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Original Article

Multiple Autoimmune Disorders in Aicardi-Goutières Syndrome

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ABSTRACT

Background: Aicardi-Goutières syndrome is an early-onset encephalopathy with presumed immune pathogenesis caused by inherited defects in nucleic acid metabolism. It is a model disease to study systemic autoimmunity, and there are many clinical, genetic, and basic science considerations that underline a possible overlap between Aicardi-Goutières syndrome and systemic lupus erythematosus.
Results: We describe a 15-year-old girl with Aicardi-Goutières syndrome due to compound heterozygous pathogenic variants in *SAMHD1* (sterile alpha motif domain and HD domain-containing protein 1). Over time, she developed multiple autoimmune diseases (vitiligo, alopecia areata, immune thrombocytopenia, positive antithyroglobulin antibodies) without positive antinuclear antibody or features of systemic lupus erythematosus. Her thrombocytopenia was refractory to treatment with corticosteroids and intravenous immunoglobulin but responded to a standard course of rituximab.
Conclusion: This is the first report of a multiple autoimmune syndrome in a patient with molecularly proven Aicardi-Goutières syndrome. This study illustrates an emerging pattern of the natural history of Aicardi-Goutières syndrome characterized by early encephalopathic presentation followed by symptoms of systemic autoimmunity.

Introduction

Aicardi-Goutières syndrome (AGS) is a rare monogenic disorder that features an inflammatory encephalopathy that clinically resembles an *in utero* viral infection. It is caused by pathogenic variants in at least seven genes (*ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1*, or *IFIH1*) encoding enzymes involved in the metabolism of intracellular nucleic acid.[1,2] With the identification of the genetic basis of AGS, the clinical phenotype has expanded to a wide spectrum of neurological and non-neurological phenotypes. More recently, AGS has been linked to systemic autoimmune disorders, particularly systemic lupus erythematosus (SLE).[3] We describe a 15-year-old with genetically confirmed AGS who developed multiple autoimmune diseases without antinuclear antibody or features of SLE.

Patient description

This girl was born at 34 weeks' gestation to a primigravida mother. Her parents were nonconsanguineous. She had intrauterine growth retardation, and at birth her weight was 1.3 kg (less than the third percentile). Pregnancy was also complicated by prolonged rupture of membranes, and she was born via Caesarean delivery. After birth, her examination was significant for a reduced level of consciousness, depression of tone and reflexes, and feeding difficulty, and she remained in the neonatal intensive care unit for four weeks. In early infancy, she exhibited severe global

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Informed consent: Informed consent was obtained from the parents of the child included in the study

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developmental delay and bilateral knee contractures. Brain magnetic resonance imaging (MRI), performed at ages one and five years, showed bilateral increased signal frontal lobe lesions with the fluid-attenuated inversion recovery and T2-weighted MRI sequences. A small 7-mm cyst was identified in the right frontal lobe (Fig). Initial extensive metabolic and genetic studies (karyotype, chromosomal microarray, methylation studies for Angelman and Prader-Willi syndromes, and sequencing of *MECP2*) were unremarkable. At age 14 years, she was evaluated by a dermatologist for well-demarcated round patches of hair loss on the scalp and scattered depigmented patches on the face, trunk, and extremities. She was diagnosed with generalized vitiligo and alopecia areata. Follow-up neuroimaging showed bilateral basal ganglia calcification (Fig).

Neurological examination was significant for severe microcephaly, spastic quadriparesis, and the presence of intermittent dyskinetic movement of upper extremities. She was nonverbal and wheelchair-bound.

Owing to the absence of a unifying diagnosis of her microcephaly, neonatal-onset encephalopathy, cerebral palsy, and multiple autoimmune diseases, next-generation sequencing was done targeting 427 genes specific to the intellectual ability, which revealed two heterozygous pathogenic variants (c.1270G>C and c.658C.T) in the *SAMHD1* (sterile alpha motif domain and HD domain-containing protein 1), consistent with AGS 5 (OMIM # 612952), an autosomal recessive condition.

A few months later, she presented with episodes of hematemesis secondary to thrombocytopenia (5000/μL). Testing for IgG and IgM direct antiplatelet antibodies was strongly positive. Bone marrow aspiration ruled out malignancy and bone marrow failure. She was diagnosed with immune thrombocytopenia, which was refractory to conventional first-line therapy including intravenous immunoglobulin and high-dose corticosteroid administration. However, she ultimately responded to a standard four-week course of rituximab with the maintenance of a normal platelet count. She had an extensive autoimmune and

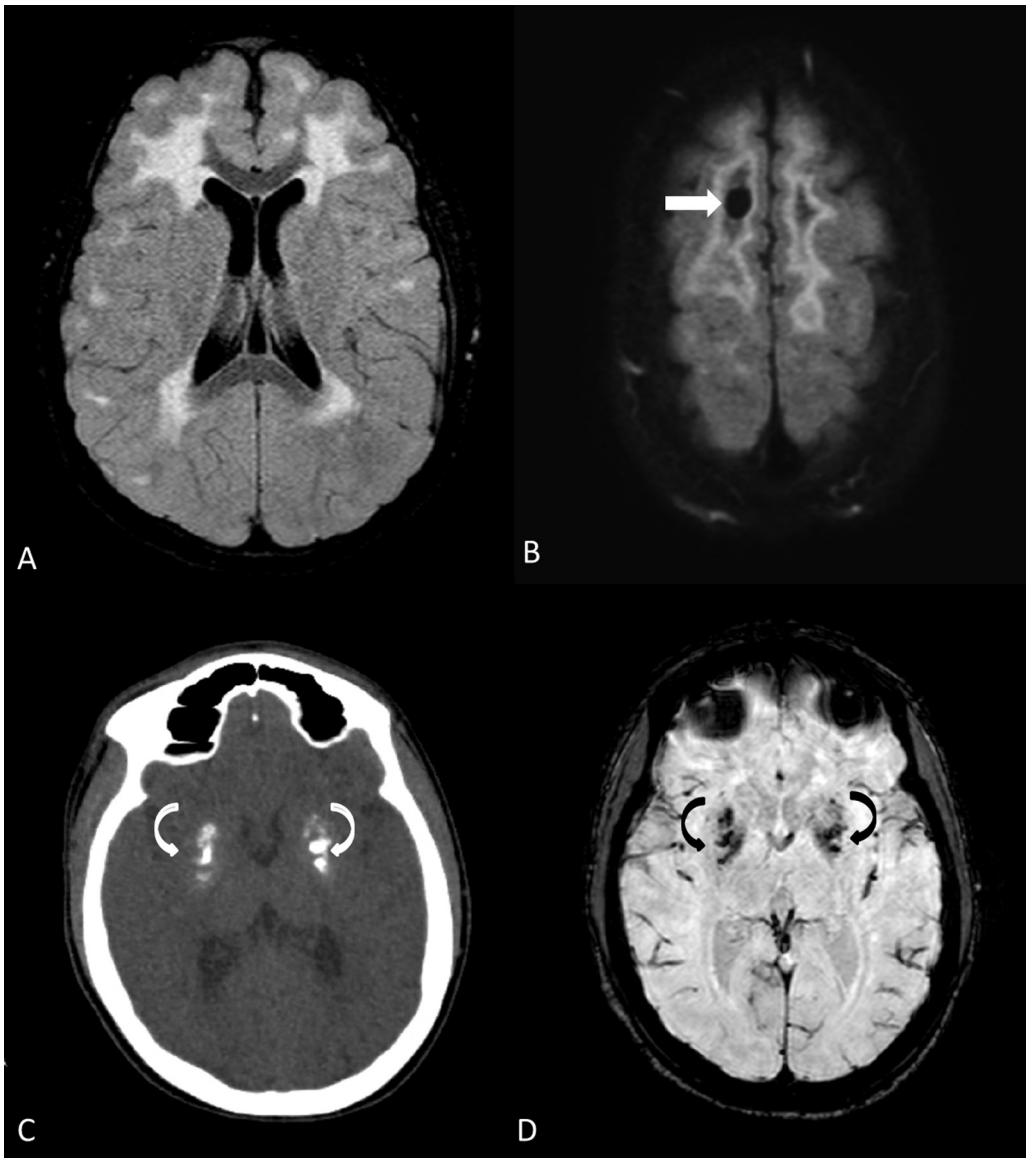

FIGURE. Axial FLAIR (fluid-attenuated inversion recovery) MRI sequence at age five years (A) shows bilateral symmetric areas of white matter hyperintensity. The white matter hyperintensity was more severe in the frontotemporal region with sparing of the internal and external capsules. Axial FLAIR image (B) at the level of the vertex showed a focal cystic change (arrow). Axial noncontrast computed tomography (C) at age 14 years shows bilateral symmetric globus pallidus calcification (curved arrows) corresponding to the reduced signal lesions (curved arrows) on the axial susceptibility sequence of the brain MRI (D).

TABLE.
Three Proposed Groups of Multiple Autoimmune Syndrome

Type I	Myasthenia, thymoma, polymyositis, and giant cell myocarditis
Type II	Sjögren syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma, autoimmune thyroid disorders
Type III	Autoimmune thyroid disease, myasthenia or thymoma, Sjögren syndrome, pernicious anemia, idiopathic thrombocytopenic, Addison disease, insulin-dependent diabetes, vitiligo, autoimmune haemolytic anemia, systemic lupus erythematosus

inflammatory evaluation, which showed either normal or negative findings except positive anti-thyroglobulin antibodies. Owing to the presence of several autoimmune diseases, such as vitiligo, alopecia areata, immune thrombocytopenia, and autoimmune thyroid disease, she was diagnosed with multiple autoimmune syndrome (MAS).

Discussion

MAS is characterized by the presence of at least three distinct autoimmune diseases in one individual.[4] Among the three types of MAS, our patient can be classified as having Type III (Table)[5]. Autoimmune skin disorders such as vitiligo and alopecia areata are commonly reported as one of the first symptoms of MAS, as noted in our patient. Autoimmune thyroid disease is also commonly present in individuals with MAS, especially in patients with vitiligo. The pathogenesis of MAS is not known, but genetic, infectious, and immunologic factors may play significant roles in the development of MAS. Owing to the diverse and complex phenotype and pathogenesis of MAS, the genetic susceptibility of this complex disease can be investigated by studying monogenic disorders, in which a single-gene defect is responsible for the phenotype.

The likely pathogenesis of AGS involves a failure in the removal process of endogenously produced nucleic acids with subsequent activation of the innate immune system.[6] In addition, AGS is considered a model disease for systemic autoimmunity.[7] Systemic autoimmunity develops from a loss of immunologic tolerance by the inability of the immune system to discriminate self from nonself. AGS also shares clinical and serologic features with SLE. Pathogenic mutations in *TREX1* (an AGS gene) is the single most common etiology of monogenic SLE. Ramantani et al. reported 12 patients with AGS (in a cohort of 20 patients) who had symptoms similar to SLE, such as thrombocytopenia, leukocytopenia, antinuclear antibodies, erythematous skin lesions, oral ulcers, and arthritis.[8] However, no examples of SLE were included in a large cohort of 123 patients with AGS.[9] This cohort contained two individuals with hypothyroidism, two with insulin-dependent diabetes mellitus, and six with an abnormal antibody profile. No patient with MAS was reported in either of these two large cohorts. It has been postulated that the autoimmune features seen in AGS are probably due to interferon-α dysregulation, a pathogenetic mechanism common with systemic autoimmunity.[10]

The diagnosis of AGS in our patient was established by the identification of biallelic pathogenic variants in *SAMHD1,* which is a deoxynucleotide triphosphohydrolase and breaks down deoxynucleoside triphosphate to deoxynucleoside and inorganic triphosphate in the catabolic process to maintain a stable deoxynucleoside triphosphate pool.[11] Nucleotide metabolism is precisely controlled inside the cell, by a balanced synthetic and catabolic pathway. A pathogenic mutation of SAMHD1 alters the intracellular degradation of endogenous nucleic acids and produces inappropriate and massive interferon response by activation of the innate immunity. Moreover, SAMHD1 acts as a negative regulator of the antiviral immune response and was shown to be upregulated in response to viral infections.[12]

At present, there is not an effective cure for AGS or MAS. Current treatment approaches for MAS include nonspecific immune suppression with corticosteroids and other cytotoxic drugs with considerable side effects. An etiologic link between AGS and MAS may also have direct implications for the clinical management. Conventional therapy with corticosteroids and immunoglobulin was not effective for our patient's immune thrombocytopenia, but she responded well to the anti-CD-20 therapy with rituximab. It is possible that recently discovered biologics that target specific lymphocyte populations, inflammatory cytokines, or other molecules may provide novel targeted therapeutic benefits in these patients.

Conclusion

MAS in a patient with molecularly proven AGS defines the immunologic disease continuum and highlights the interplay between the innate and adaptive immune systems in the pathogenesis of systemic autoimmunity. Induction of autoimmunity initiated by immune recognition of endogenous nucleic acids may represent a novel pathogenic pathway of MAS and may have direct implications on the clinical management.

References

1. Crow YJ. Aicardi–Goutières syndrome. In: Handbook of Clinical Neurology. Vol. 113. Elsevier; 2013:1629–1635.
2. Al Mutairi F, Alfadhel M, Nashabat M, et al. Phenotypic and molecular spectrum of Aicardi-Goutières syndrome: a study of 24 patients. Pediatr Neurol. 2018;78:35–40.
3. Ramantani G, Häusler M, Niggemann P, et al. Aicardi-Goutieres syndrome and systemic lupus erythematosus (SLE) in a 12-year-old boy with SAMHD1 mutations. J Child Neurol. 2011;26:1425–1428.
4. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. Maedica. 2010;5:132.
5. Humbert P, Dupond JL. Multiple autoimmune syndromes. Ann Med Interne (Paris). 1988;139:159–168.
6. Crow YJ, Rehwinkel J. Aicardi-Goutieres syndrome and related phenotypes: linking nucleic acid metabolism with autoimmunity. Hum Mol Genet. 2009;18:R130–R136.
7. Lee-Kirsch MA, Wolf C, Günther C. Aicardi–Goutières syndrome: a model disease for systemic autoimmunity. Clin Exp Immunol. 2014;175:17–24.
8. Ramantani G, Kohlhase J, Hertzberg C, et al. Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutières syndrome. Arthritis Rheum. 2010;62:1469–1477.
9. Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. Am J Hum Genet. 2007;81:713–725.
10. Fazzi E, Cattalini M, Orcesi S, et al. Aicardi–Goutieres syndrome, a rare neurological disease in children: a new autoimmune disorder? Autoimmun Rev. 2013;12:506–509.
11. Goldstone DC, Ennis-Adeniran V, Hedden JJ, et al. HIV-1 restriction factor SAMHD1 is a deoxynucleoside triphosphate triphosphohydrolase. Nature. 2011;480:379.
12. Lahouassa H, Daddacha W, Hofmann H, et al. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat Immunol. 2012;13:223.