

Aicardi Syndrome: Old and New Findings

Jean Aicardi, MD, FRCP

Abstract

Newly recognized features of Aicardi syndrome, such as ependymal cysts, choroid plexus papillomas, cortical migration abnormalities, and optic disc coloboma may be as important for diagnosis as the classic triad of chorioretinal lacunae, infantile spasms, and agenesis of the corpus callosum that may be occasionally absent in rare cases. The outcome may be less unfavorable than originally thought. *Int Pediatr.* 1998;14(1):5-8.

Key words: Aicardi syndrome, agenesis of corpus callosum, infantile spasms, cortical dysplasia, ependymal cysts

Introduction

Aicardi syndrome (AS) was originally described as featuring a triad of infantile spasms, chorioretinal 'lacunae' and agenesis of the corpus callosum.^{1,2} The condition has been recognized only in individuals with two X chromosomes; of more than 400 cases published or known to the author, only two were in boys, both with an XXY chromosomal complement (personal communication of G. Ronen, 1994).³ Aicardi syndrome is not a familial condition; only one familial instance is known involving two sisters.⁴ The actual frequency of the condition is not known. In series of infantile spasms from tertiary referral centers, 1% to 4% of cases may be due to AS.

Early cases of the syndrome were diagnosed by air encephalography which explains the diagnostic importance attributed to callosal agenesis that was the major recognizable sign using this technique. Modern neuroimaging, especially magnetic resonance imaging (MRI), has shown that a complex brain malformation is more characteristic than isolated agenesis of the callosum which does not occur in all cases.^{5,6} The use of modern neuroimaging and the accumulation of new cases has also led to the recognition of some new clinical signs and to the realization that the course of the disorder, although usually very severe, was in some cases significantly milder.⁶⁻⁸

This review focuses on some less-known clinical, EEG, ophthalmologic, pathologic, and imaging features of AS, and on the current knowledge of the etiologic aspects of the AS and related disorders.

Clinical and Imaging Features

Infantile spasms are frequently asymmetrical.⁹ Clusters of spasms are often preceded, and apparently precipitated, by a focal clonic or tonic seizure limited to the side in which the spasms predominate.¹⁰ The focal seizure is accompanied by a localized discharge of repetitive spikes and followed by a series of slow complexes usually of higher amplitude on the side opposite the clinical spasms,^{5,6,10} and with characteristics similar to those described by Gobbi et al¹¹ for 'periodic spasms.'

Variable neurologic abnormalities are often present; the most frequent is hemiparesis or hemiplegia often on the side where the spasms predominate. A degree of microcephaly may develop but the head circumference is normal at birth.

The 'chorioretinal lacunae' may be more or less extensive and are occasionally unilateral. In one recently observed girl with all the other clinical and imaging features of AS, the fundi were completely normal and, in three patients, no typical lacunae were seen although the fundi could not be regarded as completely normal because of coloboma or other abnormalities.⁵ This suggests that in rare cases this sign, usually regarded as pathognomonic, may be absent. In many cases, other ophthalmologic abnormalities are associated with the lacunae or may occur alone (at least in one eye). Coloboma of the optic disc, sometimes prolonged posteriorly as a coloboma of the optic nerve, is found in more than half the cases and may be uni- or bilateral.^{6,12} Microphthalmia, ringlike pigment deposits surrounding a colobomatous papilla (looking like the morning glory anomaly¹³), can also be observed. Despite extensive retinal involvement, total blindness is rare but no precise assessment of acuity is available. In a few cases, a relatively normal electroretinogram (ERG) could be recorded.

Magnetic resonance imaging has shown in a large majority of cases a complex central nervous system (CNS) malformation that includes, in addition to the agenesis of the callosum initially described, several abnormalities:

From the Service de Neurologie Pédiatrique, Hôpital Robert Debré, Paris, France.

Address reprint requests to Hôpital Robert Debré, 48 Blvd. Séurier, 75019 Paris, France (Dr Aicardi).

(1) areas of dysplastic cortex (present in varying degrees in most patients); (2) periventricular gray matter heterotopias; (3) gross asymmetry of the cerebral hemispheres; (4) cysts of the choroid plexus or in the vicinity of the third ventricle, pineal region, or rarely in the posterior fossa; (5) choroid plexus papillomas; (6) rarely, agenesis of hypoplasias of the cerebellar vermis.²⁵ In most cases, several of these abnormalities are present simultaneously and the overall MR appearance is suggestive at a glance even if the corpus callosum is present in totality or in part. In rare cases, only one or two features are present, the most frequent being cortical malformations and periventricular heterotopias. However, they may be absent or undetectable in a small number of otherwise typical cases. Cysts in the region of the third ventricle are very common. They are extraventricular, often multiple, and their size varies from a few millimeters to several centimeters. They give a more intense signal than cerebrospinal fluid (CSF) on T1-weighted sequences and may also appear brighter on T2-weighted sequences. In a few operated cases, they were shown to be of ependymal origin.^{6,14} Similar cysts are frequently present in the glomi of the choroid plexuses. The wall of the cyst often takes up gadolinium contrast. Choroid plexuses and periventricular cysts may coexist and cysts may also coexist with choroid plexus papillomas.¹² Multiple cysts have been reported.¹⁵ In some cases, the cysts may enlarge considerably and become compressive. In one recent case, marked hydrocephalus developed, probably as a result of aqueductal compression. There are at least 11 reports of demonstrated or probable choroid plexus papilloma in AS (Fig 1).^{6,12,16-19} Interestingly, in at least two

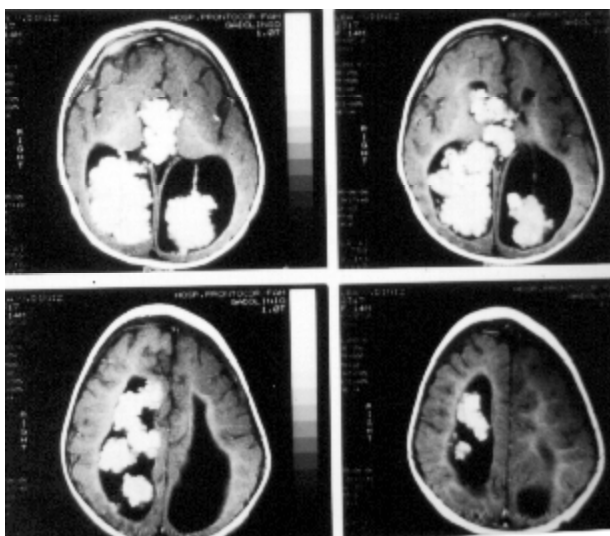


Fig 1.—Choroid plexus papillomas in both lateral ventricles and third ventricle in a girl with Aicardi syndrome (courtesy Dr Luiz Fernandez Fonseca, Porto Alegre, Brasil)

cases, there was no hydrocephalus associated with the papillomas^{12,16} and in one of these cases,¹⁶ left unoperated, no significant increase in the size of the tumors or of the ventricles was observed over a 2-year period despite the presence of bilateral papillomas. In one recent case, large papillomas filled the lateral and third ventricles.

As a consequence of these novel findings, it seems reasonable to propose new diagnostic criteria. The classic triad remains the cornerstone of diagnosis in most patients but in rare cases one of the features, especially agenesis of the corpus callosum, may be missing. The diagnosis can probably be made in such cases if two or more of the new criteria are present (Table). However, an absolutely firm diagnosis in incomplete or atypical cases will have to await the discovery of a biological (probably DNA) marker.

New Criteria for the Diagnosis of Aicardi Syndrome

Classic Triad

Infantile spasms
Chorioretinal lacunae
Agenesis of the corpus callosum (may be partial)

New Major Features *

Cortical malformations (mostly microgyria)**
Periventricular and subcortical heterotopia
Cysts around the 3d ventricle and/or choroid plexuses
Papillomas of choroid plexuses
Optic disc/nerve coloboma

Supporting Features ***

Vertebral and costal abnormalities
Microphthalmia and/or other eye abnormalities
'Split-brain' EEG (dissociated suppression-burst tracing)
Gross hemispheric asymmetry

* Present in most patients studied by MRI.

** Probably constant but may not be possible to evidence.

*** Present in some cases.

The course and outcome of AS are extremely severe. The estimated survival rate is 76% at 6 years and 40% at 14 years of age.⁷ The overall disability is usually quite marked. In one survey of 34 patients from the AS association in the United States, all patients were still having seizures at the time of survey, half of them had been hospitalized at least once for respiratory problems, 10 were unable to feed themselves and 75% were fed on baby food or pureed food.⁶ Only 8 girls could walk, 3 could run, and 1 patient could speak a few words but no sentences. Over the past several years, the existence of less severe cases has been increasingly recognized. Two pa-

tients reported by Neidich et al²⁰ were capable of using two-word sentences and I have examined at least 3 girls who were capable of using short sentences. Abe et al²¹ reported a single case of normal developmental progress and noted 10 additional cases with mild retardation in a literature survey.²¹ Menezes et al⁸ reported a child with hypoplasia of the corpus callosum and mild intellectual disability. They also noted that mild retardation was more common in cases of partial agenesis.⁷ However, one girl I recently saw had a normal developmental progress at 2½ years despite complete absence of the callosum and all the other imaging features of AS. A girl reported by Hopkins¹⁶ had typical lacunae, infantile spasms that responded completely to prednisolone and have not recurred, no visible migration abnormalities, and a normal corpus callosum. At 2½ years, she remained seizure-free and progressed normally. The spectrum of developmental problems may be wider than previously thought, although the overall outlook is rather dismal.

Pathological Findings in CNS and Retina

The pathology of AS is largely deduced from imaging findings and few actual pathological data are available.^{12,14,22-24} Post-mortem studies showed areas of abnormal gyration mostly representing unlayered polymicrogyria (Fig 2), even when apparent pachygyria was macroscopically found, resulting from fusion of the molecular layers of the apposed microconvolutions. Large pyramidal cells were found randomly distributed throughout the whole cortical thickness¹⁴ or restricted to their appropriate deep location.²² Heterotopic neurons were present in the periventricular nodules, scattered in the subcortical white matter, and in pial heterotopias. The complex of dysgenesis of the corpus callosum, cortical malformations and heterotopias is suggestive of, but not specific



Fig 2.—Cortical unlayered polymicrogyria in a case of Aicardi syndrome. Thin undulating neuronal layer under the molecular layer. Note fusion of the molecular layers of apposed convolutions.

for, AS. I believe however that the association of these anomalies with ependymal cysts or choroid plexus papilloma is probably unique to this syndrome.

The eye pathology does not feature any inflammatory lesion. The 'lacunae' are zones of thinning of the choroid and sclera with associated depigmentation of the pigment epithelium with degeneration of rods and cones.²⁵ In some cases, more extensive abnormalities are present with complete interruption of the pigment epithelium and other lesions.⁶

Genetic Data

With the exception of sporadic cases in two XXY males (G. Ronen personal communication),³ AS affects females exclusively and the hypothesis of a dominant X-linked gene lethal early in development for male conceptuses remains the most likely explanation of the data.^{2,5} Only one family with two affected sisters has been reported and this may have resulted from a germinal mutation. Otherwise the mutation seems to arise *de novo* and to be sporadic rather than hereditary. Such a mutation could even occur as a postzygotic event in early embryonic development as a set of identical twins, one with AS and one with completely normal development, has been observed.²⁶ The possibility that such a case could have resulted from uneven X chromosome inactivation in the twins was excluded by the demonstration of a very similar pattern of random inactivation in both. Preferential inactivation of one X-chromosome was reported by Neidich et al²⁰ but not confirmed in a more recent study by Hoag et al²⁷ who found a normal random pattern.

Efforts to localize the gene(s) responsible for AS have not been successful. Several patients with somewhat similar eye findings, seizures, mental retardation or agenesis of the corpus callosum were found to harbor translocations involving the short arm of X chromosome with a breakpoint at Xq22.3.^{28,29} This is also the region where the locus for the syndrome of microphthalmia with linear skin defects (MSL) has been located.³⁰⁻³³ This syndrome shares with AS a number of features (microphthalmia, chorioretinal abnormalities, seizures, and sometimes agenesis of the callosum), but not some of the most specific abnormalities of AS. The gene for MSL has been cloned and is homologous to mitochondrial holocytochrome c-type synthetases identified in other organisms.³¹ However, a mutational analysis of the human holocytochrome c-type synthetase (HCCS) gene in lymphoblasts derived from 7 patients with AS did not reveal evidence of gene rearrangements or mutations.³² Therefore, this possible candidate appears rather unlikely as a cause of AS.

Several contiguous genes may exist in the same region of the X-chromosome and various but distinct rearrange-

ments in these genes could result in either AS or MLS, which could account for the variable severity and incomplete forms of these syndromes. Further evidence is waited for with great interest.

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