Aicardi-Goutières Syndrome - Expanding the Phenotypic Spectrum

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Abstract

Aicardi-Goutières syndrome (AGS) is a rare inherited autosomal recessive condition. A number of different phenotypic presentations of AGS have been identified in recent years. This report describes an infant with AGS type 1, who presented with a neonatal lupus-like phenotype.

Introduction

First described in 1984, Aicardi-Goutières syndrome (AGS) is an inherited early onset subacute encephalopathy with basal ganglia calcification and persistent cerebrospinal fluid (CSF) lymphocytosis (Livingston et al., 2016). Neonatal presentation is not rare and often confused with intra uterine infections (Abdel-Salam et al., 2004). Availability of focused and whole exome sequencing in the last decade has added to its genotypic – phenotypic spectrum. Over time, new features often mimicking Systemic lupus erythematosus (SLE) have been recognised (Ramantani et al., 2010). Recognition of the role of the type 1 interferon pathway in the pathogenesis of AGS has explained its phenotypic overlap with SLE and it is now reclassified as a genetic interferonopathy (Eleftheriou et al., 2017). It is important for clinicians to be aware of newer features and the differential diagnosis of AGS. We describe an infant of AGS type 1 who presented with persistent skin rash resembling neonatal lupus.

Patient Details

A 6-month old boy, second born to a 5th degree consanguineous couple, with a normal antenatal history and birth weight of 2.9 kg, was brought with complaints of developmental delay and an erythematous non-pruritic skin rash observed since the last 1 month. There was history of excessive crying in the first month with normal neurological features, which subsided spontaneously. An elder male sibling, detected with intracranial calcification in the periventricular and thalamic region on brain ultrasonography in the neonatal period, and suspected to have sepsis, had expired at 20 days of age. No further details of this sibling were available.

On examination he had microcephaly, bilateral simian crease and hemihypertrophy of the right side. Systemic examination showed spasticity of all limbs with brisk reflexes, hepatosplenomegaly and a soft systolic murmur. An erythematous macular rash involving the whole body was present which was clinically suspected to be urticarial rosacea (Figure 1A). He was admitted at 10 months of age with high grade fever without localization and normal investigations, suggestive of aseptic fever.

Routine blood investigations including liver and thyroid functions were normal, except for mildly raised hepatic transaminases. Skin biopsy showed cutaneous mastocytosis suggestive of urticarial rosacea. 2 D Echocardiography detected a small atrial septal defect and abdominal ultrasound was normal. Magnetic resonance imaging (MRI) of the brain showed diffuse lack of myelination in the cerebral hemispheres, internal capsule and the cerebellar white matter. There was thinning of the corpus callosum, hypoplasia of pons and parenchymal atrophy with cortical thinning and a wide sylvian fissure. There were multiple echogenic foci in bilateral deep cerebral white matter and lentiform nuclei which were confirmed to be calcifications on a Computed tomography (CT) scan of the brain. (Figures 1B-D)

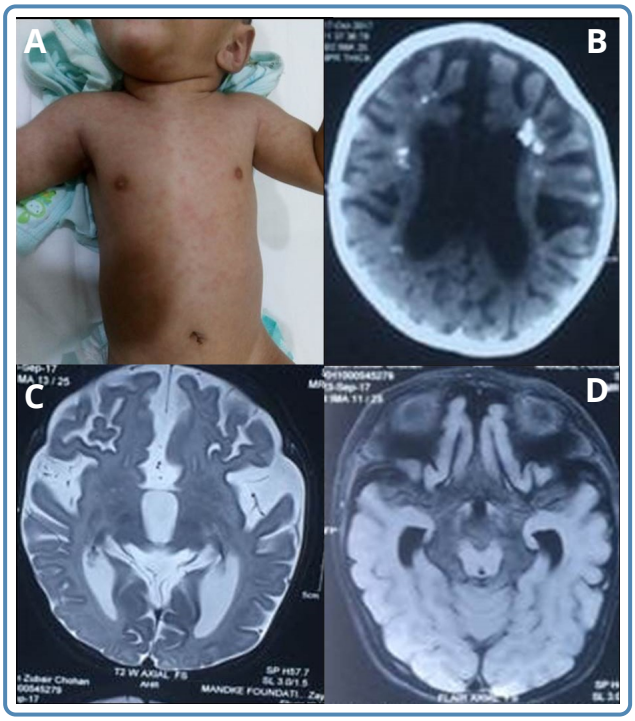

Figure 1 A - Clinical photograph showing generalized erythematous macular rash in the child. B - Axial plain CT scan image of the brain showing foci of calcification, with predominant periventricular distribution. C - Axial T2 W MRI image of the brain showing presence of abnormal white matter, hyperintense T2 signal in an irregular fashion in subcortical regions and evidence of white matter rarefaction. D - Axial FLAIR image of the brain showing temporal horn prominence and atrophic changes.

Maternal TORCH serology titers showed raised IgG levels for rubella, cytomegalovirus and herpes simplex virus. Polymerase chain reaction (PCR) test for rubella, toxoplasma, cytomegalovirus and herpes simplex virus in the proband's blood and for Zika virus in his urine were negative. Clinical exome sequencing of the child performed after informed consent revealed a homozygous variant c.377_378dup (p.Ala127Trpfs*17) in the *3-Prime Repair Exonuclease 1 (TREX1)* gene which has been described previously as disease-causing for Aicardi-Goutières syndrome (AGS) type 1 (HGMD Professional 2017) (Rice et al., 2007). This variant has previously been reported in gnomAD (Genome Aggregation Database) with a minor allele frequency of 0.000012 and is absent in the Exome Sequencing Project (ESP) and 1000 Genomes databases. It is classified as pathogenic (class 1) as per the American College of Medical Genetics and Genomics (ACMG)/ Association of Molecular Pathology (AMP) guidelines. The parents did not consent for carrier testing.

Discussion

We report a case of AGS caused by homozygous *TREX1* gene mutation who presented with the classical triad of encephalopathy, neurodevelopmental delay, white matter abnormalities with intracranial calcifications and an unusual skin rash suggestive of mastocytosis. This type is frequently associated with the neonatal presentation as seen in our case and may imply in utero onset of the disease (Livingston et al., 2016; Rice et al., 2007).

So far 7 causative genes - *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1* and *IFIH1* with largely autosomal recessive inheritance, and a few (*TREX1, ADAR1, IFIH1*) with dominant inheritance have been identified (Livingston et al., 2016) to cause the AGS phenotype. All have similar clinical and radiological features and can be differentiated only by genetic testing. These genes encode proteins involved in DNA metabolism, dysfunction of which results in accumulation of endogenous nucleic acid by-products which triggers an innate immune response and subsequent activation of the type 1 interferon pathway (Eleftheriou et al., 2017). Evidence for abnormal interferon activity has been demonstrated soon after AGS was described, by detection of elevated levels of interferon α in the cerebrospinal fluid (CSF) and in blood, along with an "interferon signature" (Abdel-Salam et al., 2004). Though we could not document it in our patient due to lack of parental consent, we had highlighted its role with other markers like 5-methyl tetrahydrofolate, biopterin and neopterin in a previous case report of AGS with a homozygous mutation in the *RNASEH2C* gene (Merchant et al., 2016).

These biomarkers help distinguish AGS from multiple acquired and genetic conditions with overlapping phenotypes of microcephaly, early onset progressive encephalopathy and intracranial calcifications. Congenital infections like TORCH and Zika virus are well known differentials which can be ruled out by negative serological markers as in our case. Pseudo- TORCH is another overlapping syndrome, distinguished by the MRI brain finding of polymicrogyria. Neonatal lupus erythematosus may show radiological features of AGS but extensive erythematous rash and normal

Table 1 Comparison of gene specific phenotype in the current patient and previously reported cases of Aicardi-Goutières Syndrome (Rice et al., 2015; Livingston et al., 2016; Merchant et al., 2016).

Features	*TREX1* gene-associated	*RNASEH2C* gene-associated	Current patient (*TREX1* gene-associated)	Patient previously reported by the authors (*RNASEH2C* gene-associated)
Developmental delay	✓	✓	✓	✓
Regression	✓	✓		✓
Epileptic seizures	✓	✓		✓
Motor disorder (dystonia/spasticity)	✓	✓	✓ (spasticity)	✓ (spasticity)
Eye movement abnormalities	✓	✓		✓
Spastic paraparesis		✓		✓
Large vessel disease (stenosis/Moyamoya disease/ aneurysms)	✓			
White matter abnormality and intracranial calcification	✓	✓	✓	✓
Cerebral atrophy	✓	✓	✓	
Recurrent sterile fevers	✓	✓	✓	
Autoimmune features	✓	✓	✓(Rash)	
Glaucoma	✓	✓		
Hematological abnormality: Neonatal thrombocytopenia/ bone marrow suppression	✓	✓		
Hypertrophic cardiomyopathy	✓	✓		
Joint contractures	✓			✓

neurologic outcome are its distinctive features (Abdel-Salam et al., 2004).

Over time the phenotype of AGS has expanded to include non-neurological features like glaucoma, cardiomyopathy and endocrine abnormalities. Amongst these, hepatomegaly, thrombocytopenia, transaminitis and hypothyroidism are common in *TREX1* mutation (Rice et al., 2007; Crow et al., 2015). They may evolve with age and should be included in health surveillance during follow up. Bilateral simian crease and right side hemihypertrophy observed in our patient have not been reported so far in AGS, but since the parents were unwilling for any additional tests, we could not do further evaluation to explain these findings. Heterozygous mutations in *TREX1* have also been reported with non AGS phenotypes namely familial chilblain lupus and retinal vasculopathy with cerebral leukodystrophy (Rice et al., 2015). Chilblain lesions are the commonest skin manifestation, reported in 40% of AGS cases (Hebbar et al., 2018). Though absent in our patient, we noted a persistent rash with histological finding of cutaneous mastocytosis which may be seen in SLE.

High prevalence of SLE features such as thrombocytopenia, leukocytopenia, antinuclear antibodies, aseptic fever, erythematous lesions, oral ulcers, and arthritis have been reported in AGS, with increased prevalence in *TREX1* and *RNASEH* mutations (Ramantani et al., 2010). Only rash and aseptic fever were present in our patient and none were found on review of our previously reported AGS with *RNASEH2C* mutation. We also compared the genotype - phenotype spectrum of these 2 patients. (Table 1)

So far only supportive management is available for AGS. Corticosteroids may show some benefit for cutaneous lesions but do not improve the

neurological outcome. Novel treatment strategies like interferon (IFN) blockers and endogenous retroviruses in activation of nucleic acid receptors are now being researched after its reclassification under interferonopathies (Eleftheriou et al., 2017).

Conclusion

This case highlights the expanding phenotypic and genotypic spectrum of AGS. We suggest that neonatal lupus should be considered as a differential for AGS in addition to intrauterine infections and other causes of intracranial calcification. Many non-neurologic features are mutation specific and evolve with age, thus genetic diagnosis is important to explain the prognosis and subsequent health surveillance. Insights derived from the pathogenesis of this disorder could open the possibility of new biomarkers and treatment strategies.

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