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Neuroimaging Aspects of Aicardi Syndrome

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Abstract

Aicardi syndrome is a rare neurodevelopmental disorder characterized by congenital chorioretinal lacunae, corpus callosum dysgenesis, seizures, polymicrogyria, cerebral heterotopias, intracranial cysts, and costovertebral defects. Cerebellar abnormalities have been described occasionally.

Aicardi syndrome is sporadic and has been observed only in females and 47,XXY males.

Therefore, it is thought to result from a mutation in an X-linked gene. Improved definition of the clinical phenotype should focus the selection of functional candidate genes for mutation analysis.

Because central nervous system abnormalities are the most prominent component of the phenotype, we performed a detailed characterization of abnormalities identified on magnetic resonance neuroimaging studies from 23 girls with Aicardi syndrome, the largest cohort to undergo such review by a single group of investigators. All patients had polymicrogyria that was predominantly frontal and perisylvian and often associated with underopercularization.

Periventricular nodular heterotopias, present in all patients, were more frequent than previously reported; 10 had single and 11 had multiple intracranial cysts. Posterior fossa abnormalities were also more frequent than previously described. Cerebellar abnormalities were noted in 95% of studies where they could be evaluated. As a novel finding, we noted tectal enlargement in 10 patients. Since mildly-affected girls with variable callosal dysgenesis have now been reported, the constellation of frontal-dominant and perisylvian polymicrogyria, periventricular nodular heterotopias, intracranial cysts, and posterior fossa abnormalities, including tectal enlargement, should prompt consideration of the diagnosis of Aicardi syndrome. We further propose that improved characterization of the neurological phenotype will benefit the selection of candidate genes for mutation analysis.

Keywords

Aicardi Syndrome; Polymicrogyria; Heterotopias; Cerebellum; Tectum; Corpus callosum

INTRODUCTION

Aicardi syndrome is a rare neurodevelopmental disorder affecting females and, very rarely, males with a 47,XXY karyotype [Aicardi, 2005; Aicardi et al., 1965; Hopkins et al., 1979].

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The diagnosis of Aicardi syndrome in boys with a 46,XY karyotype has been reported but not confirmed subsequently [Aggarwal et al., 2000; Aicardi, 1980; Curatolo et al., 1980; Hunter, 1980]. It has therefore been hypothesized that Aicardi syndrome is caused by mutations in a gene on the X chromosome that causes lethality in hemizygous males [Van den Veyver 2002; Wettke-Schafer and Kantner, 1983]. Aicardi syndrome is sporadic except for one reported pair of affected sisters [Molina et al., 1989] and a pair of affected monozygotic twins [Pons and Garcia, 2008]. Hence, linkage analysis to identify the causative gene is not possible. An alternative approach to identify the causative gene(s) for Aicardi syndrome is functional candidate gene analysis. To select the most promising candidate genes, complete and rigorous characterization of the phenotype is required.

Aicardi syndrome was first described in 1965 as a condition characterized by a triad of infantile spasms, callosal dysgenesis, and distinctive chorioretinal lacunae [Aicardi, 2005], but the phenotype is much more complex and has many additional neurological and constitutional manifestations. This recognition led to revised criteria for the clinical diagnosis of Aicardi syndrome that include cerebral malformations such as polymicrogyria, cerebral heterotopias, and cysts as major findings and gross cerebral asymmetry as a minor abnormality [Aicardi, 2005]. Other anomalies include cerebellar dysgenesis, papillomas of the choroid plexus, holoprosencephaly, and embryonic tumors [Aicardi, 2005]. Several reports have documented these brain malformations in Aicardi syndrome, but the number of affected individuals described in each report is relatively small owing to the rarity of the syndrome. In addition, some reports predate the availability of current high-resolution imaging modalities. Thus detailed information on the frequency, distribution and imaging characteristics of the intracranial findings is still limited [Barkovich et al., 2001; Donnenfeld et al., 1989; Palmer et al., 2006; Smith et al., 1996; Yamagata et al., 1990].

We recently performed clinical and genetic examinations and reviewed the brain imaging studies of a substantial number of girls with Aicardi syndrome. From these studies we reported characteristic facial and physical traits that had not been fully appreciated previously [Sutton et al., 2005]. Here we present our review of neuroimaging studies from 23 subjects. We provide a detailed study of the prevalence of previously-identified developmental brain abnormalities and identify novel manifestations. This more detailed characterization of the brain phenotype of Aicardi syndrome may lead to identification of microforms of Aicardi syndrome and to an improved candidate gene approach for the disorder.

MATERIALS AND METHODS

Subjects

This study was approved by the Baylor College of Medicine Institutional Review Board for Human Subjects Research. Subjects were included if they had the classic triad of corpus callosum dysgenesis, seizures, and chorioretinal lacunae or microphthalmia. Twenty-one patients were evaluated clinically by us and two imaging studies were submitted directly to us. The diagnosis of Aicardi syndrome for those patients was confirmed via review of their medical records. Twenty-two were female and one was a 47,XXY male. After informed consent was obtained from parents or legal guardians, the investigators reviewed brain magnetic resonance imaging (MRI) studies that had been obtained previously as a part of the assessment for these patients. No neuroimaging studies were obtained solely for this research protocol.

Neuroimaging studies

We reviewed 23 brain magnetic resonance imaging (MRI) scans (9 without contrast) with sagittal T1-weighted and axial T1 and T2-weighted images. The average age at which the studies were performed was 1.8 years (range: 1 day to 7.2 years). First we collected information about the patterns and anatomical distribution of polymicrogyria, heterotopias, callosal dysgenesis, ventriculomegaly, colpocephaly, gross cerebral asymmetry and tumors. After this initial analysis, we performed a secondary review of intracranial cysts, cerebellar abnormalities, tectum irregularities and opercular development on all but two subjects, for whom the images were available to us for only a limited time. When cysts were present, their location, MRI signal intensity on T1-weighted images, contrast enhancement and size/dimensions were recorded. Cyst diameters were measured at the widest point in the sagittal or axial planes. The length of the tectum was measured along the longest distance and its width at the widest point on a mid-sagittal image. The anterior interopercular distance was estimated as the mean distance between the posteroinferior border of the inferior frontal gyrus and the superoanterior border of the temporal lobe in the axial and sagittal planes, as described by others [Chen et al., 1995]. Opercular underdevelopment was defined as an anterior interopercular distance greater than 4.5 mm in infants and 3.5 mm in children over one year of age [Chen et al., 1995]. The reviewed studies were performed at different institutions from 1993 to 2004 and both the instrumentation and imaging techniques varied. If an available study did not offer adequate resolution, appropriate images, or scales necessary for measurement of one of the imaging parameters, it was excluded from analysis for that portion of the neuroimaging review.

RESULTS

Polymicrogyria and heterotopias

Polymicrogyria was found in the imaging studies of all 23 (100%) subjects; 21 (91%) showed greater anterior involvement, mainly in the frontal regions; 15 (65%) had perisylvian polymicrogyria, which was bilateral in 5 (22%). Although 65% of subjects had bilateral polymicrogyria, there was an asymmetric distribution in which the left frontal region was most commonly involved (Fig 1A-1C). Heterotopias were seen in all 23 (100%) imaging studies (Fig 1). The heterotopias were periventricular in all subjects, with a predilection for the body of the lateral ventricle. Three subjects also had heterotopias of the fourth ventricle, and one had bilateral thalamic nodular heterotopias. (Fig 2). One subject had subcortical heterotopias in the left frontal corona radiata (Fig 1F, Table I), and 6 had cerebellar subcortical heterotopias (Fig 1E). Heterotopias were bilateral in 19/23 (83%) and asymmetric in all subjects. Single periventricular nodules were seen in 17/23 studies (74%), confluent nodular periventricular heterotopias in 1/23 (4%) and a mixed pattern in 5/23 (22%). We found higher incidence of migration abnormalities compared to previous neuroimaging surveys of Aicardi syndrome [Palmer et al., 2006; Smith et al., 1996; Yamagata et al., 1990] (Table II), except for one study in which 5 patients were reported who all had microgyria and heterotopias [Barkovich et al., 2001]. Furthermore, the polymicrogyria consistently involved frontal and perisylvian regions. This led us to perform a more detailed, quantitative assessment of the operculum.

Opercular abnormalities

The operculum could be measured reliably in 18 studies. Widening was documented in 13 (72%) of imaging studies: the average anterior interopercular distance was 7.3 mm (1-30 mm) on the left and 7.5 mm (1.5-28 mm) on the right. The opercular abnormalities were bilateral in 9 subjects. We also found that 8 individuals with underdevelopment of the operculum also showed perisylvian polymicrogyria (Fig 1).

Intracranial Cysts

Cysts were present in 20/21 (95%) imaging studies (Figs 1, 3, Table III). Of these, 11 showed multiple cysts and 9 had single cysts. The cysts were midline interhemispheric (81%), intraventricular (29%), extra-axial (8%) or parenchymal (10%) (Table II). The cyst diameters were 1.0-5.0 cm (average 1.9 cm) for cysts within the lateral ventricles, 1.7-7.8 cm (average 4.5 cm) for extra-axial cysts and 1.0-2.0 cm (average 1.5 cm) for intraparenchymal cysts. Midline cysts were round, with an average diameter of 1.2 cm (range: 1 to 4 cm), loculated without apparent communication with the ventricles, and positioned in the pineal region or above the region where the corpus callosum should have formed. These characteristics are most consistent with those of type 2b midline cysts, according to Barkovich's classification [Barkovich et al., 2001]. Eight of the 11 studies with midline cysts that had contrast-enhanced images showed cyst wall enhancement. All 5 available contrast-enhanced MRI images of lateral ventricular cysts showed enhancement of the cyst walls. Most lateral ventricular cysts were round, well-defined, and encapsulated with a thick cyst wall. One was multiloculated with avid contrast enhancement and was contiguous with the choroid plexus, consistent with a choroid plexus papilloma (Fig 3A-3A₁). Of the extra axial cysts, only one showed cyst-wall contrast enhancement. Most were located posteriorly, 4 in the region of the cerebellum and one outside of the left occipital lobe. The two intraparenchymal cysts were also located posteriorly with one being to the left of the midline in the occipital lobe and the other being in the right cerebellar hemisphere. Both MRI studies with contrast showed contrast enhancement of the cyst walls.

Posterior fossa and cerebellar abnormalities

The posterior fossa could be evaluated reliably in 21 subjects. Cerebellar abnormalities were noted in 20 subjects (95%) (Fig 4). They included superior foliar prominence of the vermis, inferior vermian hypoplasia and dysplastic or hypoplastic cerebellar hemispheres in 13 (65%) each. Cerebellar subcortical and/or periventricular heterotopias were noted in six studies (27%). An enlarged cisterna magna was present in 11 (55%) and 4 (20%) had cerebellar cysts. Five subjects with vermis abnormalities also had an enlarged cisterna magna and none of the subjects with vermis abnormalities had an extra-axial cyst. Eight subjects with abnormalities of the cerebellar hemispheres also had enlargement of the cisterna magna with only 2 having an extra-axial cyst. Because we were impressed with the prominence of the tectum on many of the MRI studies, we measured it objectively in 18 imaging studies to document accurately the full range of neuroimaging findings in Aicardi syndrome. Normal tectal measurements have not been published for children, but based on experience with review of brain MRIs of children without neurodevelopmental abnormalities, we chose a threshold for tectal enlargement of > 15 mm in length and > 5 mm in width. The average tectal length and width were 14.0 mm (12-18 mm) and 4.7 mm (3-7 mm) (Fig 4) and did not correlate with age. The tectal length was greater than or equal to 15 mm in six patients, and the width was greater than or equal to 5 mm in 10 patients.

DISCUSSION

Our findings from a review of 23 neuroimaging studies of individuals with Aicardi syndrome indicate that polymicrogyria is present universally and that heterotopias are much more common than previously appreciated [Barkovich et al., 2001; Palmer et al., 2006; Smith et al., 1996; Yamagata et al., 1990]. We observed a consistent pattern of frontal predominance of polymicrogyria with a strong predilection for the perisylvian region. Interestingly, underdevelopment of the operculum was found in almost three-fourths of our patients and was associated frequently with perisylvian polymicrogyria. All subjects had heterotopias, which were most often found near the body of the lateral ventricles with small, single periventricular nodules present in nearly all. We further observed frontal-lobe

subcortical heterotopias and cerebellar heterotopias which have been described before [Smith et al., 1996]. We found that posterior fossa abnormalities are much more common in Aicardi syndrome (95%) than prior reports, and we describe tectal enlargement as a new finding. We confirmed that type 2b midline cysts [Barkovich et al., 2001] are the most common cysts in Aicardi syndrome, while the second most common cysts occur in the lateral ventricles. The presence of cyst wall contrast enhancement in most of the ventricular, midline, and intraparenchymal cysts mimics the contrast enhancement seen in the choroid plexus which can also contain papillomas in Aicardi syndrome, perhaps suggesting a common origin of these findings.

Although posterior fossa abnormalities have been described previously in Aicardi syndrome [Barkovich et al., 2001; Donnenfeld et al., 1989; Smith et al., 1996; Yamagata et al., 1990] (Table II), our data suggest that their prevalence and characteristics have been underappreciated thus far. This prompted a more detailed characterization of the posterior fossa and cerebellum. The cerebellar vermis abnormalities, including inferior vermian hypoplasia and superior foliar prominence, were subtle and the superior foliar prominence was also highly variable. Given that all subjects had epilepsy, these cerebellar vermis findings may be related to exposure to antiepileptic medication. However, since they were present in subjects who were less than 4 months of age (and as early as the first day of life), we speculate that superior foliar prominence and hypoplasia of the cerebellar vermis may be related to decreased cell proliferation as well as atrophy due to medication exposure. The cerebellar hemispheres were strikingly abnormal in 59% of subjects and showed unilateral hypoplasia or dysplasia with associated large cisterna magna, subcortical and/or periventricular cerebellar heterotopias, and cerebellar intraparenchymal cysts and extra-axial cysts. We did not observe that cerebellar abnormalities were associated with cyst development, but we cannot exclude that they result from enlargement of the cisterna magna and cerebellar abnormalities. This reflects the overall asymmetry in brain development which has been classically described supratentorially.

Enlargement of the tectum has not been reported before. What causes this in Aicardi syndrome is unclear. The tectum contains the inferior colliculi, which are involved in hearing, and the superior colliculi, which are involved in vision and visual motor control. Children with Aicardi syndrome have maldevelopment of their anterior visual system demonstrated by chorioretinal lacunae and optic nerve dysplasias. We speculate that secondary effects on the visual pathways may influence the size of the tectum. We have not examined an age-matched population of children with ocular or anterior segment dysgenesis to ascertain whether this finding is associated possibly with other purely ocular conditions presumably occurring at similar times in embryonic and fetal development.

We did not review callosal agenesis and dysgenesis in detail, as their presence is an inclusion criterion for the primary diagnosis, and therefore they were seen in all reviewed studies; however agenesis was found in two-thirds and dysgenesis one-third of our cohort. An individual with Aicardi syndrome and a normal corpus callosum was described recently [Iturralde et al., 2006] and other mildly affected individuals who have partial callosal agenesis, more limited brain and ocular defects and prolonged survival have also been reported [Abe et al., 1990; Matlary et al., 2004; Menezes et al., 1994; Palmer et al., 2006]. This suggests that callosal dysgenesis and other classic manifestations may not always be present in this condition [Aicardi, 2005] and it emphasizes the importance of other neuronal migration abnormalities, such as polymicrogyria and heterotopias, in the diagnosis of Aicardi syndrome. Whether microforms of Aicardi syndrome would not be diagnosed under current criteria must await the discovery of the causative gene(s). We believe that, until such time, these intracranial details will aid the differentiation of Aicardi syndrome from other neurodevelopmental disorders and should help clinicians to establish a clinical diagnosis of

Aicardi syndrome in those individuals who have an atypical presentation without callosal dysgenesis or typical chorioretinal lacunae. We propose further that the unique constellation of frontal dominant polymicrogyria (especially perisylvian involvement), nodular periventricular heterotopias, intracranial cysts, underopercularization, and posterior fossa abnormalities with vermian hypoplasia, dysplasia of the cerebellar hemispheres, and tectal enlargement should prompt further evaluation for Aicardi syndrome. This should include an ophthalmological examination, evaluation for seizures and typical EEG abnormalities, and a skeletal survey to search for costovertebral segmentation defects.

That Aicardi syndrome has been reported only in females and 47,XXY males suggests that the causative gene is located on the X-chromosome [Hopkins et al., 1979]. Despite active research for many years [Prakash et al., 1999; Schaefer et al., 1996; Schaefer et al., 1997; Van den Veyver, 2002; Van den Veyver et al., 1998; Van den Veyver et al., 2004], the gene has proven elusive. The isolated nature of the disorder precludes linkage analysis. Efforts to identify a locus that contains the Aicardi syndrome gene by array-based comparative genomic hybridization for a copy number loss or gain have not yet yielded any genomic region of interest [Yilmaz et al., 2007] (and our unpublished data). An alternative approach for gene identification is the selection of functional candidate genes for mutation analysis. Considering the high gene content of the X-chromosome, a targeted, functional, or protein interaction-based approach might offer the best candidate genes first. The findings in two other X-linked conditions are relevant to our observations. The first is X-linked bilateral perisylvian polymicrogyria, which has been mapped to Xq28 [Villard et al., 2002]. The second is oculocerebrocutaneous syndrome (OCCS), an X-linked disorder primarily affecting males that has been reported to have extensive phenotypic overlap with Aicardi syndrome [Moog et al., 2005]. Our data suggest that this clinical overlap also includes abnormalities of the cerebellum and posterior fossa. The genes for neither of these syndromes possibly allelic to Aicardi syndrome have been identified. Finally, the comparison of the intracranial features of Aicardi syndrome to those of other conditions with neuronal migration abnormalities, autosomal or X-linked, or to those of mice with specific gene inactivations, may offer valid candidate genes from relevant developmental pathways. Such an approach has been successful for other neuronal migration defects [Barkovich et al., 2005; Lian and Sheen, 2006].

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Figure 1. T2-weighted axial images from six girls with Aicardi syndrome

All have gross cerebral asymmetry. Dashed circles indicate areas of polymicrogyria (PMG): 1A-C: perisylvian PMG with most extensive involvement in 1B; 1A and 1C show frontal PMG. The solid white arrows in 1A, 1C, and 1D point to single, nodular, periventricular heterotopias. The round marker in 1C points to confluent rows of periventricular heterotopias. Arrowheads point to subcortical heterotopias in the cerebellum (1E) and in the frontal regions (1F). Underdevelopment of the operculum is seen in figures 1A, 1B, and 1C. Asterisks point to a large posterior fossa cyst in 1B; a midline interhemispheric cyst in 1C and a left-occipital intraparenchymal cyst in 1F.

Figure 2. T2 weighted axial image showing thalamic heterotopia

Bilateral thalamic heterotopia are indicated by black arrowheads. This image also demonstrates right sided underopercularization with bilateral perisylvian polymicrogyria, left frontal polymicrogyria, left lateral ventricle nodular heterotopia, ventriculomegaly, and gross cerebral hemispheric asymmetry.

Figure 3. T1 weighted axial, sagittal, and coronal images from five girls with Aicardi syndrome. 3A and 3A¹ (from the same individual) show a multiloculated contrast-enhancing hyperintense cyst in the right lateral ventricle, resembling cysts associated with choroid plexus papillomas. 3B and 3C each illustrate a round hyperintense cyst in the right lateral ventricle and a midline/interhemispheric cyst with contrast enhancement in 3B (3C was a study without contrast). 3D shows a large interhemispheric cyst. 3E illustrates an extra-axial cyst in the posterior fossa (also seen in 1B) and an intraparenchymal cyst in the right cerebellar hemisphere.

Figure 4. Cerebellar and tectal abnormalities in Aicardi syndrome

All panels demonstrate inferior vermis hypoplasia. 4A and 4B show superior foliar prominence, 4B and 4C show large cisternae magna. 4A illustrates a normal sized tectum measuring 13 mm in length and 0.4 mm in width and 4B and 4C show tectal enlargement (3B = 16 mm × 7 mm and 3C = 15 mm × 6 mm).

Table I**Heterotopias**

Pattern	N = 23 (%)
Single nodules only	17(74)
Confluent rows only	1(4)
Mixed (single nodules and confluent rows)	5(22)
Anatomical Distribution	N = 23 (%)
Periventricular	23 (100)
Frontal horn	11 (48)
Body	17 (74)
Occipital horn	11 (48)
Temporal horn	11 (48)
3 rd Ventricle	1 (4)
4 th Ventricle	3 (13)
Subcortical	7 (30)
Frontal cerebral	1 (4)
Cerebellar	6 (26)
Unilateral	4 (17)
Bilateral	19 (83)

Table II

Frequency of Neuroimaging Findings in Aicardi Syndrome

Neuroimaging Features		Current Study	Palmer et al., 2006	Barkovich et al., 2001	Smith et al., 1996	Yamagata et al., 1990	Donnenfeld et al., 1989
Number of Patients (%)		23	18	5	20	12	18
Dysgenesis of the Corpus Callosum	Complete	16/23 (70)	13 (72)	4 (80)	12/19 (63)	10 (83)	13 (72)
	Partial	7/23 (30)	5 (28)	1 (20)	7/19 (37)	2 (17)	5 (28)
Heterotopias	Periventricular	23 (100)		5 (100)	3/15 (20)	1 (8)	9 (50)
	Subcortical	7 (30)	3 (17)		9/15 (60)		
Polymicrogyria		23 (100) F/FP	3 (17)*	5 (100) F/FP	R	1 (8)	
Colpocephaly		18 (78)			R		
Ventriculomegaly		18 (78)			14/14 (100)	4 (33)	
Cerebral Asymmetry		23 (100)	6 (33)	At least 1/5	11/18 (61)		
Cysts	Midline	17/21 (81)	6 (33)	5 (100)	10/17 (59) supratentorial	3 (25) arachnoid	
	Intraventricular	6/21 (29)	7 (39)		4/17 (24) cerebellar		
	Other	EA 8/21 (38) IP 2/21 (10)	PF 2 (11) Pin 1 (5)				
Cerebellar Anomalies		20/21 (95)		At least 1/5	4/17 (24) hypoplastic vermis, posterior fossa cysts	1 (8)	1 (6)
Other		12/18 (67) Opercular Abnormalities 10/18 (56) ↑ Tectal Size 1/23 (4) CPP	4(22) ↓ WM 1(5) Hypophysis Abnormality	5/5 (100) hypoplastic falx cerebri	3/16 (19) CPP	1 (8)HPP 3 (25) P 1 (8) CPP	1 (6) CPP

F=frontal, FP=frontoparietal, : R=reported, but number affected with this feature was not provided, EA=extra-axial, IP=intraparenchymal, PF=posterior fossa, Pin=pineal gland, WM= white matter, CPP=choroid plexus papillomas, HPP=hypoplasia of the corpus callosum, P=porencephaly

* reported as cortical dysplasias

Intracranial Cysts

iso=iso-intense on T1, Hyper=hyperintense on T1, CE=contrast enhancement, No CE = no contrast enhancement, AD=average diameter (cm);