

Aicardi-Goutières syndrome: differential diagnosis and aetiopathogenesis

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Summary

Aicardi-Goutières syndrome (AGS) is a progressive encephalopathy with onset in the first year of life and a recessive autosomal pattern of inheritance. The syndrome is characterised by acquired microcephaly, basal ganglia calcifications, white matter abnormalities, chronic cerebrospinal fluid (CSF) lymphocytosis and raised interferon-alpha (INF-alpha) in the CSF. AGS is diagnosed on the basis of a clinical picture characterised by microcephaly and by the onset of encephalopathy associated with severe psychomotor delay, spasticity and extrapyramidal signs. CT is very important in the diagnosis of AGS, demonstrating clearly the presence of calcifications at basal ganglia level: these are often bilateral and symmetrical. CT scan and MRI reveal leukodystrophy and progressive cerebral atrophy. A raised level of INF-alpha in the CSF constitutes a marker of the syndrome: this level, which falls with age, is higher in the CSF than in the serum, suggesting intrathecal synthesis. Differential diagnosis in AGS is carried out to exclude the presence of other neurological and endocrinological pathologies characterised by the presence of intracranial calcification; considering the white matter abnormalities, it is necessary to exclude forms of leukodystrophy associated with metabolic defects, known or otherwise. One fundamental aspect that remains to be clarified is the aetiopathogenetic mechanism underlying AGS: the most well-founded hypotheses are reported. There does not exist, to date, any causal therapy for AGS, although genetic studies, particularly those focusing on interferon-regulating genes, may well provide some therapeutic indications.

KEY WORDS: Aicardi-Goutières, basal ganglia, brain calcification, interferon, leukodystrophy.

Definition and clinical picture

Aicardi-Goutières syndrome (AGS) is a progressive encephalopathy with onset in the first year of life and a recessive autosomal pattern of inheritance. The syndrome is characterised by acquired (or sometimes congenital) microcephaly, basal ganglia calcifications, white matter abnormalities, chronic cerebrospinal fluid (CSF) lymphocytosis and raised interferon-alpha (INF-alpha) in the CSF. Aicardi and Goutières' first description of eight cases was published in 1984 (1). Since then, the reports appearing in the literature have pointed to a certain clinical heterogeneity of the syndrome (2), describing less severe cases, later onset and a variability of the overall picture even within single families (3).

AGS is a rare pathology and its true incidence is not known. To date, 51 cases have been described (4). Of these cases, which are distributed all over the world, many are familial (5).

As we have detailed elsewhere (4), diagnosis of AGS is based on a clinical picture characterised by microcephaly (usually appearing in the first months of life) and the onset of encephalopathy associated with psychomotor delay, spasticity and extrapyramidal signs. It is also based on the presence of:

- bilateral symmetrical calcifications at basal ganglia level (involving, in particular, the putamen, the pallidus and the thalamus) visible on brain CT scan;
- cerebral white matter abnormalities: CT scan shows hypodensities and MRI a hyperintense signal in T2-weighted images, particularly at periventricular level and sometimes involving the brainstem (6) and pyramidal tracts;
- cerebral atrophy (visible on CT scan and on MRI);
- chronic lymphocytosis (>5 cells/mm³) on CSF examination, which may decrease over time and which is not accompanied by any other sign of an infectious process (7).

In most cases, raised INF-alpha is detected in the CSF and sometimes in the serum (8), although the level tends to fall after the first few years of life. Tubular reticular inclusions in endothelial skin cells (9) have been described in a few cases, particularly in subjects with high levels of circulating INF-alpha.

Pregnancy, delivery, birthweight and head circumference at birth are all normal, with the first signs of the disease tending to appear between 3 and 6 months of age; in some cases, however, symptoms are present at birth.

The first symptoms noted by parents and physicians are feeding difficulties, irritability, tremor, abnormal eye movements (e.g., nystagmus) and sometimes unexplained mild febrile episodes (38-38.5°C).

In around a third of cases, onset occurs after the age of

six months with loss of psychomotor acquisitions. Upon clinical examination, the subjects present spasticity, dystonic movements, trunk hypotonia, little or no eye contact and acquired microcephaly. Epileptic seizures are present in approximately half the subjects. Extra-neurological signs have occasionally been observed, the most significant being skin lesions affecting the toes and fingers ("chilblains" in the periungual region); sometimes lesions are also present on the earlobes, suggesting a distal vasculopathy.

The prognosis is very severe. Most AGS sufferers are profoundly disabled and unable to communicate. However, in some cases the motor and mental deficit is less severe and some scope for relational contact is conserved.

Diagnosis

As mentioned above, AGS is diagnosed on the basis of a clinical picture characterised by microcephaly (onset within the first year, usually the first months, of life), and by the onset of encephalopathy associated with severe psychomotor delay, spasticity and extrapyramidal signs (10).

Lymphocytosis is a constant feature and ranges, according to Goutières et al. (10), from 260 cells/mm³ at the first evaluation to 13/mm³ at 21 months. All affected subjects have a count of 8 or more cells in the first year of life (10-50 in most cases).

CT is very important in the diagnosis of AGS, demonstrating clearly the presence of the calcifications. The calcium deposits are often situated at the level of the thalamus, globus pallidus, putamen, caudate nucleus and dentate nucleus. Calcifications have also been described in the periventricular and subcortical regions (6) and in the cerebellum. The deposits may be punctate, but more frequently present as larger concretions. They are often bilateral and symmetrical and can present with varying intensity in different patients, even within the same family (Fig. 1).

Hypodense areas in the white matter, visible on CT scan, are situated mainly at periventricular level, but may also involve the brainstem and pyramidal tracts, giving an appearance of diffuse leukodystrophy; this feature is accompanied by a hyperintense signal in T2-weighted MR images (Fig. 2). In all cases, both MRI and CT reveal signs of severe and progressive cerebral atrophy, with enlargement of the ventricles and cortical sulci, which is generally, but not always (11), increased at subsequent follow ups.

A raised level of INF-alpha in the CSF constitutes a marker of the syndrome, being found by Aicardi and Goutières et al. in 14 out of 15 affected subjects tested (10). This level, which falls with age, is higher in the CSF than in the serum, suggesting intrathecal synthesis.

Tubular reticular inclusions in endothelial skin cells, in muscle and in lymphocytes, particularly in subjects with high levels of circulating INF-alpha, have been described in a few cases. In these cases, it is opportune to carry out a skin biopsy (9).

DNA analysis may, in a few cases, reveal genetic heterogeneity, with the locus AGS1 on chromosome 3p21 (12).

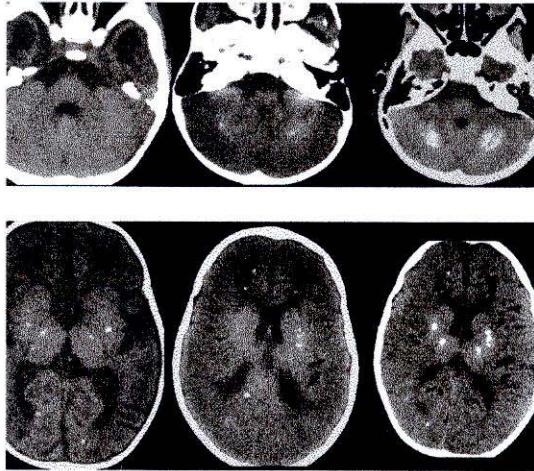


Figure 1 - Brain CT scans of the cerebellum (top) and of the basal ganglia and thalami (bottom). The images show the progression of the calcifications, visible as hyperdensities, in the course of the disease (7 months, 18 months, 3 years).



Figure 2 - Brain MRI, axial image. The figure shows areas of diffuse hyperintensity caused by the leukodystrophy affecting the temporal lobe white matter.

Differential diagnosis

Differential diagnosis in AGS is carried out to exclude the presence of other neurological and endocrinological pathologies characterised by the presence of intracranial calcification (9) situated preferentially at basal ganglia level or associated with calcification in other sites (13,14) (Table I). Furthermore, considering the white matter abnormalities, it is necessary to exclude forms of leukodystrophy associated with metabolic defects, known or unknown (15,16) (Table II).

Useful investigations for the differential diagnosis of AGS include:

- serological investigations to test for TORCH complex markers, in order to exclude the possibility of pre- or perinatal infection (15);

- measurement of lactic and pyruvic acid in the blood and CSF, in order to exclude the presence of a mitochondrial encephalopathy; when the latter is strongly suspected, muscle biopsy and investigation of respiratory chain enzymes are warranted;
- measurement of calcaemia, phosphataemia and parathormone in order to exclude hypoparathyroidism and pseudohypoparathyroidism (13);
- measurement of lysosomal enzymes on leukocytes, in order to exclude leukodystrophies associated with known metabolic defects. If Cockayne syndrome is suspected, damage to DNA repair mechanisms can be evaluated by means of ultraviolet irradiation of the fibroblasts (17);
- testing for the presence of systemic lupus erythematosus (SLE) and complementaemia autoantibodies, particularly in subjects with progressive dermatological complications (18-20).

Aetiopathogenetic hypothesis

One fundamental aspect that remains to be clarified is the aetiopathogenetic mechanism underlying AGS and, in particular, the significance of the presence of INF-alpha in the CSF of affected subjects (8,10). INF-alpha is a cytokine that, in normal conditions, protects cells against many viruses and plays an immunomodulatory role.

Akwa et al. (21) generated two lines of transgenic mice that produce INF-alpha1 chronically. These lines, GIFN-39 and GIFN-12, are characterised, respectively,

by moderate and low expression of the transgene codifying INF-alpha. GIFN-39 mice develop a progressive phenotype that is characterised by weight loss accom-

Table I - Neurological and endocrinological pathologies characterised by the presence of intracranial calcification.

Diffuse intracranial calcifications that can occasionally involve the basal ganglia	
Congenital toxoplasmosis	
Cytomegalovirus infection	
HIV infection	
Congenital rubella	
Herpes simplex infection	
Calcifications preferentially involving the basal ganglia	
Hypoxic-ischaemic encephalopathy	
Endocrine disorders:	
• Hypoparathyroidism	
• Pseudohypoparathyroidism	
Metabolic diseases:	
• mitochondrial encephalopathies (Kearns-Sayre syndrome, MERRF, MELAS)	
• biotinidase deficiency	
• carbonic anhydrase II deficiency	

Table II - Forms of leukodystrophy associated with metabolic defects, known or unknown.

Type of leukodystrophy	Transmission	Metabolic defect
Primary leukodystrophies with known metabolic defects:		
Metachromatic leukodystrophy	AR	Cerebroside sulphatase
Krabbe's disease	AR	β-galactocerebrosidase
X-linked adrenoleukodystrophy	XLR	Lignoceroyl-CoA-ligase
Canavan-Van Bogaert disease	AR	N-acetylaspartic acid
Primary leukodystrophies with no known metabolic defects:		
Pelizaeus-Merzbacher disease	XLR	Proteolipid protein synthesis defect
Alexander disease		
Cockayne syndrome		
Leukodystrophy with calcification of the central grey matter (Aicardi-Goutières syndrome)		
Leukodystrophies secondary to another metabolic disorder:		
Mucopolysaccharidosis (Hurler syndrome)	AR	L-iduronidase
Phenylketonuria	AR	Phenylalanine oxidase
Glutaric aciduria	AR	Glutaryl-CoA dehydrogenase
Other amino acid or organic acid disorders	AR	
Mitochondrial encephalopathies		
Encephalomyopathies		

Abbreviations: AR = autosomal recessive; XLR = X-linked recessive

panied by inactivity, ataxia, and epileptic fits. Death often occurs between 3-5 months. GIFN-12 mice appear normal up to the age of 10-12 months, after which some animals show a progressive but slower degeneration that can result in death.

In contrast to the beneficial anti-viral action of INF-alpha in CSF, the progressive deterioration and premature death of transgenic mice demonstrates a harmful effect of this cytokine at brain level. Indeed, abnormalities are found in the CNS of these mice that lead to a neurodegenerative pathology and bear witness to the toxicity mediated by dysregulation of intrathecal production of INF-alpha.

In the GIFN-39 mice, mineral deposits (essentially calcium and phosphorous) at cerebellar and basal ganglia level have been demonstrated. These deposits are situated both alongside and inside the walls of small blood vessels in the brain. Although the cause of these neuropathological alterations remains unknown, involvement of INF-alpha-induced calcium manipulation and/or metabolism can be hypothesised.

It is also possible that the increase in INF-alpha is not the main cause of the disease, but is itself the consequence of another, as yet unknown, mechanism, perhaps immunomediated.

Dale et al. (18) described two siblings with a congenital progressive encephalopathy associated with SLE. In the first year of life, both patients presented encephalopathy and intracranial calcifications (periventricular, subcortical, but above all, basal ganglia); one also presented hepatitis and thrombocytopenia, features suggesting a congenital viral infection. All the serological investigations (TORCH, HAV, HBV, HCV, Parovirus B19) were negative. The most likely diagnosis is thus microcephaly intracranial calcification syndrome (MICS). In the first year of life, both children presented acquired microcephaly, cortical blindness, spastic tetraplegia, myoclonias and virtual absence of psychomotor development. Small erythematous lesions appeared in both patients by the age of 10 months, by 2 years affecting the dorsum of the toes and fingers, the tip of the nose and the outer ears. This led to a clinical diagnosis of SLE, confirmed by skin biopsy of the lesions which showed a hyperkeratotic epidermis and degeneration of the basal lamina. Direct immunofluorescence studies revealed granular deposits of IgM at basement membrane level.

The early development of SLE in these subjects suggests that their cerebral pathology is part of an autoimmune process (22).

Although there are, to date, no descriptions of cases of AGS associated with autoantibody-induced activation, pathological studies have demonstrated microangiopathy (23). Tolmie et al. (9) have described, in AGS patients, skin lesions similar to those observed in two patients with MICS. In these latter patients, anti-DNA antibody values and skin biopsy confirmed the presence of lesions typical of SLE. Observing the presence of INF-alpha in the serum and CSF of these young patients, as well as the presence of vasculitic lesions comparable with those reported by other authors, it was hypothesised that AGS and MICS may be the same pathology, or different allelic expressions of a pathology that could be called alpha-interferonopathy. The systemic production of INF-alpha would presumably play a role in the

autoimmune phenomenon, whose most easily identifiable clinical manifestation is erythema pernio.

Another mechanism hypothesised as the primary cause of the disease is that of a genetic cerebral microangiopathy.

Barth et al. (23) reported post-mortem findings in an AGS patient who died at the age of 17 years. These findings included, at cerebral level, not only a severe microcephaly, but also supra- and infratentorial atrophy with inhomogenous and diffuse white matter loss. As a result, areas of cavitation and compensatory ventricular dilatation were visible.

No inflammatory signs were present, but there was thickening of the media and adventitia with small vessel calcification in the media and adventitia and perivascular spaces. The latter findings were observed in areas of the cerebral and cerebellar cortex and underlying white matter affected by microinfarctions, and accompanied by abnormal proliferation of the small vessels.

According to Barth et al. (23), these elements provide evidence that vascular insufficiency is a decisive factor both in the degenerative process, leading to functional insufficiency at the level of the small arterioles, and in the areas of microinfarction, even in the absence of frank vascular occlusions. The inhomogenous distribution of the white matter alterations (conserved areas alternating with areas of demyelination) suggests an aetiological process based on a hypoxic-ishaemic type mechanism.

The clinical studies carried out by Tolmie et al. (9) add weight to the microangiopathy hypothesis; two AGS patients are reported who, at the age of three years, developed erythematous lesions and acrocyanosis on the feet. The erythema was, strangely, not associated with cold and immunological investigations were negative. Furthermore, these lesions failed to respond to vasodilator therapy.

Ever since the appearance of the first reports of affected siblings in families in which the parents were often consanguineous, it has been hypothesised that the disease is inherited as an autosomal recessive trait (24). The gene responsible has still not been mapped, even though an alteration on the short arm of chromosome 3 has been identified in some patients and in their families.

Crow et al. (12) studied 23 children with a clinical diagnosis of AGS who originated from 13 families; the patients included in the study presented with an early-onset, progressive encephalopathy characterised by normal head circumference at birth, basal ganglia calcification, negative viral studies and CSF abnormalities (raised lymphocyte counts and/or raised INF-alpha).

By means of a linkage analysis on 13 families, these authors obtained evidence of a positive linkage for AGS on chromosome 3p21. The result was not homogeneous, however, in the sense that only some of the families gave significantly positive logarithm of odds (LOD) scores; the other families gave negative LOD scores, in particular <-2. This result provides clear evidence that the disease is genetically heterogeneous with around 50% of families showing a linkage with chromosome 3.

As far as the other families are concerned, the data reported constitute evidence supporting the existence of

at least one other locus capable of giving rise to the same clinical phenotype.

When the families showing a linkage with chromosome 3 were further analysed through the addition of other loci, the LOD score rose to 5.28, providing a definitive demonstration of the presence of a locus on chromosome 3. The region involved covers around 15 cM (centiMorgans) and is located between locus D3S1768 and D3S3721.

Treatment and future prospects

There does not exist, to date, any causal therapy for AGS, although genetic studies, particularly those focusing on interferon-regulating genes, may well provide some therapeutic indications. Other treatment hypotheses currently in the clinical experimental stage are based on symptomatic treatment (attempts to reduce the level of INF-alpha in the CNS through cycles of cortisone at high doses).

Rehabilitative therapy, on the other hand, aims to increase the wellbeing and to improve the day-to-day management of these patients. In subjects with epilepsy, anti-comitial therapy is undertaken.

Prospects for future study of AGS span the fields of genetics and immunology, although it is essential not to underestimate the importance of thorough clinical research, as it is essential to collect extremely detailed clinical histories of these patients and to document with precision their evolution.

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