Syndrome Aicardi-Goutières

Author: Professor Pierre Lebon[1]
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[1]Laboratoire de virologie, Hôpital Saint-Vincent de Paul, 74-82 Avenue Denfert-Rochereau, 75674 Paris Cedex 14, France. p.lebon@svp.ap-hop-paris.fr

Abstract
Aicardi-Goutières syndrome (AGS) is an autosomal recessive progressive encephalopathy associated with basal ganglia calcification, myelin abnormality, cerebro-spinal fluid (CSF) lymphocytosis and elevated CSF interferon (IFN)-alpha. The disease manifests similarly to fetopathy and the diagnosis is only often established at the birth of a second case in the family. The incidence of the AGS is very low, being inferior to 10 new cases per year in France. Onset occurs before 3-7 months of age in most patients. Vomiting, feeding difficulties, jitteriness, irritability, ocular jerks, and lack of progress in motor and social skills are the main symptoms, which progress to a microcephaly and a syndrome of vegetative state. Death rate is estimated to 30% between the age of 1 and 17 years. Symptoms may display an intrafamilial variability in severity. IFN-alpha is produced during months or years in the CNS and in the serum of patients in the absence of viral infection. Its synthesis is currently considered as a marker for the disease. Transgenic mice with chronic overexpression of IFN-alpha in astrocytes develop a phenotype similar to AGS with calcifications of the basal ganglia and leukodystrophy, supporting the hypothesis that abnormal secretion of IFN-alpha may be crucial in the syndrome pathogenesis. The syndrome displays genetic heterogeneity, and linkage analysis showed that 40-50% of AGS families map to the locus AGS1 on chromosome 3p21.

Keywords
Familial encephalopathy, progressive encephalopathy, CSF lymphocytosis, leucodystrophy; interferon-a; intracranial calcifications; autosomal transmission; basal ganglia calcifications, microcephaly, neonatal familial encephalopathy, childblains

Disease name and synonyms

- Aicardi-Goutières syndrome (AGS) named after Jean Aicardi and Françoise Goutières who gave the first description of the syndrome in 1984 (Aicardi and Goutières 1984)
- Familial encephalopathy with basal ganglia, with chronic CSF lymphocytosis
- Familial encephalopathy associated with a prolonged secretion of IFN-α

- Encephalopathy with chronic CSF lymphocytosis, basal ganglia calcifications, and leukodystrophy
- Familial encephalopathy with chronic CSF lymphocytosis, calcifications, and leukodystrophy
- Familial encephalopathy with chronic CSF lymphocytosis and prolonged Interferon secretion
- Intrauterine infection-like syndrome

Excluded diseases

- Viral fetopathy
- Cockayne syndrome
- Mitochondrial encephalopathies

Definition/Diagnosis criteria

AGS consists of a familial progressive encephalopathy associated with calcifications of the basal ganglia, white matter abnormalities, a chronic CSF lymphocytosis, a persistent synthesis of IFN-α in the CSF, and negative serological investigations for common prenatal infections.

All the results of serology and tissue culture for isolating TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex), varicella, adenoviruses, human T-cell leukemia virus type I and II, and human immunodeficiency virus type 1 and 2 from blood and CSF are negative.

Laboratory investigations give normal results for blood calcium and phosphorus levels, aminoacid, organic acid chromatographies, and lysosomal enzyme activities (Goutières *et al* 1998, Lebon 2002).

Electromyography, motor and sensory nerve conduction velocities, and electroretinogram are normal.

Visual evoked potentials are absent, decreased in amplitude, or delayed.

Brainstem evoked potentials show a prolonged I-V interval (Kato *et al* 1998).

CSF lymphocytosis is a consistent feature of all patients. In their review of patients with AGS, Goutières *et al* (1998) showed that all CSF samples contained 8 or more white blood cell /mm3 (WBC) and between 10 and 50 WBC in most samples in the first 12 months of life. Although lymphocytosis decreased with age, it persisted beyond the age of 2 years in two patients. One child was reported to have still 8 WBC at age 9 (McEntagart *et al* 1998), whereas one familial case showed no CSF lymphocytosis when studied at 12 months, in contrast to his affected sibling (Ostergaard *et al* 1999). In two cases related to the locus AGS1 (see "Etiology"), lymphocytosis was absent in spite of the presence of interferon in CSF (Crow *et al* 2000). CSF protein level is usually normal (<0.5 g/l), with normal electrophoresis or mild blood-CSF barrier disturbances without oligoclonal pattern.

Elevated levels of IFN-α in CSF is currently considered as a marker for the syndrome (Lebon *et al* 1988; Goutières *et al* 1998). Generally, values are higher in CSF than in serum, and they were observed to vary from 3 to 300 UI/ml (normal <2 UI/ml) in CSF of 77 tested patients (Lebon *et al* 2002). Values are higher at birth and decrease with age. However, IFN- α has been found to persist in some children after 5 years (Lebon *et al* 1988, 2002). Tubuloreticular inclusions induced by IFN-α have been observed in the skin, muscle, and lymphocytes (Lebon 1988, Goutières *et al* 1998, Barth 2002).

Basal ganglia calcifications are detected by CT scan performed without contrast in putamina, pallidum, thalami, and, in some patients, in dentate nuclei and subcortical areas. Their aspect varies from punctiform to massive, even within the same sibship (Goutières *et al* 1998; Ostergaard *et al* 1999), and is not always correlated with the severity of the status. Studies reported the absence of these calcifications on the first CT scan in 3 children at 7 weeks, 10 months, and 12 months (Aicardi and Goutières 1984; Goutières *et al* 1998; Ostergaard *et al* 1999). In addition to calcifications, CT scan show white matter hypodensities located mainly around the ventricles. They appear as hyperintense on MRI T2 sequences, they are not constant, and a diffuse leukodystrophic aspect is uncommon (Goutières *et al* 1998). Signs of severe and progressive brain atrophy with enlarged ventricles and sulci increasing on successive examinations are a constant finding on CT and MRI, and confirm the evolving nature of the disorder.

Differential diagnosis

Because of its association with lymphocytosis and calcifications, AGS can be mistaken for congenital or neonatal encephalitis caused by rubella, herpes virus, cytomegalovirus, varicella-zoster virus (VZV), toxoplasmosis or HIV. However, the predominant localization of calcifications in the basal ganglia, the negative TORCH investigations, the visceral involvement, and a lack of retinopathy, microcephaly or hydrocephaly at birth are distinguishing features of Aicardi-Goutières syndrome.

Cockayne syndrome, a familial leukodystrophy with striocerebellar calcifications caused by defective repair of transcriptionally active DNA (Nance and Berry 1992), differs from Aicardi-Goutières syndrome by special facial features, dwarfism, microcephaly, nerve deafness, retinopathy, cataract, and skin photosensitivity. Familial encephalopathy with intracerebral

calcifications, white matter lesions, growth hormone deficiency, and retinal degeneration can be differentiated from Aicardi-Goutières syndrome by the associated features (Bonnemann 1991).
In static non-progressive encephalopathy associated with basal ganglia calcification, CSF is normal, some cases resulting from neonatal anoxia (Aicardi 2002).
AGS shares many features with microcephaly intracranial calcifications (MICS) syndrome or pseudo-TORCH syndrome and the Cree Encephalitis. Both conditions are said to differ from AGS by the presence of an early onset microcephaly, disturbance of liver and thrombocytopenia and a normal CSF white cells count in pseudo-TORCH syndrome, and by the presence of systemic immune abnormalities in Cree encephalitis. However these entities are similar for IFN presence (Lebon 1996) and linked to the same locus than AGS (Crow 2003).

Epidemiology
The incidence of AGS is not known. Reports indicate that it is present at least in Europe, North Africa, North and South America, Pakistan and possibly in all the continents. In France, we collect approximately ten cases per year, but the incidence is likely to be underestimated.

Clinical manifestations
Onset occurs before 3-7 months of age in most patients, and sometimes within the first week. Weight and head circumference at birth are within the normal range, but exceptional cases with congenital microcephaly have been reported (Goutières *et al* 1998; Kato *et al* 1998). Similar cases are also termed under the name of MICS (Reardon 1994). Vomiting, feeding difficulties, jitteriness, irritability, ocular jerks, and lack of progress in motor and social skills are the main symptoms. Bouts of mild fever (38°C to 38.5°C) may lead to the erroneous diagnosis of meningitis or encephalitis (Goutières *et al* 1998).
A few children show a later onset, between 7 and 12 months of age, marked by loss of previously acquired psychomotor skills (Aicardi and Goutières 1984; Goutières *et al* 1998; Ostergaard *et al* 1999). Although almost all children have severe developmental delay and little or no communication ability, a few children show less severe impairment with relative preservation of social interaction (Goutières *et al* 1998; McEntagart *et al* 1998). There have been cases of different degrees of severity in the same sibship (McEntagart *et al* 1998; Ostergaard *et al* 1999). Seven children with AGS from a consanguineous family showed diffuse intracranial calcifications (Kumar 1998). These cases may represent also a particular phenotype of AGS.
Symptoms progress to a microcephaly (between 3 and 12 months of age) and a syndrome of vegetative state. Death rate is estimated to 30% between the age of 1 and 17 year (Aicardi 2002). On examination, the infants show diffuse neurological signs with truncal hypotonia, dystonia, pyramidal tract signs, and cortical blindness. Fundi are normal or show mildly pale papillae.
Seizures are occasional and the EEG is usually not informative.
Extraneurological signs are occasionally present: vascular necrotic cutaneous lesions of the toes looking like chilblains with acrocyanosis (Tolmie *et al* 1995; Stephenson *et al* 1997; Goutières *et al* 1998), erythematous periungual skin, puffy hands and feet, or cold feet (Goutières *et al* 1998). Transient hepatomegaly, increased levels of hepatic transaminases, and thrombocytopenia at birth have been observed in some cases (Goutières *et al* 1998).

Management and treatment
There is no cure for AGS. Treatment is symptomatic principally for treating the dystonia with orthopaedic surgery or localized botulinum toxin injection, and for relieving the pain with specific drugs. Sometimes children need intensive care during aggravation periods. Tube feeding is indicated in case of feedings difficulties.

Etiology
AGS is an autosomal recessive disorder whose gene(s) remain(s) unknown. The first genetic studies concluded to a genetically heterogeneous disease: a first genome-wide screening of 5 consanguineous families by homozygosity mapping has detected several, but different, homozygous region in affected individuals (Fauré *et al* 1999). However, genetic heterogeneity with one locus (AGS1) on chromosome 3p21 has been recently identified in 40-50% of affected families (Crow *et al* 2000). The same locus has been associated with the MICS and recently with the Cree encephalitis (Crow 2003).

Diagnostic methods
Clinical examination, CT scan, CSF analysis, measurement of interferon in CSF and in serum, viral serology, measurement of blood calcium, phosphorus, amino acid acid organic chromatography, lysosomal enzymes activities, mitochondrial enzymes activities.

Genetic counseling
The autosomal recessive inheritance of the disorder entails a risk of 1/4 for subsequent siblings in affected families.

Antenatal diagnosis
Antenatal diagnosis has not been performed so far. A genetic molecular test may be performed for the antenatal diagnosis of families associated with the locus AGS1.

Unresolved questions
Does AGS result from a primary genetic defect in IFN-α metabolism? CSF IFN- α levels are consistently raised in the early stages of the disease (Lebon1988, Lebon 2002), and of particular importance, astrocyte-specific chronic overproduction of IFN-α in transgenic mice (Campbell 1999, Akwa 1998) mimics the neuropathological findings observed in AGS (Barth 2002) and Cree encephalitis (Black 1988) with calcifications of the basal ganglia and leukodystrophy. These observations suggest that IFN-α plays a fundamental role in the pathogenesis of AGS.

References
Aicardi, J. Aicardi-Goutieres syndrome: special type early-onset encephalopathy. Eur J Ped neurol 2002; 6 (suppl A):1-7.
Aicardi J, Goutieres F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 1984;15:49-54.
Akwa Y, Hassett DE, Eloranta ML, *et al*. Transgenic expression of interferon--a in the central nervous system of mice protects against lethal neurotropic viral infection but induces inflammation and neurodegeneration. J Immunol 1998;161:5016-26.
Barth PG. The neuropathology of Aicardi-Goutieres syndrome Eur J Ped neurol 2002; 6 (suppl A):1-7
Black DN, Watters GV, Andermann E, *et al*. Encephalitis among Cree children in Northern Quebec. Ann Neurol 1988;24:483-9.
Bonnemann CG, Meinecke P, Reich H. Encephalopathy with intracerebral calcification, white matter lesions, growth hormone deficiency, microcephaly and retinal degeneration: two sibs confirming a probably distinct entity. J Med Genet 1991;28:708-11.
Campbell IL, Krucker T, Steffensen S, Akwa Y, Powell HC, Lane T, Carr DJ, Gold HG, Henriksen SJ, Siggins GR. Structural and functional neuropathology in transgenic mice with CNS expression of IFN-α. Brain Res 1999;835:46-61.
Cardenas-Mera N, Campos-Castello J, Ferrando-Lucas MT, Carreaga-Maldonado J. Progressive familial encephalopathy in infancy with calcifications of the basal ganglia and cerebrospinal fluid lymphocytosis: report of four cases. Acta Neuropediatr 1995;1:206-13.
Crow, YJ, Jackson AP, Roberts E, van Beusekom E, Barth P, Corry P, Ferrie CD, Hamel BC, Jayatunga R, Karbani *et al*. (2000). Aicardi-Goutières Syndrome displays genetic heterogeneity with one locus (AGS1) on chromosome 3p21. Am. J. Hum. Genet. 2000; 67:213-221.
Crow Y, Black D, Ali Manir, Bond J, Jackson AP, Lefson M, Michaud J, Roberts E, Stephenson JBP, Woods G, Lebon P, Cree encephalitis is allelic with Aicardi-Goutieres syndrome; implications for the pathogenesis of disorders of interferon alpha metabolism, J Medical Genetics (in press)
Fauré S, Bordelais I, Marquette C, Rittey C,Campos-Castello J, Goutieres F, Ponsot G, Weissenbach J, Lebon P. Aicardi-Goutieres syndrome: monogenic recessive disease, genetically heterogeneous disease or multifactorial disease? Clin Genet 1999;56:149-53.
Goutieres F, Aicardi J, Barth PG, Lebon P. Aicardi-Goutieres syndrome: an update and results of Interferon-alpha studies. Ann Neurol 1998;44:900-7.
Kato M, Ishii R, Honma A, Ikeda H, Hayasaka K. Brainstem lesion in Aicardi-Goutieres syndrome. Pediatr Neurol 1998;19:145-7.
Kumar D, Rittey C, Cameron AH, Variend S. A recognizable inherited syndrome of progressive central nervous system degeneration and generalized intracranial calcification with overlapping phenotype of the syndrome of Aicardi and Goutieres. Am J Med Genet 1998;75:508-15
Lebon P, Badoual J, Ponsot G, *et al*. Intrathecal synthesis of interferon alpha in infants with progressive familial encephalopathy. J Neurol Sci 1988;84:201-8.
Lebon P, Black D, Goutieres F, *et al*. Viral infection in a genetic terrain or genetic disease involving the interferon alpha system? Eur Cytokine Netw 1996;7:459
Lebon P, Meritet JF, Krivine A, Rozenberg F, Interferon and Aicardi-Goutieres Syndrome. Eur J Ped neurol 2002 ; 6 (suppl A) 47-53
McEntagart M, Kamel H, Lebon P, King MD. Aicardi-Goutieres syndrome: an expanding phenotype. Neuropediatrics 1998;29:163-7.
Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. Am J Med Genet 1992;42:68-84.
Ostergaard JR, Christensen T, Nehen AM. A distinct difference in clinical expression of two

siblings with Aicardi-Goutieres syndrome. Neuropediatrics 1999;30:38-41.
Reardon W, Hockey A, Silberstein P, *et al*. Autosomal recessive congenital intrauterine infections-like syndrome of microcephaly, intracranial calcification, and CNS disease. Am J Med Genet 1994;52:58-65.
Stephenson J, Tolmie J, Heckmatt J, Tang S, Tatnall F, Lebon P. Aicardi-Goutieres syndrome: autoimmune clues to diagnosis and pathogenesis and link to microcephaly intracranial calcification syndrome. Dev Med Child Neurol 1997;77:15.
Tolmie JL, Shillito P, Hugues-Benzie R, Stephenson JB. The Aicardi-Goutieres syndrome: familial, early onset encephalopathy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. J Med Genet 1995;32:881-4.

Références about historical cases and very similar cases for which the interferon assay was not performed

Babbitt DP, Tang T, Dobbs J, Berk R. Idiopathic familial cerebrovascular ferrocalcinosis (Fahr's disease) and review of differential diagnosis of intracranial calcification in children. Am J Roentgenol 1969;105:352-8.
Bonnemann CG, Meinecke P. Encephalopathy of infancy with intracerebral calcification and chronic spinal fluid lymphocytosis: another case of the Aicardi-Goutieres syndrome. Neuropediatrics 1992;23:157-61.
Diament AJ, Machado LR, Cypel S, Ramos JL. Síndrome de calcificações dos gànglios da base, leukodistrofia e pleocitose linfomonocitária crônica do líquido cefalorraqueano. Arq Neuropsiquiatr 1986;44:185-90.
Giroud M, Gouyon JB, Chaumet F, *et al*. A case of progressive familial encephalopathy in infancy with calcification of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Childs Nerv Syst 1986;2:47-8.
Jervis GA. Microcephaly with extensive calcium deposits and demyelination. J Neuropathol Exp Neurol 1954;13:318-29.
Hallervorden I. Über diffuse symmetrische Kalkablagerungen bei einem Krankheitsbild mit Mikrocephalie und Meningoencephalitis. Arch Psychiatr Neurol 1950;184:570-600.
Lyon G, Robain O, Philippart M, Sarlieve L. Leucodystrophie avec calcifications strio-cérébelleuses, microcéphalie et nanisme. Rev Neurol (Paris) 1968;119:197-210.
Mehta L, Trounce JQ, Moore JR, Young ID. Familial calcification of the basal ganglia with cerebrospinal fluid pleocytosis. J Med Gent 1986;23:157-60.
Melchior JC, Benda C, Yakovlev PI. Familial idiopathic cerebral calcifications in childhood. Am J Dis Child 1960;99:787-803.
Troost D, Van Rossum A. Cerebral calcifications and cerebellar hypoplasia in two children: clinical, radiologic and neuropathological studies. A separate neurodevelopmental entity. Neuropediatrics 1984;15:102-9.
Verrips A, Hiel JA, Gabreels FJ, Wesseling P, Rotteveel JJ. The Aicardi-Goutieres syndrome: variable clinical expression in two siblings. Pediatr Neurol 1997;16:323-5.