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Movement Disorders in Aicardi–Goutières Syndrome and Response to Immunomodulation

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ABSTRACT

This study characterizes movement disorders and treatment responses in seven children with Aicardi–Goutières syndrome (AGS). We retrospectively evaluated motor phenotypes, neuroimaging, and interferon signatures in patients treated with baricitinib or anifrolumab. Spasticity affected all patients, while dystonia was present in 4/7. GMFCS levels ranged from I to V. Following immunomodulation, interferon signatures normalized in 6/7 of patients, and 6/7 showed clinical stabilization or improvement, with no further regression events. These findings indicate that targeted therapy was associated with reduced systemic inflammation and stabilized disease. However, motor outcomes varied, suggesting that established CNS injury may limit functional recovery despite a biochemical response.

1 | Introduction

Aicardi Goutières syndrome (AGS) comprises a group of monogenic disorders characterized by chronic activation of the type I interferon pathway. AGS-associated genes include *TREX1*, *RNASEH2A/B/C*, *SAMHD1*, *ADAR*, *IFIH1*, *RNU7-1*, and *LSM11* [1, 2]. AGS presents with early-onset encephalopathy, mixed movement disorders, cognitive disability, epilepsy, recurrent fevers, and neuroimaging abnormalities including intracranial calcifications [1, 3]. Despite these characteristic features, genotype–phenotype correlations show remarkable variability, even between identical genotypes [4, 5]. Because of this phenotypic overlap and the rarity of AGS, affected individuals may be misdiagnosed as having cerebral palsy or hereditary spastic paraplegia [6]. With the increasing availability of targeted immunomodulatory therapies, movement disorder specialists must consider AGS early in the differential diagnosis, as timely treatment initiation may prevent or ameliorate long-term neurological disability.

JAK inhibitors and anifrolumab have emerged as a potential disease-modifying approach in type I interferonopathies, with small cohorts reporting favorable systemic outcomes. Baricitinib is an oral Janus kinase (JAK) 1/2 inhibitor that blocks downstream intracellular signaling of type I interferons and other inflammatory cytokines [7, 8]. Anifrolumab is a monoclonal

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antibody that directly antagonizes the type I interferon receptor (IFNAR), providing potent, targeted suppression [9]. Seminal multicenter studies have established the safety and systemic efficacy of JAK inhibitors in large pediatric AGS cohorts, demonstrating substantial improvements in systemic inflammatory markers; however, neurological and movement-related benefits remain variable and incompletely defined [7, 8]. In addition, anifrolumab use in AGS patients has not been described.

We characterize movement and motor disorder phenotypes in seven patients with AGS, describe their response to immunomodulation, and explore genotype–phenotype relationships. We hypothesized that while targeted therapy effectively reduces systemic interferon signatures, motor outcomes remain heterogeneous and are primarily dependent on the extent of baseline neurological injury.

2 | Methods

Following informed consent (Boston Children's Hospital IRB #P00033016), we reviewed seven cases of genetically confirmed AGS. We assessed longitudinal changes in motor phenotype, neuroimaging, treatments (baricitinib, anifrolumab), CSF neopterin, and adverse events. Interferon scores reflect CD169 expression on monocytes via flow cytometry through testing at Cincinnati Children's Hospital or at Boston Children's Hospital [10]. Prior to initiating JAK inhibitors, patients underwent evaluation for latent infections, including polymerase chain reaction (PCR) evaluations for Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV6). In addition, pretreatment evaluation was performed for infection with hepatitis B, hepatitis C, herpes simplex virus (HSV), human immunodeficiency virus (HSV), or *mycobacterium tuberculosis*. During treatment, BK virus levels in the urine and blood were regularly monitored, and other viral PCRs were tracked longitudinally as clinically indicated.

3 | Results

3.1 | Demographic and Molecular Spectrum

Seven patients with a median age of 10 years (range: 22 months–13 years) were included. Genotypes comprised *RNASEH2B* ($n=4$), *ADAR* ($n=1$), *TREX1* ($n=1$), and *IFIH1* ($n=1$) (Table 1). Median age at onset was 3.6 months (range 0–1.25 years) and median age at diagnosis was 1.7 years (range 0.2–10.25 years). Mean diagnostic delay was 3.15 years (range 0.2–9.25 years).

3.2 | Movement Disorders and Neurological Features

Movement and motor disorders were categorized into isolated and mixed phenomenologies. Spasticity was universal throughout the cohort (7/7). Isolated spasticity occurred in three patients (*RNASEH2B* ($n=2$), *IFIH1* ($n=1$)). A mixed movement disorder characterized by concurrent spasticity and dystonia was present in four patients (*ADAR* ($n=1$), *RNASEH2B* ($n=2$), *TREX1* ($n=1$)). Three patients had spastic tetraparesis (e.g., Patient 1, Video S1), three had spastic paraparesis (e.g., Patient 2, Video S2), and one had mild unilateral leg spasticity and weakness (Patient 3, Video S3). Axial hypotonia with appendicular hypertonia affected 6/7. Three patients had generalized dystonia (Patient 4, Video S4), one (Patient 5, Video S5) had focal lower-extremity dystonia that progressed to generalized involvement of the limbs, jaw, and neck, and three patients did not experience dystonia (Figure 1A). Pyramidal signs included hyperreflexia (6/7) and ankle clonus (6/7). Fine motor impairment was present in all patients, ranging from severe limitations with minimal hand use to mild impairments with preserved self-feeding abilities. Dysarthria or phonatory dysfunction occurred in 5/7, including two nonverbal patients. Seizures occurred in 4/7 patients and microcephaly in 5/7 patients (z-score range: −2.71 to −2.29).

3.3 | Functional Severity

Three patients were non-ambulatory with minimal head and trunk control (GMFCS V). Two individuals were wheelchair-dependent but retained partial truncal control (GMFCS IV), and one was ambulatory with limitations (GMFCS II). One had nearly age-appropriate mobility (GMFCS I). Ambulatory patients commonly exhibited toe-walking or spastic gait.

3.4 | Neuroimaging Findings

Neuroimaging demonstrated white matter signal and volume abnormalities and basal ganglia calcifications in 6/7 patients. Imaging findings remained stable in 5/7. One patient developed progressive cerebral volume loss despite treatment. Another patient, who presented with multiple early strokes, had no additional infarcts over 8.5 years of baricitinib therapy (Figure S1).

3.5 | Response to Immunomodulation

All patients received weight-adjusted baricitinib (2–8 mg daily in divided doses), with treatment durations ranging from 7 months to 8.5 years. Three patients transitioned to anifrolumab (5.5 mg/kg monthly) because of persistently elevated interferon signatures or treatment-limiting side effects. Interferon signatures normalized in 6/7 patients: four on baricitinib and two on anifrolumab. One patient demonstrated persistently elevated interferon scores 6 months after baricitinib initiation; however, concurrent persistent EBV viremia may have contributed to the elevated levels. CSF neopterin was elevated in most tested patients prior to immunomodulation (3/4). Repeat CSF testing after treatment initiation was not performed. Four patients (4/7) experienced pre-treatment episodes of developmental regression. No further acute regression events occurred after initiation of immunomodulatory therapy (Figure 1B).

Most patients (6/7) on immunomodulatory therapy had disease stabilization and no further regression events after treatment initiation. Patient 3 (*RNASEH2B*-related AGS) displayed resolution of chilblains and preservation of age-appropriate development (GMFCS I) with interferon normalization. Patient 6

TABLE 1 | Demographic, genetic, clinical, and neuroimaging features of seven children with Aicardi–Goutières syndrome.

Variable	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Gene	RNASEH2B	IFIH1	RNASEH2B	RNASEH2B	ADAR	RNASEH2B	TREX1
Variant	NM_024570.4: c.529G>A, (p.Ala177Thr) Homozygous	NM_022168.4: c.2336G>A (p.Arg779His) Heterozygous	NM_024570.4: c.529G>A (p.Ala177Thr) Homozygous	NM_024570.4: c.428_434delAGGAAAA (p.Glu144ValfsTer5)/ c.529G>A (p.Ala177Thr) Compound heterozygous	NM_015841.4: c.164C>T (p.Pro55Leu)/ c.3223A>T (p.Lys1075Ter) Compound heterozygous	NM_024570.4: c.529G>A (p.Ala177Thr)/ c.128C>A (p.Pro43His) Compound heterozygous	NM_033629.6: c.341G>A (p.R114H) Homozygous
AGS	AGS-2	AGS-7	AGS-2	AGS-2	AGS-6	AGS-2	AGS-1
Sex	F	F	M	F	M	M	F
Race/ethnicity	Asian	Hispanic	White	n.a.	n.a.	White	White
Birth history	Term, uncomplicated	Term, uncomplicated	Term, uncomplicated delivery, transposition of great arteries	Term, shoulder dystocia, brief NICU stay for meconium aspiration	Pre-term (33wk), NICU for feeding	Term, uncomplicated	Term, decreased fetal movements, low APGARs
Age at Onset	4 m	3 m	0 m	3w	1y	15 m	0 m
Initial Symptoms	Developmental delay, irritability, poor feeding	Hypotonia, developmental delay	Microcephaly at birth	Recurrent fevers, developmental delay, irritability	Developmental delay	Developmental delay	Hearing impairment, seizure, poor feeding
Age at Diagnosis	9 m	9y	1y	1y	10y	1y	2 m
Age at last follow up	5 y	13y	3y	10y	13 y	11y	22 m
Motor							
Spasticity	Spastic Tetraparesis	Spastic Paraparesis	Spastic Uniparesis	Spastic Paraparesis	Spastic Tetraparesis	Spastic Tetraparesis	Spastic Paraparesis
Dystonia				Generalized	Progressive generalized	Generalized	Generalized
Axial Hypotonia	+	+	+	+		+	+
Ambulatory		+	+				
GMFCS Level	V	II	I	IV	V	IV	V

(Continues)

TABLE 1 | (Continued)

Variable	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Fine motor impairment	Severe	Moderate	Moderate	Severe	Moderate	Mild	Severe
Hyperreflexia	+	+	+	+	+	+	
Cognitive							
History of Developmental Delay	+	+		+	+	+	+
History of Regression				+	+	+	+
Intellectual disability	+	+		+	+	+	
Phonatory dysfunction	Nonverbal	Normal	Normal	Dysarthria	Severe dysarthria	Mild dysarthria	Nonverbal
Language	Nonverbal	Minimally verbal	Verbal	Minimally Verbal	Minimally verbal	Verbal	Nonverbal
Other symptoms							
Seizures	+	+			+		+
Microcephaly	−2.43 (at 24 months)	−2.54 (at 26 months)	−2.31 (at 21 months)	−2.71 (at 23 months)			−2.29 (at 24 months)
Exaggerated Startle	+			+			+
Neuroimaging							
Basal ganglia calcification	+	+		+	+	+	+
Other calcifications	Parieto-occipital	Substantia nigra; red nucleus		Right frontal cortex		Periventricular	
White matter changes	+	+		+	+	+	+
Parenchymal volume loss	+	+			+		+
Thinning corpus callosum	+			+			+

(Continues)

TABLE 1 | (Continued)

Variable	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Other features		Cavum septum pellucidum	Nonspecific tiny foci of susceptibility signal in left frontal operculum and sylvian fissure			Multifocal infarcts; hemorrhagic foci; abnormal cauda equina clumping	
CSF Neopterin	n.a.	Elevated (120 nmol/L) prior to Baricitinib	Normal (13 nmol/L) prior to Baricitinib	n.a	Elevated (41 nmol/L) on Baricitinib prior to Anifrolumab	Elevated (n.a.) prior to Baricitinib	n.a.
Age at treatment initiation							
IVIG						1y	
Baricitinib	1y	13y	2y	1y	10y	2y	3 m
Anifrolumab				8y	12 y		1y
Treatment duration	4y5m	7 m	8 m	8y6 m (Baricitinib) 1y2 m (Anifrolumab)	2y2 m (Baricitinib) 1y (Anifrolumab)	2d (IVIG) 8y8 m (Baricitinib)	1y7 m (Baricitinib) 6 m (Anifrolumab)
Symptomatic treatment	Baclofen				Baclofen Botox injections Trihexyphenidyl Clonazepam	Botox injections	Trihexyphenidyl Clonazepam Clonidine
IFN Signature	Normalized	Elevated	Normalized	Normalized	Normalized	Normalized	Normalized
Imaging Changes	Stable	Stable	Stable	Stable	Stable	Stable	Progressed
Adverse Events on baricitinib	Thrombocytosis, Anemia, Hyperlipidemia, Elevated CK	Anemia	Elevated CK, Weight Gain	Elevated CK	Thrombocytosis, Elevated CK	Anemia	Hyperlipidemia, Weight Gain

(Continues)

TABLE 1 | (Continued)

Variable	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Treatment Discontinued or Wean	No	No	No	Transition from baricitinib to anifrolumab due to persistently elevated IFN and concern for neurological progression.	Transition from baricitinib to anifrolumab due to persistently elevated IFN and concern for neurological progression.	No	Transition from baricitinib to anifrolumab due to persistently elevated IFN, anemia and concern for neurological progression.

(*RNASEH2B*-related AGS), who had multiple early cerebral infarcts prior to treatment, had no further strokes or stroke-like episodes over more than 8 years of baricitinib and continued cognitive gains with interferon normalization. Patient 1 (*RNASEH2B*-related AGS) had improved alertness, disease stabilization, and interferon score normalization. Patient 4 (*RNASEH2B*-related AGS) showed improved engagement and vocalizations, along with disease stabilization and interferon signature normalization. Patient 2 (*IFIH1*-related AGS) remained clinically stable despite a persistently elevated interferon score. Patient 7 (*TREX1*-related AGS) had a mixed course: dystonia initially improved on baricitinib, which occurred concurrently with interferon signature normalization on a high dose of 2 mg QID. Despite the early motor response, cerebral volume loss progressed, and the patient developed severe side effects, prompting a transition to anifrolumab. The interferon signature has remained normal on anifrolumab for the 3 months since initiation with some improvement in irritability and autonomic instability.

One patient demonstrated clinical progression despite partial biochemical response. Patient 5 (*ADAR*-related AGS) had developmental regression episodes prior to baricitinib that did not recur after treatment initiation; however, spasticity and dystonia worsened over 3 years despite dose escalation and improvement (though not normalization) of interferon signature. After switching to anifrolumab, the interferon signature normalized, and while disease progression slowed, dystonia and functional status (GMFCS V) remained unchanged.

Adverse reactions to baricitinib included thrombocytosis (2/7), anemia (3/7), hyperlipidemia (2/7), elevated creatine kinase (4/7), and weight gain (2/7). These side effects were treatment-limiting in three patients and led to transition to anifrolumab. Anifrolumab was well tolerated, with no major adverse events reported. All 3 patients on anifrolumab were able to reduce the dose of baricitinib (2/3) or stop baricitinib (1/3) and maintain normalized interferon signature and clinical stability.

3.6 | Notable Individual Cases

Two patients sharing the *RNASEH2B* p.Ala177Thr homozygous variant (Patients 1 and 3) had markedly different clinical trajectories. Patient 1 developed severe encephalopathy in early infancy (onset 4 months) with developmental plateau, mixed hypertonia, and extensive basal ganglia calcifications, and remains profoundly impaired (GMFCS V) despite baricitinib initiation at age 2. In contrast, Patient 3, who had microcephaly at birth, was milder at baseline and followed a milder course (onset 2 years). After starting baricitinib at 2.5 years, he maintains age-appropriate development with independent ambulation (GMFCS I).

4 | Discussion

This case series refines the characterization of movement disorders in AGS and highlights both the potential and limitations of immunomodulatory treatment. Spasticity was a universal feature (7/7) yet has been infrequently quantified in

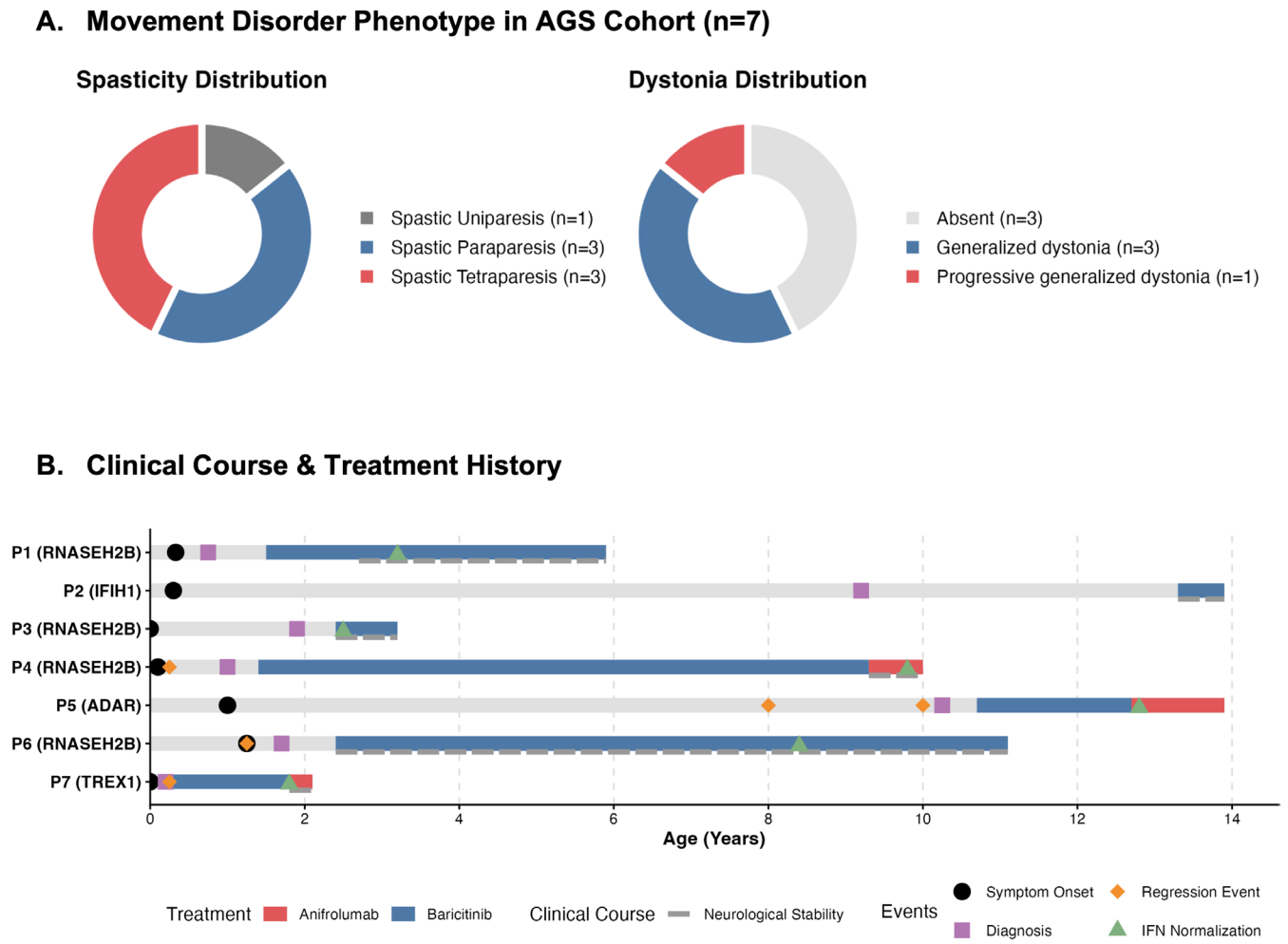

FIGURE 1 | Movement disorder phenotypes and clinical course in pediatric type I interferonopathies. (A) Distribution of motor phenotypes in the study cohort ($n = 7$). Spasticity was the predominant feature (7/7), presenting as spastic para- or tetra- or, in one case, mild unilateral leg spasticity. Dystonia was present in 4/7 of patients, ranging from focal to generalized forms. (B) Clinical timelines and treatment history stratified by genotype. Horizontal bars represent the duration of immunomodulation with baricitinib (blue) or anifrolumab (red). Markers indicate key clinical events: Symptom onset (black circles), molecular diagnosis (purple square), acute developmental regression (orange diamonds), and time point of interferon signature normalization (green triangles). The dashed horizontal gray line represents the documented period of neurological stability following the initiation of effective immunomodulatory therapy. Note the absence of new regression events following treatment initiation.

prior literature. Our findings underscore spasticity as a principal contributor to disability in AGS, with half of patients demonstrating lower extremity–predominant involvement and more than one third exhibiting spastic tetraparesis, closely mirroring published rates [11].

Extending beyond spasticity, dystonia was also prominent, affecting approximately two-thirds of patients (4/7), with a broad range of severity and progression. Mixed axial hypotonia with peripheral hypertonia (6/7) aligns with the largest published series ($n = 167$), in which dystonia and axial hypotonia were reported in 73.7% and 86.8% of patients, respectively [11].

The discordance between interferon normalization and clinical response echoes published experience with JAK inhibition in AGS [7, 8]. Although most patients in our cohort showed normalization of interferon signaling, only a subset experienced meaningful gains in dystonia or motor function. These observations support the potential limitations with interferon signaling inhibition. Limited clinical responses despite biochemical normalization may relate to poor central nervous system penetrance, particularly for large monoclonal antibodies like anifrolumab. However, another important limitation is the efficacy of interferon inhibition in the setting of established CNS injury, irreversible basal ganglia damage acquired before treatment. While the natural history trajectories in AGS include spontaneous disease stabilization, this timeline is variable and early targeted therapy is likely advantageous and can potentially prevent further irreversible injury and accumulation of motor deficits (e.g., Patient 5; see Appendix S1).

The striking severity difference between the two *RNASEH2B* p.Ala177Thr homozygous patients highlights the heterogeneity of AGS and the limited prognostic value of genotype alone [5, 12]. Despite relatively early intervention in both, differences in baseline CNS injury likely shaped long-term outcomes, emphasizing the limitations posed by the contribution of prenatal injury in some patients as well as the need for early recognition and treatment before further irreversible injury may occur.

Three patients transitioned to anifrolumab, a type I interferon receptor–blocking antibody that achieves robust interferon suppression in other interferonopathies, although AGS-specific data are limited [9]. Interferon normalization was achieved in two patients and was successfully maintained in one patient despite reductions in baricitinib dose, suggesting potential utility for individuals with persistent interferon activation or intolerance to JAK inhibition.

Regular peripheral interferon monitoring can guide decision making, particularly after dose adjustments. JAK inhibitors remain first-line given their established safety profile, while transition to anifrolumab is indicated for treatment-limiting adverse events or inadequate interferon suppression despite optimized dosing. The necessary duration of interferon suppression in AGS patients has not yet been defined, but at this time we consider treatment to be lifelong, as it has been observed that abrupt discontinuation can lead to neurological worsening [13]. Any necessary dose reductions should be gradual and accompanied by interferon signaling monitoring.

Limitations include the small retrospective cohort, variable treatment timing, and the lack of standardized goal-setting frameworks or objective neuropsychological assessments to formally quantify the pre-treatment disease burden and subsequent cognitive trajectories. Nevertheless, this detailed longitudinal phenotyping adds granularity to the emerging AGS literature. Overall, our findings suggest that interferon suppression may be associated with disease stabilization, though the disconnect between biochemical and motor responses suggests that factors beyond systemic interferon suppression, such as the timing of intervention and baseline CNS injury, critically shape motor outcomes. However, given the heterogeneity of AGS, distinguishing true therapeutic stabilization from the natural history of milder phenotypes remains challenging. Early genetic diagnosis and initiation of targeted therapy are still thought to be important clinically, and larger prospective studies are needed to define predictors of motor response and optimize treatment strategies.

Author Contributions

Enrique Gonzalez Saez-Diez and Monica Ferrer Socorro: Research Project: Design, Execution; Statistical Analysis: Design, Execution, Review and Critique; Manuscript Preparation: Writing of the First Draft, Review and Critique. Kathryn Yang, Zainab Zaman, Mariko Bennett, Andeline Vanderver, Pui Y. Lee and Lauren Henderson: Research Project: Execution; Statistical Analysis: Review and Critique; Manuscript Preparation: Review and Critique. Milena Andzelm: Research Project: Conception, Design, Execution; Statistical Analysis: Review and Critique; Manuscript Preparation: Review and Critique. Darius Ebrahimi-Fakhari: Research Project: Conception, Design, Execution; Statistical Analysis: Review and Critique; Manuscript Preparation: Writing of the First Draft, Review and Critique.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Clinical Vignettes. **Figure S1:** Neuroimaging findings in pediatric type I interferonopathies. (A) Axial CT image of Patient 1 with *RNASEH2B*-related AGS at 2 years 8 months (top) demonstrating basal ganglia and periventricular calcifications and axial T2/FLAIR MRI at 3 years 4 months (bottom) showing hypomyelination/demyelination in the subcortical white matter of the frontal lobes and periatrial regions with mild thinning of the corpus callosum; both studies were obtained during baricitinib treatment. (B) Axial T2/FLAIR MRI image of Patient 5 with *ADAR*-related AGS at 10 years 3 months (top) showing atrophy and abnormal signal of the putamina and caudate nuclei, scattered subcortical white matter T2 hyperintensities, and mild sulcal enlargement. Axial SWI images demonstrates basal ganglia calcifications. Imaging was obtained prior to baricitinib initiation. **Video S1:** Patient 1: A 5-year-old girl with homozygous RNASEH2B (NM_024570.4:c.529G>A;p.Ala177Thr) variants. The video, obtained at the last follow-up (age 5 years), demonstrates axial hypotonia and weakness with appendicular spasticity, and wheelchair dependence (GMFCS level V). **Video S2:** Patient 2: A 13-year-old girl with a heterozygous de novo IFIH1 (NM_022168.4:c.2336G>A; p.Arg779His) variant. The video, obtained at the last follow-up (age 13 years), demonstrates mild bilateral lower-extremity "predominant spasticity and mildly impaired gait" (GMFCS level II). **Video S3:** Patient 3: A 3-year-old boy with homozygous RNASEH2B (NM_024570.4:c.529G>A; p.Ala177Thr) variants. The video, obtained at the last follow-up (age 3 years), demonstrates independent ambulation (GMFCS level I) with a mild right-predominant spastic gait. **Video S4:** Patient 4: A 10-year-old girl with compound heterozygous RNASEH2B variants (NM_024570.4:c.428_434delAGGAAAA; p.Glu144ValfsTer5 / NM_024570.4:c.529G>A; p.Ala177Thr). The video, obtained at the last follow-up (age 10 years), demonstrates axial hypotonia, appendicular spasticity, and generalized dystonia, with wheelchair dependence (GMFCS level IV). **Video S5:** Patient 5: A 13-year-old boy with compound heterozygous ADAR variants (NM_015841.4:c.164C>T; p.Pro55Leu/NM_015841.4:c.3223A>T; p.Lys1075Ter). The video, obtained at the last follow-up (age 13 years), demonstrates prominent cervical dystonia, action-induced upper-limb dystonia, intermittent oromandibular dystonia, and lower-limb spasticity. The patient is wheelchair-dependent (GMFCS level V), with impaired fine motor skills and severe dysarthria.