DNA and RNA binding protein) which is located on chromosome region 21q22.[1] *SON* encodes a protein involved in multiple cellular processes, including transcription, premessenger RNA splicing, and cell cycle regulation, but much is still unknown about its function.[2] Global developmental delay has been seen in all cases.[1] Manifestations also include dysmorphic facial features, musculoskeletal abnormalities, abnormal brain MRI findings, hypotonia, eye anomalies, seizures, and short stature in more than 50% of cases.[1] Less common manifestations include cardiac, gastrointestinal, and genitourinary abnormalities.[1] Management of these conditions remains supportive. With only 60 known cases of ZTTK syndrome,[1] reports which expand the clinical phenotype will help inform clinicians of previous findings, diagnoses, and management strategies. In this study, we report 2 unrelated individuals who presented to our institution with a metabolic stroke. Although not widely described, we have identified one report of another individual with ZTTK syndrome who experienced a metabolic stroke.[3] Metabolic stroke is classically known as a rapid-onset central neurologic deficit in the absence of a vessel occlusion, with brain MRI confirming ischemia not confined to a vascular territory.[4] Metabolic stroke has not been commonly reported as a clinical manifestation of ZTTK syndrome, but mitochondrial dysfunction seen within *SON* may be implicated.[5,6]

Case 1

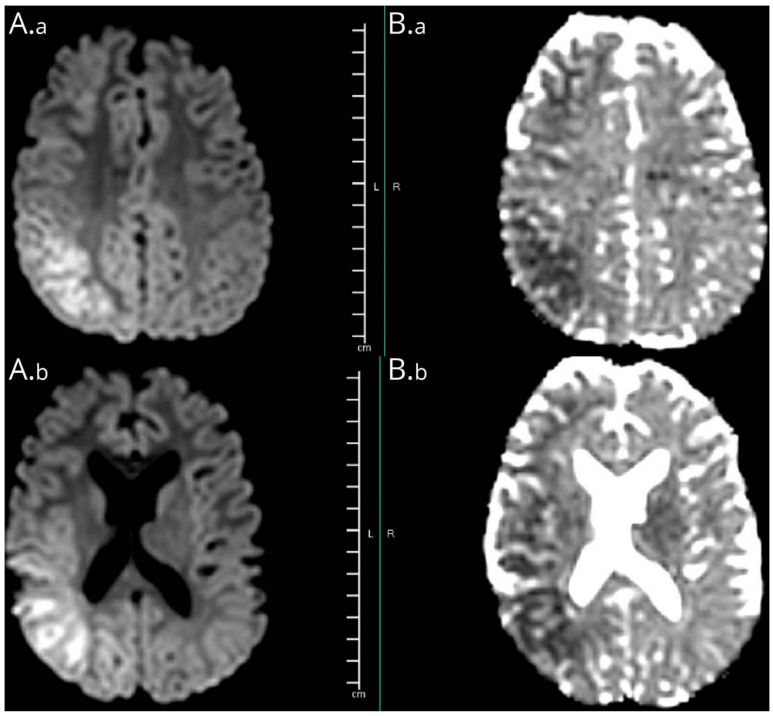
A 12-year-old adolescent girl presented to our institution with sudden-onset left hemiplegia. She carried a diagnosis of ZTTK syndrome since 6 years given her clinical characteristics of global developmental delay, dysmorphic facial features, musculoskeletal abnormalities, abnormal brain MRI, hypotonia, seizures, and short stature. Along with a whole-genome single nucleotide-polymorphism (SNP) microarray revealing a homozygous 589 KB interstitial deletion of arr[hg19] 21q22.11(34,841,458-35,430,729), which includes *SON, TMEM50B, GART, DONSON, CRYZL1, ITSN1,* and *ATP50*. After discharge, subsequent testing for combined mitochondrial genome, mitochondrial focused nuclear gene panel/sequencing and deletion/duplication testing returned negative for mitochondrial disease. On admission, her examination was notable for severe encephalopathy; fixed right gaze preference; and left lower face, arm, and leg paralysis. Extensive workup was significant for MRI obtained on the sixth day of symptomology and revealed diffusion restriction throughout the entire right hemisphere that is not confined to a single vascular territory, which is most likely consistent with a metabolic stroke (Figure 1). MRI scans obtained on the first and fourth days of symptomology also revealed subtle diffusion restriction that progressively worsened. EEG tracings showed initial severe right hemispheric attenuation, slowly giving way to periodic lateralized epileptiform discharges from the ipsilateral

Figure 1 Case 1



MRI of the brain (Aa-Ab axial diffusion weighted images [DWI]; Ba-Bb axial apparent diffusion coefficient [ADC] images) demonstrating diffusion restriction throughout the entire right hemisphere that is not confined to a single vascular territory, which is most likely consistent with a metabolic stroke.

Figure 2 Case 2



MRI of the brain (Aa-Ab axial diffusion weighted images [DWI]; Ba-Bb axial apparent diffusion coefficient [ADC] images) demonstrating diffusion restriction in the right parietal and occipital areas that is not confined to a single vascular territory, which is most likely consistent with a metabolic stroke.

region days after her admission. Two days before presentation, she experienced her typical seizure involving staring and left-sided weakness, but without her typical recovery in 10–12 hours, therefore prompting the family to seek medical attention. One clinical seizure occurred on the sixth day of symptomology and was described as abnormal movements of her left face, tongue, drooling, and left gaze preference with nystagmus. During her symptomatic period, her plasma lactate was between 0.8 and 3.0 mmol/L (0.5–2.2 mmol/L) and her pyruvate level was measured as 0.3 mmol/L (0.3–0.7 mmol/L). Her CSF lactate and pyruvate levels were not checked. She was treated with arginine, carnitine, and ubiquinone similarly to how some metabolic strokes are treated in individuals with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes. She recovered close to her previous functional baseline before the metabolic stroke by 2 weeks after the onset of symptoms.

Case 2

An 11-year-old adolescent girl presented to our institution with sudden-onset left hemiplegia. At that time, she had the clinical characteristics of ZTTK syndrome, global developmental delay, dysmorphic facial features, musculoskeletal abnormalities, abnormal brain MRI, hypotonia, seizures, cardiac abnormalities, gastrointestinal abnormalities, eye anomalies, and hearing loss. Whole-exome sequencing revealed a heterozygous p.R10X or C.27dupT leading to a de novo nonsense sequence variation in *SON*, a pathogenic variant. Later, she was diagnosed with ZTTK syndrome when the association was found between her clinical characteristics and genetic abnormality. On admission, her examination was notable for severe encephalopathy; fixed right gaze preference; and left lower face, arm, and leg paralysis. Extensive workup was significant for brain MRI findings demonstrating diffusion restriction in the right parietal and occipital areas, which is not confined to a single vascular territory, which is most likely consistent with a metabolic stroke (Figure 2). EEG tracings showed right central parietal sharp waves superimposed on right hemispheric slowing and disorganization. During her symptomatic period, her laboratory test results revealed a CSF lactate level of 1.3 mmol/L and a plasma pyruvate level of 0.13 mmol/L (0.08–0.16 mmol/L). Her CSF pyruvate and plasma lactate levels were not checked. She recovered close to her previous functional baseline before the metabolic stroke by 1 week after the onset of symptoms.

Discussion

In this study, we describe 2 individuals with ZTTK syndrome who presented to our institution with sudden-onset left hemiplegia and right gaze preference and were found to have a metabolic stroke. The association between ZTTK syndrome and metabolic stroke has not been commonly reported. Previously, a case was reported of a 10-month-old girl who presented with left hemiplegia, status epilepticus, and abnormal MRI findings suggestive of a corresponding cerebral infarction, which involved multiple vascular territories, ultimately suspicious for metabolic stroke. This patient recovered within 2 months after rehabilitation.[3] Pathogenic variants in *SON* have been hypothesized to cause mitochondrial

dysfunction[5,6]; however, the underlying mechanism remains unclear. Further research may support a link between mitochondrial dysfunction, epilepsy, ZTTK syndrome, and metabolic strokes. In the 2 new cases described here and one reported elsewhere, all individuals had good functional recovery. Case 1 received arginine therapy, sometimes used in metabolic strokes caused by a mitochondrial disorder.[5] Metabolic strokes carry significant clinical and therapeutic implications. Further studies are needed to assess how metabolism is impaired in ZTTK syndrome, the role of epilepsy in ZTTK syndrome, and whether arginine therapy would be beneficial when a metabolic stroke occurs.

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Name	Location	Contribution
Angie El-Said, BS	University of Central Florida College of Medicine, Orlando, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
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Neha Longani, MD	Department of Pediatric Critical Care Medicine, Nemours Children's Health, Orlando, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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