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Ophthalmologic findings in Aicardi syndrome

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Abstract

Background—Aicardi syndrome is a rare X-linked disorder that has been characterized classically by agenesis of the corpus callosum, seizures, and the finding of chorioretinal lacunae. This triad has been augmented more recently by central nervous system and ocular findings. The goal of this study is to determine how frequently other ophthalmologic findings are associated with Aicardi syndrome.

Methods—A single ophthalmologist recorded the ocular and adnexal findings of 40 girls with this disorder at the annual meeting of an Aicardi syndrome family support group. For each subject, the examiner performed facial anthropometrics, portable biomicroscopy, and, where feasible, indirect ophthalmoscopy.

Results—The most common findings were chorioretinal lacunae in 66 (88%) of 75 eyes and optic nerve abnormalities in 61 (81%) of 75 eyes. Other less common findings included persistent pupillary membrane in 4 (5%) of 79 eyes and anterior synechiae in 1 of 79 eyes (1%).

Conclusions—Although the ophthalmic hallmark and defining feature of Aicardi syndrome is the cluster of distinctive chorioretinal lacunae surrounding the optic nerve(s), the spectrum of ocular, papillary, and retinal anomalies varies widely, from nearly normal to dysplasia of the optic nerve and to severe microphthalmos.

Aicardi syndrome is a rare genetic disorder with a worldwide prevalence of approximately 1 in 100,000.¹ It affects mostly girls, presumably inherited in an X-linked dominant fashion. Initially it was characterized by a classic triad of agenesis of the corpus callosum, chorioretinal lacunae, and seizures, predominantly infantile spasms. The full spectrum of this disorder has now been recognized to be much wider. Patients often have other central nervous system abnormalities, such as heterotopias, pachygyria, and polymicrogyria, midline cysts and cerebellar abnormalities, skeletal abnormalities, gastrointestinal

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Study conducted at Baylor College of Medicine.

dysfunction, and usually significant developmental and intellectual disability. They may also be at risk for developing rare tumors compared to healthy children of similar ages.²

While the hallmark ophthalmologic finding of Aicardi syndrome has been the presence of chorioretinal lacunae,³ a number of other ophthalmologic features have been considered typical of the syndrome. Microphthalmos, anomalous retinal vessels, retinal detachment, dysplasia or coloboma of the optic nerve, persistent pupillary membrane, iris synechiae, posterior staphylomas of the iris or choroid, and cataracts, are seen with varying frequency in affected individuals. Morning glory–like anomalies, involving ring-shaped pigment deposits surrounding or within a colobomatous or staphylomatous optic nerve head, have also been described.^{4–5} We are aware of no similar large-scale evaluation of Aicardi syndrome cases by a single clinician with description of the clinical ophthalmologic features that often factor so prominently in establishing a diagnosis. Our study endeavors to expand the current understanding of Aicardi syndrome by reporting the ophthalmologic features of 40 girls and investigating a possible correlation with aspects of neurological and developmental severity.

Subjects and Methods

Subjects were evaluated during a family conference of the Aicardi Syndrome Foundation, a family support group (<http://www.aicardisyndrome.org/site/node/13>). That conference included families with more and less severely affected persons. There is no fee for membership, and low-income families can receive financial support to attend the conference.

Subjects provided informed consent to participate in our research study and sent or brought us their medical records; some signed a release form to permit our requesting medical records from their physicians. Subjects were seen by an experienced clinical geneticist, a pediatric neurologist, and an experienced ophthalmologist. Other findings from this survey have been reported previously.²

We characterized the frequency and variations of the significant ophthalmologic findings relevant to the clinical diagnosis of Aicardi syndrome with an ophthalmologic evaluation of 40 affected girls as part of a multidisciplinary team survey.² The research protocol was approved by the Baylor College of Medicine Institutional Review Board for Human Subject Research, and all participants, parents, or legal guardians of the research participants provided informed written consent. Subjects (and their families) sent or brought us their medical records.² For each participant, the diagnosis of Aicardi syndrome was confirmed by ophthalmological evaluation, review of the medical records, related neuro-imaging studies, and parental interview (n = 40), augmented by relevant physical and neurological examinations (n = 20). The patients were evaluated by a multidisciplinary team including an experienced clinical geneticist, a pediatric neurologist, and an experienced ophthalmologist. and the diagnosis was confirmed by consensus based on clinical criteria set forth by Aicardi.⁶ The facial features of the patients described in this paper have been reported previously.²

Ophthalmologic Evaluation

A single ophthalmologist evaluated each girl with portable diagnostic equipment. The examination included a note on the external, adnexal, anthropometric, and binocular biomicroscopic examination and dilated retinal examination by indirect portable equipment. The globe measurement was performed with a handheld millimeter ruler held close to the globe in the horizontal meridian, with the greatest measurement estimated by comparison. Due to the nonclinical environment, biometry and precise measurements were not feasible.

We specifically attempted to note the presence or absence of the following known features: microphthalmia (the measured horizontal diameter of the globe <20 mm),⁷ persistent pupillary membrane(s), anterior synechiae, iris colobomata, chorioretinal lacunae, colobomata of the optic nerve (near “crater holes” of massively malformed nerve heads), pale or atrophic optic nerves, optic nerve hypoplasia, optic nerve dysplasia, pseudoadenomatous proliferation of the retinal pigment epithelium, papilla nigra (extensive hyperpigmentation within the sclera-choroidal rim), retinal detachment, and abnormalities of the retinal vessels. Refraction was not attempted and retinal photographs were not taken during the examinations since the children were not sedated and they were examined in a nonclinical setting. Five eyes were so severely microphthalmic that no detailed anterior segment analysis was feasible and no posterior segment could be seen. Therefore these could not be counted in these analyses.

The data were entered into a secure Microsoft Access database for storage and efficient retrieval. Descriptive statistics defined the specific features. With Microsoft Excel, the fraction of eyes with each scored feature of interest was calculated.

Results

Of the 40 girls enrolled, 31 (77.5%) were younger than 10 years of age, and 2 were younger than 1 year. The median age was 5 years, and the mean age was 5.7 years at the date of examination. Of these 40 subjects, 39 had seizures within the first 6 months of life. All 40 had partial or complete agenesis of the corpus callosum.

Two participants were examined in a private ophthalmology office; the remainder were evaluated at the conference. Chorioretinal lacunae, followed by abnormalities of the structure of the optic nerve, were the most common ophthalmic findings. Of 75 evaluated eyes, 66 (88%) were found to have lacunae. Abnormal retinal vessels were observed in 1 (1.3%) of the left eyes of the 75 eyes examined; no examined eyes were found to have retinal detachment.

The fractions of children with various optic nerve abnormalities are shown in Table 1, divided by laterality. Of the 75 eyes, 61 (81%) were found to have at least one form of optic nerve abnormality (Table 2). The most common optic nerve anomaly observed was coloboma, observed in 29 (39%) out of 75 eyes evaluated.

Severe microphthalmia limited the ability to examine some eyes fully. In the 40 individuals surveyed, microphthalmia occurred in 9 right eyes (22.5%) and 5 left eyes (12.5%). Microphthalmia was bilateral in 4 individuals and was more severe on the right in each participant with bilateral microphthalmos. In 4 children, the severity of the microphthalmos in the right eye made evaluation of the retina and optic nerve on that side impossible. The extent of microphthalmos of the left eye precluded evaluation of the retina and optic nerve in only one subject. Of note, in addition to having a horizontal globe diameter of <20 mm, all 14 individuals had a horizontal corneal diameter was also <10 mm. Other findings seen with less frequency in this series included persistent pupillary membrane, observed in 3 (7.5%) of 40 right eyes and 1 (2.5%) of 39 left eyes. Anterior synechiae were seen rarely (1 of 40 right eyes examined and left eyes). These iris anomalies were developmental and no eye showed evidence of an inflammatory response. Classic iris colobomata were rare, absent in the 40 right eyes, and seen in only 1 of the 39 left eyes.

Discussion

Ophthalmologists were likely the first physicians to describe Aicardi syndrome^{8,9}; among the earliest is a case report published in 1946^{10,11} of a girl whose clinical description and

findings at autopsy were consistent retrospectively with Aicardi syndrome. In 1965 Aicardi, for whom it is now known eponymously, first described the broader aspects of the syndrome.¹²

The clinical presentation of Aicardi syndrome is variable. Thanks to improvements in imaging^{13–15} and detailed pathological evaluation¹⁶ we have learned that the central nervous system phenotype is more complex than originally believed. Agenesis of the corpus callosum may be partial or complete, and affected individuals may exhibit neurological findings, including microcephaly, microgyria, cysts, cortical heterotopia, psychomotor or developmental delay, axial hypotonia, bilateral pyramidal signs, and swallowing difficulties.^{10,17} Aicardi syndrome is often accompanied by severe complex seizures and anomalies on electroencephalography (EEG).¹⁸ Many small series and case reports further cite the presence of skeletal anomalies in affected girls.^{17–19} Up to 5% of affected girls have tumors or other disturbances in tissue differentiation.²⁰ Choroid plexus papillomas, arachnoid cysts, and retrobulbar cysts in the central nervous system have reported. Outside the central nervous system, benign teratomas in the soft palate, palatal hemangioma, gastric polyposis, scalp lipomas, angiosarcomas, embryonal carcinomas, and hepatoblastomas have all been observed.²⁰

Ophthalmologic findings in patients with Aicardi syndrome have been described earlier, but all have been small series or have not resulted from systematic evaluation by a single ophthalmologist. We found that the two most common findings were chorioretinal lacunae and optic nerve colobomata. Microphthalmia was present in 13 eyes and was more prevalent on the right side than the left. Severe microphthalmia prevented evaluation of the retina and optic nerve in only 5 eyes. Recently Cabrera and colleagues²¹ described the eye findings and brain MRI findings of 26 children with Aicardi syndrome. In that study, significantly more brain lesions were noted on the right side than on the left side of the brain, and it was more likely for ocular lesions to be on the right side compared to the left.

We found unilateral or bilateral lacunae in 39 of the 40 girls. These present as rounded, flat lesions of the retina found mostly in the peripapillary area of the posterior pole and are usually yellow or white because of the excavation of the retinal pigment epithelium through the choroid to the bare sclera. The lacunae vary in size from half to three times the disk diameter and have not been documented to change in number or size over time.^{22,23} They are not associated with retinal edema or subretinal fluid and in general they do not affect the vision of the affected individual unless they affect the central foveal area. Thus despite the often dramatic aspect of these lesions, total blindness is rare. Histologically, the lesions are limited to the retinal pigment epithelium and choroid; photoreceptor folds at the edges of the lacunae have been reported.^{19,24} Though sometimes considered pathognomonic of Aicardi syndrome, chorioretinal lacunae have also been found in patients with oral-facial-digital syndrome, and lacunae are absent in some girls with Aicardi syndrome. McMahon and colleagues²⁵ point out notable differences between the lacunae associated with Aicardi syndrome and the hypopigmented and nonpigmented islands on the retinal pigment epithelium that occur in other conditions such as high myopia, toxoplasmosis, and the geographic atrophy of the dry form of age-related macular degeneration. These other conditions often have additional features, including sclerosis of choriocapillaris, fibrovascular proliferation, Bruch's membrane anomalies, fibrous metaplasia, and inflammatory cells. Another difference is the more distinct margin of the Aicardi-associated lacunae.²⁵

Based on our current knowledge of Aicardi syndrome as an isolated, likely malelethal condition, seen only in females or in males with a 47,XXY karyotype, a mutation at a locus undergoing X-inactivation is suspected as the causative genetic factor. Mutations in genes

that undergo X-inactivation have been found in various developmental disorders with a wide spectrum of phenotypes.²⁶ Among these are Rett syndrome (MECP2), alpha-thalassemia with mental retardation (ATRX), incontinentia pigmenti (IKBKG, also known as NEMO), and X-linked mental retardation with epilepsy (ARX). The variable severity and phenotypic presentation characteristic of Aicardi syndrome possibly could be explained by the presence of a mutation in a gene that undergoes X-chromosome inactivation (XCI). During early embryogenesis in females, either the maternally or paternally derived chromosome is “turned off” in each cell to compensate for the presence of only a single chromosome in males. The choice of which chromosome is turned off in a cell is initially random, but is maintained in all of its daughter cells upon cell division. Typically in “random” XCI, approximately 50% of cells have the maternally derived chromosome turned off, and 50% have the paternally derived chromosome is turned off. Skewed inactivation is present if this ratio favors one or the other chromosome. It can be seen in diseases caused by a mutation on one of the chromosomes, presumably because of reduced survival of cells carrying a deleterious mutation on their “active” chromosome. The variable phenotypic presentations and severity of X-linked disorders may be explained by the percentage of mutation-containing chromosomes that are turned off; the smaller the percentage, the more severe the disease. This is supported by our data that there is increased skewing of XCI in girls with Aicardi syndrome, compared to the general population.²⁷

Detailed clinical characterization of a large cohort of patients, including careful description of ophthalmologic features presented here, may provide guidance regarding the best research direction to pursue for the identification of this devastating neurodevelopmental disorder. We feel that the subject population that we evaluated is representative. Although the membership numbers of the Aicardi Syndrome Foundation are unknown, patients with varying severity of involvement were members, and low-income families receive financial support to attend. Still, because this was not a population survey, it is possible that the study population is self-selected and thus possibly biased. Because the gene has not yet been identified, we cannot rule out the possibility that phenocopies were included in this cohort. Until a gene is identified, better characterization of the phenotype may assist physicians to diagnose this phenotypically variable condition.

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Table 1

Optic nerve anomalies

	Number of eyes evaluated with anomaly (percentage) ^a		
	Right eyes (n = 36)	Left eyes (n = 39)	Total (n = 75)
Pale/atrophic	3 (8.3)	1 (2.6)	4 (5.3)
Hypoplasia	0 (0.0)	1 (2.6)	1 (1.3)
Coloboma	12 (33.3)	17 (43.6)	29 (38.7)
Severe dysplasia	7 (19.4)	6 (15.4)	13 (17.3)
Pseudoadenomatous proliferation of RPE	6 (16.7)	5 (12.8)	11 (14.7)
Papilla nigra	1 (2.8)	3 (7.7)	4 (5.3)
Glial proliferation	9 (25)	5 (12.8)	14 (18.7)
Staphyloma	1 (2.8)	3 (7.7)	4 (5.3)

RPE, retinal pigment epithelium.

^aFour right eyes and one left eye could not be evaluated due to severe microphthalmia.

Table 2

Frequency of multiple optic nerve anomalies

Number of anomalies ^a	Number of right eyes (percentage)	Number of left eyes (percentage)
0	7 (19.4)	7 (17.9)
1	19 (52.8)	23 (60)
2	10 (27.8)	9 (23.1)

^aFour right eyes and one left eye could not be evaluated due to severe microphthalmia.