Case study

Aicardi–Goutiéres syndrome presenting atypically as a sub-acute leukoencephalopathy


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A B S T R A C T

Aicardi–Goutiéres syndrome is an autosomal recessive encephalopathy characterised by acquired microcephaly, basal ganglia calcifications, leukodystrophy, cerebral atrophy, chronic cerebrospinal lymphocytosis, and raised titres of interferon alpha in the cerebrospinal fluid. The disease onset is generally within the first months of life. We here report a case of Aicardi–Goutiéres syndrome presenting atypically as a sub-acute leukoencephalopathy following satisfactory psychomotor development up to the age of 16 months. This case highlights the importance of considering Aicardi–Goutiéres syndrome in the differential diagnosis of an unexplained leukoencephalopathy and the possibility of later onset of the disease.

1. Introduction

Aicardi–Goutiéres syndrome (AGS) is an autosomal recessive disorder characterised by acquired microcephaly, intracranial calcification, cerebral white matter abnormalities, cerebral atrophy, chronic cerebrospinal fluid (CSF) lymphocytosis (>5 cells/mm³) and elevated level of CSF interferon alpha (IFN-alpha), features mimicking those of acquired in utero viral infection. Typically, the disease onset is in the first year of life, in most patients before four months of age. The main symptoms at presentation are feeding difficulties, irritability, unexplained low-grade fever and a loss of motor and social skills. Neurological examination usually reveals truncal hypotonia, severe pyramidal and extrapyramidal tract signs (dystonia, buccal-lingual dyskinesia) and abnormal eye movements. After the early, sub-acute manifestations, the clinical picture appears to stabilise often by the end of the second year of life.

AGS is a genetically heterogeneous disorder: following the identification of two AGS loci, AGS1 on chromosome 3p21 and AGS2 on chromosome 13q14.3, Crow et al. recently identified four genes responsible for the disease. AGS may result from a dysregulation of intrathecal production of IFN-alpha giving rise to the immunological features of AGS which include sterile pyrexias, polygammaglobulinaemia, Coombs positive haemolytic anaemia, and the characteristic chilblain-like lesions seen in some cases.

Here, we report the case of a female child with an atypical presentation of AGS characterised by the sub-acute onset of a...
severe leukoencephalopathy following satisfactory psychomotor development until the age of 16 months. Our case highlights the importance of considering AGS in the differential diagnosis of an unexplained leukoencephalopathy and the possibility of later onset cases occurring in childhood and beyond.

2. Case study

This girl, the only child of healthy unrelated white Italian parents, was born by spontaneous vaginal delivery at 41 weeks gestation. The pregnancy was characterised by threatened premature birth at 30 weeks. Ultrasound examination at this time was normal and biochemical and infectious investigations were negative (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus types 1 and 2). The birth weight was 3.250 g (25th percentile), length 51 cm (50th percentile) and head circumference 35.2 cm (50th percentile). Apgar scores were 8 at 1 min and 9 at 5 min. The perinatal and neonatal periods were normal except for the presence of mild gastro-oesophageal reflux at the age of 4 months. Head control was acquired at 4 months and sitting at 7 months. When the child was 15 months old she was able to stand with support although independent walking was never achieved. Her language was normal and appropriate for her age (first words before 12 months). She underwent routine vaccinations without complications (her last vaccination being the MMR at 15 months of age).

She was healthy until age 16 months, when, following an episode of otitis media, she developed hypersomnia, generalised asthenia and pallor with increased irritability. Within a week the clinical picture showed a rapid worsening with onset of a high-grade fever (over 38 °C) unresponsive to therapy with paracetamol, antibiotics, and steroids. The child was hospitalised and underwent diagnostic investigations. EEG examination documented diffuse slowing of background activity and mild and non-specific bilateral white matter hypointensities were seen on T2 weighted MRI without contrast enhancement. There was no evidence of cerebral calcifications on CT scan (Fig. 1). CSF analysis revealed a white cell count of 10 cells/mm³. On the basis of a suspected undefined encephalitis, antibiotics and high-dose steroid therapy was started. When this proved ineffective, 3 weeks after her initial hospitalisation, the child was transferred to a specialist neurological hospital. At that time, her fever was unremitting and the neurological examination was characterised by severe irritability, drowsiness, axial hypotonia with pyramidal signs and loss of all milestones. Further analysis of her CSF (12 weeks after the onset of her illness) confirmed a pleocytosis (32 cells/mm³; reference <5), with lymphocytes accounting for 30%. Cytchemistry, immunochemical protein analysis, IgG immunoblot, and PCR were all normal. Measurement of CSF biogenic amines and metabolites showed decreased folates (51.8 nmol/l; reference 63–111) and highly elevated biotin (242 nmol/l; reference 10–30) and neopterin (1206 nmol/l; reference 9–30). Extensive laboratory and metabolic investigations (including routine blood examination, CRP, ESR, total immunoglobulin levels, complement, HVA, VMA, quantitative plasma and CSF amino acids, urinary organic acids, pyruvate, lactate, plasma and CSF ketones, screening for succinylpurines, arylsulfatase A, galactocerebroside, VLCFA, mucopolysaccharides, FTH, ammonium, ENA, ANA, HIV, HBV and HCV) were performed and were all unremarkable. Laboratory investigations ruled out infection with TORCH complex, HSV6, Mycoplasma pneumoniae, influenza virus, parainfluenza virus, borrelia, enterovirus (adenovirus, rotavirus, coxsackie A-1-2-4-7-9-10-21, echovirus 2-3-4-6-7-14-16-8-30-31), toksana virus, Q fever, orinthosis, psittacosis, RSV, poliovirus 1-2-3, rubella, measles, parotitis, diphertheria and tetanus.

Repeat EEG revealed diffuse slowing of background activity. ABRs, VEPs, SEPs, motor and sensory conduction velocity were all normal. Ophthalmological examination was normal; abdominal US scan was non-contributory except for a mildly increased spleen size (length 7 cm) whilst chest X-ray, spinal MRI and bone marrow biopsy were all negative. At this time, a repeat MRI demonstrated an extension of the previously observed white matter abnormalities (Fig. 1). Considering the neuroradiological picture and an altered CD4/CD8 ratio, a diagnosis of erythrophagocytic lymphohistiocytosis was considered and then ruled out on the basis of normality of perforin expression test and cytotoxic NK cell activity.

At this stage, 5 months after the onset of her disease, the clinical examination was characterised by recurrent and periodic fevers (every 5–8 days), which were attenuated to some extent following IVig and levsulpiride therapy. The child’s head circumference showed no evidence of decline. She remained extremely irritable with limited and sporadic social interaction and absent verbal function. She showed a spastic tetraplegia with dystonic features.

A further CT scan, 3 months after the initial examination, revealed bilateral calcifications in the lentiform nuclei (Fig. 1). Examination of the previously stored CSF sample demonstrated an elevated IFN-alpha level (150 pg/ml, reference <10). Mutation analysis of the AGS2/RNASEH2B gene revealed the child to be homozygous for the recurrent exon 7 c. 529G>A (p.A177T) mutation.

At 32 months of age, 18 months after the onset of her disease, the child’s clinical picture is characterised by truncal and neck hypotonia, pyramidal and extrapyramidal tract signs (dystonia, buccal-lingual dyskinia and ‘startle reactions’ even to minor acoustic stimulations). There has been no recovery of her previously acquired psychomotor abilities. Her head circumference remains on the 50th percentile. She is still irritable, although less so than at the onset of her illness. She shows improved social interaction, moderate gastro-intestinal problems, and complete remission of the febrile episodes. There are no cutaneous signs.

3. Discussion

We describe a case of AGS atypically presenting as leukoencephalopathy at 16 months of age following previously satisfactory psychomotor development. Classically, AGS has been described to occur in the first year of life, usually within the first 4 months, and with a more insidious presentation than the sub-acute onset observed in the case we report here. In view of the sub-acute onset, recurrent fevers, diffuse

slowing of background activity on EEG and white matter abnormalities, a provisional diagnosis of a leukoencephalitis was pursued. Of note, a CSF lymphocytosis was observed at presentation but the significance of this result only became evident with the appearance of the intracranial calcifications approximately 3 months after an initially normal CT scan. There are reports of cases in which intracranial calcification was absent at the first observation and, indeed, discordance for this sign between siblings was noted in the original description of the disease. However, to our knowledge, this is the first case in which it has been possible to establish the time course between onset of the inflammatory vasculitic process and the appearance of basal ganglia calcification. Interestingly, this evolution is consistent with the pathogenetic mechanism hypothesised for the experimental transgenic mouse model of CNS expression of IFN-alpha.

More generally, our case illustrates the importance of considering AGS in the differential diagnosis of an undefined leukoencephalopathy. The similarity between the white matter abnormalities described and those seen in erythrophagocytic lymphohistiocytosis led us to consider that condition as a differential diagnosis. It is of note that the pathogenetic mechanism of erythrophagocytic lymphohistiocytosis, in a subgroup of patients, is in some ways similar to that hypothesised for AGS. In particular, in both diseases the production of a large quantity of cytokines, including IFN-alpha, may play an important part in the activation of macrophages responsible for tissue damage. On the other hand, acute disseminated encephalomyelitis (ADEM) was considered unlikely on account of the neuroimaging findings, which included a progressive leukoencephalopathy with symmetrical involvement of the cerebral hemispheres, lack of grey matter involvement, and calcifications, and none of which are suggestive of ADEM. We also considered the possibility of a mitochondrial cytopathy, which may present with a somewhat similar neuroimaging picture; however, laboratory investigations failed to reveal any biochemical abnormalities consistent with such a diagnosis.

Fig. 1 – Neuroradiological findings: upper left, axial CT scan obtained at presentation does not reveal any abnormality; upper right, axial CT scan obtained after 3 months shows punctuate basal ganglia calcifications (arrows); lower left, axial T2-weighted MR image obtained 15 days after initial presentation shows abnormal white matter hyperintensity in the parietal and posterior frontal lobes (open arrows) with sparing of the anterior frontal lobes; lower right, axial T2-weighted MR image obtained after 1 month shows anterior progression of signal abnormalities (arrows).
The fact that the child did not develop microcephaly is another atypical aspect of her picture. However, the absence of microcephaly has been reported in a small number of cases of AGS with preserved intellect.10 The finding in this case may be attributable to the fact that the disease had an onset after the first year of life. We note that repeat MRI examination have not yet demonstrated evidence of cerebral atrophy. It will be interesting to determine if a slowing of the rate of growth of the head circumference and atrophy on MRI become evident on follow-up examinations.

Given the likely involvement of the immune system in the pathogenesis of AGS, the possible triggering stimulus of a vaccination with live attenuated virus a month prior to the onset of the symptoms, or of the reported episode of otitis media, is of interest. However, it is also of note that our patient has suffered significant neurological sequelae despite treatment with high-dose steroid therapy and immunoglobulin. Finally, our case also highlights the usefulness of finding raised levels of CSF neopterin as a marker of AGS.10

REFERENCES


