Review article

Aicardi–Goutières syndrome

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Abstract

Aicardi–Goutières syndrome is a familial progressive early onset encephalopathy with basal ganglia calcifications, chronic CSF lymphocytosis and high level of interferon-α in CSF. Cutaneous necrotic lesions and the neuropathological aspect of microangiopathy and microinfarctions suggest a vascular process in relation to elevated interferon-α. A genetic defect in the regulation of its synthesis may be the causal factor of the disorder.

Keywords: Familial encephalopathy; Basal ganglia calcifications; CSF lymphocytosis; Interferon-α

1. Introduction

The Aicardi–Goutières syndrome (AGS) was first described in 1984 by these authors who reported on eight infants from five families suffering from an early onset familial encephalopathy with chronic CSF lymphocytosis and basal ganglia calcifications, mimicking an intrauterine infectious process but with negative TORCH investigations [1]. In the first family observed, a misleading genetic counselling had been given to the consanguineous parents after the birth of an affected child erroneously thought suffering from a viral foetopathy and a second child similarly affected was born. Clinically, the patients showed bilateral spasticity, dystonia, ocular jerks, acquired progressive microcephaly with a rapid course towards profound deterioration and death. In addition to basal ganglia calcifications, computerized tomography (CT) scan showed diffuse and progressive brain atrophy and deep white matter hypodensities. The authors suggested a probable genetic condition with autosomal recessive inheritance. They identified in the literature nine previously reported possibly similar cases of unclassified leukodystrophy with calcifications [2–5]. Following the publication of similar cases [6–9], the disorder was listed under the eponym AGS by McKusick as autosomal recessive 22,575 [10]. In 1988, Pierre Lebon [11] impressed by the chronic CSF lymphocytosis and the cerebral calcifications had the idea to study interferon-α (inf-α) previously shown to be elevated in congenital rubella and in acquired herpetic encephalitis. Inf-α was detected in the CSF from five of the six patients tested and was not detected in 44 control infants with various neurological syndromes of non-infectious nature. Since this study, elevated CSF inf-α is considered as the best marker for the syndrome and systematically looked for in patients in whom this diagnosis is suspected. It is currently considered as a cue to the diagnosis [12]. After their initial publication of eight children [1], the authors reviewed 19 additional patients [13] and numerous other cases have been reported so far [14–25]. This list included the familial cases of Kumar [22] who are reported as distinct from AGS. These cases, in my opinion, raise a nosological problem that is discussed below. An important series of 21 Italian cases has been published recently [26]. To date, 74 cases have been reported throughout the world. AGS is present, at least in Europe, in North Africa, in North and South America, in Japan and possibly in Pakistan.

2. Clinical manifestations

The clinical presentation is a very early progressive encephalopathy. Onset is before 4 months of age in most patients, in some within the first week. Weight and head circumference at birth are within the normal range, but occasional cases with congenital microcephaly are on record [7,9,13,19,24]. One patient showed deceleration of
head growth in utero suggestive of a prenatal onset [14]. Others without microcephaly at onset presented with a reduction of the cranial circumference within the first year of life. Vomiting, feeding difficulties, jitteriness, ocular jerks, lack of progress in motor and social skills are the main symptoms. Bouts of low-grade fever (38–38.5°C) may lead to the erroneous diagnosis of meningitis or encephalitis [13]. About a third of cases have a later onset, between 4 and 12 months of age marked by loss of previously acquired motor and mental skills and appearance of spasticity [13,18,21]. On examination, all infants show diffuse neurological signs with truncal hypotonia, limb hypertonia, pyramidal tract signs, extrapyramidal signs with dystonia, buccal-lingual dyskinesia and persistence of asymmetric tonic neck reflexes, abnormal eye movements probably associated with reduced or absent vision. Optic fundi are normal or show mildly pale papillae. Occasional epileptic seizures (generalized tonic-clonic, massive myoclonic jerks) occur in about 25% of children [26]. Almost all children have severe developmental delay and no or only a poor contact with surroundings. Several patients also have extra neurological features. The most striking of these are vascular necrotic cutaneous lesions of the toes, fingers, ear lobes looking like chilblains, with acrocyanosis, erythematous periungual skin, puffy hands and feet, and cold feet [13,17,23,27]. Transient hepatosplenomegaly at birth has been noticed [13].

Transient hepatosplenomegaly at birth has been noticed [13]. The course of the condition is usually marked by loss of previously acquired motor and mental skills and appearance of spasticity [13,18,21]. On examination, all infants show diffuse neurological signs with truncal hypotonia, limb hypertonia, pyramidal tract signs, extrapyramidal signs with dystonia, buccal-lingual dyskinesia and persistence of asymmetric tonic neck reflexes, abnormal eye movements probably associated with reduced or absent vision. Optic fundi are normal or show mildly pale papillae. Occasional epileptic seizures (generalized tonic-clonic, massive myoclonic jerks) occur in about 25% of children [26]. Almost all children have severe developmental delay and no or only a poor contact with surroundings. Several patients also have extra neurological features. The most striking of these are vascular necrotic cutaneous lesions of the toes, fingers, ear lobes looking like chilblains, with acrocyanosis, erythematous periungual skin, puffy hands and feet, and cold feet [13,17,23,27].

Transient hepatosplenomegaly at birth has been exceptionally noticed [13]. The course of the condition is very severe. Death occurred in 1/4 of the reported patients between 9 months and 17 years of age [6,9,13]. However, a few children showed less severe impairment with relative preservation of social interaction in some [13,18,20] and different degrees of severity in the same sibship [18,20,21,23]. In the familial case of McEntagart et al. [20], one presented with non-progressive spastic diplegia, appropriate head growth and normal intelligence at the age of 9 years while his brother had dyskinetic cerebral palsy with cognitive delay and progressive microcephaly.

3. Imaging features

Calcification of the basal ganglia is the hallmark of the syndrome and a major diagnostic clue. Calcifications were detected in all the 27 patients observed by Goutières and Aicardi [13]. They are better detected by CT scan which is the first choice imaging investigation rather than magnetic resonance imaging (MRI). They affect the putamina, which are mostly involved, the pallidum, the thalami and in some patients, the dentate nuclei and the subcortical areas. Their aspect varies from punctiform to massive even in the same sibship [12,21] (Fig. 1), and is not correlated to the severity of the status. They were lacking on the first CT scan in two patients of the author at the age of 7 weeks and 10 months [13] and in one patient of Østergaard et al. at 12 months [21]. In addition to calcifications, CT scan shows white matter hypodensities located mainly around the ventricular horns; they are of various intensity and appear as increased signal on MRI T2 sequences (Fig. 2). They are not constant and a diffuse leukodystrophic aspect is uncommon [13]. Signs of severe and progressive brain atrophy with enlarged ventricles and sulci increasing on successive examinations are a constant finding. They confirm the evolutive nature of the disorder.

4. CSF findings

Chronic CSF lymphocytosis is the third main characteristic of AGS. In my experience, all CSF samples contained eight or more lymphocytes per cubic millimeter in the first 12 months of life (between 10 and 50 in most patients). Lymphocytosis varied at first examination from 260 mm<sup>–3</sup> at the age of 3 days in one patient to 6 mm<sup>–3</sup> at 19 months in another, with normal subset of lymphocytes. It decreases with age but persisted beyond the age of 2 years in two patients [13]. One patient of McEntagart et al. had still eight white blood cells (WBC) at the age of 9 years [20]; one familial case had no cell when studied at 12 months, pleocytosis being present in his sibling [21]; another familial case had 1650 WBC at the postmortem examination at the age of 10 months [22]. CSF protein is usually normal (only 12 of 27 children observed by the author had CSF protein of 0.50 g/l or more), with no oligoclonal banding or evidence of intrathecal protein synthesis. The presence of high titers of inf-α in CSF was first demonstrated by Lebon et al. [11] and has proved to be a major characteristic of AGS. Values are consistently higher in CSF than in serum. They varied from 3 to 75 IU/ml (normal <2) in 14 children aged 4 years 10 months or less [13]. Values are higher at birth and decrease with age; inf-α was still present in two children at 5 years [11]. According to the onset of the disease, the average of inf-α levels appear to be very high in patients with early onset whilst they are lower when the disease begins after 3 months [28]. Tubulo-reticular inclusions associated with the presence of inf-α have been observed in the skin, muscle and lymphocytes [13].

5. Other laboratory data investigations

They give normal results for blood calcium, phosphorus, amino acid and organic acid chromatographies, immunoglobulins and lysosomal enzymes activities. Virological research in blood and CSF for TORCH, varicella, adenovirus, human T-cell leukemia virus type I and II, human immunodeficiency virus type I and II are negative [13]. Anemia with microcytosis [22], increased levels of hepatic transaminases and thrombocytopenia at birth [13,26] have been exceptionally noticed. Brain auditory evoked potentials may show a prolonged I–IV interpeak interval [19]. The EEG is usually not informative. Muscle and liver biopsies performed in three patients were normal,
Fig. 1. CT scan of familial cases. (A) The older sibling at the age of 22 months showing discrete basal ganglia calcifications and atrophy. (B) The younger sibling at the age of 23 months, with massive basal ganglia, periventricular and subcortical calcifications, severe cortical and subcortical atrophy and hypodensity of the white matter in the frontal lobes. (C) Cerebellar calcifications in dentate nuclei and white matter.
ruling out a mitochondrial or peroxysomal disorder [13–18]. Recently, the presence in blood of antibodies consistent with the diagnosis of lupus erythematosus was reported in two patients [29]. In these cases, the serologic picture of lupus erythematosus appeared several years after the initial period in which all the signs of the syndrome had been present.

Neuropathological lesions are those of cerebral and cerebellar microangiopathy with diffuse non-homogeneous myelin loss without signs of storage or myelin breakdown, astrocytosis, calcifications in white matter and basal ganglia and cortical wedge-shaped microinfarcts with calcifications in the walls and periventricular spaces of small cerebral vessels [30,31].

6. Genetics

AGS is inherited as autosomal recessive. A genome-wide linkage analysis of 23 children from 13 families has demonstrated linkage to chromosome 3p21 in a proportion of the families but not in all [32]. This suggests the existence of at least one additional disease locus. This hypothetical genetic heterogeneity may possibly correspond to clinical heterogeneity [33].

7. Differential diagnosis and nosological issues

The diagnosis includes a large number of disorders as the symptoms are not characteristic. Intrauterine infections due to rubella, herpes virus, cytomegalovirus or toxoplasmosis are frequently misleadingly suspected because of the lymphocytosis and calcifications; they are the first diagnoses to be excluded as erroneous genetic counselling might ensue. Cockayne syndrome (CS), a familial leukodystrophy with striato-cerebellar calcifications caused by defective repair of transcriptionally active DNA, differs by its special facial features, dwarfism, retinitis pigmentosa and skin photosensitivity [34]. The familial encephalopathy with intracerebral calcifications, white matter lesions, growth hormone deficiency and retinal degeneration [35] may well be a milder form of CS whose nosological independence is not proven. The inherited syndrome of progressive central nervous system degeneration and generalized intracranial calcification described by Kumar et al. [22] in seven children with a high number of lymphocytes and extensive calcifications does not appear very different from AGS. Inf-α was checked in only one patient and was found mildly elevated. In my opinion, these cases represent very severe forms of AGS and not a different entity. Two familial disorders share with AGS very early onset encephalopathy, basal ganglia calcifications, leukencephalopathy and brain atrophy mimicking an infectious process: the congenital intrauterine infection-like or pseudo TORCH syndrome, known as microcephaly, intracranial calcification syndrome (MICS) [36,37] and the familial ‘encephalitis’ reported in Indian Cree children in Northern Quebec [38].

The patients of Reardon et al. suffering from MICS [37] presented at birth with marked microcephaly and extraneurological involvement with transient edema, hepatomegaly, jaundice, elevated liver enzymes and thrombocytopenia. Necrotic skin lesions with the appearance of vasculitis and tubuloreticular inclusions in skin biopsy have been observed in two patients [23] and an elevated level of inf-α in CSF in one [28]. The clinical features of MICS are of uncertain significance: Lanzi et al. [26] observed five patients with early onset AGS confirmed by elevated inf-α who showed as MICS affected children, microcephaly (2), thrombocytopenia (1), elevated transaminases (5) and hepatosplenomegaly (2). This is in conformity with our experience in two patients. Indian Cree children with familial ‘encephalitis’ manifested from birth failure to thrive, recurrent infections, elevated serum immunoglobulins, lymphocytic abnormalities and CSF lymphocytosis. These children had also microcephaly, hepatosplenomegaly, thrombocytopenia and severe acrocyanosis with chronic ulcerations of the phalanges similar to the cutaneous ‘childblainlike’ lesions observed in AGS and in MICS. In three Indian Cree patients, an elevated level of inf-α was detected in CSF and a linkage to the locus AGS1 in 3p21 was demonstrated [39]. These data strongly suggest
that the three conditions may be closely related both clinically and genetically. From a practical point of view, the differential diagnosis between these disorders has no major consequences as the three are inherited in the same autosomal recessive way and, unfortunately, no treatment has proven efficacy in AGS. Corticosteroids lower the levels of inf-α in blood and CSF in the few patients treated so far but no clinical improvement resulted.

8. Physiopathology

The origin of the disorder is still unknown but the main lesions appear to be a calcifying vasculitis that affects both brain and systemic vessels. This vasculitis is similar to that observed in mice receiving astrocyte-targeted inf-α which develop a progressive encephalopathy with basal ganglia calcifications similar to the neuropathological lesions in AGS [40]. In addition, cutaneous vascular lesions bearing similarities to the chilblains observed in AGS, in MICS and in Cree ‘encephalitis’ have been reported during treatment with inf-α [41,42] and experimentally, inf-α induces the appearance of tubuloreticular inclusions in the fibroblasts and white cells similar to those described in AGS and in lupus erythematosus [43].

This suggests that the high level of inf-α might be a causal factor for the encephalopathy and that there may be some relationship between the vasculitis of lupus and that found in the syndrome. The origin of this high level is unexplained. The concentration in CSF suggests an intrathecal synthesis that may result from a genetic defect in its regulation.

9. Conclusions

There exist a group of disorders with similar clinical features and that share a number of biological features. In these cases in which adequate investigations have been performed, AGS was the first of these conditions and remain the best studied so far. Although its mechanisms are not fully understood, the role of the high levels of inf-α as a probable cause of diffuse vasculitis seems established. One likely hypothesis is that the basic mechanism could be a dysregulation of production and control of inf-α. A similar or related mechanism is likely to be at play in MICS and Cree ‘encephalitis’. Although these diseases are rare, they may represent a new category of disorders related to the regulation of inf-α production.

References

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