Clinical and neuroradiologic variability of Aicardi-Goutiéres syndrome: Two siblings with RNASEH2C mutation and a boy with TREX1 mutation

Emek Uyur-Yalçın, Hülya Maraş-Genç, Bülent Kara
Division of Child Neurology, Department of Pediatrics, Kocaeli University Faculty of Medicine, Kocaeli, Turkey.
E-mail: emekuyur@gmail.com
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Aicardi-Goutières syndrome (AGS) is a rare, autosomal recessively inherited, immune-mediated neurodevelopmental disorder. The syndrome causes infantile-onset progressive encephalopathy characterized by the neuroradiologic features of basal ganglia and periventricular white matter calcification, leucodystrophy and cerebral atrophy. Lymphocytosis and elevated levels of interferon alpha (IFN-alpha) in the cerebrospinal fluid are supplementary findings of AGS. It is frequently misdiagnosed as sequelae of congenital infection (pseudo-TORCH) and mostly recognized later. We describe three AGS cases with different clinical presentation, two male siblings with RNASEH2C mutation and a boy with TREX1 mutation. These cases highlight the importance of considering AGS in the differential diagnosis of unexplained leukoencephalopathy and developmental delay. We suggest to search for intracranial calcification, especially if there are more than one affected cases in a family.

Key words: Aicardi-Goutiéres syndrome, intracranial calcification, pseudo-TORCH, TREX1, RNASEH2C.

Aicardi–Goutières syndrome (AGS) is a rare, usually early infantile-onset, inflammatory disorder most typically affecting the brain and the skin. Typical neuroradiologic findings are calcification of the basal ganglia, abnormalities of the cerebral white matter and diffuse brain atrophy\(^1\). AGS clinically resembles in-utero-acquired viral infection, and some characteristics of the condition also overlap with systemic lupus erythematosus (SLE)\(^2\). The transmission of AGS is autosomal recessive, but there are rare “de novo” autosomal dominant cases. Disease-causing allelic variants in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, or ADAR genes are identified in approximately 90% of individuals with consistent clinical and radiological findings of AGS\(^3\). It seems that, these genes are involved in nucleic acid reparation mechanisms and consequently in a secondary activation of innate autoimmunity, but our information about pathogenesis is still inadequate\(^4\).

About 20% of patients with AGS present in the neonatal period with microcephaly, seizures, jitteriness, cerebral calcifications, white matter abnormalities, cerebral atrophy, hepatosplenomegaly, elevated transaminases and thrombocytopenia. These clinical features mimic congenital infections, especially cytomegalovirus (CMV). Therefore, many AGS patients are misdiagnosed. The later onset form of AGS presents at the age of approximately four months, frequently after an apparently normal development. These children develop features of an encephalopathy with irritability, persistent crying, poor feeding, an intermittent fever (without obvious infection), dystonia, an exaggerated startle response and sometimes seizures\(^3, 5\).

Here we present three cases with AGS, and aim to discuss intrafamilial clinical and neuroradiologic heterogeneity of AGS, due to different gene mutations.
Case Reports

Case 1
An eight-month old boy, born at term after an uneventful pregnancy to consanguineous parents, presented with developmental delay. The neonatal period was uneventful. The physical examination revealed microcephaly, axial hypotonia, limb hypertonia, and hyperactive deep tendon reflexes. He did not have head control or eye contact. There were no dysmorphism, organomegaly or neurocutaneous stigmata. Visual and audiological examinations were normal. Complete blood count, routine biochemistry, plasma ammonia and lactate, tandem mass spectrometry, urinary organic acids, blood and urine quantitative amino acids were normal. The cranial magnetic resonance imaging (MRI) revealed mild cerebral atrophy and thin corpus callosum. Cerebrospinal fluid (CSF) protein and glucose levels were within normal limits and there was no pleocytosis. Karyotype analysis was 46, XY. He was followed as global developmental delay of unknown etiology. Seizures started at the age of 2 years, and were easily controlled with valproic acid. When Case 1 was 3.5 years old, he had a new brother (Case 2).

Case 2
He was born at 37 weeks of gestation with a birth weight of 2,640 g (25-50th p), height 49 cm (75th p) and head circumference 33 cm (50th p). He was hospitalized in the neonatal intensive care unit because of hepatosplenomegaly, generalized petechia, elevated transaminases, and persistent thrombocytopenia. His primitive reflexes were depressed, and spontaneous motility was decreased at birth. He had sepsis-like clinical features. Cerebral ultrasonography showed periventricular hyperechogenicity compatible with calcification, and cranial computerized tomography (CT) revealed bilateral symmetric periventricular white matter and basal ganglia (Fig. 2). Molecular analysis revealed homozygous mutation at RNASEH2C gene [c.196C>T (p.Arg66Cys)] in both siblings and the parents were heterozygous.

At the last follow-up, Case 1 was 6 years old. He could follow object, but he had still no head control. His seizures were under control with valproic acid. Case 2 was 2.5 years old. He had frequent aspiration pneumonias and also gastroesophageal reflux disease. He was feeding via gastrostomy tube. At the age of 2 years he developed glaucoma. He had no seizures. He had no eye contact or head control.

Case 3
A two and a half year old boy was referred to our clinic with developmental delay. He was the third living child of parents with second degree cousin consanguinity. His sister died when she was 2 years old with an unknown etiology, and she had microcephaly. Prenatal and natal history of the patient was uneventful. He was born at term with a birthweight of 2800 g. The physical examination revealed microcephaly, truncal hypotonia, and spastic tetraparesis. He could follow objects, but had no head control, nor could he say a word. Complete blood count and routine biochemical tests and screening for inborn errors of metabolism (tandem mass spectrometry, urinary organic acids, plasma ammonia and lactate) were normal. Visual examination and hearing tests were normal. Cranial MRI revealed diffuse white matter abnormality in deep and subcortical white matter and bitemporal subcortical cysts (Fig. 3 a, b, c). Cerebellar white matter was spared. Cranial CT showed calcification in the cerebral and cerebellar white matter, especially in the left hemisphere (Fig. 3 d, e, f). AGS was suspected because of neuroradiologic findings, family history of a microcephalic sibling and history of consanguinity. Molecular analysis confirmed the diagnosis, which revealed homozygous mutation in TREX1 gene [c.341G>A (p.Arg114His)]. At the last follow-up he was 3.5 years old, and had no seizures. He had no head control, but he could follow objects. His visual examination was normal and there was no cutaneous finding.

Discussion
We reported three Turkish cases from two families with AGS. Case 1 had been followed with global developmental delay of unknown
etiology, until his newborn brother (Case 2) presented with TORCH-like findings including hepatosplenomegaly, elevated transaminases, thrombocytopenia and intracranial calcification. As MRI has become the first imaging modality of choice, cranial CT has been performed less frequently. In our patients, cranial CT guided the diagnosis of AGS. Livingston JH et al.\textsuperscript{6} suggest that CT should always be considered in children with an undiagnosed neurological disorder if MRI is uninformative. If cranial CT was obtained soon after non-specific MRI findings in Case 1, the diagnosis of AGS would have been confirmed earlier.

Our second case presented was in the neonatal period. His clinical features were highly suggestive of congenital infections, but serology was negative. The lack of retinal abnormalities and hearing loss were also useful differentiating features from congenital infections. In AGS hearing is almost always normal, vision may be normal or there may be cortical blindness, but ocular structures are normal. However, there is a risk of glaucoma, it may be present at birth, or develop later and patients should be followed for later onset glaucoma\textsuperscript{7}. In our young sibling (Case 2), glaucoma was detected at the second year and he needed an operation.

The clinical presentation was heterogeneous even in the same family. The latter one had neonatal onset with TORCH-like clinical picture, while the older brother had a late presentation with global developmental delay and pyramidal signs. They were found to be homozygous for the common RNASEH2C c.196C>T [p.(Arg66Cys)] mutation, and the parents were heterozygous. Vogt et al.\textsuperscript{8} described a family with a recurrent Asian founder mutation in RNASEH2C and striking intrafamilial variability. In this family, one female child had a severe AGS phenotype with an onset in infancy and profound developmental delay, and the older sister was of normal intellect with a normal head circumference and

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Fig. 1. Axial computerized cranial tomography image of Case 2 shows bilateral symmetric periventricular white matter and basal ganglia calcification of the younger brother during neonatal period.

Fig. 2. Axial computerized cranial tomography of Case 1 shows bilateral basal ganglia calcification, triventricular hydrocephalus and diffuse cerebral cortical atrophy of the older brother at the age of 3.5 years.

Fig. 3. Cranial MRI and tomography of Case 3 at the age of 2 years. T2-weighted axial images (a-c) show cerebral atrophy, enlarged ventricles, hyperintensity in periventricular deep white matter, and bitemporal subcortical cysts and cranial tomography. Axial images (d-f) show calcification of periventricular white matter (d), basal ganglia (e) and cerebellar hemisphere (f) more prominent in the left.
was only diagnosed because of the presence of chilblains and a mild hemiplegia. These findings support the phenotypic variability of AGS due to the same gene mutation, in the same family.

The clinical presentation of Case 3 was similar with the first case with onset at the age around six months, after an apparently normal development; however, cranial MRI findings were different including leucodystrophy and bitemporal subcortical cysts. These findings are seen frequently in AGS, but the differential diagnoses in terms of MRI include Alexander disease, megalencephalic leucoencephalopathy with subcortical cysts, and childhood ataxia with central nervous system hypomyelination/vanishing white matter disease. Macrocephaly is present in the first two diseases, and intracranial calcification is not seen in all three diseases.

The typical pattern of intracranial calcification in AGS is of symmetrical, spot-like lesions in the basal ganglia and the deep white matter of frontal and parietal lobes. Calcifications due to congenital infection are often periventricular, in the ependymal or subependymal region, and often asymmetrical. They completely outline the ventricles. On the other hand, true periventricular calcifications are relatively rare in AGS. Livingston JH et al. suggest that these features may be useful in the discrimination of these two entities. In Case 1 basal ganglia calcification was more prominent with rare periventricular calcification. In Case 2, periventricular calcification was more diffuse and symmetrical in addition to basal ganglia calcification.

It has been shown that in patients with AGS, increased levels of lymphocyte neopterin and interferon-alpha are found and these findings may guide the diagnosis. We did not perform lumbar puncture in Case 2, because of resistant thrombocytopenia. There was no CSF-lymphocytosis in Case 1 and Case 3. We could not test interferon-alpha and neopterin in our cases.

Because of possible relation between SLE and AGS, AGS can be viewed as a model disease for systemic autoimmunity. Over time, up to 40% of patients develop any time so-called chilblain lesions, most typically on the toes and fingers and occasionally also involving the ears. Chilblains can occur in association with mutations with any of the genes, but heterozygous mutations in TREX1 cause additional inflammatory phenotypes characterized by autoimmunity, including autosomal dominant familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus and autosomal dominant retinal vasculopathy with cerebral leucodystrophy. There was no chilblain in our cases at the last follow-up examinations, but it may also appear later in the course.

In conclusion, all three cases highlight the importance of considering AGS in the differential diagnosis of patients with unexplained global developmental delay, leucoencephalopathy, and TORCH-like clinical and radiologic features with negative serology. As MRI has been the initial imaging modality in most centers, calcifications may go unnoticed. If MRI is uninformative in patients with global developmental delay and/or leucoencephalopathy, cranial CT should be ordered. Most patients may be misdiagnosed as congenital TORCH infections or a sequel of TORCH infections resulting in erroneous counseling. The absence of hearing loss and retinopathy, CSF lymphocytosis, elevated interferon alpha levels in CSF or increased expression of interferon-stimulated genes in peripheral blood may all guide to diagnose AGS. The heterogeneity of the syndrome even between siblings in the same family is worth emphasizing.

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REFERENCES


