Movement Disorders
CLINICAL PRACTICE

CASE SERIES

Diagnosis of Aicardi-Goutières Syndrome in Adults: A Case Series

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ABSTRACT: Introduction: Aicardi-Goutières syndrome (AGS) is a genetic disease presenting with early-onset encephalopathy, generalized dystonia, spasticity, and cognitive disability. Diagnosis may be difficult in adults, as the clinical course seems static from infancy.
Methods: AGS patients from an adult movement disorders outpatient clinic were retrospectively analyzed.
Results: A total of 5 patients and 1 asymptomatic carrier from 3 different families were identified. All had a homozygous c.529G>A,p.A177T mutation in exon 7 of the *RNASEH2B* gene. Two patients had neonatal-onset AGS, 2 had later onset forms, and 1 was slightly symptomatic. All were diagnosed in adulthood after chilblains, and basal ganglia calcifications were identified on computed tomography scans.
Discussion: AGS patients have marked phenotypic variability regarding psychomotor development and morbidity. The present series included 1 asymptomatic carrier and 1 slightly symptomatic patient, both with homozygous *RNASEH2B* mutations. Chilblains and basal ganglia calcifications identified on computed tomography scan (but not on magnetic resonance imaging) are important clues for late diagnosis.

Aicardi-Goutières syndrome (AGS) is a genetic disease first described as a triad of basal ganglia calcifications, white matter abnormalities, and raised levels of interferon-α in the cerebrospinal fluid (CSF).[1] It is caused by mutations in several genes (*TREX1*, *RNASEH2A*, *RNASEH2B*, *SAMHD1*, *IFIH1*, among others) with a predominantly autosomal recessive inheritance.[2] The condition usually presents with early-onset encephalopathy followed by generalized dystonia, spasticity, and frequent cognitive disability.[3] Because the clinical course seems static from infancy and imaging findings are nonspecific, diagnosis can be challenging, and some patients may be misdiagnosed with cerebral palsy.[4] In this study, a series of 5 patients diagnosed with AGS in adulthood and the case of 1 asymptomatic homozygous carrier are described, and clinical findings relevant for diagnosis are reported, namely chilblain lesions and basal ganglia calcifications.[1]

Methods

Data from an adult movement disorders outpatient clinic were retrospectively assessed, and 5 patients from 3 different families (A–C) with genetic diagnoses of AGS were identified. A total of 3 patients were primarily diagnosed through clinical presentation (patients 1, 3, and 5); 2 other patients (patients 4 and 6) and 1 homozygous asymptomatic carrier (patient 2) were further identified following sibling evaluation. All had a homozygous c.529G>A,p.A177T mutation in exon 7 of the *RNASEH2B* gene (Table 1). One asymptomatic sibling had a negative genetic result, and 2 other asymptomatic siblings refused evaluation. No history of consanguinity was apparent. All individuals had experienced normal pregnancies and labor. Except for patient 3, none had microcephaly or dysmorphias. No patient presented with systemic lupus erythematosus (SLE) or any other auto-immune disorder.

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TABLE 1 *Clinical data of 5 Aicardi-Goutières patients and 1 asymptomatic patient*

	Patient						
	1	2	3	4	5	6	Freq/Aver
Family	A	A	B	B	C	C	
Sex	M	F	F	F	F	F	
Age, y	36	42	26	44	39	37	37,3
Age at diagnosis, mo	35	41	21	40	34	32	33,8
Previous diagnosis	Dystonia	–	CP	–	CP	CP	
Labor/pregnancy issues	–	–	+	–	–	–	1/6
Encephalopathy, mo	5	–	3	–	0	7	3,8
Clinical picture at onset	Mixed	–	Mixed	–	Mixed	Diplegia	
Severity	+	–	++	–	++	+	
Cognitive dysfunction	–	–	++	–	++	–	2/6
Dystonia	++	–	++	–	++	+	5/6
Pyramidal signs	++	–	++	–	++	++	4/6
Epilepsy	–	–	+	–	–	–	1/6
CSF pleocytosis	–	NA	+	NA	–	–	1/6
Abnormal MRI	–	NA	+	NA	+	–	2/6
CT calcification	+	NA	++	–	++	+	4/6
Chilblain lesions	+	–	+	+	+	+	5/6
RNASEH2b mutation	+	+	+	+	+	+	6/6

Freq, frequency; Avg, average; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CT, computed tomography; *RNASEH2b*, Ribonuclease H2, subunit B; M, male; F, female; CP, cerebral palsy; NA, not available.
The last column displays frequency, except for time data, which are presented as averages.

Results

Family A

Patient 1 had normal psychomotor development until the age of 5 months, when he experienced subacute encephalopathy with significant neurological regression. Over the years, he developed generalized dystonia and spastic tetraparesis with dubious progression. Extensive diagnostic workup including cerebral magnetic resonance imaging (MRI) and CSF analysis was normal. By the age of 30 years, the patient was referred to our outpatient clinic for botulinum toxin treatment. He presented fixed generalized dystonia with pyramidal signs and normal cognitive functions (Video S1). Chilblains on hands and feet were present since adolescence and aggravated during winter (Fig. 1). This prompted a computed tomography (CT) scan that showed basal ganglia calcifications. Subsequent genetic testing identified a homozygous c.529G>A,p.A177T mutation in exon 7 of the *RNASEH2B* gene. Patient 1 is currently wheelchair bound but maintains normal cognition and completed university graduation.

Patient 1's only sister, patient 2, is 42 years old and asymptomatic. She has normal neurological examination and no history of chilblains, abnormal labor or development, visual or hearing problems, arthropathy, hypothyroidism, or diabetes mellitus. She was referred to genetic counseling, where the same homozygous mutation was identified.

Family B

Patient 3 is a 26-year-old woman, the youngest of 4 siblings. Her pregnancy included gestational hypertension during the third trimester followed by an uneventful delivery. Delayed psychomotor development was noted since the first days of life. Encephalopathy emerged at 3 months and spontaneously resolved after a few weeks. Serum analysis and karyotype were normal. CSF analysis showed mild pleocytosis, and MRI

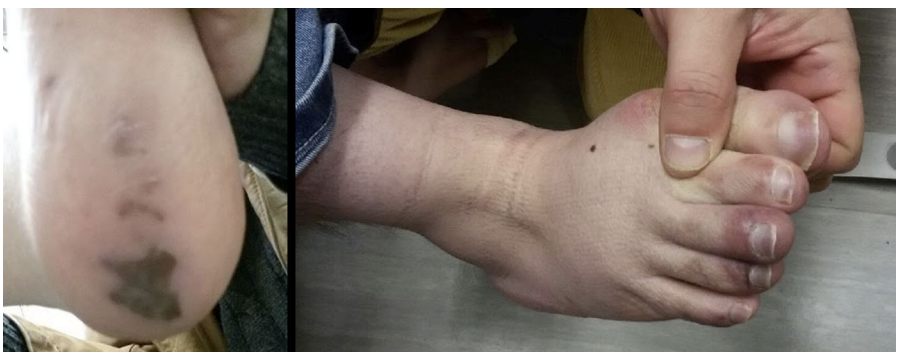

FIG. 1. Patient 1 with chilblain lesions on the toes and heels.

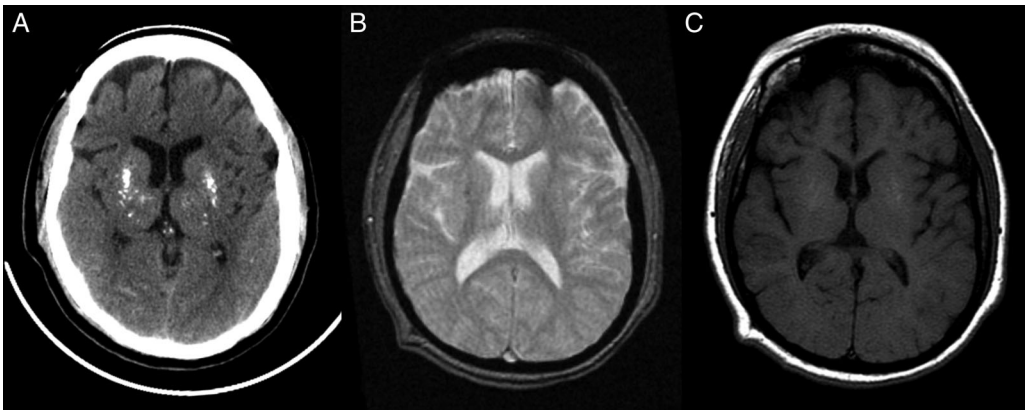

FIG. 2. (**A**) Axial nonenhanced computed tomography scan image revealing obvious calcification in lenticular nuclei. (**B**) T2*-weighted axial magnetic resonance imaging showing hypointense foci corresponding to calcification on computed tomography scan. (**C**) T1 weighted axial magnetic resonance imaging showing small hyperintensities in lenticular nuclei.

revealed T2 hyperintensity on lenticular nuclei. No diagnosis was established at that time. On reevaluation at the age of 21, the patient presented generalized dystonia and spastic tetraparesis (Video S2), severe cognitive and behavioral dysfunction, and chilblain lesions on both feet. A CT scan revealed extensive basal ganglia calcifications, and subsequent genetic testing identified a homozygous *RNASEH2B* mutation. The patient developed autoaggressive behavior and restlessness that prompted the institution of antipsychotic therapy.

Patient 4 is the 44-year-old sister of patient 3. She has latent dystonic posturing of both hands and chilblains on the ears, hands, and feet during winter. Similar to patient 2, there is no history of systemic disease. A CT scan showed no calcifications, and genetic testing revealed homozygosity for the *RNASEH2B* mutation.

The remaining siblings are described as neurologically asymptomatic and have no history of chilblains.

Family C

Patient 5 is the oldest of 3 siblings. Jitteriness, hypotonia, and severe cognitive impairment were present since birth. Control of the head and language skills were never acquired. A pyramidal syndrome ensued early, associated with progressive generalized dystonia with predominant oromandibular involvement. No study was performed during infancy, and the patient was diagnosed with cerebral palsy. Chilblains on the hands and heels appeared late in childhood. Clinical study performed at the age of 29 revealed normal serum and CSF analysis, and MRI showed lenticular calcifications subsequently confirmed on CT scan (Fig. 2). Genetic testing for AGS was ordered, and a homozygous c.529G>A,p.A177T mutation in exon 7 of the *RNASEH2B* gene was identified. Clinically, the response to levodopa or trihexyphenidyl was unsatisfactory.

Patient 6 is a 37-year-old female whose clinical case had been previously published (image and video available).[5] She had normal psychomotor development until the age of 7 months, when subacute encephalopathy ensued. The patient subsequently developed a spastic diplegia with preserved cognition, having completed 9 years of regular school by the age of 19 years. At 24, she developed generalized dystonia and chilblains on the toes were noted for the first time. Cerebral MRI and laboratory study with CSF analysis were normal. At that time, AGS diagnosis was suspected after her sister was diagnosed with the condition. A CT scan was ordered, disclosing basal ganglia calcifications, and subsequent genetic testing was positive for the c.529G>A,p.A177T mutation. The patient currently receives regular botulinum toxin treatment and maintains her job.

The middle sister of this family is 42 years old. She is asymptomatic, with normal neurological condition, no chilblains, and negative genetic testing for the *RNASEH2B* mutation.

Discussion

AGS is characterized by a wide phenotypical variability. Presentation may range from severe neonatal forms, with total functional impairment, to later onset forms, with milder phenotypes.[1] Neonatal forms may be associated with several mutations, with *RNASEH2B*, *SAMHD1*, and *ADAR* more commonly associated with milder AGS phenotypes and better cognitive performance.[6] Cases with marked intrafamilial differences are uncommon. One study reported the case of 2 siblings with a homozygous mutation in the *RNASEH2C* gene, 1 with hemiplegia and normal intellect and the other with severe encephalopathy.[7] Another study reported the case of 2 asymptomatic adults with *IFIH1* mutations.[8]

Cases of asymptomatic carriers or mildly disabled patients with *RNASEH2B* homozygous mutations, such as patients 2 and 4 of this series, are rare. Importantly, despite carrying the same *RNASEH2B* homozygous mutation, both patients had impaired

siblings with full AGS phenotypes. On the other hand, siblings 5 and 6 of family C had disabling AGS with different progressions: 1 had late-onset AGS with intellectual preservation, whereas the other had neonatal AGS with severe disability since birth. Although the cause of this remarkable intrafamilial variability is unknown, it is acknowledged that genetic or environmental factors may result in different syndrome presentations.[7]

In this series, all patients were adults at the time of AGS diagnosis. A total of 3 patients had previous cerebral palsy diagnoses and were referred to our clinic for botulinum toxin treatments. However, basal ganglia calcifications on CT scan and chilblains raised the suspicion of an alternative diagnosis.

Skin lesions, brain calcifications, and white matter abnormalities are a consequence of brain exposure to high levels of interferon-α.[3] Interferon-α is a proinflammatory cytokine produced in response to viral infections, restricting viral replication. However, nucleic acids can also trigger an autoimmune interferon-mediated response, as occurs in SLE pathogenesis.[3] AGS-implicated mutations affect the gene coding for proteins involved in removing endogenous nucleic acid debris from cells.[1] Failure to do so results in the accumulation of nucleic acid products, activation of the innate immune system, and an increase in interferon-α levels, accounting for the similarity between AGS and congenital infections.[1] This response extends over the years, suggesting an ongoing inflammatory process.[9]

Basal ganglia calcifications are suggestive of congenital infection, but alternative diagnostics—such as AGS or Cockayne syndrome—should be considered if there is no evidence of infection.[1] Currently, head MRI is frequently used as primary imaging modality in children, but it may underestimate or even miss cerebral calcifications,[3,5] as occurred in patients 1 and 3. Therefore, a CT scan should be performed in patients with a clinical presentation suggestive of AGS. Moreover, smaller calcifications may correlate with better cognitive function, as observed in patients 1 and 6 and previously reported.[2]

Chilblain lesions are reported in approximately 40% of patients and may be associated with mutations in any of the previously mentioned genes.[2,6] Although not reported in the original syndrome description[10] and possibly developing only late in adolescence, chilblains are an important clue for a retrospective diagnosis,[4] as in the present series. Therefore, when examining a patient with a previous diagnosis of cerebral palsy, it is important to inquire about previous encephalopathy episodes and the presence of chilblains. The presence of basal ganglia calcifications should be investigated on CT scan despite normal head MRI.

In conclusion, the present study highlights the intrafamilial and interfamilial variability of AGS and documents the case of patients with asymptomatic or slightly symptomatic homozygous presentation forms. In addition, it emphasizes the important role of chilblains and CT imaging for a correct diagnosis.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

G.V.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
M.J.M.: 1C, 2C, 3B
I.L.: 1C, 2C, 3B
R.M.: 1B, 1C, 2C, 3B
R.T.: 1C, 2C, 3B
M.M.: 1A, 1B, 1C, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Patients or their parents gave informed consent prior to inclusion in this report.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. Segment 1: Patient 1 speaking about his current job as a web designer (in Portuguese); he had mild hypophonia and spastic dysarthria, whereas cognition and language were normal. Segments 2 and 3: generalized dystonia involving all limbs with fixed postures and a brisk pyramidal syndrome.

Video S2. Patient 3 with spastic tetraparesis and generalized dystonia.