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Original Research Paper

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HETEROZYGOUS *RNASEH2B* (p.Ala177Thr) VARIANT IN A CHILD WITH RECURRENT HEADACHES AND EPILEPTIFORM EEG: DIAGNOSTIC CHALLENGES IN SUSPECTED AICARDI–GOUTIÈRES SYNDROME (AGS)

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ABSTRACT Aicardi–Goutières syndrome (AGS) is a genetically mediated type I interferonopathy characterized by early-onset encephalopathy, intracranial calcifications, and leukodystrophy. Mutations in *RNASEH2B* are among the most frequent causes of AGS type 2 (AGS2); however, heterozygous carriers are asymptomatic and do not manifest disease. We report a 4-year-old girl with normal early development who presented with recurrent occipital headaches, sleep disturbance, and occasional vomiting. MRI brain and metabolic evaluation were normal, while EEG showed frequent generalized epileptiform discharges. Headache frequency improved significantly with divalproate prophylaxis. Genetic testing revealed a heterozygous *RNASEH2B* c.529G>A (p.Ala177Thr) pathogenic variant, confirming a carrier state rather than AGS. This case underscores the importance of cautious interpretation of heterozygous interferonopathy-related variants in children presenting with nonspecific neurological symptoms.

KEYWORDS : RNASEH2B, Aicardi–Goutières syndrome, carrier state, headache, childhood epilepsy.

INTRODUCTION

Aicardi–Goutières syndrome (AGS) is a genetically determined type I interferonopathy that typically presents in early infancy with subacute encephalopathy, irritability, developmental regression, feeding difficulties, microcephaly, and seizures[1]. Neuroimaging commonly reveals basal ganglia calcifications, leukodystrophy, and cerebral atrophy[2]. Seven genes-*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, and *IFIH1*-are known to cause AGS, all of which disrupt nucleic acid processing and lead to chronic interferon pathway activation[3].

Among these, *RNASEH2B* variants are the most frequently identified worldwide. The c.529G>A (p.Ala177Thr) allele is particularly common and represents one of the most well-recognized AGS2-causing mutations[4]. However, AGS follows an autosomal recessive inheritance pattern, and individuals with heterozygous mutations are clinically unaffected[4 5]. With increasing use of genetic testing in children presenting with nonspecific neurological symptoms, heterozygous pathogenic variants are often detected incidentally, raising concern for misdiagnosis when clinical features are not supportive.

This case illustrates the importance of careful interpretation of heterozygous *RNASEH2B* variants in children presenting with common neurological complaints.

Case Report

A 4-year-old girl, born to third-degree consanguineous parents, presented with recurrent occipital headaches for several months. Her birth and developmental history were normal. The headaches were described as heaviness in the head, frequently disturbing sleep, and sometimes associated with vomiting. She initially experienced three to four episodes per week. She had a remote history of a febrile generalized tonic–clonic seizure, and family history was notable for childhood seizures in her father and paternal uncle.

Physical examination and vitals were normal. Laboratory evaluation, including metabolic testing, was unremarkable. MRI brain showed no calcifications, no white-matter abnormalities, and no cerebral atrophy—findings strongly inconsistent with AGS[1 2]. EEG revealed frequent generalized epileptiform discharges without clinical seizures. A diagnosis of probable migraine with an epileptiform EEG pattern was made, and prophylactic divalproate therapy was initiated. Her headaches improved significantly, decreasing to one episode per month to every two months.

Because of the abnormal EEG and family history, genetic testing was performed. The results revealed a heterozygous *RNASEH2B* c.529G>A (p.Ala177Thr) pathogenic variant. Given that AGS requires biallelic pathogenic variants, this result confirmed the child as an asymptomatic carrier rather than an affected individual. Her normal neurodevelopment, normal neuroimaging, absence of regression, and lack of systemic features (such as chilblains) further supported the interpretation that the heterozygous variant was incidental. Parents were counselled regarding autosomal recessive inheritance and the benign nature of carrier status.

DISCUSSION

The classical AGS phenotype presents in infancy with severe neuroinflammation, progressive microcephaly, spasticity, dystonia, and seizures[1,3]. Neuroimaging abnormalities-including basal ganglia calcifications and leukodystrophy-are highly characteristic and present in nearly all affected individuals[2,6]. CSF findings typically include lymphocytosis and elevated interferon-α and neopterin[7].

Newer reports describe a wider range of AGS presentations, including attenuated or later-onset forms, but all confirmed cases involve homozygous or compound heterozygous mutations[2,4,8]. Even patients with milder AGS2 caused by *RNASEH2B* mutations exhibit at least subtle developmental abnormalities, neuroimaging changes, or chronic neurological deficits[4,8,9].

The p.Ala177Thr variant is the commonest *RNASEH2B* pathogenic allele and is strongly associated with milder AGS2 when present biallelically[4]. However, extensive clinical and biochemical studies show that heterozygous carriers do not develop AGS[3,5]. Functional analyses demonstrate that one functional allele is sufficient to maintain RNase H2 enzymatic activity, preventing aberrant nucleic acid accumulation and interferon pathway activation[5,8].

The present case aligns with this evidence. The child's recurrent headaches and generalized epileptiform EEG discharges are far more consistent with migraine and benign epileptiform activity than with interferonopathy. Her normal neurodevelopment and normal MRI are particularly important, as radiological abnormalities are present in almost all AGS cases-even atypical forms[6,9,10].

Thus, the heterozygous *RNASEH2B* variant should be regarded as an incidental genetic finding, not explanatory for her symptoms. Misinterpreting heterozygous pathogenic variants risks unnecessary investigations, anxiety, and inappropriate labelling of benign clinical presentations.

CONCLUSION

This case underscores the importance of clinical context when interpreting heterozygous pathogenic variants in interferonopathy-associated genes. The *RNASEH2B* A177T variant, although pathogenic in homozygosity, represents a benign carrier state when heterozygous. Clinical evaluation and neuroimaging remain central to distinguishing true AGS from incidental genetic findings. Accurate genotype-phenotype correlation prevents misdiagnosis and supports appropriate counselling for families.

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