Aicardi-Goutieres Syndrome-A Case Report

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Abstract:

Aicardi Goutieres Syndrome is an early-onset leukoencephalopathy with a presumed immune pathogenesis caused by inherited defects in nucleic acid metabolism. It is an inflammatory disorder resulting from mutation of multiple genes. Majority of the affected individuals experience physical as well as intellectual disability. Here we discuss a case of A 2-year old girl of consanguineous marriage diagnosed as Aicardi Goutieres Syndrome who was presented with the sudden loss of motor and cognitive skills after an acute febrile illness. This syndrome was diagnosed by clinical exome sequencing and RNAEH 2A mutant gene identification.

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Introduction:

Aicardi-Goutieres Syndrome (AGS) is an early onset neurodevelopmental disorder. It has an autosomal-recessive Mendelian inheritance pattern and its origin is derived from the mutations that undergo the different genes encoding the RNAses, in charge of degrading intracellular RNA chains. Mutations in these genes result in the cytoplasmic accumulation of nucleic acids, which acts as an error signal of ongoing viral infection and initiates type I IFN production and that is responsible for AGS. This condition generally suffer from progressive microcephaly associated with severe neurological symptoms, such as hypotonia, dystonia, seizures, severe developmental delay and spastic quadriplegia.

Aicardi-Goutieres Syndrome can be of two types on the basis of onset: early and late onset form. Early onset is very severe and affects 20 percent of the infants. These infants are born with liver (elevated liver enzymes and enlargement of the liver and spleen) and neurological abnormalities. But infant with later-onset, begin their symptoms after first few weeks or months of normal development, which projects as muscle spasticity, decline in head growth, developmental and cognitive delays. The risk to siblings are only less than 1%.

Diagnosis of AGS minimally suggested by intracranial calcifications with abnormal CNS white matter and no infectious explanations and /or CSF findings of leukocytes, pterins or interferon alpha. Molecular confirmation of mutations in TREX1, SAMHD1, and RNAseH2A,B and C gene is helpful. Effective treatment have not yet been developed. Supportive and symptomatic treatment should be given.

Case Report:

A 2-year old female child of consanguineous marriage parents was presented with loss of her acquired developmental milestone for last 1 year. She was developmentally normal up to 1 year of age, then she developed regression of all milestone of development after acute febrile illness. Now she could stand by holding objects and could speak 10 to 12 words. Mother also noticed that her child cried excessively following this events. There was history of fever prior to this illness which was high grade continuous in nature. The child was delivered by normal vaginal delivery with no perinatal and postnatal complication. There was no history of convulsion, unconsciousness, breathing problem, vomiting, abnormal body and urine odour, hearing and visual problem. On examination she was conscious, oriented and vitally stable. Nervous system examination reveals increased tone in all four limbs, exaggerated deep tendon reflexes (Biceps, knee, ankle) and bilateral planter extensor. There was no sign of meningeal irritation. Her biochemical report shows serum ammonia-57 micro mole / L, Lactic acid 4.74 mg/dl. EEG report was normal. Brain MRI T1 weighted image showed...
hypointense signal and T2 weighted image showed hyper intense signal around the periventricular region which resembled to leukodystrophy. Gene analysis (Clinical exome sequencing) was done and found in location Exom 3, variant c.322C>T, classification likely pathogenic and homozygous mutation of RNASEH 2A gene and diagnosed as a case of AGS.

This child was treated with Levodopa/ carbidopa, multiminerals and with physiotherapy. Now she is on regular follow up.

Fig.-1: MRI of Brain, T1 with Flare image axial section showing periventricular white matter hyper intensity.

Fig.-2: Report of clinical exome sequencing
Aicardi-Goutieres syndrome is a rare, early onset, predominantly autosomal recessive neurodegenerative disorder. The combined findings of early-onset encephalopathy, dystonia, seizures, spasticity and progressive microcephaly, psychomotor retardation associated with basal ganglia calcification, cerebral atrophy, white matter abnormalities and cerebrospinal fluid lymphocytosis as well as elevated interferon alfa are characteristics for AGS with neonatal onset. Feeding difficulties, vomiting, ocular jerks and lack of progress in motor and social skills are the main symptoms. Our patient presented with sudden loss of motor and cognitive skills and seizures after febrile episode.

Cutaneous findings are the most prominent extraneurologic features of AGS. They include characteristics Chilblain-like lesions (pernio), associated acrocyanosis and nail abnormalities with erythematous periungual skin. Puffy hands and feet, and distal tapering of digits, have also been described. Congenital glaucoma and brain stem atrophy by radiography describe by Crow et al.

MRI of brain show high T2 signal intensity and low T1 signal intensity in the white matter, most prominently in frontal and temporal lobe, and atrophy may be significant. Brain MRI of our patient shows hypointense signal in T1 and hyper intense signal around the periventricular region T2 image which was resemble to leukodystrophy.

Although AGS is a monogenic disorder, it is genetically heterogeneous, with seven genes implicated to date, encoding several nucleic acid processing enzymes and a cytosolic nucleic acid sensor. These comprise the RNASEH2A, RNASEH2B and RNASEH2C proteins of the RNase H2 endonuclease complex as well as TREX1, SAMHD1, ADAR and IFIH1. Heterozygous mutations in the three RNase H2 genes and TREX1 are also associated with systemic lupus erythematosus.

Our patient shows RNASEH2A gene mutation by clinical exome sequencing.

Partial loss-of-function biallelic mutations in the RNase H2 genes are the major cause of AGS, accounting for over half of all cases. RNase H2 is ubiquitously expressed and functions alongside RNase H1 to degrade cellular RNA: DNA heteroduplexes.

As there is currently no recommended treatment for AGS, Our patient was treated with Levodopa, multiminerals and physiotherapy.

Conclusion:
There are no direct treatment options for Aicardi-Goutieres Syndrome. Instead, we treat the associated symptoms. Physical and occupational therapies can also improve the conditions. Aicardi-Goutieres syndrome can cause endocrine (hypothyroidism) as well as vision problems (glaucoma). So periodic check-up is very essential.

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