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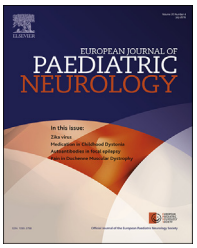

Case study

Variable clinical phenotype in two siblings with Aicardi-Goutières syndrome type 6 and a novel mutation in the *ADAR* gene

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ABSTRACT

Aicardi-Goutières syndrome (AGS) is a hereditary inflammatory encephalopathy resulting in severe neurological damage in the majority of cases. We report on two siblings with AGS6 due to compound heterozygosity for a known and a novel mutation in the *ADAR* gene and a strikingly variable phenotype. The first sibling presented at 12 months of age with a subacute encephalopathy following a mild respiratory infection. The child developed a spastic tetraparesis, generalized dystonia and dysarthria. In contrast, the younger sibling presented with an acute episode of neurological impairment in his third year of life, from which he recovered without sequelae within a few weeks. These findings illustrate a striking intrafamilial phenotypic variability in patients with AGS6 and describe the first case of a full recovery from an acute encephalopathy in an AGS patient. Our findings also suggest that AGS should be considered as an important differential diagnosis of an infection-triggered encephalopathy in infancy despite the absence of typical neuroimaging findings.

Abbreviations: AGS, Aicardi-Goutières syndrome; ADAR, adenosine deaminase, RNA-specific; CSF, cerebrospinal fluid; dsRNA, double-stranded RNA.

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1. Introduction

Aicardi-Goutières syndrome (AGS) is a genetically determined inflammatory encephalopathy with onset in infancy.[1] Clinically, AGS resembles congenital viral infection and is associated with lymphocytosis and raised levels of the antiviral cytokine interferon-α in the cerebrospinal fluid (CSF). Neuroimaging findings include basal ganglia calcifications, myelin defects and brain atrophy. In most cases, AGS is inherited as an autosomal recessive trait. Depending on the underlying mutated gene, seven AGS subtypes can be distinguished so far. Thus, loss-of-function mutations in the genes encoding the exonuclease *TREX1* (MIM*606609, AGS1), the three subunits of ribonuclease H2 (MIM*610181; AGS2, MIM*610329; AGS3, MIM*610333; AGS4), the phosphohydrolase *SAMHD1* (MIM*606754, AGS5) and the adenosine deaminase *ADAR* (MIM*146920, AGS6) as well as gain-of-function mutations in *IFIH1* (MIM*606951, AGS7) encoding the RNA-sensor MDA5 have been shown to cause AGS.[1] Mutations in these genes lead to disturbances of the metabolism or the sensing of intracellular nucleic acids resulting in activation of an innate immune response with constitutive type 1 interferon signalling.[2] AGS and related disorders are therefore also referred to as type 1 interferonopathies. As a result of chronic inflammatory processes, most AGS patients exhibit severe global developmental delay that can be accompanied by various extra-neurological manifestations such as cutaneous chilblain lesions.

Mutations in *ADAR* (AGS6) are more likely to be associated with a later onset and milder symptoms than other AGS subtypes.[3] Besides the classical AGS phenotype, cases presenting with bilateral striatal necrosis or spastic paraparesis with preserved cognitive function have been described.[1]

Here, we present the clinical course of two siblings with AGS caused by compound heterozygosity for two *ADAR* mutations and a highly variable intrafamilial phenotype.

2. Case studies

Patient 1 was born after an uncomplicated pregnancy to healthy non-consanguineous Caucasian parents. The girl was born at term with weight, length and head circumference within normal limits. Psychomotor development was normal until the age of 12 months, when she presented with a subacute encephalopathy following a mild respiratory infection with fever and generalized exanthema. She was not able to walk or crawl anymore and showed decreased head control, tremor and opisthotonos. There was no evidence for an infectious cause. EEG, CT and MRI of the brain comprising MR-angiography were normal. Metabolic analyses of organic acids, oligosaccharides and glycosaminoglycanes were unremarkable. Following the initial encephalopathic episode, no further infection-triggered crises were noted. However, the patient was never again able to stand or walk and exhibited truncal hypotonia with poor head control, spastic tetraparesis, generalised dystonia and athetosis.

At the age of three years, the girl had an occipitofrontal head circumference (OFC) <10 percentile with height and weight below the third percentile. ENT examination revealed mild conductive hearing loss. Psychological averbal testing showed normal cognitive development. A brain MRI was again without pathological findings. CSF analysis revealed normal values for protein, glucose, lactate, immunoglobulines, amino acids and neurotransmitters. CSF lymphocytes were slightly elevated at 0.89 (normal range 0.6–0.8 MPt/L). The patient was suspected of L-Dopa responsive dystonia. However, genetic testing of the *GTP-Cyclohydrolase-1* gene revealed no mutation, and L-dopa treatment over several months did not ameliorate the clinical condition. At the last follow-up at 14 years of age, a brain MRI demonstrated mild cerebral atrophy with bilateral atrophic putamen and hypoplasia of the corpus callosum (truncus) (Fig. 1A). Her cognitive development was mildly impaired with good speech perception, but severe dysarthria.

Patient 2 is the younger brother of patient 1. The boy was born after an uncomplicated pregnancy. Psychomotor development was normal until the age of 26 months. The child had a pneumonia which was treated with antibiotics. Following recovery, he exhibited a sudden onset of agitation, tremor and an ataxic gait pattern. Within the next days, the boy exhibited a severe encephalopathy, he lost the ability to walk or stand and had recurrent episodes of intensive agitation and restlessness. The child was noted to have an OFC on the 4th percentile with weight and height within normal limits. A brain MRI, EEG and a CSF analysis were unremarkable. The boy completely recovered within 2 weeks after the onset of symptoms. At the age of 2 years and 10 months neurological examination was normal.

Because of the family history of an early-onset infection-triggered encephalopathy with extrapyramidal movement disorder further genetic testing was initiated. Panel sequencing using the TruSight One kit (enrichment of coding exons of 4813 genes associated with known clinical phenotypes, so called OMIM genes; Illumina, San Diego, CA) revealed two heterozygous mutations in *ADAR* (NM_001111.4), c.1A>G (p.Met?) and c.577C>G (p.Pro193Ala), in both siblings (Fig. 1B and C) which were confirmed by Sanger sequencing. Both parents were found to carry only one of the two mutations consistent with compound heterozygosity for both mutations in the affected children. Based on the genetic findings, the diagnosis of AGS6 was made. While the first mutation (p.Pro193Ala) has been described as the most common pathogenic variant in AGS6,[4] the second mutation (p.Met?) has previously not been associated with a disease phenotype and is not listed as variant in the ENSEBL, ExAc or gnomAD databases.

Both children were subsequently tested for an interferon signature in blood. While the older child exhibited a strong interferon signature, the younger child showed no significant upregulation of interferon-stimulated genes in blood (Fig. 1D).

3. Discussion

We describe the highly variable clinical course in two siblings with AGS6 due to mutations in the *ADAR* gene. Both patients experienced a subacute onset of an encephalopathy during infancy following a respiratory infection. While symptoms in the first child started at 12 months of age and resulted in

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