RNASEH2B Pathogenic Mutation Presenting with Pure, Apparently Non-Progressive Hereditary Spastic Paraparesis

Sir,

Hereditary spastic paraparesis (HSP) is a group of heterogeneous conditions leading to spastic paraparesis, with or without additional neurological deficits.[1] Pure HSP presents with spastic paraparesis with bladder impairment and mild sensory impairment of the lower limbs alone.[1] Any additional neurological deficits are classified as complicated HSP. The inheritance patterns of HSP are diverse (autosomal dominant, autosomal recessive, mitochondrial, and X-linked), and genotype-phenotype correlations can usually be made based on the presenting features. Aicardi-Goutières Syndrome (AGS) is an autosomal recessive disorder usually presenting with early-onset encephalopathy resulting in severe intellectual impairment and physical disabilities.[2] It can result from pathogenic mutations in any of the following genes: *ADAR, RNASEH2A, RNASEH2B, RNASEH2C, TREX1, or SAMHD1*.[2] The presentation of *RNASEH2B*-associated AGS syndrome as an HSP phenotype is extremely rare, with only five reported cases globally.[3-5] We report the first such case from India.

A 16-year-old girl presented with complaints of difficulty in walking since she became independently ambulant at the age of 2 years. Although her walking difficulty was apparently non-progressive since onset, she complained of urinary urgency and occasional urge incontinence for the past 5 years (having achieved complete bladder control at the age of 4 years). She was born at term by vaginal delivery to non-consanguineous parentage, with normal developmental milestones for her age. There was no regression of milestones. She did not report any impairment in her cognitive abilities, hearing or vision, or other neurological deficits. There was no history of toxin exposure. Her family history was negative for similar illnesses.

Neurological examination revealed spastic paraparesis involving both lower limbs. The power of bilateral hips, knees, and ankles was 4/5 on the modified research council (MRC) score with grade 2 spasticity (modified Ashworth scale). Her lower limb reflexes were exaggerated without any clonus along with bilateral extensor plantar response. There was no sensory loss. Neurological examination of the upper limbs was normal. The ophthalmological examination did not reveal any optic atrophy.

Her routine investigations, including hemogram, hepatic, renal, and thyroid function tests, vitamin B_{12}, and folate levels, and serology for HIV were within normal limits. Magnetic resonance imaging (MRI) of the brain and spine were normal. Nerve conduction studies were normal [Figure 1]. A possibility of the pure form of hereditary spastic paraparesis (HSP) was considered. Whole exome sequencing revealed the presence of pathogenic compound heterozygous mutations on exon 7 of the *RNASEH2B* gene (c.529G>A and c.617-3C>G). This was confirmed by Sanger sequencing in her and her parents leading to a diagnosis of Aicardi-Goutières Syndrome. She was treated with oral baclofen for spasticity and is symptomatically better at one-year follow-up, with no increase in motor impairment.

AGS is a rare pediatric disorder. The classical features of AGS include early encephalopathy, profound intellectual impairment, spasticity, dystonia, microcephaly, skin lesions, organomegaly, and can resemble congenital infections. However, clinically milder and atypical forms are also reported, although genotype-phenotype correlation remains unclear. *RNASEH2B*-associated sporadic, pure HSP has previously described in five published cases to date[3-5] [Table 1]. Two patients were of Italian, two of Egyptian, and one of North African ancestry. We report the first case of Indian descent. All published cases so far presented in very early childhood and demonstrated the same pathogenic variant as our patient (c.529G>A) and presented with a similar phenotype of non-progressive spastic paraparesis without involvement of other neurological systems. We suggest that there may be a genotype-phenotype correlation between the c.529G>A variant, and a relatively benign course of HSP.

Table 1: Published cases of *RNASEH2B*-associated pure HSP phenotype

Ethnicity	Age of onset (years)	Clinical presentation	Consanguinity	Nucleotide alteration	Amino acid alteration	MRI Brain	Publication
Italian	Birth	Non-progressive pure HSP	No	c.529G>A	p.Ala177Thr	normal	Spagnoli C, *et al*.[5] 2018 Dec; 49(6):419
Egyptian	1	Non-progressive pure HSP	No	c.529G>A	p.Ala177Thr	normal	Crow YJ, *etal*.[3]Neuropediatrics 2014;45(06):386-393
Egyptian	2	Non-progressive pure HSP	No	c.529G>A	p.Ala177Thr	normal	
North African	1.5	Non-progressive pure HSP	No	c.529G>A	p.Ala177Thr	Diffuse, non-specific high signal on T2 weighted imaging	
Italian	2	Non-progressive pure HSP	Not known	c.529G>A	p.Ala177Thr	normal	Traveglini L, *et al*.[4] Neurogenetics 2018;19(02):111-121

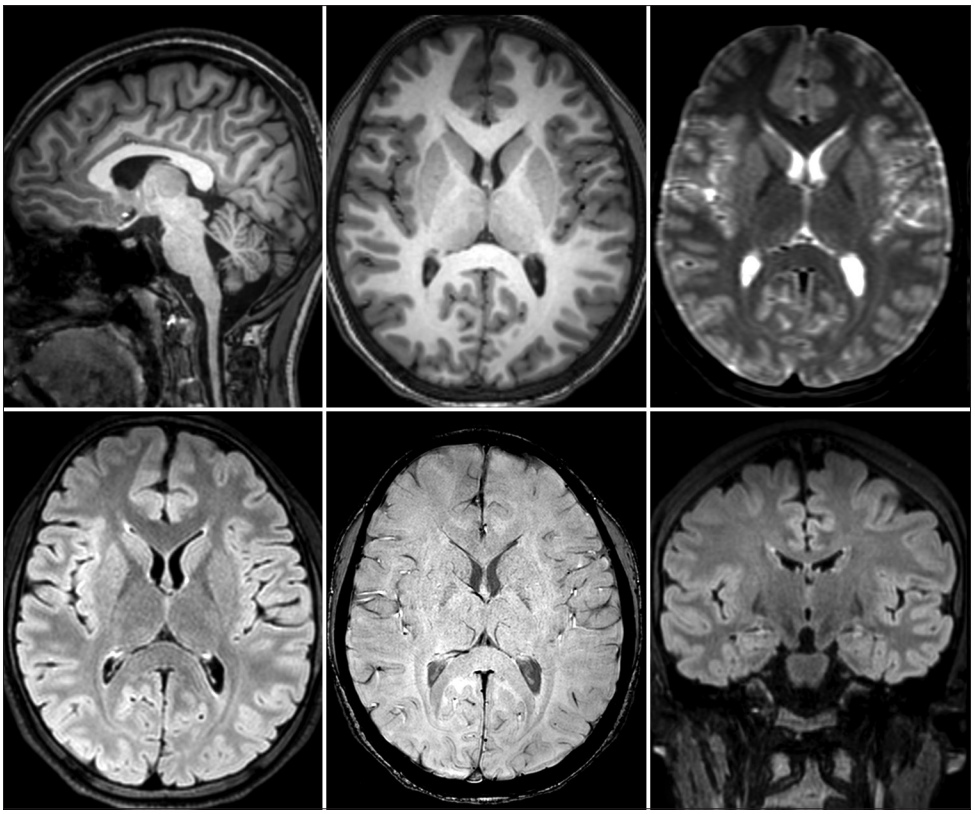

Figure 1: Normal MRI Brain

RNASEH2B-associated AGS is milder than AGS associated with other pathogenic variants.[6]

It may be worthwhile to consider AGS as a differential in patients presenting with apparently non-progressive HSP with onset in early childhood, especially in the presence of MRI features of thinning of the corpus callosum or 'ear of the lynx' sign, which are classically reported with certain HSP subtypes.

Learning objective:

- Aicardi-Goutieres syndrome should be considered as a differential in patients presenting with the non-progressive, pure form of hereditary spastic paraparesis.

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.

Ayush Agarwal, Divyani Garg, Ajay Garg[1], Achal K. Srivastava

Departments of Neurology and [1]Neuroradiology, AIIMS, New Delhi, India

Address for correspondence: Dr. Divyani Garg, Assistant Professor, Department of Neurology, AIIMS, New Delhi, India.
E-mail: divyanig@gmail.com

References

1. Finsterer J, Loescher W, Quasthoff S, Wanschitz J, Auer-Grumbach M, Stevanin G. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. J Neurol Sci 2012;318:1-18. doi: 10.1016/j.jns.2012.03.025.
2. Crow YJ. Aicardi-Goutières syndrome. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, *et al*., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2023.
3. Crow YJ, Zaki MS, Abdel-Hamid MS, Abdel-Salam G, Boespflug-Tanguy O, *et al*. Mutations in ADAR1, IFIH1, and RNASEH2B presenting as spastic paraplegia. Neuropediatrics 2014;45:386-93.
4. Travaglini L, Aiello C, Stregapede F, D'Amico A, Alesi V, Ciolfi A, *et al*. The impact of next- generation sequencing on the diagnosis of pediatric-onset hereditary spastic paraplegias: New genotype-phenotype correlations for rare HSP-related genes. Neurogenetics 2018;19:111-21.
5. Spagnoli C, Frattini D, Salerno GG, Fusco C. RNASEH2B pathogenic gene variant in uncomplicated hereditary spastic paraplegia: Report of a new patient. Neuropediatrics 2018;49:419.
6. Rice G, Patrick T, Parmar R, Taylor CF, Aeby A, Aicardi J, *et al*. Clinical and molecular phenotype of Aicardi-Goutières syndrome. Am J Hum Genet 2007;81:713-25.

Submitted: 08-Aug-2023 **Revised:** 25-Aug-2023 **Accepted:** 01-Sep-2023
Published: 25-Sep-2023

DOI: 10.4103/aian.aian_707_23