Child Neurology: Aicardi-Goutières Syndrome Presenting as Recurrent Ischemic Stroke

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Abstract

Aicardi-Goutières syndrome (AGS) is a rare, single-gene disorder, characterized by neurologic and skin involvement with an increased level of interferon-α (IFN-α) in the CSF. We describe the case of a young patient presenting with recurrent ischemic stroke. Evaluation revealed the presence of chilblains, white matter abnormalities, cerebral atrophy, and raised IFN-α in the CSF. Compound heterozygous variants of *TREX1* were detected, confirming a diagnosis of AGS. After excluding other causes, we attributed the stroke to AGS. Tofacitinib, a Janus kinase inhibitor, was administered to our patient in addition to antiplatelet drugs. There was no recurrence of stroke during 3-month follow-up. This is a rare case of recurrent stroke in *TREX1*-mutated AGS. Small vessel involvement has been previously demonstrated to play a significant role in the pathogenesis of AGS. This microvascular mechanism might explain the occurrence of ischemic stroke in our patient. For young patients with stroke and multiple system involvement, genetic disorders including AGS should be considered.

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Section 1

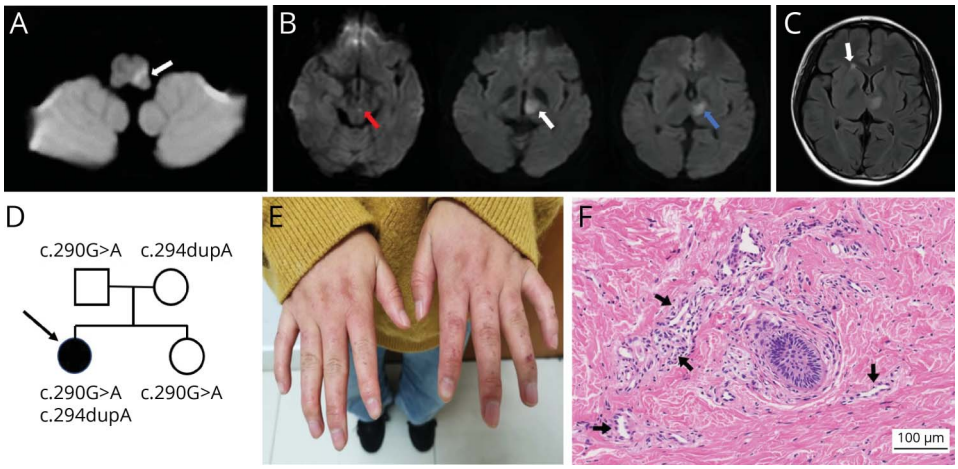
A 16-year-old Chinese girl was referred to our center for sudden onset of right upper and lower limb weakness, double vision, and cognitive decline. No limb numbness, aphasia, or vertigo was reported. She had experienced left medullary infarction (Figure, A) 1 year ago without sequelae. Since then, she had been prescribed aspirin and atorvastatin. She had undergone surgical repair of a ventricular septal defect at age 2 years. Family history was negative.

Neurologic examination demonstrated cognitive impairment with a Mini-Mental State Examination score of 17/30. Ocular movements were normal except for partial limitation of infraduction of the left eye. There was no ptosis. Mydriasis was evident in the left eye, with sluggish pupillary light reflex. Central right facial palsy was noted. Strength was 4/5 in the right limbs, with normal muscle tone and reflexes. Babinski sign was positive on the right. No signs of sensory disturbance and ataxia were found.

Questions for Consideration:

1. Where do you localize the lesion?
2. What is the most likely cause of this presentation?

Figure Brain MRI, Pedigree, Chilblains, and Histopathologic Result of the Skin Biopsy



1(A) Diffusion-weighted MRI showed acute medullary infarction (white arrow) at age 15 years. (B) Diffusion-weighted MRI showed acute infarction involving the left thalamus (blue arrow), thalamo-mesencephalic junction (white arrow), and oculomotor nerve fascicles (red arrow) at age 16 years. (C) T2 fluid-attenuated inversion recovery (FLAIR) MRI showed mild white matter abnormalities (white arrow). (D) The patient carried 2 *TREX1* variants (c.290G>A, p.R97H and c.294dupA, p.C99Mfs*3) (NM_033629), inherited from her father and mother, respectively. (E) Chilblains on the hands of the patient. (F) Histopathologic examination of the skin lesions showed perivascular lymphocyte infiltration (black arrows).

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Section 2

Cognitive impairment suggested the involvement of cortices or essential subcortical structures such as thalamus. The upper motor neuron paralysis of the right limbs and face was localized to the left pyramidal tract (above the nucleus of the facial nerve). Infraduction limitation and mydriasis of the left eye was localized to the left oculomotor nerve or midbrain.

CT of the head showed mild cerebral atrophy. MRI revealed acute infarction involving the left thalamus, thalamo-mesencephalic junction, and oculomotor nerve fascicles (Figure, B), consistent with our clinical localization. Mild white matter hyperintensities around bilateral ventricles (Figure, C), lacunes in the brainstem, and mild cerebral atrophy were also demonstrated. Given the acute onset of symptoms, previous ischemic stroke, and typical radiologic findings, acute ischemic stroke was diagnosed.

CT angiography of the neck, MR angiography of the head, and high-resolution MR vessel wall imaging of the vertebral and basilar arteries were normal (eFigure, links.lww.com/WNL/C188). Holter monitoring for 24 hours was unremarkable. Both noncontrast and contrasted transthoracic echocardiogram were unremarkable except for previous repair of ventricular septal defect, showing no right-to-left shunt. Her laboratory profile was normal, including blood counts, renal and hepatic function, coagulation function, and thyroid function. Antinuclear antibodies were positive with a titer of 1:100. Extractable nuclear antigen antibodies, anti-neutrophil cytoplasmic antibodies, anticardiolipin antibody, lupus anticoagulant, β-2 glycoprotein 1 antibody, and rheumatoid factor were all negative. Erythrocyte sedimentation rate was 41 mm/h (normal ≤ 15 mm/h) with normal C-reactive protein and anti–streptolysin O levels.

Questions for Consideration:

1. How would you further investigate the cause of recurrent stroke?

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Section 3

Negative results of large vessel and cardiac evaluations prompted us to seek uncommon causes of recurrent stroke in an adolescent patient. Additional history revealed that starting at age 5 years, the patient had chilblains—erythematous skin lesions—which were located in the hands, legs and feet, and more severe in the winter. She had experienced mild mental retardation and blurred vision since childhood. During this hospitalization, we observed chilblains in the above-mentioned areas, most severe in the hands (Figure, E). Ophthalmologic consultation was obtained. Best-corrected visual acuity was 20/25 OD and 20/40 OS. Optical coherence tomography showed thinning of the retinal nerve fiber layer in the left eye.

Given the multiple organ (brain, skin, and eyes) involvement from childhood, we suspected a genetic disorder. Whole-exome sequencing was performed, revealing compound heterozygous variants of *TREX1*, 1 missense variant (c.290G>A, p.R97H) and 1 frameshift variant (c.294dupA, p.C99Mfs*3) (NM_033629) (Figure, D). Sanger sequencing confirmed the maternal origin of c.294dupA and paternal origin of c.290G>A.

Questions for Consideration:

1. How would you diagnose the patient?
2. What would be the appropriate management strategy?

GO TO SECTION 4

Section 4

Both variants have been identified in Aicardi-Goutières syndrome (AGS).[1] AGS is a rare, genetic disorder characterized by neurologic manifestations and skin involvement (mainly chilblains) with an increased level of interferon-α (IFN-α) in the CSF. Skin biopsy of the lesions on the hand of our patient was performed, and histopathologic examination showed perivascular lymphocyte infiltration (Figure, F). Lumber puncture demonstrated an opening pressure of 120 mmH_2O, leukocytes of 6 cells/mm^3, elevated protein of 1,165 mg/L, and glucose of 2.4 mmol/L (paired plasma glucose 6.2 mmol/L). CSF oligoclonal bands were negative. Tumor cells or pathogens were not found. IFN-α in CSF was elevated at 4.5 pg/mL (normal range: 0–0.2 pg/mL).

In the presence of mental retardation, recurrent stroke, chilblains, ophthalmologic findings, cerebral atrophy, an elevated INF-α level in the CSF, and compound heterozygous variants in *TREX1,* the diagnosis of AGS was confirmed. A case of *TREX1*-mutated AGS with stroke has been previously reported.[2] After excluding other causes of stroke, we favored that our patient's recurrent stroke was attributed to AGS.

Janus kinase (JAK) inhibitors have been reported to be effective in treating patients with AGS.[3,4] Therefore, our patient was placed on tofacitinib, a JAK inhibitor, in addition to antiplatelet drugs. Her neurologic symptoms including limb weakness, diplopia, and cognition impairment improved markedly 1 month after the stroke. There was also substantial improvement of her chilblains. There was no recurrence of stroke during 3-month follow-up.

Table Causative Genes and Clinical Features of Aicardi-Goutières Syndrome

Causative genes and clinical features of Aicardi-Goutières syndrome	
Genes	*TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR,* and *IFIH1*
Clinical symptoms	Onset age: Usually younger than 1 year (age at diagnosis may be up to 40s)
	Neurologic symptoms: psychomotor delay, spasticity, dystonia, epileptic seizures and microcephaly, stroke, and visual problems
	Skin symptoms: Chilblains
	Other organ involvement: Anemia, thrombocytopenia, interstitial lung disease, pulmonary hypertension, hepatosplenomegaly, elevated liver transaminases, intermittent sterile pyrexias, hypothyroidism, insulin-dependent diabetes mellitus, scoliosis, cardiomegaly, and glaucoma
Neuroimaging	White matter abnormalities
	Cerebral calcification (may be absent in the late-onset patients)
	Brain atrophy (may be absent in the late-onset patients)
CSF	Chronic lymphocytosis (>5 cells/mm^3)
	Raised interferon-α in the CSF

Discussion

AGS is a rare, juvenile-onset, multisystem, single-gene disorder. AGS can be diagnosed by confirmed genetic variants, or when no molecular confirmation is available, a clinical and laboratory phenotype suggestive of AGS[5] (Table).

There are at least 7 genes associated with AGS. Variants in the *TREX1* gene account for approximately 24% of all AGS cases. Other causative genes include *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH*.[1] AGS is mainly inherited in an autosomal recessive pattern but occasionally can be autosomal dominant.[6,7]

AGS varies in severity, from a severe neonatal form to a milder, late-onset type.[8] Typically, patients have onset of symptoms in the early age of life, especially for those carrying variants in *TREX1*, and often present with an acute encephalitic phase and failure to progress in motor and mental skills.[9] Around 1 in 4 patients die between the age of 1 and 17 years. Some patients have survived past 40 years of age.[10] Our patient presented with a milder, later-onset phenotype.

AGS most commonly affects the brain and the skin.[6] Neurologic manifestations include feeding difficulties, irritability, epileptic seizures, generalized dystonia, spasticity, cognitive disability, and microcephaly.[6] Stroke and visual problems have also been reported in late-onset patients.[9] Chilblains, which are erythematous skin lesions usually at acral locations triggered by cold temperature, are present in more than 40% of patients with AGS and are associated with variants in all the 7 causative genes, especially *TREX1*.[7,8] Other extraneurologic features include hepatosplenomegaly, anemia, thrombocytopenia, and elevated liver transaminases.[9]

Brain calcification, white matter abnormalities, and cerebral atrophy are the classic radiographic features of AGS.[11] In some of the late-onset patients, classic calcifications and cerebral atrophy are lacking.[12]

Lymphocytosis with more than 5 cells/mm^3 and/or an elevated IFN-α level in the CSF has been documented in the diagnosis criteria of AGS.[5] Lymphocytosis and an elevated IFN-α level are permanent CSF findings in most patients, although the extent diminishes slightly with age.[10]

Stroke has been previously reported in several other cases of AGS.[2] Most of the cases were caused by *SAMHD1* variants, and 1 case associated with *TREX1* variant has been reported.[2] This patient with *TREX1*-mutated AGS was a child, carrying the same *TREX1* variant of c.290G>A as our patient.[2] However, the stroke was revealed by MRI, and the timing of the ischemic event was unclear.[2] To our knowledge, this is the first

description of recurrent stroke in *TREX1*-mutated AGS, expanding the clinical spectrum of AGS.

Pathophysiologic mechanisms of AGS are not fully understood. The hypothesis is that a mutated protein could lead to an accumulation of cytosolic nucleic acids and subsequently trigger an INF-α–mediated immune response.[10] Postmortem evidence of thrombotic microangiopathy was reported in the brain of a patient with AGS.[13] The small vessel involvement played a significant role in the pathogenesis of AGS based on brain autopsy.[14] Chilblain is a kind of distal small vessel disease of the skin.[15] With histopathologic evidence of cerebral and extracerebral vascular involvement, AGS may be considered to be a genetic microvascular disease.[15] The microvascular mechanism might explain the recurrence of ischemic stroke in our patient.

Baricitinib, a JAK inhibitor, which blocks interferon activation, proved to be effective in the treatment of chilblains in patients with AGS.[3] Tofacitinib, another JAK inhibitor, has also been reported to be effective in the treatment of skin lesions.[4] However, JAK inhibitors' effect on stroke prevention is unknown.

Herein, we report recurrent ischemic stroke as a novel clinical manifestation of *TREX1*-mutated AGS. For young patients with stroke with multiple system involvement, genetic disorders including AGS should be considered.

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Disclosure

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