Aicardi–Goutières syndrome (AGS)

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\textbf{Abstract}

In 1984, Jean Aicardi and Françoise Goutières described 8 children showing both severe brain atrophy and chronic cerebrospinal fluid lymphocytosis, with basal ganglia calcification in at least one member of each affected family. The course was rapid to death or a vegetative outcome. Aicardi and Goutières correctly predicted that the disorder would be genetic, but emphasised that "some features, especially the pleocytosis, may erroneously suggest an inflammatory condition". The increased interferon-alpha in affected children (Pierre Lebon, Paris) mimicked congenital viral infection, but the associated chilblains (pernio) pointed to lupus erythematosus and an autoimmune mechanism. Genetic research led by Yanick Crow has clarified these puzzling relationships in Aicardi–Goutières syndrome, a syndrome that now includes conditions previously known as microcephaly-intracranial calcification syndrome, pseudo-TORCH and Cree encephalitis. At the time of writing, Crow’s team has discovered that over 80% of families with Aicardi–Goutières syndrome have mutations in one of four nuclease genes, the exonuclease TREX1 and the genes for all three subunits of the ribonuclease H2 enzyme complex. Aicardi–Goutières syndrome is both genetically and phenotypically heterogeneous, with a range of severity from life-threatening perinatal illness to mild late infancy onset. All infants of whatever genotype have increased interferon-alpha in the first year of life and this appears to be the final common pathway that links Aicardi–Goutières syndrome, congenital virus infection and systemic lupus erythematosus.

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1. Introduction

In 1984, Jean Aicardi and Françoise Goutières of Paris described 8 children showing both severe brain atrophy and chronic cerebrospinal fluid lymphocytosis, with basal ganglia calcification in at least one member of each affected family.\(^1\) The course was rapid with death or a vegetative outcome in all. Aicardi and Goutières thought that the disorder was probably genetic, but emphasised that “some features, especially the pleocytosis, may erroneously suggest an inflammatory condition”.\(^1\) By inflammatory condition they meant an infective condition, in particular congenital viral infection.

Soon afterwards Pierre Lebon and colleagues\(^2\) demonstrated the presence of interferon-alpha (IFN-\(\alpha\)) in the CSF and/or serum in 7 of 8 patients with what was then called progressive familial encephalopathy associated with calcifications of the basal ganglia and white matter alterations. Intrathecal synthesis of IFN-\(\alpha\) was demonstrated in some of these patients by the CSF IFN-\(\alpha\) level being higher than the serum, and prolonged secretion of IFN-\(\alpha\) was demonstrated by its presence up to several years after birth.\(^3\)

The term Aicardi–Goutières syndrome (AGS) was first used in a case report in 1992,\(^3\) and the newly characterised syndrome was reviewed in depth in 1995.\(^4\) Tolmie et al.\(^4\) showed not only a picture of a floppy infant with AGS but also an image of his severe chilblains. This was the first description and illustration of chilblains\(^4\) that have since been shown to be a major extra-neurological feature of AGS.\(^5\)

A family from Dublin extended the phenotype with the demonstration that brain atrophy was not obligatory, there need be no clinical progression (that is to say, regression was not inevitable) and intelligence could be normal.\(^6\) Intrafamilial variability,\(^6,7\) had already been known since the original description,\(^1\) but a report from Denmark extended the limits of AGS by finding a persistently normal CSF cell count in one of two affected.\(^7\)

The familial condition described by Dale et al.\(^8\) as systemic lupus erythematosus (SLE) and “congenital infection-like syndrome” provoked considerable interest.\(^9\) The diagnostic criteria for SLE were fulfilled,\(^8\) with circulating autoantibodies, but the clinical features were otherwise those of AGS\(^5\) and the lesions on the toes and elsewhere which Dale et al.\(^8\) called discoid lupus looked exactly the same as what others call chilblains.\(^4,10,11\)

2. The genetic revelation

It was tempting to head this section “The genetic revolution”, but whichever word is applied the recent advances in the genetics of AGS hold promise of advances in the wider fields of medicine and science. In a short space of time the team led by Yanick Crow has moved from the recognition of genetic heterogeneity, with one locus on chromosome 3p21 (AGS1),\(^12\) to the discovery of four of the genes responsible.\(^13,14\)

Before these actual genes were identified, the first major spin-off from the genetic research derived from the finding that so-called Cree encephalitis of Northern Quebec\(^15\) was allelic with AGS1.\(^16\)

The original report\(^15\) was of a condition confined to a highly inbred native community. Onset was from the neonatal period to age 6 months, with a median age at death of 20 months. Clinically, there was a failure to thrive, irritability, fever, delay, arching posture, failure of head growth, spasticity, and lack of developmental gains, and often hepatosplenomegaly. Investigations revealed basal ganglia calcifications, white matter hypodensities and cerebral atrophy on CT scans, CSF lymphocytosis (2–3560 /ml, median 24), and IgG and autoimmune abnormalities. Recurrent viral infections were a prominent feature. The immunological abnormalities argued against the disorder being the same as AGS, and the authors judged at the time that ‘Cree encephalitis’ resulted from a combination of a genetic factor and a virus infection.\(^15\)

For the 2003 paper,\(^16\) 7 of the available 14 Cree children were studied. All 7 showed progressive microcephaly, intracerebral calcification and severe delay. Of note, only 5/7 had CSF WCC >5 cells/mm\(^3\) though in 3 of 3 tested CSF IFN-\(\alpha\) was raised, including the two children with normal CSF white cell counts (in one child the serum IFN-\(\alpha\) was greater than the CSF IFN-\(\alpha\) level). Crow et al.\(^16\) predicted that the nature of the AGS1 gene would give insights into control of IFN-\(\alpha\) production and the role of IFN-\(\alpha\) in congenital viral infection and SLE.

A by-product of this study was that what had previously been regarded as separate conditions and called microcephaly-intracranial calcification syndrome or pseudo-TORCH are probably also examples of AGS.\(^16\)

For the studies that culminated in the identification of the first four genes for AGS\(^13,14\) all affected individuals demonstrated:

1. progressive neurological dysfunction,
2. onset in the 1st year of life,
3. intracranial calcification involving the basal ganglia,
4. negative investigations for common perinatal infections, and
5. CSF lymphocytosis (>5 cells/mm\(^3\)) and/or raised CSF IFN-\(\alpha\) (>2 iu/ml)

these criteria having been derived from Goutières et al.\(^10\)

It transpired that AGS1 was a DNA exonuclease TREX1\(^13\) and AGS2-4 were genes encoding ribonuclease H2 subunits, such that AGS2 = RNaseH2B, AGS3 = RNaseH2C and AGS4 = RNaseH2A.\(^14\) Analysis of a much larger number of pedigrees\(^5\) showed that in over 80% of families there were biallelic mutations in one of these four genes, whilst in 17% no mutations were found—and so at least one further gene for AGS remains to be discovered.

Despite the demonstrated genetic (and phenotypic) heterogeneity, it was remarkable that clinical features such as chilblains occurred in all those with all four mutated genes.\(^5\)

An additional elaboration was the finding of de novo ‘dominant’ mutations, as in a Scottish child with a heterozygous mutation in TREX1\(^17\) and in those with familial chilblain lupus.\(^17\)
3. Clinical diagnosis of AGS

There is a beautiful paradox within the diagnostic criteria for AGS. Most of the early criteria for diagnosis no longer apply. Neurological dysfunction is not necessarily progressive. Onset is not always in the first year of life. Calcification of the basal ganglia is not inevitable. CSF lymphocytosis need not be present. But if it had not been for the original compilation of Jean Aicardi and Francine Goutières it would not have been possible to prosecute the scientific studies that have allowed our present understanding of the expanded phenotype (Fig. 1).

Broadly speaking, there are two main presentations of AGS, the neonatal and the later onset forms. In the neonatal form, typically due to mutations, neurological illness is manifest at birth or in the first few days, frequently with features suggesting congenital infection, but with negative virology. In the later onset form a period of normal development precedes subacute regression, commonly with extreme irritability and ‘sterile’ pyrexias, followed by loss of skills and slowing of head circumference growth. This later onset presentation is associated with a more prolonged course, with stabilisation and low mortality: the gene most often implicated is RNaseH2B.

The clinical sign is most likely to point to the diagnosis of AGS later in the first year of life, and from then on is the appearance of chilblains. Chilblains or pernio appear as purple-red swellings, sometimes scaly or necrotic, on the toes or fingers and sometimes on the earlobes or elbows. Colour illustrations are available on http://www.nature.com/ng/journal/v38/n8/extref/ng1845-s1.pdf. Chilblains are present in over 40% of mutation-positive individuals with AGS and seem to be a highly specific diagnostic sign (http://www.simulconsult.com/).

Congenital glaucoma is a non-specific finding but seems to be a part of the AGS phenotype.

4. Diagnostic investigations

The investigations most likely to be helpful are brain imaging and CSF examination.

Cerebral calcification, basal ganglia and otherwise, may still be better seen on CT than on MRI, though MRI shows the leukoencephalopathy more dramatically, and may also reveal (non-specific) brainstem atrophy. CSF lymphocytosis is easy to determine, but a normal CSF cell count at any age does not rule out the diagnosis of AGS. IFN-α is increased in all cases of AGS in the first year of life, but at the time of writing few outside Pierre Lebon’s laboratory in Paris are able to estimate IFN-α reliably. Pterins are another index of intrathecal inflammation and are increased in the CSF in AGS.

Biopsies of chilblains have shown granular deposition of immunoglobulins in the basement membrane, but of more fundamental importance is the finding of tubuloreticular inclusions (TRI) on electron microscopy in cells and biopsies. When Lebon et al. wrote in their abstract “IFN-α was detected in cerebrospinal fluid and/or sera from 7 of 8 patients with a progressive familial encephalopathy associated with calcifications of the basal ganglia and white matter alterations”, that was short-hand for IFN-α or an IFN-α marker (my italics). In one of the 7 patients, IFN-α was not measured in CSF or serum but instead TRI were noted in endothelial cells on skin biopsy, and as previously shown the presence of TRI is a reliable marker of circulating IFN-α. Of the 18 patients tabulated with IFN-α values in Goutières et al. four (three without CSF or serum IFN-α estimations)
showed “Tubuloreticular inclusions related to the presence of interferon” (my italics), two in endothelial cells in skin biopsy, one in muscle biopsy, and one in CSF lymphocytes. It is surprising that TRI—well known as an electronmicroscopic feature of SLE and virus infections such as HIV—have not been reported outside of Paris as a marker of AGS.

Finally, direct genetic diagnosis of AGS from DNA samples may be relatively easy.10

5. Concluding remarks

Neonates and young infants with AGS look as if they have prenatally acquired virus infection, because the result of innate autoimmunity on the brain (and many other tissues) seems to be the same.

From a biological perspective, the unification of the IFN-a-mediated responses to endogenous “self” nucleic acids and to virus is a fascinating synthesis. As Alarcon-Riquelme wrote,24 (after Crow et al.13,14) “The identification of genes defective in AGS opens new avenues of research into the homoeostasis of the innate immune system and the pathogenesis of SLE and autoimmunity.” What intellectual excitements from such a rare disorder!

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As a medical student in 1959, I was greatly inspired by “The Clonal Selection Theory of Acquired Immunity” by Sir Macfarlane Burnet. My more recent inspiration has come from the work and kindness of Dr. Yanick Crow.

REFERENCES