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CASE REPORTS

A RARE CASE OF AICARDI-GOUTIÈRES SYNDROME WITH NOVEL RNASEH2C GENE MUTATION: A COMPREHENSIVE CLINICAL AND MOLECULAR ANALYSIS

Deepak Mulchandani, Vaishali Singh, Omkar Shelke.

Department of Paediatrics, Bombay Hospital, Mumbai.

ABSTRACT

Aicardi-Goutières syndrome (AGS) is a rare autosomal recessive disorder characterized by early-onset encephalopathy, intracranial calcifications, white matter disease, and elevated interferon-alpha levels in cerebrospinal fluid. This case report presents the clinical and molecular details of a 9-month-old male infant with AGS, harboring mutations in the RNASEH2C gene. The patient exhibited global developmental delay, hearing impairment, and a family history of similar presentations. Whole exome sequencing identified two pathogenic variants in RNASEH2C. This report provides insights into the varied phenotypic features of AGS and emphasizes the importance of genetic testing for accurate diagnosis.

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Introduction

Aicardi-Goutières syndrome (AGS) is a rare inherited encephalopathy, known for its clinical heterogeneity and genetic basis. It is characterized by intracranial calcifications, white matter abnormalities, and elevated levels of interferon-alpha in the cerebrospinal fluid.[1] Chilblain lesions on the hands, feet and intermittent sterile pyrexias have been reported and can be clues for the diagnosis of AGS.[2] AGS is associated with mutations in several genes, including RNASEH2C. Here, we present a case of AGS with RNASEH2C gene mutations in an infant with a complex clinical history.

Case Report

A 9-month-old male infant, born to non-consanguineous parents, was evaluated for global developmental delay and bilateral sensorineural hearing loss. The child's birth history revealed a term, intrauterine growth-restricted baby with low birth weight. Early life was marked by recurrent, unexplained fevers and developmental regression starting at 3 months of age, reminiscent of AGS characteristics. Interestingly, two elder male siblings also exhibited similar clinical features and died in early adolescence. In contrast, a 3-year-old female sibling was neurologically normal. Clinical examination of the infant revealed microcephaly, light coloured hair, no response to sound and spastic quadriparesis. Routine blood investigations along with thyroid profile, serum lactate and serum ammonia were normal. Urine gas chromatography and Tandem mass spectrometry was also normal. Fundus examination showed left gaze preference with mildly hypopigmented fundus showing inadequate response to bright light. BERA was suggestive of retrocochlear involvement affecting both auditory pathways at upper and lower brain stem level with increased hearing threshold. VEP revealed positive replicable response but no fixation and no response to bright light. TORCH titres were negative and EEG was normal. Magnetic resonance imaging (MRI) was suggestive of cerebral atrophy and intracranial calcifications. CSF studies were unremarkable. Genetic analysis through whole exome sequencing identified two heterozygous variants in RNASEH2C: a novel variant (c.178G>T, p.Glu60) and a known pathogenic variant (c.205C>T, p.Arg69Trp).

Discussion

Aicardi-Goutières syndrome is a rare disease which is transmitted through autosomal recessive mode of inheritance. It has a prevalence of 1-5 in 10,000 newly live births.[3] The disease should not be confused with Aicardi Syndrome which is a rare genetic malformation syndrome characterized by the partial or complete absence of a key structure in the brain called the corpus callosum, the presence of retinal lacunes, and epileptic seizures in the form of infantile spasmsand is almost exclusively seen in females suggesting a X-Linked dominant disorder.[4] In contrast, Aicardi Goutieres Syndrome presents with variable clinical features often resembling cerebral palsy and congenital intrauterine infections like TORCH group of infections. RNASEH2C (Ribonuclease H2 Subunit C) is a protein coding gene which encodes a ribonuclease H subunit that can cleave ribonucleotides from RNA:DNA duplexes. Mutations in this gene cause Aicardi-Goutieres syndrome type 3. Genetic testing such as whole exome sequencing, plays a crucial role in accurate diagnosis. We identified 2 types of RNASEH2C variants, a novel likely pathogenic variant and a pathogenic variant which were consistent with AGS type 3. These variants lead to impaired RNASEH2C function and have been previously associated with AGS. The patient on whole exome testing had one copy (heterozygous) of a non-sense variant, Variant 1 (c.178G>T; p.Glu60) in RNASEH2C gene which is predicted to cause premature truncation of the protein. The variant has been reported in dbSNP database with an identification number: rs941076637.[5] This variant seems to be novel as it has not been previously reported in literature. Since, this variant is predicted to produce a

Address for Correspondance:

Deepak Mulchandani, Room no 1103, MRC wing, Bombay Hospital, 12, new marine lines, Mumbai - 400042.

Email: elfagieh@yahoo.com

truncated protein which might result in loss-of-function and other truncating variants in this gene are also known to cause similar phenotype, therefore, this variant was labelled as Likely Pathogenic. Another mutation in RNASEH2C gene labelled as Variant 2 (c.205C>T; p.Arg69Trp) which affects the protein function was also detected. The variant has been reported in dbSNP database with an identification number: rs78635798 and in the Genome Aggregation Database (gnomAD) with a rare allele frequency of 0.009169%. Also, ClinVar database reports the clinical significance of this variant as 'pathogenic' (VCV000001260.31). The identified variant has been previously identified in patients affected with Aicardi-Goutieres syndrome 3 in heterozygous state.[6] However, the parents did not give consent for further carrier testing.

Conclusion

This case report highlights the clinical and molecular aspects of Aicardi-Goutières syndrome, emphasizing the importance of genetic testing in diagnosing this rare disorder. The clinical variability and novel mutations observed in this case further underscores the challenge of distinguishing AGS from other conditions. Increasing awareness of AGS and its genetic underpinnings can aid in early diagnosis and management.

Compliance with Ethical Standards
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