LETTER TO THE EDITOR

To the Editor

SAMHD1 Mutations Are Also Responsible for Aicardi–Goutières in the Cree Population

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Aicardi–Goutières syndrome (AGS) is a progressive inflammatory encephalopathy with multi-organ involvement. There are seven genes known to be responsible for AGS (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH1*). The most common is *TREX1*, typically presenting as neonatal encephalopathy with cystic leukoencephalopathy and calcifications on brain imaging. Affected infants may present with hepatosplenomegaly, transaminitis, and thrombocytopenia and are often presumed to have a congenital viral infection. However, many children with AGS present within the first weeks of life following a normal neonatal period. Clinical manifestations include developmental regression, difficulty feeding, microcephaly, spasticity, seizures, and sterile pyrexias.

First described in 11 Cree children from a Northern Quebec village, Cree encephalitis is thought to be an immune condition possibly triggered by a prenatal viral or retroviral infection in a genetically predisposed population.[1] Currently, only *TREX1* mutations have been implicated in Cree encephalitis.[2] A pathogenic variant affecting *SAMHD1* has not been described in Cree children. We report a case of a Cree boy with phenotypic severe AGS and a homozygous *SAMHD1* mutation. Consent was obtained from his biological parents. The AGS phenotype due to the common mutation in the Cree population has traditionally been referred to as Cree encephalitis but is allelic to AGS in some patients. Therefore, Cree encephalitis is likely part of the AGS spectrum of disorders.

Our patient is a 5-year-old boy born at term by caesarean section to a healthy gravida-5/para-5 mother after an uncomplicated pregnancy and delivery. Prenatal ultrasounds were normal. He required no resuscitation, and there were no postnatal complications. To the parents, he appeared developmentally normal for the first 2 months of life with normal head control and feeding. However, he never learned to smile, coo, or reach for objects. Between the age of 2 and 3 months, he had an arrest of gross motor development and lost head control. He developed spastic quadriplegia with opisthotonus. At 6 months, he required a gastrostomy tube for feeding, through which he is now exclusively fed. At 12 months, he developed myoclonic seizures. He was diagnosed with glaucoma at 2 years and is cortically blind. He has several hospital admissions for aspiration pneumonia and status epilepticus. Other issues included hypertension, secundum atrial septal defect, and recurrent fevers of unknown origin.

Physical examination at 3.5 years revealed severe microcephaly (<2%), spastic quadriplegia with severe contractures of all limbs, spontaneous clonus, dystonic posturing, upgoing plantar responses bilaterally, and hepatosplenomegaly. He demonstrated small violaceous palpable lesions on his nose and right great toe. Currently, at age 5, he smiles in response to his parents' voice and occasionally coos, but he has no spontaneous movements. He continues to have intermittent fevers without infections. His seizures are under control.

Both parents are of Cree origin and reside in northeastern Ontario along James Bay, and are from different communities. The mother had two male cousins via her maternal aunt with developmental delay and seizures, both of whom died at age 8 months. No other family member has had neurological issues.

Head MRI at age 1 year showed tiny periventricular white matter and basal ganglia T1 hyperintensities (Figure 1). Findings on T2-weighted imaging included frontal predominant periventricular hyperintensities extending into the subcortical U-fibers, anterior temporal lobe and bifrontal subcortical cysts, frontal encephalocele, cavum septum pellucidum, abnormal myelination of external capsules and the internal capsule, and a thin corpus callosum, as well as brainstem and cerebellar atrophy. These findings persisted at 26 months with further cortical and brainstem atrophy. There was no enhancement on gadolinium. MR spectroscopy demonstrated lactate peak and an increased choline-to-NAA ratio. No vessel imaging was acquired.

Chromosomal microarray done at age 1 year was normal. Initial testing for Cree encephalitis (*TREX1*) followed by testing for *RNASEH2A*, Cree leukoencephalopathy (*eIF2B5)*, leukodystrophies, and fibroblasts for respiratory chain analysis were negative. He was then tested for an AGS panel including *TREX1*, *RNASEH2A/B/C*, and *SAMHD1*, and was found to have a homozygous sequence variant at c1265T > A; p.Leu422Gln in *SAMHD1*, which has not been previously reported in the literature. Both parents are carriers of this variant. In-silico analysis was done using four different programs (Align GVGD, SIFT, MutationTaster, and PolyPhen-2). Based on the current available information, SAMHD1:c.1265T > A is classified as a "variant of uncertain significance" (VUS, ACMG 3). Evidence supporting pathogenicity (PM2, PP3, PP4), falls short of being sufficient to classify the variant as "likely pathogenic" (ACMG 4). A different amino acid substitution has been reported at the same position (c.1265T > C, p.Leu422Pro) in a case of gastric adenocarcinoma (COSMIC ID: COSM4098095). Based on the in-silico FATHMM algorithm, this variant is classified as "pathogenic." This evidence (PM5) was not included in the final ACMG classification because the pathogenicity of the c.1265T > C (p.Leu422Pro) variant was based entirely on in-silico predictions. If this additional information is considered (PP5), the SAMHD1:c.1265T > A variant would be classified as "likely pathogenic" (ACMG 4).

Homozygous and compound heterozygous mutations in *SAMHD1* were first implicated in AGS patients in 2009.[3] Approximately 13% of AGS is caused by mutations in *SAMHD1* (including missense and null mutations as well as large deletions).[3,4] The majority of these patients have a normal neonatal course with neurological symptoms presenting in the first year of life. *SAMHD1* mutations have been found in Amish populations,[5] Maltese patients,[6] Ashkenazi Jews,[6] and patients of Northern European, North American, Asian, and Australian descent.[4]

The phenotypic similarities between AGS and Cree encephalitis are well-described. Currently, only *TREX1* mutations have been identified in Cree encephalitis.[2] To our knowledge, there are no reports of *SAMHD1* mutations in Cree children.

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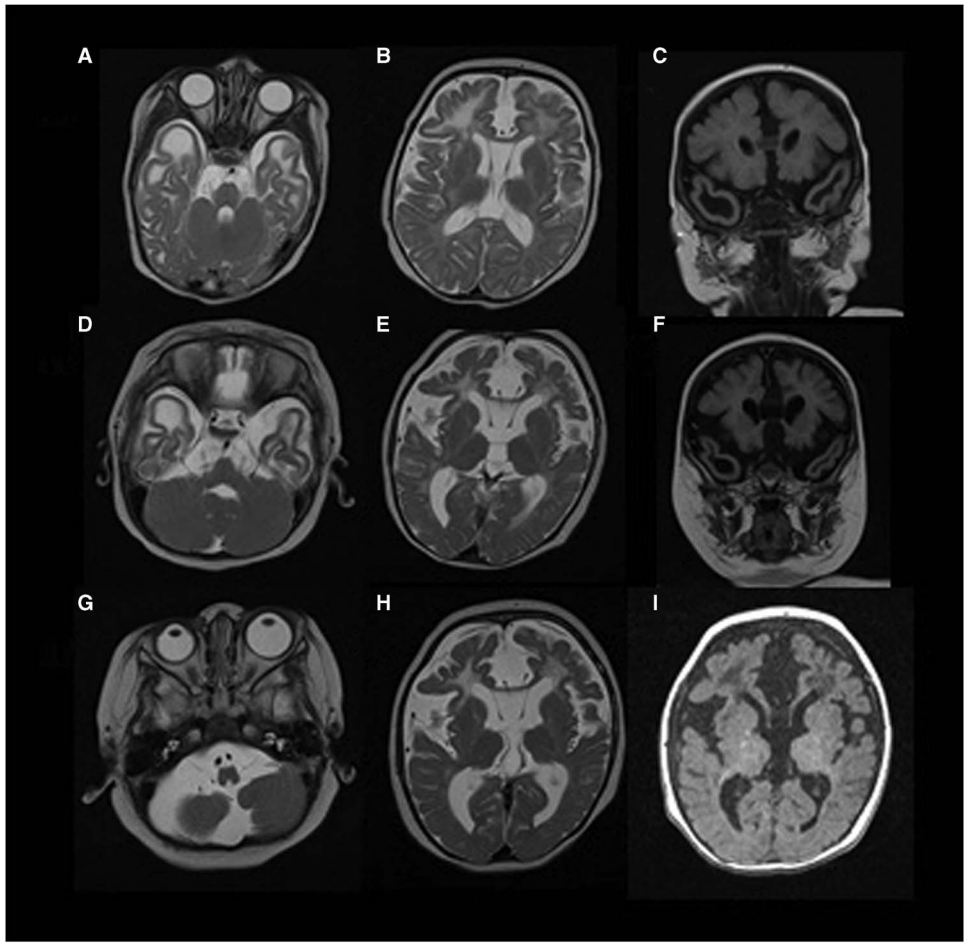

Figure 1: *A through C, age 4 months, T2W and T2 FLAIR axial images demonstrating temporal and frontal cysts; D through F, age 11 months, T2W and T2 FLAIR axial images demonstrating temporal and frontal cysts and abnormal myelination status; G, age 18 months, T1W axial image demonstrating left glaucoma; H, age 18 months, T2W axial image demonstrating ongoing cerebral atrophy; I, age 18 months, T1W axial image demonstrating basal ganglia calcifications.*

Several conditions are associated with AGS, including glaucoma, autoimmune diseases, familial chilblain cardiomyopathy, intracerebral vasculitis,[7] and arthropathy.[4] Among AGS patients, those with *SAMHD1* mutations have a higher likelihood of developing glaucoma and chilblains. They are also the only group to develop intracerbral vasculopathy and arthropathy. In a series of five patients with *SAMHD1* mutations, all had both a cerebral arteriopathy and peripheral vasculopathy with chilblains, and two had leukocytoclastic vasculitis on skin biopsy.[7] These findings were convincing for a role for *SAMHD1* in systemic inflammation. Therefore, for this subgroup of AGS, anti-inflammatory therapies and immunosuppression may help prevent disease progression.

Patients with AGS display increased interferon activity in cerebrospinal fluid and serum.[8] This was not investigated in our patient due to his deteriorating condition.

Currently, in Canada, *TREX1* testing for the common mutation is typically done first-line in patients suspected of having Cree encephalitis. If negative, an AGS panel (including *SAMHD1*) or individual *SAMHD1* testing should be performed. A wider genetic screen of the Cree population may help elucidate the carrier rate of *SAMHD1* in this population. If additional cases are identified, it would assist in defining the pathogenicity of the variant. This testing would be particularly important, as AGS with *SAMHD1* mutations can have potential complications, including glaucoma and arteriopathy, requiring anticipatory screening and treatment. Furthermore, immunosuppressive therapies may play a role in the management of this subgroup of AGS patients.

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Disclosures

Ashraf Kharrat, Jennifer MacKenzie, and Sunita Venkateswaran do not have anything to disclose.

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