The Aicardi-Goutières syndrome was first described in 1984 (1) in a Portuguese family in which the first child was affected with calcification of the basal ganglia and a severe encephalopathy. It was thought, at the time, that this represented cytomegalovirus infection (CMV infection) because of the clinical presentation and despite the fact that we were not able to demonstrate any viral infection.

Unfortunately and despite the relatively favourable genetic counselling that we had given to this family, another child was later born and was also affected with the same condition, which led us to recognize that it was not cytomegalovirus infection, but probably genetic condition not known at that time. This family later had a third affected child despite correct counselling.

The parents were consanguineous, suggesting strongly a recessive autosomal condition, as both boys and girl were affected. Currently about 30 cases of the syndrome have been reported (2), even though many more cases certainly exist. In fact one can find mention of similar cases in the old literature not recognized as a specific syndrome.

The present study is based on 28 cases, 19 of these were seen by Dr Goutières and myself us and if there is a discrepancy between my two slides is because I’ve recently added a 28th case to the 27 that were recently reported by doctor Goutières and myself. The remaining cases were shown to us by colleagues, especially Prof. Barth, Prof. Di Rocco, Prof. Stephenson in Scotland, whom we wish to thank.

We now know of 12 familial cases in 20 families. In 3 families at least; and probably a fourth one, consanguinity was present. There was no history of significant perinatal events or of abnormal events in pregnancy except in a few cases. Finally, as this will be developed later by Dr Crow, one locus has been mapped on chromosome 3p21 in about half of the cases so far studied.
Neurological Features
The major features of the syndrome are relatively common, despite some striking characteristics.

The first one is the existence of a progressive encephalopathy of early onset, often actually present from birth, but that may begin later on. But almost always in the first year of life.

The second most striking feature is the presence of calcifications which are located mostly in the basal ganglia but can extend into the white matter, the cerebellum and very occasionally, only in a few cases, also to the cortex. The third feature which is of great diagnostic importance, is the presence of an abnormal CSF with the presence of a lymphocytosis, varying from a few to many cells, and associated in about half of the cases with a relatively elevated level of protein.

The fourth point which is a negative one but very important for the diagnosis, is the negativity of all etiological investigations, and especially those that are directed toward the diagnosis of fetal infections.

The last feature, which was demonstrated by professor Lebon, is the presence of an elevated level of interferon alpha in the CSF and in the blood, although consistently the titre of interferon is much higher in the CSF than it is in the blood. The clinical characteristics of these neuro-developmental features will be described in more detail by professor Lanzi. All patients had a severe developmental delay, except two patients in whom the mental affectation was less severe. All patients also had diffuse neurological signs, involving hypertonus, pyramidal tract signs, abnormal eye movements and, especially in some cases, attacks of opisthotonus that were precipitated by minor external stimuli.

Eight patients had epileptic seizures at the time of observation and most patients developed a microcephaly which was not present at birth, but become evident after months or years, to generally exceed 3 standard deviations below the mean. Abnormal
eye movements, which are probably associated with the reduced or absent vision, were present in a high proportion of the patients. Pyramidal tract signs were consistently observed; truncal hypotonia was common; ocular jerks were present in about half the patients; absent gaze in the same proportion. No significant abnormality of the fundi was seen. Clear extrapyramidal signs, with prominent dystonic movements and in some patients a very marked buccal-lingual dyskinesia were present. Persistence of asymmetrical tonic neck reflexes was common. Figure 1 illustrates the attitude of one patient with congenital involvement, showing the hypertonus which was particularly marked in this case.

Extraneurological features
Several patients also have extraneurological features. The most prominent of these are the cutaneous lesions which mainly affect the fingers and toes, sometimes also the ear lobes, in the form of scaly erythematous rash with swelling of the digits and an acrocyanotic appearance closely reminiscent of childblains. This may be complicated, at times, by periungual infection.

In addition to these cutaneous signs, which may be very prominent, there was in some patients a transient hepatomegaly, and transaminases were slightly elevated a few infants. A mild thrombocytopenia was found in two of them. This is interesting in view of the probable relationship of these cases with the syndrome of microcephaly-intracranial calcifications, the so-called MICS syndrome which will be alluded to below.

Recently, the presence in blood of antibodies consistent with the diagnosis of lupus erythematosus was reported in two patients by Scottish colleagues (3). In these cases, the serologic picture of lupus erythematosus appeared after several years, following a first period in which, all the symptoms and signs of the syndrome had been present. Unfortunately, interferon alpha was not looked for in these cases. Fig. 2 illustrates the aspect of the hands and feet of a patient; and I am indebted to Prof. Barth for giving me these photographs.

Imaging Features
Imaging features are quite remarkable and calcification of the basal ganglia is a cardinal sign of the condition and a major diagnostic clue. Calcifications in the basal ganglia, were observed in all our 28 patients. The involvement of the various areas is somewhat variable. The putamen is mostly involved, less often the pallidum. The caudate is frequently affected. The thalamus is less commonly involved but was interested in 15 of our patients. In the cerebellum, prominent calcification of the dentate nucleus may be present.
The calcification are well demonstrated by CT scans but are usually less obvious on MRI (figures 3 – 5).

Fifteen patients in this series had calcification of the hemispheric white matter, usually less dense than in the basal nuclei and often of a punctate character. White matter hypodensities, apparently reflecting absence or insufficient deposition of myelin was found in 21 of 28 patients. They predominated in the periventricular area and in the frontal lobe. They are much more evident on MRI than on CT that may not demonstrate them well.

Atrophy of the brain is present in virtually all cases, with ventricular dilatation of variable severity. In some cases, when repeated examinations were done, an increasing degree of atrophy could be shown.

Not all the imaging features need be present in all cases. Of particular interest are those cases in which calcifications of the basal ganglia are not seen. This as been our experience in two cases for which by CT showed brain atrophy and white matter hypodensity but no obvious calcification. In one of these patients, a repeat CT showed faint punctate calcification in the putamen.

In the second case, a second CT, one year later demonstrated clearcut calcifications thus indicating that progrtession of calcium deposition can take place and that, in rare cases, calcifications may be delayed so their absence does not exclude the diagnosis. Note, however, that the CT’s of these patients were not normal, but showed significant degrees of atrophy.
fig. 3 CT scan of another infant: calcification of the basal ganglia. Note also diffuse brain atrophy and hypodensity of the white Matter.

fig. 4 Symmetrical calcifications of the dentate nuclei

fig. 5 MRI of another infant showing marked decrease of white matter signal especially in the frontal lobes and diffuse hemispheric atrophy.

CSF Findings.

The third important feature of the syndrome is the presence of abnormalities in the CSF. The cerebrospinal fluid is grossly normal, but lymphocytosis was found in 20 of our cases. All cases that were examined before 1 year of age had from 6 to 260 cells per cubic milliliter and this persisted to over the age of 3 years in at least 3 cases. It appears therefore that lymphocytosis of variable degrees is a consistent feature of all infants with this syndrome. However, the duration of persistence of pleiocytosis is probably quite variable and the length of persistence of the lymphocytosis remain to be defined more precisely. The lymphocytes found in CSF are normal subsets of lymphocytes but their exact characteristics have not been well defined, so far.
Protein was elevated in only 12 patients; we did not find any oligoclonal banding or evidence of intrathecal synthesis in the CSF.

The presence of high titers of interferon alpha in the blood and, above all, in the CSF was demonstrated by professor Lebon a number of years ago (4) and has proved to be a major characteristic of Aicardi-Goutières syndrome. It has become an essential diagnostic finding and is probably consistently present, at least in the early stage of the disease. Anb elevated titer of interferon alpha was demonstrated in 15 of 16 patients in whom it was measured. The titer were quite variable but always higher in CSF than in plasma. Among those cases in which interferon was not directly measured, indirect evidence for interferon synthesis was given by the presence of tubular reticular inclusions in endothelial cells in the skin biopsy of 2 children. These inclusions are regarded as being the morphological correlate of the presence of interferon.

The only other laboratory results of interest are those of TORCH investigations that were always found negative. No IGM antibodies against cytomegalovirus were found.

The visual evoked potentials were absent in two cases. Muscle and liver biopsies done in 2 patients were normal as was the study of the mitochondrial and peroxisomal functions. Immunological studie in the cases studied were normal.

**COURSE**

The course of the condition is very severe. To our knowledge, eight patients were dead at ages varying between slightly over 1 year and 17 years. Nineteen were still alive at the time of our last follow-up: 6 of these being over the age of 10 years, indicating that the prognosis, although unfavourable, is not necessarily extremely bad in terms of survival in the first year of life.

We were able distinguish two types of course. Nineteen infants had an early onset before the age of 4 months, usually at birth or almost immediately after birth. They were quite irritable, had frequent vomiting, fever and were in poor general conditions and obviously ok very severely ill from onset. In these cases ther is more than purely neurological involvement and systemic affectation is marked and often responsible for an early death.

Eight children, in contrast, had a later onset with a normal initial development followed by regression which was clearly demonstrated in some of these cases, by a clearcut loss of previously acquired skills, taking place usually before the age of 2 years and most often even at the end of the first year.

Among the severe cases of early onset, 10 patients had feeding difficulties, convulsions, fever, marked systemic involvement, especially feeding difficulties and vomiting that was a prominent feature in these cases. In contrast, cases in group 2, that is of the late onset group of 8 patients, the onset was between a few months to about 1
year of age and the first symptoms were generally neurological; the presentation was that of a slowly progressive encephalopathy, without the marked systemic involvement which was observed in the early onset group.

ATYPICAL VARIANTS
A number of atypical cases have been published or observed. Some cases without calcification of the basal nuclei or without lymphocytosis. Mild forms, probably more frequent, have been reported in recent years (5). Such mild forms can go unrecognised for some time in patients who exhibit slight or moderate retardation, very mild neurological signs or no neurological signs at all. These patients do not necessarily have microcephaly, but they all have some degree of neurodevelopmental dysfunction. Some of these patients are siblings of typical severe cases, thus indicating that they definitely suffer from the same condition.

On the contrary there are severe forms, with severe cerebral atrophy and systemic manifestations including anaemia with microcytosis, e.g. the cases reported by Kumar et al. (6). These authors considered that their cases could represent a different condition. I tend to think that these cases differ only in severity not in nature, as they fulfil all the criteria for the diagnosis of the syndrome. At this point, I think it preferable to include among the atypical cases only those in whose families another typical case is recognised. However, in Kumar’s family all affected children had a severe type, but these cases can still be included on the basis of their clinical features.

DIFFERENTIAL DIAGNOSIS
There is a large differential diagnosis as the symptoms are not characteristic. The most frequent problem is that of other conditions which also feature calcification of the basal ganglia. Calcification of the basal ganglia is a very common finding; with at least 50 disorders that can produce it.

The first and most important diagnosis is obviously that of intrauterine infections of the TORCH group, especially the cytomegalovirus infection. This is the first diagnosis to be excluded, because the diseases of this group are frequent and some, especially toxoplasmosis or CMV infection are amenable to treatment and must be recognised because of the consequences, both therapeutic and genetic, of the diagnosis. Another diagnostic problem is raised by the microcephaly-intracranial calcification syndrome or MICS (7, 8), which shares many features with Aicardi-Goutières syndrome. Some patients with MICS may also have thrombocytopenia and several subtypes have been recognised. The literature on this group not particularly clear and patients with thrombocytopenia, hepatosplenomegaly, and cataracts have been reported. Still another syndrome features, in addition to calcification of the basal ganglia, cerebellar hypoplasia and thrombocytopenia. Whether these syndromes are really distinct conditions is not yet perfectly clear but they clearly raise the issue of whether some of them might be identical to Aicardi-Goutières syndrome.
Finally the largest group is that of children with calcification of the basal ganglia associated with static nonprogressive encephalopathy. In such cases the CSF is normal. We have followed some such children for 10 to 15 years without their showing any suggestion of aggravation so they seem to represent a distinct condition but one not easily distinguishable from Aicardi-Goutières syndrome.

A less common and less difficult diagnosis is Cockayne’s syndrome and related conditions. This syndrome includes intracranial calcification, retinopathy and systemic features.

A disorder very similar to the syndrome has been reported among the Cree Indians of Northern Quebec (9). I had the opportunity to see one of these patients with Frederick Andermann in Montreal and the similarity to the syndrome is indeed striking. In fact, in one of these patients, a high level of interferon was found and in another patient, a linkage to the same locus was demonstrated.

The last diagnosis I wish to discuss is that of lupus erythematosus. In fact the two cases first reported demonstrated all the features of Aicardi-Goutières syndrome and the lupus appeared much later and was probably secondary. These cases are of great interest as they suggest that there may be some relationship between the vasculitis of lupus and that which has been found in the syndrome. It seems likely that Aicardi-Goutières syndrome, MICS syndrome and related syndromes, and the Cree encephalitis may be the same or at least overlapping conditions and, indeed, the presence of high titer of interferon alpha has been demonstrated in isolated cases of the two latter diseases.

**PHYSIOPATHOLOGY**

Physiopathology will be more extensively discussed by other much more competent speakers and I am not going to dwell on this issue. One point pathologically important is that the main lesions appear to be a calcifying vasculitis that involves both brain and systemic vessels. This vasculitis is very similar to that induced in mice receiving astrocytes-targeted interferon. But this is limited to the central nervous system where the lesions obtained are remarkably similar to those in humans (10) with a progressive encephalopathy with an angiopathy and calcification of the basal ganglia. If involvement of interferon in the pathogenesis of the disorder appears highly probable, the cause of the high interferon levels is not known. The impression of several investigators is that is may be due to a dysregulation by a mutated gene of the production of interferon.

**CONCLUSIONS**

The practical interest of the syndrome is quite clear. The major interest is to separate this condition from intrauterine infections because of the genetic and therapeutic consequences so their diagnosis is really essential.
Another interest of the syndrome, despite its rarity, is that its study can contribute to the understanding of some mechanisms of CNS calcification and in a broader perspective in that of chronic encephalopathies with dysregulation of immune mechanism, a chapter that is currently the subject of much investigation.

A number of problems remain regarding the syndrome. From an etiological point of view, is the syndrome a single entity or is it a collection of related disorders with similar manifestations? This possibility is supported by the fact that there must be additional loci as about half of the cases appear not to be linked to chromosome 3pr, only half appear to be linked to chromosome 3p21.

Another point of possible discussion is how broad is the clinical spectrum of the syndrome. The existence of mild or very mild cases makes the limits of the syndrome still imperfectly defined, especially when the patients are seen at a time when the lymphosytosis in the CSF may have decreased or disappeared and interferon is no longer present.

We do not know at what age the absence of some features like CSF lymphocytosis and possibly absence of calcification rules out the diagnosis of that condition. This has yet to be determined.

Other problems are raised by the mechanisms of the condition. What are the mechanisms responsible for the calcifying encephalopathy, the cutaneous lesions and of visceral lesions when present? The origin of the vasculitis is not known, but seems to be related to the dysregulation of the production or secretion of interferon, as suggested by animal experiments.

Much more work of the syndrome is required to try to improve our current knowledge.

REFERENCES


