Neurologic Phenotypes Associated with Mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, and *IFIH1*: Aicardi–Goutières Syndrome and Beyond

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Abstract

The Aicardi–Goutières syndrome (AGS) was first described in 1984, and over the following years was defined by the clinical and radiological features of an early onset, severe, neurologic disorder with intracranial calcification, leukoencephalopathy, and cerebral atrophy, usually associated with a cerebrospinal fluid (CSF) pleocytosis and elevated CSF interferon α activity. It is now recognized that mutations in any of the following seven genes may result in the classical AGS phenotype: *TREX1* (AGS1), *RNASEH2A* (AGS2), *RNASEH2B* (AGS3), *RNASEH2C* (AGS4), *SAMHD1* (AGS5), *ADAR1* (AGS6), and *IFIH1* (AGS7). All of these genes encode proteins involved in nucleotide metabolism and/or sensing. Mutations in these genes result in the induction of type 1 interferon production and an upregulation of interferon stimulated genes. As more patients harboring mutations in these genes have been described, in particular facilitated by the advent of whole exome sequencing, a remarkably broad spectrum of associated neurologic phenotypes has been revealed, which we summarize here. We propose that the term AGS has continued clinical utility in the designation of a characteristic phenotype, which suggests relevant diagnostic investigations and can inform outcome predictions. However, we also suggest that the use of the term "type 1 interferonopathy" is appropriate for the wider spectrum of disease consequent upon dysfunction of these genes and proteins since it implies the possibility of a common "anti-interferon" approach to therapy as such treatments become available.

Keywords
- Aicardi–Goutières syndrome
- type 1 interferonopathies
- interferon signature

Introduction

In 1984, Jean Aicardi and Francoise Goutières described eight children with an early onset, progressive, and severe neurologic disorder demonstrating imaging features of intracranial calcification (ICC), leukoencephalopathy, cerebral atrophy, and a cerebrospinal fluid (CSF) pleocytosis.[1] Despite the resemblance to congenital infection, the occurrence of affected siblings and consanguinity in some families suggested a genetic basis to this phenotype. In 1988, elevation of CSF and serum interferon α was demonstrated in these patients.[2] Further cases were

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subsequently reported, cutaneous features and autoimmune disease were noted, and the condition became known as Aicardi–Goutières syndrome (AGS).[3–8]

In the past decade, the genetic basis of AGS has been determined, and it is now recognized that mutations in any of seven genes can be associated with this phenotype, namely, *TREX1* (AGS1),[9] *RNASEH2A* (AGS2), *RNASEH2B* (AGS3), *RNASEH2C* (AGS4),[10] *SAMHD1* (AGS5),[11] *ADAR1* (AGS6),[12] and *IFIH1* (AGS7).[13] Mutations in these genes account for around 95% of patients with classical AGS. In most cases, inheritance is autosomal recessive; however, specific heterozygous gain-of-function mutations have been observed in *TREX1* and *ADAR1*, and all AGS-related mutations in *IFIH1* are dominant.

Although experience suggests that AGS "runs true" in most families, marked intrafamilial variation in disease expression is also well recognized. By way of illustration, Vogt et al described a family harboring homozygous *RNASEH2C* mutations in which one child had a severe AGS phenotype, whereas a sibling with the same mutations demonstrated chilblains and a very mild hemiparesis, with completely preserved cognitive function and a virtually normal magnetic resonance imaging (MRI).[14] Furthermore, and of particular note here, extended genetic screening, in particular through the use of whole exome sequencing, has revealed a remarkably broad spectrum of disease phenotypes associated with mutations in the AGS-related genes.[15]

The preceding observations raise important points of nosology, with practical implications for both clinicians and families. We have recently suggested the use of the term "type I interferonopathies" as a novel disease grouping, encompassing all monogenic phenotypes associated with a pathological upregulation of type I interferon signaling, including those due to mutations in *AGS1–7*.[16] Such a proposal has its justification in the recognition that therapies directed toward reducing type I interferon production and/or blocking type I interferon-induced signaling might be relevant to any patient with mutations in these genes. At the same time, as physicians, we recognize that diseases present as clinical scenarios, and phenotypic classification can inform prognosis.

Summary papers relating to the genotype–phenotype correlation and pathogenesis of the type I interferonopathies have been published recently.[15,17] Here, then, we have decided to describe the range of currently recognized stereotyped clinical scenarios that can present to the pediatric neurologist due to mutations in the seven AGS-related genes

Table 1 Summary of major clinical features associated with mutations in *TREX1, RNASEH2A/B/C, SAMHD1, ADAR1*, and IFIH1

Genotype	*TREX1*	*RNASEH2 A/B/C*	*SAMHD1*	*ADAR1*	*IFIH1*
Neurologic					
Developmental delay	•	•	•	•	•
Regression	•	•	•	•	•
Epileptic seizures	•	•	•	•	•
Motor disorder (dystonia/spasticity)	•	•	•	•	•
Eye movement abnormalities	•	•	•	•	•
Spastic paraparesis		•		•	•
Large vessel disease (stenosis/moyamoya/aneurysms)	•		•		
Bilateral striatal necrosis				•	
Neuroimaging					
Intracranial calcification	•	•	•	•	•
White matter abnormality	•	•	•	•	•
Cerebral atrophy	•	•	•	•	•
Other					
Recurrent (sterile) fevers	•	•	•	•	•
Autoimmune features	•	•	•	•	•
Glaucoma	•	•	•		•
Neonatal thrombocytopenia/bone marrow suppression	•	•	•	•	•
Hypertrophic cardiomyopathy	•	•			•
Chronic lymphocytic leukemia			•		
Premature dental loss					•
Aortic calcification					•
Joint contractures	•		•		•

Note: Aortic calcification occurs in the Singleton–Merten syndrome (SMS) caused by mutations in *IFIH1*. Patients with overlapping features between SMS and Aicardi–Goutières syndrome have recently been reported.[31]

(►**Table 1**). In some cases, these phenotypes represent distinct clinical entities, triggering different clinical trains of thought, differential diagnoses, investigative strategies, and prognostic considerations. At the same time, we also highlight the fact that an overlap of core features can be observed, encompassing the clinical signs of spasticity and dystonia, and the radiological features of ICC and white matter disease, which can thus serve as vital clues to the true underlying diagnosis.

Prenatal Onset Aicardi–Goutières Syndrome

Mutations in any of the seven AGS genes may result in this phenotype. However, *TREX1* mutations are most commonly associated with a true neonatal presentation that is, with onset of disease in utero. This clinical scenario represents a remarkable clinical mimic of transplacentally acquired infection (pseudo-TORCH)—associated with disturbed neurology at birth including irritability, feeding difficulties, jitteriness, microcephaly, abnormal movements, and epileptic seizures—as well as hematological disturbance such as major thrombocytopenia with petechia and anemia, and liver dysfunction. Although these systemic features can resolve after a few weeks, such a presentation is invariably associated with profound developmental effects and a markedly increased risk of death in infancy.

Infantile Onset Aicardi–Goutières Syndrome

Demonstrating essentially the same features as the neonatal form described previously, AGS most frequently has a clinically obvious onset after birth, with patients initially leaving hospital and then presenting in the first few months of life. In this scenario, parents frequently report the relatively abrupt onset of irritability and crying, with the children being apparently inconsolable and sometimes experiencing recurrent episodes of sterile pyrexias. In some cases, it is clear that development has been completely normal prior to this point, and disease onset is associated with a loss of previously acquired skills. In others, the initial level of development is difficult to gauge. Whatever the case, neurologic abnormalities commonly seen include evolving limb hypertonia with truncal hypotonia, dystonia, excessive startle, eye movement abnormalities, and epileptic seizures. The encephalopathic stage typically lasts for several months, during which time there is neurologic regression and a slowing of head growth. This clinical scenario, the most frequent presentation of AGS, can be associated with mutations in any of the AGS-related genes, although mutations in *RNASEH2B* represent the most frequent genotype seen in this context.

In both scenarios described previously, the major clue to the diagnosis usually comes from neuroimaging with a highly characteristic pattern comprising diffusely abnormal white matter often with swelling of temporal or frontal lobes, cerebral atrophy, particularly involving anterior temporal lobes, and ICC (►**Fig. 1**).[18–20] This combination of features is essentially pathognomonic.[21]

Later Onset Aicardi–Goutières Syndrome

Although effectively comprising the similar clinical and radiological markers, we highlight here that mutations in *AGS1–7* can present beyond the first year of life with the abrupt/subacute onset of profound neurologic regression.[5,6,22,23] As an example, we have seen a male with a de novo heterozygous mutation in *IFH1* who showed completely normal development until the age of 15 months, at which time he could walk and had 6 to 10 words. After this point, he developed intermittent posturing and rigidity of his legs, and then of the upper extremities. He also developed exaggerated startle. He subsequently experienced a relentless loss of motor and intellectual skills, and by the age of 24 months, he was unable to sit unsupported and had lost the ability to swallow. Between 15 months and 4 years of age, he demonstrated a fluctuating pattern of poor sleep, with persistent whining and crying. Now, at the age of 13 years, he has no useful hand function, cannot sit independently, and has limited words, although his understanding is relatively preserved. Calcification of the basal ganglia and white matter were observed on cranial CT imaging at the age of 2 years, with abnormal high signal of the deep white matter seen on T2 weighted MRI. Similar cases have been described in the context of mutations in *RNASEH2B* and *ADAR1*.

Bilateral Striatal Necrosis

Dystonia represents a significant component of the neurologic phenotype in classical AGS.[17] Following the identification of mutations in the *ADAR1* gene as the cause of AGS6, it was recognized that some patients with otherwise typical AGS also had imaging evidence of bilateral striatal necrosis (BSN).[24] Furthermore, some patients were identified who had presented with an acute or subacute onset of dystonia with imaging features of BSN rather than classical AGS. A review of patients with unexplained severe dystonia identified further cases with this phenotype; therefore, it is now recognized that *ADAR1* mutations are an important cause of BSN.[25] Most patients are normal before the rapid onset of dystonia associated with MR features characteristic of BSN. Importantly, in many cases, the onset of disease was preceded by an infectious illness. The clinical course can be severe, with progressive dystonia and early death in some patients. Of note, disease onset can occur early or much later in life (we are aware of one child with disease onset in her sixth year). ICC is not invariable in this situation; therefore, we strongly recommend that ADAR1-related disease be considered in any child presenting with BSN or otherwise unexplained subacute onset dystonia.

Hereditary Spastic Paraparesis

Peripheral hypertonia is invariable in patients with classical AGS. However, recent experience, informed particularly by the results of whole exome sequencing, has shown that patients with "idiopathic spastic paraparesis" can be identified due to mutations in *ADAR1, IFIH1*, and *RNASEH2B*.[26] We emphasize here that neuroimaging can be completely normal. Our experience to date indicates that this phenotype can be slowly progressive over

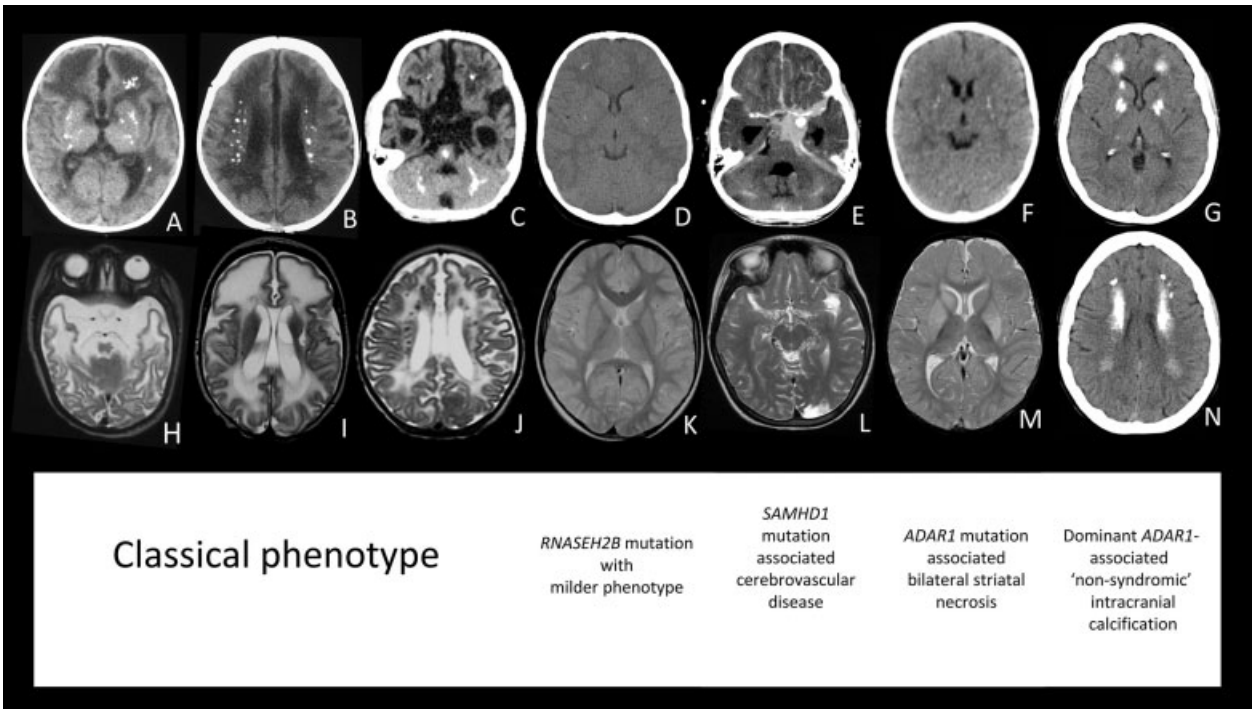

Fig. 1 Imaging features associated with mutations in Aicardi–Goutières syndrome (AGS) related genes. (**A–C**) Computed tomography (CT) and (**H–J**) T2 magnetic resonance (MR) images of the classical AGS phenotype demonstrating (**A, B**) spot calcification of basal ganglia, thalami, and deep white matter and (**C**) calcification of pons and cerebellum. (**H, I**) Abnormal white matter with swelling of anterior temporal and frontal lobes. Also note the characteristic pattern of atrophy involving the anterior temporal lobes. Calcification is apparent on the (**J**) T2 MR image as low signal spots within the deep white matter. (**D**) CT and (**K**) MR image of a patient with a milder phenotype associated with *RNASEH2B* mutations showing subtle spot calcification in the putamen and deep frontal cortex (**D**) and normal MR appearances (**K**). Large cerebral artery disease is particularly associated with *SAMHD1* mutations. (**E**) CT showing a subarachnoid hemorrhage and a large aneurysm of the left carotid artery. (**L**) MR image from a different patient shows old ischemic damage in the left occipital region and extensive moyamoya type basal neovascularization. (**F**) CT and (**M**) MR image of a patient with *ADAR1* mutation-associated bilateral striatal necrosis. The CT shows bilateral calcification in the putamen. The T2 MR image shows bilateral high signal and swelling in the caudate and putamen. (**G, N**) Widespread deep white matter and basal ganglia calcification is demonstrated in these CT images from a mildy symptomatic adult harboring a dominant *ADAR1* mutation. Her son, carrying the same dominant mutation (p.G1007R), has a typical AGS phenotype.

many years, being apparently confined to the lower limbs, and in the context of completely preserved intellect. The oldest known patient demonstrating this clinical scenario is now aged 34 years and clinically has an isolated lower limb spasticity.

SAMHD1-Related Cerebrovascular Disease

Although biallelic mutations in *SAMHD1* can be associated with classical AGS, we have observed a marked variability in the clinical features associated with this genotype, which we discuss separately here. We emphasize that SAMHD1-related disease can be associated with a degree of developmental delay typical of classical AGS or with completely preserved normal intellect. Our experience suggests that extraneurologic involvement (see later), particularly skin disease and glaucoma, is frequently presently in the context of this genotype. A particular feature of SAMHD1-related disease is the risk of intracerebral large vessel involvement, including moyamoya, aneurysms, stenosis of single vessels with infarcts, and intracerebral hemorrhage.[27] By way of illustration, we know of a child with clinical and radiological features of typical AGS whose older sister, harboring the same homozygous mutation in *SAMHD1*, is completely intellectually normal with an unremarkable medical history except for recurrent winter chilblains. Remarkably, and in contrast to her younger sibling, this young woman was identified to have significant cerebral large vessel disease on magnetic resonance angiography following the diagnosis of AGS in her sister.

Further Clues to the Diagnosis: Nonneurologic Features

Skin lesions, most frequently referred to as chilblains, are an important feature of mutations in *AGS1–7*.[7,8,17,28] They are exacerbated by cold temperature and are thus more commonly seen in the winter months. Glaucoma is also a recurrent feature, which can present in the neonate or later[17,29]; therefore, currently we recommend screening at least annually. Features of autoimmunity, most commonly thyroiditis and less frequently lupus-like disease, can also occur.

Is Aicardi–Goutières Syndrome a Progressive Disorder?

Although initially considered a neurodegenerative, progressive disease, as more patients have been studied longitudinally, this point has come into question. In our opinion, the most classical clinical course is of a period of several months

of neurologic regression in infancy associated with progressive radiological changes. For most patients, the disease then stabilizes, leaving the child with profound disabilities. Death in childhood occurs in a proportion of patients; however, for most, the course is one of survival without further evident deterioration. A recent review of 374 patients with mutations in the seven AGS-related genes identified 67 (19.3%) patients who had died (half before the age of 5 years), 68 (19%) who had lived beyond 15 years of age, and 8 beyond the age of 30 years.[17] Of the almost 300 patients, where data were available, 210 (74%) had profound neurodisability (with no useful motor, speech, or intellectual function). Considering the fact that skin involvement can be recurrent and evidence of upregulated interferon signaling can be lifelong, "why" the disease is not more "obviously progressive" is unknown. Thus, the possibility of very slow progression and/or disease flares remains. Clear progression has been observed in the context of the single dominant G1007R mutation in *ADAR1* and in certain patients with spastic paraparesis.

The Concept of the Type 1 Interferonopathies

All of the seven genes that cause AGS are involved in nucleotide metabolism and/or sensing. *TREX1* and *RNASEH2A/B/C* are nucleases targeting deoxyribonucleic acid (DNA) and DNA–ribonucleic acid (RNA) hybrids, respectively. *SAMHD1* has a role in regulating cytosolic deoxynucleotides, *ADAR1* is a double-stranded RNA (dsRNA) editing enzyme, and *IFIH1* is a cytosolic receptor for dsRNA. Mutations in any of these genes can result in an induction of type 1 interferon production and an upregulation of interferon-stimulated genes. At a cellular level, this is analogous to the type 1 interferon response following exposure to viral DNA or RNA, thus perhaps explaining why the clinical features of AGS may resemble those of a viral infection. However, in contrast to exogenous viral infection, AGS is considered to represent an abnormal response to endogenous or self-derived nucleic acids.[15,16]

The detection of elevated levels of interferon α in the CSF and blood of patients with AGS was recognized soon after the disorder was described.[2] More recently, evidence for abnormal interferon activity in AGS has been demonstrated by identifying an "interferon signature" in peripheral blood. The interferon signature measures the expression of interferon stimulated genes and has been identified in almost 100% of patients with mutations in *TREX1*, *RNASEH2A*, *RNASEH2C*, *SAMHD1*, *ADAR1*, and *IFIH1*.[30] Of note, depending on the age at testing, up to 30% of patients with mutations in *RNASEH2B* might not show an interferon signature.

Conclusion

The unraveling of the genetic basis and pathogenesis of AGS has confirmed the original hypothesis of Aicardi, Goutières, and Lebon concerning the pathogenic similarity of the disease to congenital infection and the central role of interferon. At the same time, the phenotypic diversity described previously raises several important and currently unanswered questions including why are some genes more frequently associated with specific phenotypic features than others? What genetic or environmental factors determine the sometimes marked intrafamilial and between-gene variability of disease expression and penetrance?

We hold that the term AGS has clinical utility as the designation of a characteristic phenotype, which suggests relevant diagnostic investigations and can inform predictions of outcome. However, the diverse phenotypic spectrum associated with mutations in the AGS-related genes also indicates that the possibility of a genetic interferonopathy needs to be considered in the workup relating to several clinically distinct neurologic scenarios. The presence of telltale clinical features such as ICC and chilblains is diagnostically suggestive. However, the absence of such features does not exclude the diagnosis. The more widespread availability of whole exome/genome sequencing is likely to identify further patients in whom the identification of mutations in one of the AGS-related genes comes as a clinical surprise.

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