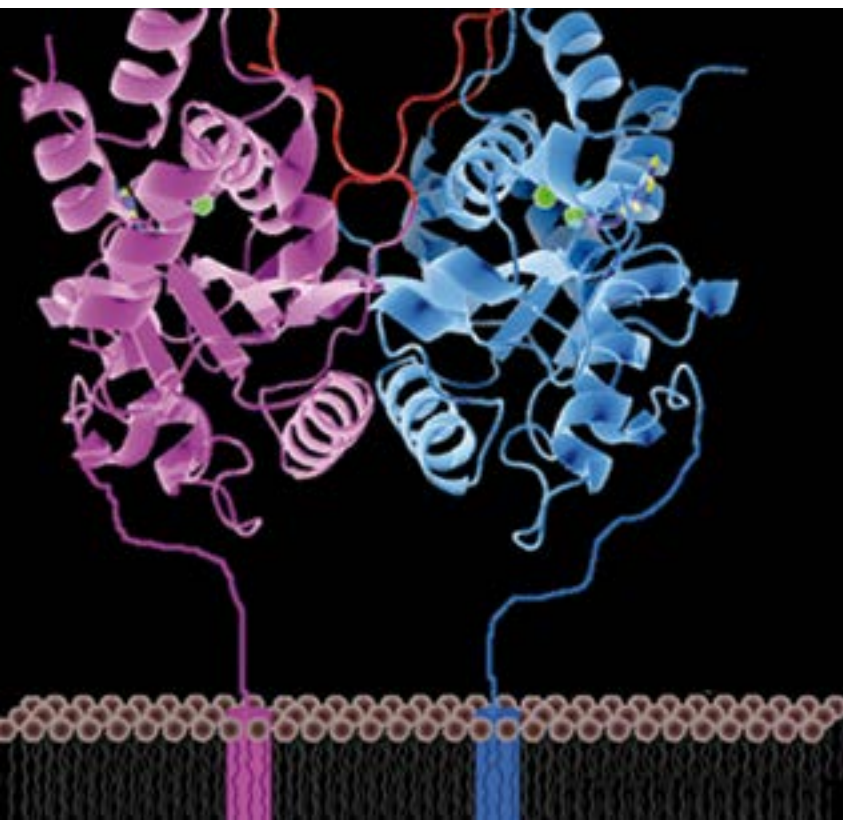


SWISS SOCIETY OF NEONATOLOGY

Aicardi-Goutières Syndrome

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Small-for-gestational age, thrombocytopenia, mild ventriculomegaly, echogenic lenticulostriate vessels and intracranial calcifications are nonspecific findings in neonatology with a broad differential diagnosis covering chromosomal anomalies, infectious diseases or they may present the first clues to rare genetic disorders.

A female infant was delivered by elective caesarean section at 35 weeks to a 29-year-old G1/P1. The parents were consanguineous with the baby's father and maternal grandfather being first cousins. The pregnancy was unremarkable until the 33rd week when mild ventriculomegaly and growth retardation were diagnosed. A fetal MRI performed a week prior to delivery confirmed the ventriculomegaly and showed loss of white matter but no anomalies of gyration. Due to a pathological fetal Doppler exam, a caesarean section was performed at 35 weeks.

The initial transition was normal and birth weight at 1835 g was on the 5th percentile for age and head circumference on the 15th percentile. Physical examination on admission was unremarkable expect for moderate generalized hypotonia and mild hepatomegaly. Initial laboratory tests showed a thrombocytopenia of 81 G/L and mild neutropenia with an ANC of $1130 \times 10^6/L$. Hemoglobin was normal at 152 g/L. Platelet and neutrophil counts normalized within 3 weeks.

Cranial ultrasound demonstrated small bilateral subependymal hemorrhages and slightly dilated lateral ventricles. In addition, there were multiple echodense calcified parenchymal and echogenic lenticulostriate vessels (Fig. 1, 2). An MRI confirmed the ultrasound findings, localizing the calcifications to the basal ganglia, and showed signs of leukodystrophy (Fig. 3). Aside from small retinal hemorrhages, the ophthalmological examination was normal as was the otoacoustic screening.

Maternal HIV was negative and CMV, rubella and toxoplasmosis IgG were positive with negative IgM for both mother and baby. CMV culture and PCR in the baby's urine were negative on repeated testing. Metabolic screening tests including organic acids, amino acids, calcium and phosphate were normal.

A lumbar puncture performed during the second week of life showed a cell count of $22 \times 10^6/l$ all of which were lymphocytes. CSF protein concentration was 1.13 g/L. PCR for CMV and toxoplasmosis were negative. Aicardi-Goutières syndrome was also considered in the differential diagnosis. CSF interferon- α was measured and found to be markedly elevated at 150 IU/ml (normal < 2 IU/ml) (Professor Pierre Lebon, Hôpital Saint Vincent de Paul, Université René Descartes, Paris).

Placenta histology was normal without any evidence of villitis. Genetic testing was done but to date none of

the known mutations for Aicardi-Goutières syndrome have been identified.

During the course of the hospitalization the baby demonstrated persistent muscular hypotonia and feeding problems as well as repeated desaturations. She was discharged home at the age of one month with a monitor and is being followed regularly by physiotherapy and pediatric neurology.

Cranial ultrasound on day 2 of life (coronal view): small subependymal hemorrhages in cystic transformation, ventriculomegaly, dilated lateral ventricles, periventricular calcification.

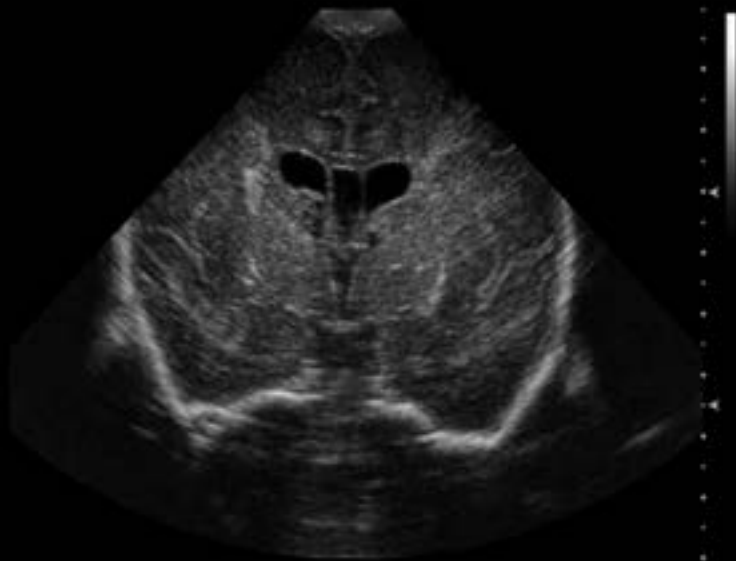


Fig. 1

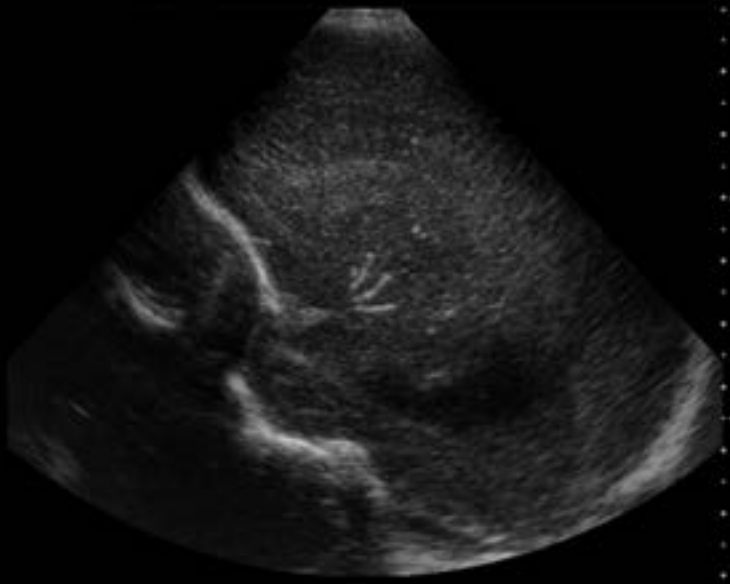


Fig. 2

Cranial ultrasound day 11 of life (left sagittal view):
calcification of lenticostriatal vessels.

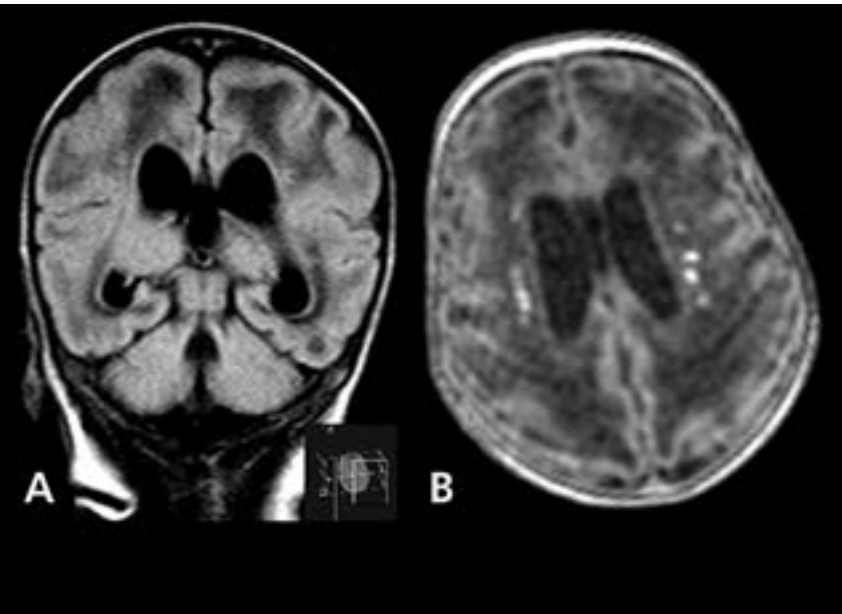


Fig. 3

Magnetic resonance imaging: A) coronal T1 weighted MRI: hypointensity of the white matter as a sign of leukodystrophy, B) axial FLAIR MRI: hyperintense periventricular calcifications, ventriculomegaly.

DISCUSSION

The combination of persistent thrombocytopenia and intracranial calcification in the basal ganglia-thalamic region can be associated with one of the TORCH infections especially CMV, toxoplasmosis or HIV, all of which we were able to rule out (1). The differential diagnosis of conditions in which basal ganglia calcification is a prominent feature include Aicardi-Goutières syndrome, Cockayne syndrome, mitochondrial diseases, parathyroid hormone metabolism disorders, and biotinidase deficiency, to mention a few (2-5).

The clinical and radiological findings in our patient, together with the CSF findings of an elevated interferon- α and lymphocytosis, are highly suggestive of Aicardi-Goutières syndrome (2, 4-8).

Aicardi-Goutières syndrome was first described in 8 children from 5 families in 1984 by Jean Aicardi and Françoise Goutières as an early onset encephalopathy of presumed genetic origin and associated with leukodystrophy, basal ganglia calcification and CSF lymphocytosis (2, 6, 9). The association with an elevated interferon- α in CSF was first noted in 1988 by Pierre Lebon (10, 11) and is considered to be the best marker for Aicardi-Goutières syndrome (2-4, 10). Many cases have subsequently been described. It is a genetically and phenotypically heterogeneous disorder (5,8). The clinical presentation is usually an early progressive encephalopathy with feeding difficulties, vomiting, jitteriness, slowing of head growth and recurrent epi-

sodes of low-grade fever over several months (1, 2, 4-7, 9, 12). In cases of later onset (4-12 months), loss of attained milestones has been described as well as spasticity (7, 12). Long-term, most infants show diffuse neurological signs including truncal hypotonia, limb spasticity, dystonic posturing, abnormal eye movements and seizures in about 50% of patients (3). Non-neurological manifestations include chilblain-like lesions of fingers, toes and earlobes in about 25-43% of patients. Autoimmune disorders such as diabetes (IDDM) and hypothyroidism have been described in a few patients (2, 3, 5, 7, 10).

Interestingly, CSF pleocytosis is variably present at diagnosis and CSF interferon- α remains elevated (>2 IU/ml) over months to years with normalization over the first few years of life. The levels are especially high when the diagnosis is made during the first month of life (1,3,5,8,10). Prenatal diagnosis in affected families has also been described in fetuses, which showed the typical findings on MRI and elevated interferon- α in fetal blood (13,14).

Since the original description of Aicardi-Goutières syndrome, two forms of the disorder have been identified: early neonatal onset and late onset, most of which are diagnosed around the age of 4 months (3-5, 10). About 20% of cases have a neonatal presentation and are most likely to be confused with TORCH infections with microcephaly, intracranial calcifications, neurological si-

gns, transitory hepatosplenomegaly with raised transaminases, transient thrombocytopenia and anemia. Of note, as in our patient, these patients have normal hearing and no chorioretinitis, which could be an early clue to the diagnosis (3,4).

Currently, 4 gene mutations have been identified by Crow YJ et al. and these can be found in 83% of patients. The first gene (AGS 1), discovered in 2000, was a TREX1 mutation on chromosome 3 and is particularly associated with the neonatal form (3-5, 10). The remaining 3 gene mutations (AGS 2-4), discovered in 2006, RNASEH2B, RNASEH2C and RNASEH2A are found on chromosomes 13, 11 and 9, respectively. It is believed that at least one gene mutation (AGS 5) remains to be identified in the remaining 17% of cases (3, 5, 10). Our patient probably belongs to the latter group and further mutations are being sought. In most cases, the patients are homozygous and the inheritance is autosomal recessive. The pathogenesis of this disorder and its phenotypic resemblance to certain congenital infections has been well-described by Crow YJ and co-workers (3, 4). An interferon- α mediated innate immune response can be triggered by both viral nucleic acids (DNA and RNA) as well as by endogenous nucleic acids, which the host recognizes as foreign. TREX1 and RNASEH2 complex proteins are nucleases which remove endogenous nucleic acids produced during normal cell processes. Failure of these nucleases, as it is thought to be the case in Aicardi-Goutières

syndrome, results in the host recognizing the endogenous nucleic acids as foreign, with subsequent inappropriate triggering of the innate immune system and activation of the interferon- α pathways (3, 4).

Aicardi-Goutières syndrome should always be considered in neonates with symptoms suggestive of congenital infection but negative screening for infections as genetic counselling is essential for the families concerned (2-5). Cordocentesis and measurement of fetal serum interferon- α could be useful in fetuses with fetal ultrasound or MRI findings suggestive of Aicardi-Goutières syndrome and a positive family history (13, 14).

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