Recurrent Encephalopathy with Spinal Cord Involvement: An Atypical Manifestation of Aicardi–Goutières Syndrome

Debopam Samanta, Raghu Ramakrishnaiah[1]

Department of Pediatrics, Division of Child Neurology, University of Arkansas For Medical Sciences, [1]Division of Neuroradiology and Pediatric Radiology, University of Arkansas For Medical Sciences, Little Rock, Arkansas, USA

Abstract

Aicardi–Goutières syndrome (AGS) is a rare, genetic inflammatory disease due to mutations in any of the seven genes discovered to date (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH1*). Clinical onset is seen most commonly *in utero* or in infancy; irritability, feeding difficulties, jitteriness, microcephaly, abnormal movements, seizures, bone marrow suppression, and liver dysfunction are seen either during the neonatal age group or within the first few months of life with abrupt onset of neurologic regression and slowing of head growth. Diffusely abnormal white matters with swelling of frontal or temporal lobes, cerebral atrophy, and intracranial calcification are typical neuroradiologic abnormalities. However, *ADAR* mutation, a recently discovered AGS gene, can cause late-onset acute or subacute onset of severe dystonia and features of bilateral striatal necrosis on neuroimaging, in the absence of other typical features of AGS.

Address for correspondence: Dr. Debopam Samanta, 1 Children's Way, Little Rock, Arkansas 72202, USA.
E-mail: dsamanta@uams.edu

DOI: 10.4103/aian.AIAN_12_18

We report a detailed description of a 5-year-old boy who had a recurrent encephalopathic presentation in the setting of infection. Magnetic resonance imaging (MRI) of brain revealed prominent and fairly symmetrical signal abnormalities in the cerebellar peduncles, thalamus, midbrain, and pons. His throat swab was positive for influenza B, and he was initially diagnosed with influenza encephalopathy. He had a recurrence after 18 months of his initial presentation, and his brain MRI showed extensive areas of signal abnormality similar to, but more extensive than, his previous scan. Extensive spinal cord swelling was also seen. His chronic skin finding was recognized as dyschromatosis symmetrica hereditaria (DSH), and genetic testing revealed compound heterozygous mutations of *ADAR* gene – causative for AGS. This is the first presentation of recurrent acute encephalopathy in the setting of documented *ADAR* mutation with the longest interval documented between two acute presentations. This is also the first documentation of extensive spinal cord involvement, which will expand its phenotype. This case also highlights the importance of early identification of DSH, a subtle but characteristic skin lesion of *ADAR* mutations, for prompt diagnosis of this rare condition.

Keywords: Acute necrotizing encephalopathy, ADAR mutation, Aicardi–Goutières syndrome, dyschromatosis symmetrica hereditaria, influenza encephalopathy

Introduction

Aicardi–Goutières syndrome (AGS) classically presents as early-onset encephalopathy with severe intellectual disability, abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, or more slowly evolving severe encephalopathy characterized by extreme irritability, intermittent sterile pyrexias as well as regression in the development and slowing of the head growth.[1] This is a genetically heterogeneous disease with mutations involving seven genes (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH1)* causing accumulation of endogenous nucleic acid species and inappropriate stimulation of the innate immune system by a robust interferon (IFN) response. This increase in IFN level produces inflammatory encephalopathy with more than 90% cases present in the early infancy.[2] However, atypical late-onset and acute/subacute dystonia can be a presenting feature, and the true extent of the phenotype is currently unknown. We describe a child with recurrent encephalopathy, initially thought to be influenza-associated encephalopathy and later recognized as an atypical case of AGS secondary to *ADAR* mutations. He also had severe spinal cord involvement which had not been reported with this condition, as per our knowledge.

Case Report

A 5-year-old boy with past medical history of cerebral palsy and influenza encephalopathy presented to our hospital with fever, decreased appetite, and lethargy in December 2016. He was born at 30 weeks of gestation and had a diagnosis of mild spastic diplegia. In March 2015, in the setting of low-grade fever and sore throat, he had acute unresponsiveness and extensor posturing. Magnetic resonance imaging (MRI) brain revealed prominent and fairly symmetrical T2/fluid-attenuated inversion recovery signal abnormalities in the cerebellar peduncles, thalamus, midbrain and pons, and to a lesser extent in the left caudate [Figure 1]. His throat swab was positive for influenza B by polymerase chain reaction, but spinal fluid (0 cell, protein 67, and glucose 137) was negative for any pathogen. He had marked improvement over the next several months and recovered to around 80% of his developmental milestones, ambulating with minimal assistance and speaking in sentences. Repeat brain MRI after 2 months showed resolution of restricted diffusion and enhancement, but areas of calcification were seen in the posterior aspects of the putamen [Figure 2].

On the 2nd day of hospital admission in December 2016, he had acute worsening with unresponsiveness, decerebrate posturing, and eye deviation to the right similar to his first admission 18 months ago. He was intubated to protect his airway. Electroencephalogram showed encephalopathy with no seizure activity. He was febrile to 39.6°C. Brain MRI showed extensive areas of signal abnormality similar to, but more extensive than, his previous scans in March 2015 during his presumed influenza encephalopathy diagnosis [Figure 3]. Spinal tap revealed lymphocytosis (white blood cell 13 with 80% lymphocyte) and increased protein of 103 mg/dl. Cerebrospinal fluid (CSF) Gram stain was negative, meningitis/encephalitis panel was negative, and culture was negative. Rapid strep culture, respiratory pathogen panel, urine and blood cultures, and CSF pathogen studies were negative. Liver enzymes were elevated at 150–200 units per liter. He was also treated with high-dose methylprednisolone and intravenous immunoglobulin. He remained unresponsive to verbal stimuli but would react to painful stimuli on lower extremities and had intermittent posturing of arms and legs. Repeat MRI brain with spectroscopy and spinal cord [Figures 3 and 4] revealed extensive spinal cord swelling with hyperintensity of the central gray matter as well as elevated lactate doublet in the spectroscopy. He had a 2.5-month course in the intensive care and intermediate care units with numerous episodes of autonomic instability and dykinetic crisis manifested as hypertension, diaphoresis, tachycardia, and refractory 4-limb dystonia which was managed with propranolol, clonidine, diazepam, trihexyphenidyl, morphine, and lorazepam. Dermatology was consulted for hypo and hyperpigmented macules which had been progressively worsen (the lighter spots had lightened and the darker spots had darkened) on the dorsum of the hands and legs over the last 4 years as well as the development of new lesions over his cheeks. These lesions were suspected to be dyschromatosis symmetrica hereditaria (DSH) which is secondary to a mutation in the

double-stranded RNA-specific adenosine deaminase (*ADAR1*) gene. Mutations in the *ADAR1* gene can also cause AGS. Whole-exome and mitochondrial genome sequence analysis were performed, and compound heterozygous for the c. 1493_1494delAG pathogenic variant and the E1193K-likely pathogenic variant in the *ADAR* gene were detected. At the time of discharge, the patient was nonverbal, bedridden, and had marked spasticity and 4-limb dystonia. Intermittent orofacial dyskinesia was also present.

Discussion

Acute necrotizing encephalopathy, predominantly reported in Japan and Taiwan, characterized by rapidly deteriorating febrile illness and associated with multifocal, symmetric brain lesions affecting bilateral thalami, brainstem tegmentum, periventricular white matter, and posterolateral putamen. The differential diagnosis of acute necrotizing encephalopathy is extensive and includes mitochondrial disorders, inborn errors of metabolism, hypoxic-ischemic injury, Japanese and dengue encephalitis, neurodegenerative diseases, osmotic myelinolysis, hemolytic-uremic syndrome, and toxin such as carbon monoxide exposure. Infection-induced acute necrotizing encephalopathy can be due to a heterozygous pathogenic variant in the RAN binding protein 2 causing bilateral symmetric thalamic, midbrain, and/or hindbrain lesions within days following the onset of an acute viral illness.[3] IIAE4, influenza-associated encephalopathy, can also cause acute neurologic decompensation following influenza infection, but brain MRI shows no abnormalities or diffuse swelling. Thermolabile alleles of carnitine palmitoyltransferase II can act as susceptibility factor in these patients.[4] Acute bilateral striatal necrosis precipitated by *Mycoplasma pneumoniae*, mitochondrial disorders such as Leigh syndrome, and POLG-related disorders can have similar clinical presentation. Acute disseminated encephalomyelitis can also mimic similar presentation though classically, infection/vaccination precedes encephalopathy by weeks. Asymmetric radiologic finding and predominant involvement of white matter also help to distinguish this condition.

AGS is a genetic inflammatory disease due to mutations in any of the seven genes discovered to date (AGS1–AGS7). Prenatal (*in utero*) or infantile onset is the most common presenting feature. Irritability, feeding difficulties, jitteriness, microcephaly, abnormal movements, seizures, bone marrow suppression, and liver dysfunction are seen either during neonatal age group or within the first few months of life with abrupt onset. Neurologic regression and slowing of head growth can be seen in the infantile presentation. Diffusely abnormal white matter with swelling of frontal or temporal lobes, cerebral atrophy, and intracranial calcification along with typical clinical features can be helpful for a prompt diagnosis. However, <10% cases can have later onset or other atypical presentations such as bilateral striatal necrosis and refractory 4-limb dystonia.[2] *ADAR1* (AGS6) mutation, another recently discovered cause of AGS, can increase immunoreactive dsRNA with suppression of IFN induction.[5] Bilateral striatal necrosis, a distinct neuroradiologic phenotype, has also been described secondary to *ADAR1* mutations. Two distinct phenotypes of bilateral striatal necrosis were seen: a subacute presentation seen in the 1st year of life or an acute presentation following an infection.[6]

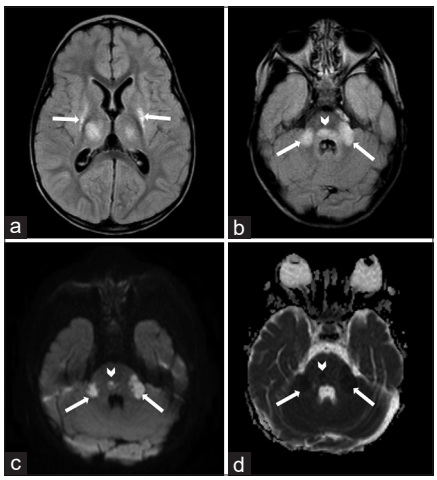

Figure 1: Initial magnetic resonance imaging of brain. Axial fluid-attenuated inversion recovery image (a) through the basal ganglia shows symmetric hyperintensity in the thalamus and basal ganglia (arrows). Axial fluid-attenuated inversion recovery image (b) through the posterior fossa shows symmetric hyperintensity in the dorsal pons (arrowhead) and in the cerebellar peduncles (arrows). The axial diffusion-weighted image (c) and the apparent diffusion coefficient map (d) show areas of diffusion restriction in the cerebellar peduncles and pons. The diffusion-weighted images also showed restriction in bilateral basal ganglia (Images not provided)

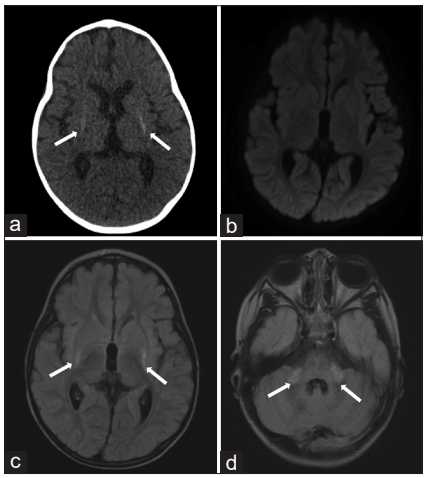

Figure 2: A 2-month follow-up computed tomography and magnetic resonance imaging studies. Axial noncontrast computed tomography image (a) shows diffuse cerebral parenchymal volume loss and areas of calcification in the posterior aspects of the putamen (arrows). (b) Diffusion-weighted sequence shows normalization of the signal abnormalities in the basal ganglia. Axial fluid-attenuated inversion recovery images (c and d) show residual hyperintensity in the basal ganglia and the middle cerebelar peduncles (arrows)

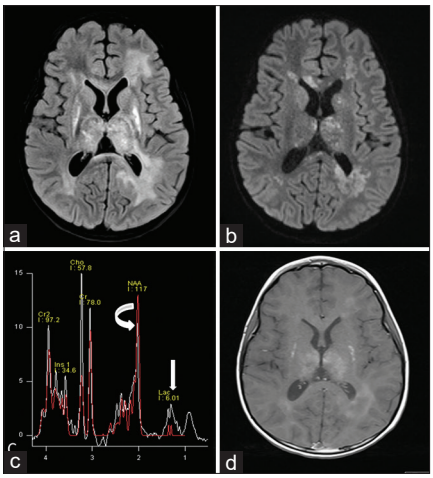

Figure 3: Repeat magnetic resonance imaging. Axial fluid-attenuated inversion recovery image (a) through the basal ganglia shows extensive hyperintensity in the thalamus, basal ganglia, central and deep white matter, and the corpus callosum. The axial diffusion-weighted images (b) show corresponding areas of diffusion restriction (arrows). (c) The magnetic resonance spectroscopy shows elevated lactate doublet (arrow) and dampening of the NAA (curved arrow) metabolite peaks. (d) Axial postcontrast T1-weighted image shows areas of amorphous enhancement corresponding areas of fluid-attenuated inversion recovery signal abnormality. Notice the posterior putaminal T1 hyperintensity corresponding to the areas of calcification seen on the prior computed tomography scan (image a, Figure 2)

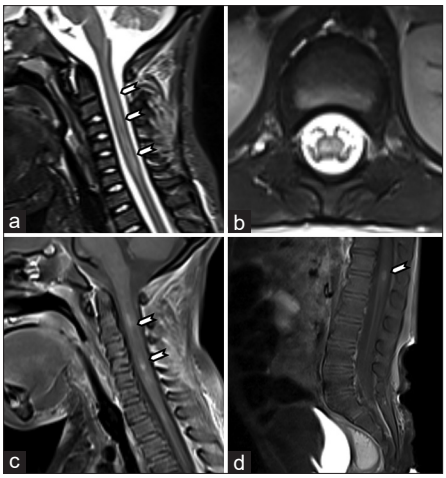

Figure 4: Sag T2-weighted through the cervical spine (a) and axial T2-weighted through the conus medullaris (b) show spinal cord swelling and hyperintensity of the central cord matter. Postcontrast T1-weighted of the cervical spine (c) and lumbar spine (d) show focal areas of intramedullary enhancement

A report by Crow *et al*. described phenotypes in association with mutations in different genes associated with AGS (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH1*) in 374 patients from 299 families.[2] *In utero* (74 patients; 22.8%) and infantile (223 patients; 68.6%) presentation constituted more than 90% patients with AGS. Twenty-eight patients (8.6%), however, presented after the age of 1 year, with 35% of them had mutations in *ADAR*. Out of 374 patients, 13 patients (3.6%) had *ADAR* mutations with the acute or subacute onset of severe dystonia and features of bilateral striatal necrosis on neuroimaging, in the absence of other features of AGS. The latest age at presentation in that group was a child with a p. Gly1007Arg mutation in *ADAR* who developed subacute dystonia beginning at the age of 5 years. Livingston reported 9 *ADAR1* mutation-positive patients from seven families demonstrating 5 acute and 4 subacute presentation of refractory 4-limb dystonia starting between 8 months and 5 years of age.[7] No patient had a prolonged remission except a 5-year-old that made a full recovery for 1 week followed by progressive deterioration over a period of several weeks.

Developmental delay, regression, epileptic seizures, dystonia, eye movement abnormalities, spastic paraparesis, bilateral striatal necrosis, intracranial calcification, white matter abnormality, cerebral atrophy, recurrent sterile fevers, autoimmune features, and bone marrow suppression were reported with *ADAR1* mutations, but prolonged recovery over several months and extensive spinal cord involvement had not been reported in the literature, to the best of our knowledge.

Classically, AGS-associated neurological injury is seen at birth or in early infancy with cessation of pathological process some months after the onset; however, intermittent or recurrent manifestation can be seen in some aspects of the AGS such as chilblains, intracerebral vascular disease, and autoimmune disease. This is the first report of distinct recurrent encephalopathic presentation in AGS. Early and rapid diagnosis may be crucial for the management of AGS. Although irreversible neurological damage is impossible to recover, aggressive treatment against inflammation in the early stages of the disease may be beneficial. This patient has intracranial calcification which was initially thought to be related to his premature birth, and his skin finding of DSH (typical of *ADAR1* mutation) remained undiagnosed until late. Some neuroradiology features such as lactate peak may erroneously point to the diagnosis of primary mitochondrial disease, though mitochondrial dysfunction, particularly marked reduction of complex III activity can be seen in AGS.[8]

Effectiveness of broad-spectrum anti-inflammatory and immunomodulatory therapies is unknown due to different available regimens, their use in different stages of the disease, and several genotypes responsible for the disease, but more specific treatment plan involving type 1 IFN blockade, reverse transcriptase inhibition, depletion of B and T-cells, and availability of biomarkers such as IFN alpha levels to assess the ongoing disease activity and treatment efficacy can change the landscape of the treatment of this devastating disease in the future.[9]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Crow YJ, Livingston JH. Aicardi-Goutières syndrome: An important Mendelian mimic of congenital infection. Dev Med Child Neurol 2008;50:410-6.
2. Crow YJ, Chase DS, Lowenstein Schmidt J, Szynkiewicz M, Forte GM, Gornall HL, *et al.* Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 2015;167A: 296-312.
3. Gika AD, Rich P, Gupta S, Neilson DE, Clarke A. Recurrent acute necrotizing encephalopathy following influenza A in a genetically predisposed family. Dev Med Child Neurol 2010;52:99-102.
4. Shinohara M, Saitoh M, Takanashi J, Yamanouchi H, Kubota M, Goto T, *et al.* Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. Brain Dev 2011;33:512-7.
5. Rice GI, Kasher PR, Forte GM, Mannion NM, Greenwood SM, Szynkiewicz M, *et al.* Mutations in ADAR1 cause Aicardi-Goutières syndrome associated with a type I interferon signature. Nat Genet 2012;44:1243-8.
6. La Piana R, Uggetti C, Olivieri I, Tonduti D, Balottin U, Fazzi E, *et al.* Bilateral striatal necrosis in two subjects with Aicardi-Goutières syndrome due to mutations in ADAR1 (AGS6). Am J Med Genet A 2014;164A: 815-9.
7. Livingston JH, Lin JP, Dale RC, Gill D, Brogan P, Munnich A, *et al.* A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1. J Med Genet 2014;51:76-82.
8. Crow YJ, Vanderver A, Orcesi S, Kuijpers TW, Rice GI. Therapies in Aicardi-Goutières syndrome. Clin Exp Immunol 2014;175:1-8.
9. Barnérias C, Giurgea I, Hertz-Pannier L, Bahi-Buisson N, Boddaert N, Rustin P, *et al.* Respiratory chain deficiency in a female with Aicardi-Goutières syndrome. Dev Med Child Neurol 2006;48:227-30.