# AICARDI-GOUTIERES SYNDROME: A DESCRIPTION OF 21 NEW CASES AND A COMPARISON WITH THE LITERATURE

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Abstract

The International Aicardi-Goutières Syndrome Association (IAGSA) was founded in 2000, its aim being to collect and analyse all available information on this rare syndrome (whose true incidence is not known) in order to increase knowledge of the pathology and the number of reported cases.

We analysed the clinical, neuroradiological and biological characteristics of 21 new Aicardi-Goutières syndrome subjects (7 observed directly and 14 on whom we gathered detailed clinical information) and compared our findings with literature data.

The main clinical symptoms (pyramidal and extrapyramidal symptoms, psychomotor delay, microcephaly) and neuroradiological features (basal ganglia calcification, atrophy, white matter alterations) observed show a greater homogeneity in our subjects than in the literature cases, which indicates an improvement in the diagnostic accuracy of AGS. Other symptoms, such as feeding difficulties and irritability are less frequent, but characteristic and present early (even at onset of the disease). In the literature, doubts are expressed as to whether lymphocytosis and/or raised interferon-alpha in CSF are crucial for a diagnosis of AGS. Our data suggest that they are, and in particular that an important role is played by raised interferon-alpha.

The clinical course seems to show different stages: early onset, rapid progression, severe deterioration, stabilisation. Our follow-up seems to indicate a trend not necessarily towards a worsening, but instead towards a stabilisation or even a slight improvement of the clinical picture.

Key words: Aicardi-Goutières syndrome, basal ganglia calcifications, clinical course, interferon-alpha, chronic lymphocytosis, leukodystrophy

Aicardi-Goutières syndrome (AGS) is a progressive encephalopathy, possibly with a recessive autosomal pattern of inheritance [1,2], which has onset in the first year of life and is characterised by acquired microcephaly (sometimes congenital), basal ganglia calcifications, white matter abnormalities, chronic lymphocytosis in the cerebrospinal fluid (CSF) and raised interferon-alpha (INF-alpha) in the CSF. Reports appearing in the literature, since Aicardi and Goutières' first description of 8 cases in 1984[3], have revealed a certain clinical heterogeneity of the syndrome, which presents in some cases a less severe clinical course[4], a later onset[5] and a variability of the overall picture even within single families[6,7,8].

| Author(s) | Year | No. of cases described |
|---|---|---|
| Aicardi and Goutières | 1984 | 8[a] |
| Troost | 1984 | 2 |
| Giroud | 1986 | 1 |
| Diament | 1986 | 1 |
| Metha | 1986 | 2 |
| Bönnemann | 1992 | 1 |
| Verrips | 1997 | 2 |
| Goutières and Aicardi | 1998 | 27[a] |
| Østergaard | 1998 | 2 |
| McEntagart | 1998 | 2 |
| Kato | 1998 | 1 |
| Kumar | 1998 | 7 |
| Barth | 1998 | 1[a] |
| Koul | 2001 | 2[b] |
| Polizzi | 2001 | 1[b] |

[a]The eight cases reported by Aicardi and Goutières in 1984 and Barth's case described in 1998 are included in the 27 cases reported by Goutières and Aicardi in 1998.
[b]After the date of the meeting a further three cases appeared in the literature: Polizzi reported one case and Koul two cases in 2001. This takes the total number of new cases to 51, but we compared our cases with the 48 detailed in the text.

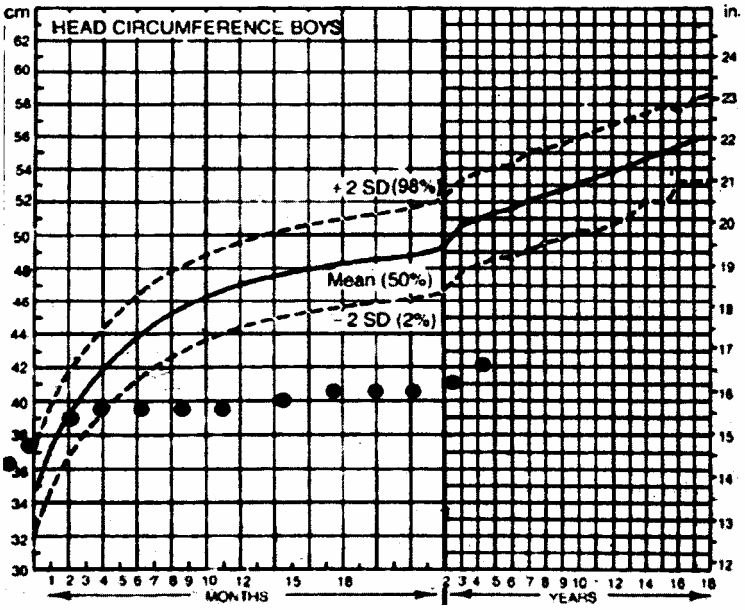
Aicardi-Goutières syndrome is an extremely rare pathology whose true incidence is not known. The total number of published cases is also difficult to establish, due to difficulties over the definition of AGS and also because of overlapping reports, for example, the 27 cases described by Aicardi and Goutières in 1998[9] include their eight cases reported in 1984[3] (the first ones to be described). To date, the literature reports 51 cases throughout the world, many of which are familial (Table 1). [3,4,6,7,8,9,10,11,12,13,14,15,16,17,18,19] To avoid swelling artificially the number of described cases, this figure was reached by counting only detailed clinical cases, and not those collected in broader immunological, genetic and neuropathological studies, such as the papers published by Crow[20], Lebon[21] and Barth[18], or those reported only briefly [10].

The diagnosis of AGS, according with literature, is based on: [9]

1. A clinical picture characterised by microcephaly (appearing in the first months of life) and by the onset of encephalopathy associated with psychomotor delay, spasticity and extrapyramidal signs.

2. The presence of bilateral, symmetrical calcifications[14] at basal ganglia level (in particular in the putamen, the pallidus and the thalamus) visible upon brain CT scan. [22]
3. The presence of cerebral white matter alterations upon neuroradiological investigation: [22] hypodensities on CT scan and, in MRI, a hyperintense signal in T2-weighted images, above all at periventricular level and sometimes also involving the brainstem[16] and pyramidal tracts.
4. The presence of cerebral atrophy (documented by CT scan and MRI) [22]
5. The presence of chronic lymphocytosis (>5 cells/mm$^3$) on CSF examination, which may decrease over time, and which is not accompanied by any other sign of an infectious process. [13,15]

| | New cases (no.21) | Literature cases (no.48) |
|---|---|---|
| Sex ratio (male/female) | 1.3 | 2.4 |
| – males | 12 (57%) | 34 (71%) |
| – females | 9 (43%) | 14 (29%) |
| Consanguinity | 2 (10%) | 16 (33%) |
| Mean age 1st observation | 4.2 months [range: 1 week–12 months] | Not available |
| Normal prenatal period | 19 (90%) | 41 (85%) |
| Normal perinatal period | 16 (76%) | 41 (85%) |
| Normal neonatal period | 19 (90%) | 43 (89%) |
| Age at onset | | |
| 0–3 months | 16 (76%) | 25 (52%) |
| 0–6 months | 4 (19%) | 14 (19%) |
| >6 months | 1 (5%) | 9 (19%) |
| Microcephaly | 18 (85%) | 38 (79%) |
| – acquired | 16 (76%) | 32 (67%) |
| – congenital | 2 (9%) | 6 (13%) |
| Pyramidal symptoms | 21 (100%) | 47 (98%) |
| Extrapyramidal symptoms | 18 (85%) | 24 (50%) |
| Psychomotor delay | 11 (100%) | 48 (100%) |
| Epileptic seizures | 5 (24%) | 14 (29%) |
| Other clinical signs | | |
| – feeding difficulties | 18 (85%) | 17 (35%) |
| – irritability | 17 (81%) | 8 (17%) |
| – liver dysfunction | 7 (33%) | 4 (8%) |
| – fever | 6 ( 28%) | 14 (29%) |
| – skin problems | 5 (24%) | 4 (8%) |
| Follow-up | mean 3 years 11 months [range 4 months– 10 years 4 months] | mean 6 years 6 months [range 6 months– 17 years 8 months] |




Most cases present with a raised INF-alpha level in the CSF and sometimes in the serum. [21,23] However, this level tends to fall after the first years of life.

Tubular reticular inclusions in endothelial skin cells, particularly in subjects with high levels of circulating INF-alpha, have been described in a few cases. [24,25,26]

Onset of AGS usually occurs, following a normal pregnancy and neonatal period, in the first year of life, often within the first six months; sometimes, however, the first symptoms are already present at birth. [9]

Primary onset symptoms include feeding difficulties, irritability, abnormal eye movements and recurrent febrile episodes that have no apparent cause and occur in the presence of normal laboratory investigations. Acquired, and more rarely congenital, microcephaly[27] is a cardinal sign, as is severe psychomotor delay accompanied by hypotonia, pyramidal signs and dystonic movements. Opisthotonic postures, oral-facial dyskinesias and absence of eye contact complete the clinical picture. Epileptic seizures occur in around 20% of subjects.

More recently, skin problems (erythema, acrocyanosis and chilblain-like lesions) have been reported, affecting the fingers and outer ears. [18,28] The pathogenesis of these lesions is debated, as is their true specificity to the clinical picture of AGS. [28]

| Sex of patient | ↓CC | ↓PLT | HS | ↑Ast-alt | Skin problems |
|---|---|---|---|---|---|
| M | | | | + | + |
| M | | | | + | |
| M | + | + | + | + | + |
| F | | | | + | |
| M | | | | + | + |
| M | + | | | + | |
| M | | | + | + | + |
| F | | | | | + |

M = male; F = female; CC = cranial circumference; PLT = platelets; HS = hepatosplenomegaly; Ast-alt = liver transaminases

Children affected by AGS present with severe neurological and cognitive impairment. However, some cases have been described, even within single families, in whom the disease

course is less severe and not characterised by a marked deterioration, and in whom there is a measure of scope for relational contact and the acquisition of some minor milestones. [4]

The differential diagnosis[9] between this syndrome and other early-onset pathologies, in particular static encephalopathies resulting from prenatal infections (cytomegalovirus, rubella, HIV, etc.), is based on the presence of basal ganglia calcifications and negative serological investigations, but progressive metabolic and mitochondrial encepahalopathies must be excluded. [29,30] There exist several rare, inherited syndromes that resemble AGS in many aspects, [17] but which have a more complex symptomatology (for example the presence of growth hormone deficit, [31] thrombocytopenia and signs of liver or immunological disorders). [32] The relationship of these syndromes with AGS is as yet unclear. [33]

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. Interferon-alpha is a cytokine that, in normal conditions, protects cells against many viruses and plays an immunomodulatory role. [34,35,36] Given that the prolonged presence of INF-alpha in the central nervous system can, in rats, [37,38] cause a progressive encephalopathy with basal ganglia calcifications, [39] it has been hypothesised that INF-alpha may be involved in the pathogenesis of the syndrome (that there may, for example, be a genetic defect in the mechanism that controls the production of INF-alpha and its response to various pathogenic agents).

But it is also possible that the increase in INF-alpha is not the main cause of the disease but, rather, a consequence of some as yet undisclosed pathogenetic mechanism (perhaps immuno-mediated). [28,40,41,42]

Another hypothesis is that the primary cause of the disease is an inherited cerebral microangiopathy. [18]

Ever since the first reports were published of families with more than one child diagnosed with AGS – in these families the parents of the affected subjects were often consanguineous – a recessive autosomal pattern of inheritance has been suggested. To date, the gene responsible has not been mapped, even though an alteration of the short arm of chromosome 3 has been found in some patients and in their families. [20] The most recent studies suggest that the syndrome could, in fact, have a heterogenic basis, in other words that there may be several genes, probably involved in the regulation of the same pathogenetic mechanism, whose alteration could give rise to the disease. [9,20]

The aim of our study was to gather new cases of AGS and to analyse, in detail, the clinical, neuroradiological and biological characteristics of these subjects, and to compare our findings with the data in the literature.

## MATERIALS AND METHODS

In the year 2000, in response to the wishes of families of affected children, the International Aicardi-Goutières Syndrome Association (IAGSA) was founded. The aim of the association is to collect and analyse all available information on cases of AGS in order to increase the number of known cases and improve knowledge of the pathology. From the cases that came to the notice of IAGSA in the year 2000, we selected only those who fulfilled the diagnostic criteria proposed by Aicardi and Goutières in their 1998 study. [9] These criteria are:

- progressive neurological disorder with onset in the first year of life;
- basal ganglia calcifications;
- chronic CSF pleocytosis;
- negative TORCH;
- no evidence of metabolic disorders, in spite of extensive investigation.

Of these cases we considered only those not described elsewhere in the literature. We observed 7 cases directly and collected, from families and specialist colleagues abroad, detailed clinical information on a further 14 cases. The total number of new cases gathered thus totalled 21. Of these, ten were Italian, five German, one Brazilian, two Scottish, one Canadian and two were from the United States.

For each subject we compiled a detailed clinical dossier based on the following information: 1) pre-perinatal history and neonatal period, 2) general characteristics (sex, age at onset, consanguinity), 3) symptoms at onset (for example, fever, irritability, feeding difficulties, psychomotor delay), 4) clinical picture at the time of observation, 5) microcephaly (and age at onset if present), 6) neurological signs, 7) general medical signs (paying particular attention to the presence or absence of skin lesions and hepatosplenomegaly), 8) neuroradiological findings (CT scan, MRI, looking in particular for basal ganglia calcifications, cerebral atrophy, and white matter alterations), 9) neurophysiological examinations (EEG, VEPs, BAEPs), 10) examination of the fundus oculi, and 11) laboratory examinations (for example liver transaminases, CSF examination, serum and CSF INF-alpha).

We compared the findings presented by our 21 patients with the data (when available) relating to the cases described in the literature. In view of the fact that the 27 cases reported by Goutières and Aicardi in 1998[9] include the first 8 cases described in 1984 by the same authors, [3] the literature cases that we considered numbered 48. Three further cases have since been published[8,19] (Table 1).

RESULTS

*Clinical data*

The main characteristics and clinical data of our sample compared with the available literature data are reported in Table 2.

The male/female ratio of our sample was 1.3 (12/9; 57%/43%), while the literature indicates a higher proportion of males to females (34/14; 71%/29%) giving a ratio of 2.4. Parental consanguinity was present in only 2 of our sample (9%) as opposed to 16 (33%) of the cases reported in the literature.

The mean age of our subjects at first observation was 4.2 months, ranging from one week to 12 months, and their mean age at diagnosis was 17.5 months (range: 7-60 months). Precise age-at-onset data are not available for all the 48 literature cases.

Forty-one (85%) of the literature cases indicated normal pregnancy and birth, while these aspects were normal in 19 (90%) and 16 (77%) of our cases respectively. The neonatal period was normal in around 90% of the subjects in both groups (in 19 of the new cases and 43 of the known cases).

The literature cases reveal 7 pathological pregnancies (15%): 2 cases of bleeding and 1 each of herpes zoster viral infection, maternal pneumothorax, echographic evidence of microcephaly, toxic state and intrauterine growth retardation.

In our sample, we found 2 cases (9%) of intrauterine growth retardation.

The literature also reports 7 pathological deliveries (15%) - premature birth in 4 cases (8%), ventouse delivery in 2 (4%) and acute foetal distress in 1 (2%) - as opposed to 5 (24%) in our sample: 2 cases (9%) of acute foetal distress, 2 (9%) preterm deliveries, and 1 case (5%) of dynamic dystocia.

Pathological neonatal periods emerged in 5 literature cases: 3 (14%) presented with feeding difficulties, 1 (5%) with irritability and 1 (5%) with congenital microcephaly. Of the new cases, only 2 (9%) showed a pathological neonatal period, characterised by microcephaly with hepatosplenomegaly and, in one of the cases also by thrombocytopenia.

The onset of AGS is early, occurring within the first three months of life in 16 (76%) of our cases vs 25 (52%) of the literature subjects. Symptoms at onset in our sample were: psychomotor delay (11 cases; 52%), irritability (9 cases; 42%), feeding difficulties (8 cases; 38%), altered muscle tone (6 cases; 28%), febrile episodes (5 cases; 24%), nystagmus (3 cases; 14%), hepatosplenomegaly (2 cases; 9%), and hypersomnia (1 case; 5%). All the subjects presented with at least three of these symptoms at onset.

Precise symptoms-at-onset data are not available for all the literature cases.

Microcephaly was present in 38 (79%) of the cases described in the literature, having congenital onset in 6 (12%), while head circumference in the other 10 (21%) was normal. Microcephaly was found in 18 of our 21 patients (85%), in 2 cases present from birth. Of the 3 subjects (14%) without microcephaly, 2 presented a reduction of the cranial circumference from the $90^{th}$ percentile at birth to the $50^{th}$ percentile at 12 months. The other, at 10 months, presented a cranial circumference equivalent to the $25^{th}$ percentile, while at birth it had been

normal. Once apparent, the microcephaly was progressive until 2 years of age, probably being related to the development of the cerebral atrophy (Fig.1). Congenital microcephaly could point to a prenatal onset of the pathology.

The neurological signs were essentially pyramidal and extrapyramidal in both samples. Spasticity was a constant feature, present in 47 of the literature cases (98%) and in all 21 of our subjects (100%). Distal hypertonia and hyperreflexia presented with different degrees of severity in the various patients and were associated with trunk hypotonia evident from birth. The extrapyramidal symptomatology was characterised by: fluctuating muscle tone, opisthotonic spasms, oral dystonias, dystonic postures, distal dyskinesias and a persistent asymmetrical tonic reflex of the neck. These aspects, variable over time and more difficult to evaluate than the spasticity, were less frequent in the literature sample, being present in 24 (50%) cases vs 18 (85%) members of our group.

Psychomotor delay was a constant finding in both samples, but precise information was available only in relation to our sample: at the time of observation, head control was present in only 3 subjects (14%), partial in 15 (72%) and absent in 3 (14%). Trunk control was attained by only two of the subjects (9%) observed by us, and only one (5%) was able to sit unsupported. Epileptic seizures were infrequent, occurring in 5 (24%) of our subjects. These were mainly focal tonic spasms. EEG was altered in 6 patients (28%), all showing slow background activity with focal anomalies in 5 cases, and multifocal in one. The literature reported 14 cases (29%) of seizures but no details regarding the semeiology of these seizures are available. Language was absent in all our cases, while cognitive aspects could not be evaluated due to the severity of the clinical picture. We can only say that smiling was present in all of them, and is also reported in many of the literature cases.

Neurophthalmological aspects of the syndrome have never been examined in depth. Photomotor response was present in all the new cases, but sluggish in 5 (24%). Fixation and tracking was present, but inconstant, in our subjects, while abnormal eye movements, such as nystagmus and saccadic abnormalities, were observed in 11 (52%) and strabismus was found in 6 (28%). Fundus oculi was pathological in 3 children (14%) with optic nerve atrophy, but only one of our cases showed a depigmentation of the fundus. Visual evoked potentials (VEPs) were abnormal in 5 (10%) of the literature cases and in none of the new cases. No more precise data are available. Brain evoked potentials (BAEPs) were abnormal in one of the literature cases (2%) and in 5 (24% ) of our sample, in two case associated with otitis and in three case characterised by delay in stimulus conduction, perhaps related to leukodystrophy.

Other frequently encountered clinical characteristics were: fever, irritability and feeding difficulties. These are primary onset symptoms that often tend to decrease after the first year of life, although feeding difficulties, which include dysphagia, difficulty chewing and gastroesophageal reflux, generally persist and can become so severe as to necessitate recourse to nasal-gastric tube feeding. Skin lesions, such as acrocyanosis, chilblain-like lesions and erythema, were present in 5 (24%) of our subjects as opposed to just 4 (8%) of the literature cases. Signs of liver dysfunction (raised transaminase levels) were present in 7 (33%) of our subjects, 2 of whom also presented with hepatosplenomegaly.

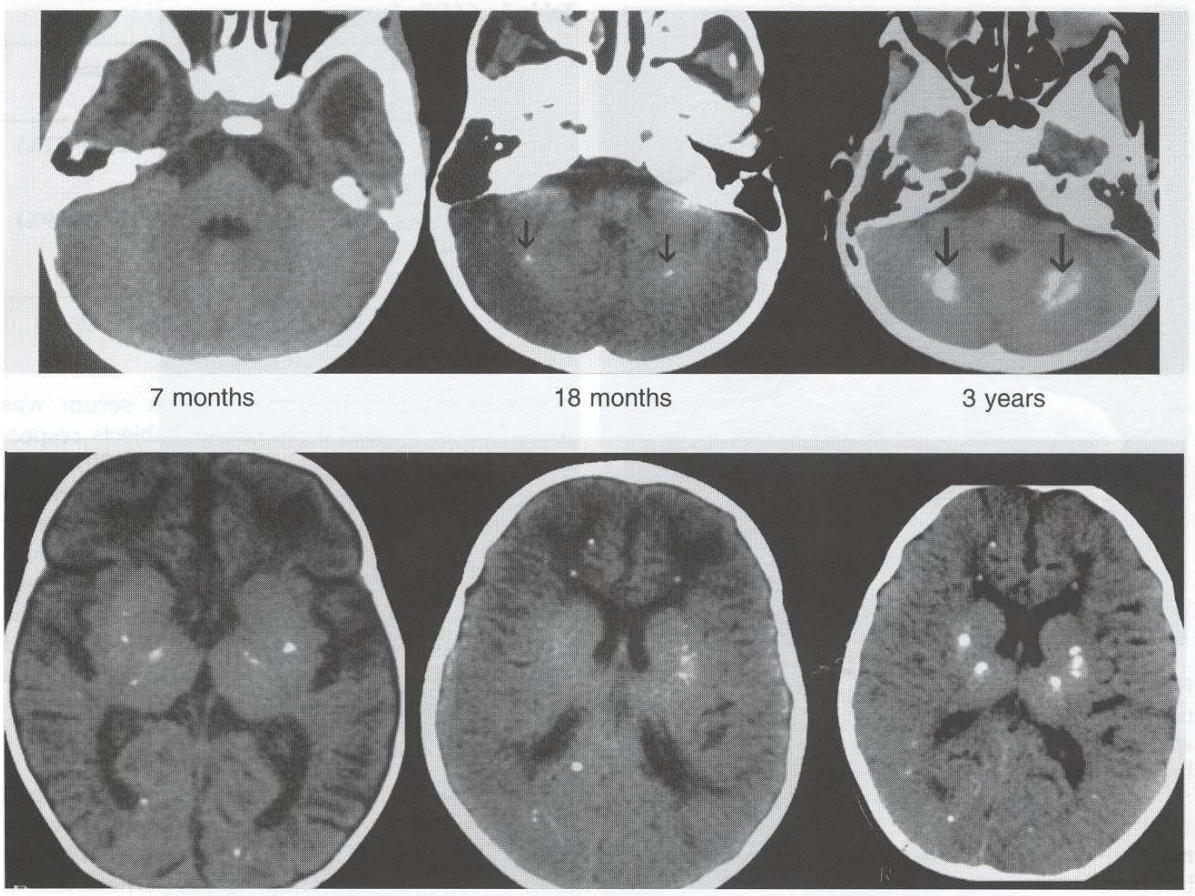
In our sample 8 cases (38%) had atypical characteristics that raise the question of the differential diagnosis between AGS and other forms of early-onset encephalopathy with cerebral calcification, such as pseudo-TORCH syndrome. These characteristics were: congenital microcephaly, neonatal signs of liver dysfunction and thrombocytopenia (Table 3). Notwithstanding these anomalies, all 8 presented CSF pleocytosis and the 7 investigated for INF-alpha presented raised levels in the CSF.
In 5 (24%) of these atypical cases we also found skin lesions (Table 3): acrocyanosis in 2 (9%), chilblains at the extremities in 2 (9%), and a rash on the ear in 1 (5%). Skin biopsy performed in 2 of these patients revealed tubular reticular inclusions.

*Neuroradiological findings*

The main neuroradiological findings are presented in Table 4. Calcifications are a typical feature of this syndrome (Fig. 2). Calcium deposits are most often reported in the globus pallidus, putamen, caudate nucleus and dentate nuclei. Additionally, calcium deposits have been reported in the white matter, in particular in the periventricular area alongside the ventricle wall. The deposits are often punctate, but may also form larger concrements.

| | New cases | Literature cases |
|---|---|---|
| BG calcifications | 21 (100%) | 43 (90%) |
| – isolated | 5 (24%) | 19 (40%) |
| – BG+ other sites | 16 (76%) | 24 (50%) |
| Cerebral atrophy | 21 (100%) | 45 (94%) |
| Leukodystrophy | 16 (76%) | 37 (77%) |

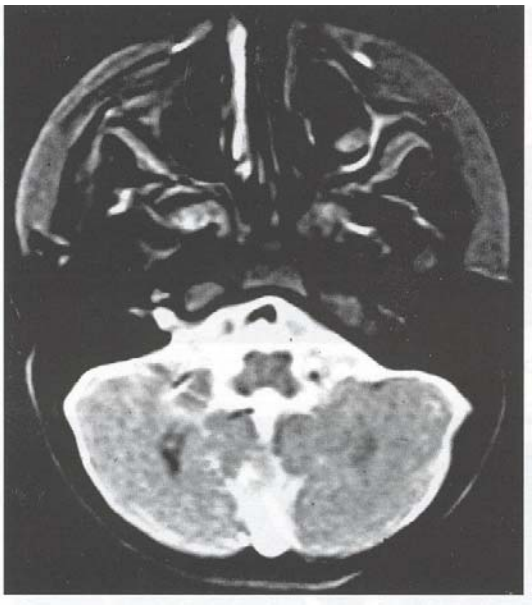
BG = basal ganglia




Marked calcifications of the dentate nuclei can be seen in the posterior fossa. They are best illustrated by the CT scan (Fig. 2), but are also visible on MRI (T2-weighted images) as hypointense areas in the same site (Fig.3).

The calcifications are punctate in the basal ganglia but more widespread in the white matter. In the literature, 43 cases (90%) have basal ganglia calcifications (of the other 5 subjects, 4 were negative and one did not undergo CT scan), while in our sample they were found in all 21 (100%). Of these, 5 (24%) showed calcification restricted to the basal ganglia (mainly the putamen and the thalamus) and in 16 (76%) they were also found in the cerebellum, especially in the dentatum, and in the white matter. Calcifications present at diagnosis in the first year of life tend to remain stable over time, but in 5 out of 12 subjects who repeated the CT scan, they were seen to increase. This may be the expression of a previous infectious process or the result of a vasculitis; the number and size of the calcifications are not strictly linked to the clinical course, nor do they reflect the pattern of the cerebral damage.

Leukodystrophy is described by Aicardi as hypodense areas on CT scan and diffuse hyperintensity in T2-weighted images, localised prevalently around the ventricle horns (Fig. 4). Regarded by Aicardi as a typical sign of the syndrome, leukodystrophy was present in 16 (76%) of our subjects. Of the 5 cases (24%) not presenting leukodystrophy, 1 was negative, 2 did not undergo brain MRI and 3 showed a slight delay of myelination upon MRI examination at 6 months. Of the previously reported cases, 37 (77%) presented white matter alterations and of the 11 cases (23%) who did not show signs of leukodystrophy, only one, [17] who died at 3 months of age, did not undergo neuroradiological investigations. The other 10 [3,6,17] were found to be negative for leukodystrophy on CT examination, but none of them underwent MRI.



Cerebral atrophy, described by Aicardi as enlargement of the ventricles and of the cortical sulci, was present in all 21 (100%) of our subjects as opposed to 46 (94%) of the literature cases. It was absent in one of Kato's subject studied by means of brain MRI and it was not investigated in Kumar's patient who died at 3 months. A characteristic of the neuroradiological picture is cystic degeneration seen in cortical areas (Fig. 5).

*Laboratory investigations*

Chronic lymphocytosis in the CSF is defined as the finding, in at least two serial CSF examinations, of >5 cells per $mm^3$ (cubic millimetre) (Table 5). Thirty-two (72%) of the cases in the literature gave positive findings, while in our sample, 19 (90%) tested positive (values ranging from 12-170 cells/$mm^3$). The two who did not, tested at the end of the first year of life, both showed increased INF-alpha in the liquor. In a third of our cases, in whom the liquor was analysed several times (at least 3), lymphcytosis was seen to decrease (even reaching normal levels in some cases).

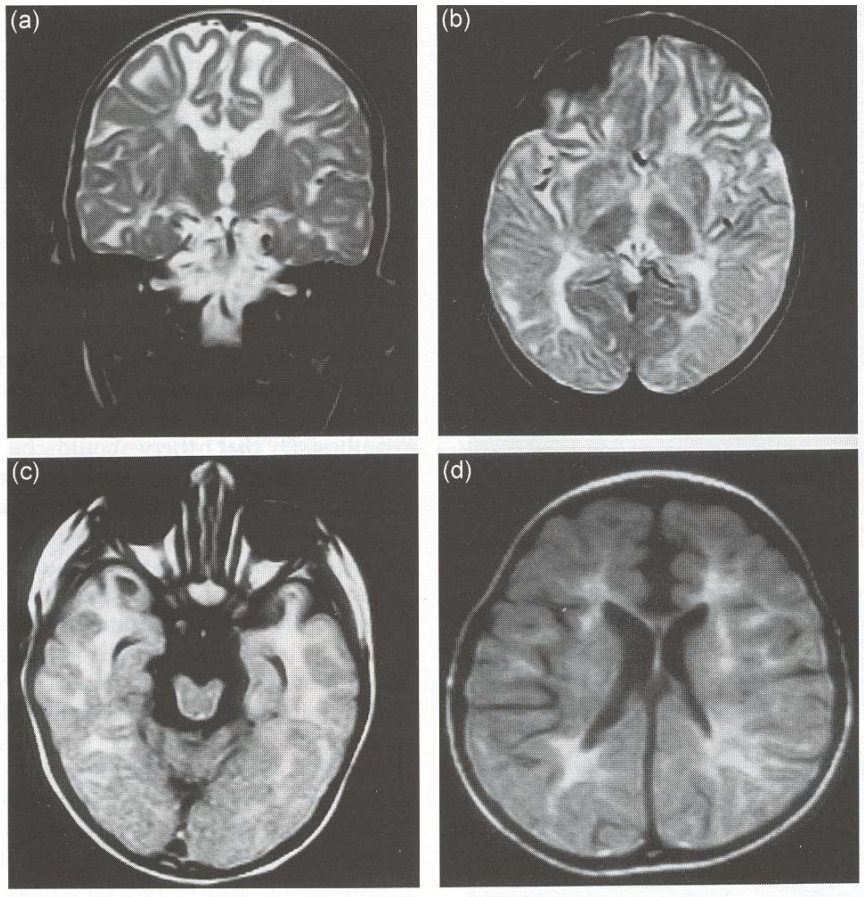
INF-alpha in liquor and in serum was measured in 14 and 8 of our subjects respectively and found to be raised in 14 (100%) and 7 (87%) (Table 5). All those not showing raised INF-alpha nevertheless presented chronic lymphocytosis. In the literature, raised INF-alpha was found in the CSF in 17/19 (89%) cases and in the serum in 9/14 (64%). INF-alpha volumes with a value of >2 IU/ml are considered increased. Our sample gave CSF values showing a range of 6-150 IU/ml (mean: 54 IU/ml) and serum values with a range of 4-25 IU/ml (mean 9.2 IU/ml).

Two of our cases underwent INF-alpha evaluation twice, and in these cases we observed a drop in the value. It is to be recalled that raised INF-alpha can be observed in herpetic and in other viral forms of encephalitis, as well as in viral meningitis and as a neurological complication of HIV infection and systemic lupus erythematosus (SLE).

In all but two of our cases, INF-alpha in the serum was lower than in the liquor. The reproducibility of these trends needs to be verified through repeated evaluations and further follow-up.

*Follow up*

Clinical follow up in the literature ranges from 6 months to 17 years and 8 months (mean: 6 years and 6 months), while in our sample it ranged from 4 months to 10 years and 4 months (mean: 3 years and 11 months).
The clinical course was found to be stable in 10 (47%) of our subjects as opposed to 16 (33%) of the literature cases. A pattern of regression was observed in 3 (14%) of our subjects vs 11 (22%) of the known cases and an improvement in 8 (38%) vs 5 (10%). No members of our sample died, whereas the literature reports 16 (33%) deaths.

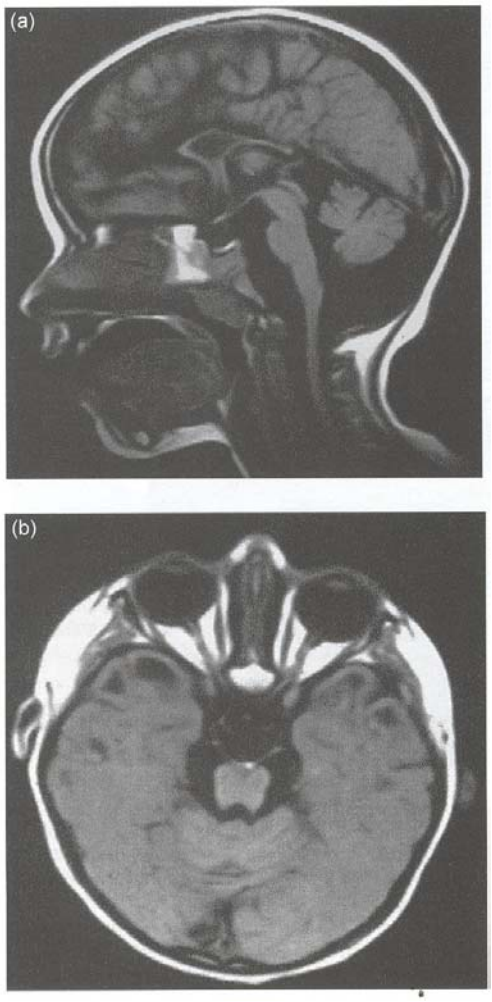



DISCUSSION

In this study we have described 21 new cases of AGS, taking the total number of reported cases worldwide to 69 (a further three have since been reported).[8,19] Even though AGS is a rare pathology, it is important to diagnose it early and correctly as there is a high probability that its signs and symptoms, both clinical and instrumental, may be confused with the neurological sequelae of non genetic congenital infections. Differential diagnosis vs TORCH syndrome, carried out in all our patients, was negative in all of them.

Although parental consanguinity was found in only 2 members of our series, the sex ratio (which is close to 1) suggests that the disease is probably not sex-linked, but has instead, as confirmed by recent genetic reports[20] , an autosomal recessive pattern of transmission.

The normality of the pre-perinatal and neonatal period reported by some authors[3,9] is confirmed by our data. Onset is mainly in the first trimester of life, a finding more frequent in our sample than in the literature. It is interesting to note that some symptoms at onset are very frequent, such as feeding difficulties. Even though the neurological symptoms such as microcephaly and spasticity can also appear in the second half of the first year, the gathering of a detailed history should allow certain non specific symptoms present from the very first months of life, and even in some cases from the first days of life (symptoms such as feeding difficulties, irritability and recurrent febrile episodes) to be picked up on. This is an important aspect emerging from our experience, which is not stressed in previous reports.




We feel that the importance of the microcephaly must be underlined. First of all, it is a very frequent and typical feature of AGS; second, it must be recognised, with particular attention paid to the congenital onset forms, in order to identify atypical cases, apparently characterised by a more severe clinical course, and to allow a correct differential diagnosis of AGS versus Pseudo-TORCH syndrome.[2,32] Pseudo-TORCH presents not only basal ganglia calcifications, but also microcephaly at birth, liver dysfunctions, thrombocytopenia, signs that are present in some AGS patients.

The most recent report [32] on the Pseudo-TORCH syndrome included five cases: CSF pleocytosis, tested in only two patients, was absent, while INF-alpha was not investigated at

all. Differently, CSF INF-alpha was raised in all our atypical cases who could present a Pseudo-TORCH syndrome (Table 3), and this seems to be a strong point in favour of a diagnosis of AGS. Our data appear to agree with Crow's hypothesis[20] that there could be an overlap between the clinical picture of pseudo-TORCH syndrome and AGS, which in turn points to "the possibility that these clinical phenotypes may represent a single disorder."

Another familial pathology with many similarities with AGS was described by Black *et al*[33] in Cree Indians in Quebec, and in one of these cases Lebon[21] demonstrated the presence of raised INF-alpha. The manifestations of Cree encephalitis are severe mental delay, cerebral atrophy with white matter alterations, basal ganglia and cerebellar calcifications, immune system abnormalities and acquired microcephaly. Severe acrocyanosis is also sometimes present, and in one patient caused chronic ulceration leading to the amputation of several fingers. It is also interesting to note that some Cree children are affected by recurrent infections, both viral and bacterial. In this regard it is interesting to consider that patients diagnosed with Cree encephalitis present recurrent infections, systemic immunological abnormalities and congenital microcephaly as typical signs, and also that INF-alpha was not tested systematically in these subjects. In our patients presenting a similar symptomatology, on the other hand, we did not find any immunological anomalies or recurrent infections while they did present raised CSF INF-alpha, a typical sign supporting a diagnosis of AGS.

This variability of clinical expression could stem from a genetic heterogeneity, as has been suggested by both haplotype[1] and linkage studies.[20]

Crow *et al,*[20] in a linkage analysis of 13 families (including both AGS and Pseudo-TORCH syndrome cases) obtained evidence of a positive linkage for AGS on chromosome 3p21. Taken together, these findings suggest that AGS, Pseudo-Torch syndrome and Cree encephalitis could all belong to a group of pathologies characterised by a form of microangiopathy demonstrated by Barth[18] in a cerebral biopsy. This microangiopathy could be present in other tissues too, particularly cutaneous tissue.

Skin lesions are also sometimes reported in children with AGS.[9] In our sample we found them in one-fourth of the cases, all presenting with atypical features.

The severity of these manifestations is variable: the fingers can present only swelling or clear skin lesions with evidence, upon biopsy, of vasculitis. This aspect appears to open up the question of the relationship between AGS and autoimmune pathologies.

Dale *et al*[43] recently described 2 patients born of consanguineous parents and affected by SLE. The diagnosis was based on the characteristic autoantibody profile that the two children developed between the ages of 2 and 4 years. In addition to this, they also presented with an early-onset encephalopathy with calcifications at CNS level. The skin lesions observed by Dale are similar to those presented by some AGS patients and affect above all the toes, fingers and outer ears.

Dale's 2 cases resemble in some respects the AGS subjects described both in the literature and in our series, although they were not investigated for INF-alpha**.** Furthermore, all the AGS cases undergoing immunological investigations for SLE gave negative results. To decide whether the case of Dale et al. constitutes a subgroup within the AGS/Pseudo-TORCH/Cree group, we will have to wait for the results of studies on the autoimmune mechanisms that regulate these pathologies. An appropriate approach would be systematically

to look for autoantibodies and to measure the complement components in the serum, particularly in patients who have cutaneous manifestations. [44,45] We conducted an investigation of this kind in one of the subjects belonging to the set of new cases; although findings were negative, it would probably be opportune to repeat the analyses when the skin lesion becomes more marked.

The main symptoms observed in AGS (basal ganglia calcifications, spasticity, psychomotor delay, microcephaly, lymphocytosis in the CSF, raised INF-alpha in the CSF) show a greater homogeneity in our subjects than in the literature cases, which indicates an improvement in the diagnostic accuracy of this disease. In the literature, doubts are expressed as to whether lymphocytosis is mandatory for a diagnosis of AGS. Our view, in accordance with other authors, [9] is that it may be an age-dependent sign that is present in the first year of life, and can decrease thereafter, while the role of the raised INF-alpha appears to be very significant.

The neurological symptoms are initially progressive, becoming stable by the end of the second year of life. The clinical course seems to be characterised by different stages: an early onset and rapid progression followed by severe deterioration and then a stabilisation. Follow up seems to indicate a trend not necessarily towards a worsening, but instead towards a stabilisation or even a slight improvement of the clinical picture. Serial measurements, too, seem to support the hypothesis of a stabilisation of the disease. Pleocytosis and raised INF-alpha in the liquor, which can reach very high levels in the first months of life, tend to decrease over the years.

In relation to the serological data, we feel it is important not to underestimate the importance of carrying out repeated and standardised measurements both of INF-alpha in CSF and serum, and of CSF pleocytosis, as increases and decreases in these values could show correlations with clinical trends.

There exists experimental evidence that raised levels of INF-alpha could play a role in the mechanism of the vasculitis and that the interferon itself is one of the causes of the encephalopathy. Akwa[37] and Campbell[38] created transgenic mice whose astrocytes are chronic producers of INF-alpha. These animals develop a progressive encephalopathy with basal ganglia calcifications and vasculitis, characteristics very similar to the neuropathological lesions encountered in patients with AGS. The encephalopathy demonstrated in mice is probably of hypoxic-ischaemic origin, like that occurring in the human pathology. The same authors have demonstrated the presence of tubular reticular and cylindrical inclusions in mouse endothelial cells. The presence of tubular reticular inclusions, in vivo, in the endothelial cells of patients affected by AGS was confirmed, in few cases, by Lebon [21] and by us and it could be correlated with the presence of circulating INF-alpha. [41] It would appear that INF-alpha stimulates activation of the cerebrovascular endothelial cells producing a significant upregulation in the expression of the ICAM-I type adhesion molecules, thus contributing to the inflammatory state seen in CSF. As well as alterations of the endothelial cells, which show deposits of amorphous material in their cytoplasm, it is possible to observe gliosis and functional and structural activation of the astrocytes and microglia.

Finally, consideration must also be given to the diagnostic criteria for AGS. In our view, these could be defined as essential, supportive and exclusion criteria.

On the basis of our results, we suggest that the following criteria might be regarded as essential for a diagnosis of AGS at the end of the first year of life (these symptoms are present in 100% of cases):

1) endocranial calcifications at basal ganglia level bilaterally;
2) psychomotor delay;
3) spastic signs;
4) cerebral atrophy;
5) raised INF-alpha in the CSF.

The following symptoms present in at least 75% of cases can be regarded as criteria strongly supporting a diagnosis of AGS:

1) secondary microcephaly revealed during the first year of life;
2) symptoms with early onset such as feeding difficulties and irritability;
3) extrapyramidal signs;
4) leukodystrophy;
5) endocranial calcifications in sites other than the basal ganglia: cortical, subcortical, periventricular, dentate nuclei;
6) chronic CSF lymphocytosis.

Obviously, exclusion criteria are :

1) Evidence of pre- perinatal infection: positive TORCH investigations.
2) Evidence of metabolic diseases or neurodegenerative disorders.

Our experience, described in this report, underlines the importance of continuing research efforts in this field in order to increase understanding of the aetiopathogenetic mechanisms underlying this disorder. It is our sincere hope that in the coming years we will be able, through IAGSA, to obtain increasingly conclusive results that might benefit children affected by AGS and their parents who, with great courage, are supporting us so generously in our research endeavours.

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Table 1 – Literature reports of Aicardi-Goutières Syndrome

| Author(s) | Year | No. of cases described |
|---|---|---|
| Aicardi and Goutières | 1984 | 8 [a] |
| Troost | 1984 | 2 |
| Giroud | 1986 | 1 |
| Diament | 1986 | 1 |
| Metha | 1986 | 2 |
| Bönnemann | 1992 | 1 |
| Verrips | 1997 | 2 |
| Goutières and Aicardi | 1998 | 27 [a] |
| Østergaard | 1998 | 2 |
| McEntagart | 1998 | 2 |
| Kato | 1998 | 1 |
| Kumar | 1998 | 7 |
| Barth | 1998 | 1 [a] |
| Koul | 2001 | 2 [b] |
| Polizzi | 2001 | 1 [b] |

[a] : the eight cases reported by Aicardi and Goutières in 1984 and Barth's case described in 1998 are included in the 27 cases reported by Goutières and Aicardi in 1998.

[b] : after the date of the meeting a further three cases appeared in the literature: Polizzi reported 1 case and Koul 2 cases in 2001. This takes the total number of new cases to 51, but we compared our cases with the 48 detailed in the text.

Table 2 - Characteristics and main clinical symptoms of 21 new and 48 known cases of AGS

| | NEW CASES (no.21) | LITERATURE CASES ( no.48) |
|---|---|---|
| Sex ratio (male/female) | 1.3 | 2.4 |
| - male s | 12 (57%) | 34 (71%) |
| - females | 9 (43%) | 14 (29%) |
| Consanguinity | 2 (10%) | 16 (33%) |
| Mean age 1st observation | 4.2 mths (range: 1wk – 12 mths) | Not available |
| Normal prenatal period | 19 (90%) | 41 (85%) |
| Normal perinatal period | 16 (76%) | 41 (85%) |
| Normal neonatal period | 19 (90%) | 43 (89%) |
| Age at onset | | |
| 0-3 mths | 16 (76%) | 25 (52%) |
| 0-6 mths | 4 (19%) | 14 (19%) |
| > 6 mths | 1 (5%) | 9 (19%) |
| Microcephaly | 18 (85%) | 38 (79%) |
| - acquired | 16 (76%) | 32 (67%) |
| - congenital | 2 (9%) | 6 (13%) |
| Pyramidal symptoms | 21 (100%) | 47 (98%) |
| Extrapyramidal symptoms | 18 (85%) | 24 (50%) |
| Psychomotor delay | 11 (100%) | 48 (100%) |
| Epileptic seizures | 5 (24%) | 14 (29%) |
| Other clinical signs | | |
| - feeding difficulties | 18 (85%) | 17 (35%) |
| - irritability | 17 (81%) | 8 (17%) |
| - liver dysfunction | 7 (33%) | 4 (8%) |
| - fever | 6 ( 28%) | 14 (29%) |
| - skin problems | 5 (24%) | 4 (8%) |

| | | |
|---|---|---|
| Follow-up | mean 3yrs 11mths<br>Range 4mths-10yrs 4mths | mean 6yrs 6mths<br>Range 6mths-17yrs 8mths |

Table 3 - Atypical cases

| Sex of Patient | ↓CC | ↓PLT | HS | ↑Ast-alt | Skin problems |
|---|---|---|---|---|---|
| M | | | | + | + |
| M | | | | + | |
| M | + | + | + | + | + |
| F | | | | + | |
| M | | | | + | + |
| M | + | | | + | |
| M | | | + | + | + |
| F | | | | | + |

Abbreviations: M = male; F = female; CC = cranial circumference; PLT = platelets; HS = hepatosplenomegaly; Ast-alt = liver transaminases

Table 4 - Neuroradiological data (CT scan, MRI)

| | New cases | Literature cases |
|---|---|---|
| BG calcifications | 21 (100%) | 43 (90%) |
| - isolated | 5 (24%) | 19 (40%) |
| - BG+ other sites | 16 (76%) | 24 (50%) |
| Cerebral atrophy | 21 (100%) | 45 (94%) |
| Leukodystrophy | 16 (76%) | 37 (77%) |

Abbreviations: BG = basal ganglia

Table 5 – CSF Findings

| | New cases | Literature cases |
|---|---|---|
| Chronic lymphocytosis (> 5 cells/$mm^3$) | 19/21 (90%) | 32/44 (72%) |
| Raised INF-alpha[a] (> 2 IU/ml) - liquor | 14/14 (100%) | 17/19 (89%) |
| [a]Raised INF-alpha in serum: | 7/8 (87%) | 9/14 (64%) |

FIGURE LEGENDS

Fig. 1 – Cranial circumference growth curve in a patient with AGS

Fig. 2 – Calcification demonstrated by CT-scan.
Axial scans of the cerebellum (top images) and of the basal ganglia and thalamus (bottom images) performed at: 7 months, 18 months, 3 years of age (from left to right of image).
The images show the progression of the calcifications, visible as hyperdensities, in the course of the disease.

Fig. 3 – Calcification demonstrated by MRI
The calcifications in the cerebellum, clearly visible in the CT scan, also appear in T2-weighted magnetic resonance images as small hypointense areas (arrows).

Fig 4 - Brain MRI : white matter abnormalities
A-B: T2-weighted MR images of the basal ganglia.
Coronal image: the hyperintense signal around the lateral ventricles is clearly evident in the anterior region.
Axial image: this clearly shows the diffuse signal hyperintensity of the white matter around the lateral ventricles.
Neither image shows clear evidence of basal ganglia calcifications
C-D: Axial MR images (proton density).
Figures C and D show areas of widespread hyperintensity of the temporal lobe white matter in C and around the lateral ventricles in D.

Fig. 5 – Brain MR image of cerebral atrophy
A: Sagittal T1-weighted image showing marked cortical and cerebellar atrophy
B: Axial T1-weighted image showing marked brainstem atrophy