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Laterality of brain and ocular lesions in Aicardi Syndrome

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Abstract

This study reports a large case series of children with Aicardi syndrome. A new severity scoring system is established to assess sidedness of ocular and brain lesions. Thirty-five children were recruited from Aicardi syndrome family conferences. All children received dilated ophthalmologic exams, and brain MRI's were reviewed. Ocular and brain MRI Aicardi lesion severity scores were devised. A linear mixed model was used to compare each side for the ocular and brain MRI severity scores of Aicardi associated disease. Twenty-six children met inclusion criteria for the study. All subjects were female, ages 3 months to 19 years. Rates per child of optic nerve coloboma, severe lacunae, and microphthalmos in one or both eyes (among those with complete fundus exams available) were 10/24 (42%), 8/22 (36%), and 7/26 (27%), respectively. Ocular and brain MRI asymmetry was found in 18% (4/22) and 58% (15/26) of subjects, respectively, with more right sided brain lesions than left (V=52, P=0.028). A significant correlation between sidedness of brain disease and microphthalmos was seen (T = 2.54, P = 0.02). This study substantiates the range and severity of Aicardi syndrome associated ophthalmologic and brain MRI lesions from prior smaller case series.

Introduction

Aicardi syndrome is defined by the clinical triad of infantile spasms, agenesis of the corpus callosum, and chorioretinal lacunae [1]. Affected individuals tend to have severe mental retardation and decreased life expectancy, although severity of disease is variable. The disorder appears to affect nearly exclusively females with a small handful of previous case reports in males primarily with XXY karyotypes [2-6]. Aicardi syndrome is, therefore,

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hypothesized to be X-linked dominant, although the exact genes involved have not yet been isolated and the pathogenesis is poorly understood [2].

Ocular findings in Aicardi syndrome include characteristic chorioretinal punched out lesions, known as lacunae, which vary in size and location but are most often peripapillary. They are typically round or ovoid, yellowish or whitish, flat, have variable pigment at their borders and correspond with histopathologically identified areas of hypopigmented retinal pigment epithelium with overlying disorganized retina [7]. Iris and optic nerve colobomas are common, as are persistent fetal vasculature and microphthalmos [8], which are typically unilateral.

Along with corpus callosum agenesis, brain involvement in Aicardi syndrome includes periventricular and subcortical heterotopias (probably due to arrested radial migration of recently born neurons), polymicrogyria, choroid plexus papillomas, cerebellar dysmorphia and both posterior fossa and type II interhemispheric cysts [2].

A hallmark of Aicardi syndrome is the variability and asymmetry of both brain and ocular findings [7, 9, 10]. However, no previous study has established a correlation between sidedness of ocular and brain findings. Here we report a large case series of Aicardi syndrome patients in which we specifically investigate whether there is a correlation between asymmetric lesions in the eye and brain. Laterality of ocular and brain disease may provide a better understanding of disease pathogenesis.

Study Design and Methods

Subjects

Fifteen subjects were recruited in 2006 followed by 20 additional subjects in 2008, for a total of 35 subjects recruited for a one-time examination. Families registered for the National Aicardi Syndrome conferences were offered the opportunity to participate in research. Medical records, including a copy of the brain MRI (magnetic resonance imaging), were retrieved for each subject. Subjects were included with a previous diagnosis of Aicardi syndrome. Children were excluded if medical records and/or brain MRI were unavailable or if their families refused dilating eye drops. Children with an unclear diagnosis based on our assessment of dilated fundus examination, clinical findings, and imaging were also excluded. Diagnostic criteria used in this study are described by Aicardi et al [2]. Children were not excluded if microphthalmos or poor pupillary dilation prevented a good fundus examination; however, all efforts were made to obtain previous records of ophthalmologic exams, particularly examinations under anesthesia, and fundus photographs. Insitutional review board approval was obtained, including compliance with HIPAA regulations. Informed consent was obtained by participants' legal guardians.

Procedures

At each conference, a single examiner (MC or BW) performed all eye examinations without knowledge of the neurological examination or MRI results. The anterior segments were examined with a penlight exam, documented and photographed. Children were then given one drop of tropicamide 1% and phenylephrine 2.5% in each eye. Drops were repeated 15 minutes later if inadequate dilation was noted. A 30 Diopter lens was used for all fundus indirect ophthalmoscopy and findings were noted. Whenever possible, portable fundus photography was obtained. After examinations were completed, the examiner reviewed any prior ophthalmology reports to identify inconsistencies and fill in missing data.

Blinded to MRI results, a pediatric neurologist (ES) performed a neurological examination of all subjects, assessing for motor and language function. Motor and language impairment

were classified in the following way, accounting for age: Motor impairment: NA = too young, potential to achieve motor milestones (<11 months); Mild = walks; Mild/Moderate = rolls, potential to walk (<4 years and rolled by 11 months); Moderate = rolls, no potential to walk (<4 years or did not roll by 11 months); Severe = does not walk or roll. Language impairment: NA = too young, potential to have words (<16 months or <4.5 years and cooed by 16 months); Mild = puts words together; Mild/Moderate = has words, potential to put words together (<6.5 years); Moderate = has words, no potential to put them together (>6.5 years); Severe = no words (>4.5 years); Profound = no cooing or words (>16 months).

A pediatric neurologist (ES) and neuroradiologist (AJB) read all brain MRIs, blinded to patient identity and ocular findings. All scans were evaluated for the extent of cerebral commissure (corpus callosum, anterior commissure, hippocampal commissure) anomalies, presence or absence of malformations of cortical development including heterotopia (subcortical and periventricular) and polymicrogyria [11], presence of midbrain/hindbrain anomalies [12], anomalies of the choroid plexus, and extraparenchymal cysts. Consensus between the two observers was established for each MRI.

An ocular severity score was derived from relative Pearson correlations between each of the 3 ocular findings and clinical neurological outcomes in a previous case series of 14 patients [7]. The Pearson correlation of each finding to clinical severity of neurological disease in that study for optic nerve coloboma, microphthalmos, and chorioretinal lacunae were 0.146, 0.367, and 0.654, respectively. Roughly based on these correlation coefficients and diagnostic categories devised by Menezes et al [7], the point system was determined in the following way: presence or absence of optic nerve coloboma (1 point), presence or absence of microphthalmos (2 points), and severity of retinal lacunae - none (0 points), all lacunae less than 1 disk diameter in size and ≤4 in number (1 point), largest lacunae 2-3 disk diameters in size or 4-7 in number (2 points), largest lacunae >3 disk diameters in size or >7 in number (3 points) regardless of location. Although iris coloboma was not reported in the prior case series, it was included in the grading system as a known Aicardi syndrome associated ocular finding. The presence or absence of iris coloboma was assigned 1 point. Due to the almost ubiquitous presence of nonspecific optic nerve anomalies (dysplastic, hypoplastic, pigmented) in Aicardi syndrome [7], these were excluded from the scoring. While chorioretinal colobomas not involving the optic nerve have been reported in Aicardi syndrome, these were excluded from scoring in the present study because they have been documented infrequently (no cases in the present study nor in that of Menezes et al) [7].

A grading system was also devised for lateralizing cerebral cortex MRI findings based on both size and number of lesions and the relative clinical significance of each finding, with the notion that polymicrogyria and subcortical heterotopias were more likely to have adverse effects than periventricular heterotopias [13]: Polymicrogyria (<1 lobe involvement 1 point, full lobe involvement 3 points, ≥2 lobe involvement 5 points), periventricular heterotopias (1-2 nodules 0.5 point, 3-5 nodules 1 point, >6 nodules 2 points), presence or absence of subcortical heterotopias (5 points), and dysplasia NOS (3 points), defined as gyration and sulcation abnormalities not consistent with definite polymicrogyria.

Statistics

The sum of severity scores for each ocular finding was used to determine the ocular severity score. The brain MRI severity score was determined from the sum of each brain finding score. A linear mixed model was used to compare the same side's ocular severity scores to that side's brain MRI severity scores adjusted for 2 observations per person. A p-value of <0.05 was considered statistically significant.

Results

A total of 35 subjects were recruited and examined at Aicardi syndrome conferences, 15 in 2006 and 20 in 2008. All subjects were female, ages 3 months to 19 years (median age 6). Fundus photos were obtained for 12 subjects. Twenty-six subjects met study criteria and were included in the final analysis. Three subjects were excluded because MRI and/or ocular findings were found not to be consistent with Aicardi syndrome. Excluded patients included one 9 year old who lacked chorioretinal lacunae and a 10 year old who had a complete corpus callosum on brain MRI. Six subjects were excluded because MRI's were not available or of poor quality. One 6 year old was excluded because the ocular examination results were lost.

Twenty-four of 26 subjects had complete or partial agenesis of the corpus callosum on brain MRI and 2 subjects had a thin corpus callosum. Twenty-four of 26 subjects had infantile spasms and 2 had unavailable EEG findings. All subjects were taking anti-epilepsy medications. Table 1 shows the ocular and brain MRI severity scores for each patient along with motor and language impairment scores, accounting for age. Fifty-three percent (10/19) of subjects with measurable motor or language impairment scores had severe or profound impairment in one or both categories.

Table 2 shows the results for ocular findings compared to a previous study by Menezes et al [7]. All 7 cases of microphthalmos were monocular. Including only those subjects with views to the fundus, ocular asymmetry, defined as an ocular severity score point difference of 3 or more between the two eyes, was found in 18% (4/22) of subjects in the present study. Completely monocular chorioretinal lacunae were seen in 18% (4/22) of subjects. Thirty-eight percent (10/26) of subjects were able to fix and follow with at least one eye, 38% (10/26) of subjects had no fix and follow behavior in either eye, 12% (3/26) of subjects had visual acuity of 20/40 or better in at least one eye, and 12% (3/26) of subjects did not have visual acuity data available.

The frequencies of brain MRI findings are shown in Table 3 compared to 2 recent case series. Brain MRI asymmetry, defined as a difference of 3 or more between the total severity scores of each hemisphere, was seen in 57.7% (15/26) of subjects.

A mixed model found a statistically significant correlation between the ocular severity score and brain MRI severity score for a particular side, accounting for two findings from each subject ($T = 2.19$, $P = 0.04$). In this analysis, 4 subjects with no view of the fundus were assumed to have maximal severity in funduscopic findings (3 out of 4 were microphthalmic). In this study, 4 out of 4 microphthalmic eyes with views of the fundus were found to have severe posterior segment disease. When we assumed minimal disease for eyes with no view of the fundus (lacunae and coloboma score of zero), the correlation between ocular and brain MRI severity score sidedness only trended toward significance ($T = 1.526$, $P = 0.14$).

Among ocular findings, the microphthalmos severity score was statistically significantly correlated with brain MRI sidedness ($T = 2.54$, $P = 0.02$). Optic nerve coloboma, iris coloboma, and retinal lacunae were not correlated with sidedness of brain disease (data not shown). No individual brain MRI finding was independently correlated with the sidedness of ocular severity scores (data not shown). Significantly more disease was found in the right brain in MRIs of this cohort compared to the left brain (Wilcoxon test: $V=52$, $P=0.028$). No significant tendency toward one particular side was seen in ocular disease although a trend toward right-sided disease was present ($V=47.5$, $P=0.298$).

Discussion

This case series found significant asymmetry of both ocular and brain lesions of Aicardi syndrome. Previous case series have documented laterality of ocular findings [7, 14, 15]. Similar to one previous study, this study found marked asymmetry in all patients with microphthalmos [7]. Eighteen percent of subjects in the current study had monocular lacunae. Other studies have demonstrated completely monocular chorioretinal lacunae in 8% to 21% of patients with Aicardi syndrome [1, 7, 14]. An association between brain and eye lesion laterality has not been previously assessed. Sidedness of microphthalmos was associated with sidedness of brain lesions in this series. A correlation between overall sidedness of ocular and brain disease is more difficult to ascertain due to the lack of adequate fundus examination in 4 subjects (3 of whom had microphthalmos, which can be associated with a high rate of posterior disease). We suspect that a correlation exists ($T = 2.19$, $P = 0.04$, when assuming maximal posterior segment disease in all subjects lacking a view of the fundus), but this would likely be largely due to microphthalmos as no other ocular findings were independently correlated with brain MRI laterality.

This study found a predilection for right-sided brain lesions on MRI. Periventricular heterotopias are known to occur more commonly in the right hemisphere, due to later migration of right-sided neuroblasts [16]. A previous study characterizing 23 brain MRI's of children with Aicardi syndrome noted that polymicrogyria tended to be asymmetric; however, that study found lesions most commonly in the left frontal lobe, rather than the right. That study also found asymmetric periventricular heterotopias in all subjects, although not with a particular side preference [9]. Put together, these studies strongly suggest that asymmetric brain involvement is a common finding in Aicardi syndrome. Asymmetric specification of function is known to occur in the brains of normal individuals, for example with semantic language centers most commonly occurring on the left side, and language prosody localized more heavily to the right hemisphere. This may be secondary in part to asymmetric gene expression of the right and left hemispheres during development, as evidenced by asymmetric cortical mRNA expression seen in embryonic human brains in one prior study [17]. Development of asymmetric abnormal pathology may therefore reflect timing of disease development when normal asymmetric gene expression is occurring.

The frequency of ocular findings in this study was similar to that of the series of 14 patients reported by Menezes *et al*, except for a higher frequency of ocular colobomas in the present study (10/24, 42% in the present study compared to 3/14, 21% from the Menezes *et al* study) [7]. (see Table 2). Menezes *et al* did not report iris colobomas while the present study found 2 cases, including one that was temporally located, which has not been previously reported in Aicardi syndrome. Brain anomalies on MRI were found at a similar rate in the present study compared to recent previous reports [9, 18, 19]. (see Table 3) The lower quality of MRI's prior to 2000 may explain a decreased frequency of lesions reported in the literature prior to 2000 [20-22].

A wide range of severity in neurological functioning was seen in this case series, as has been seen in prior reports of patients with Aicardi syndrome [1, 7, 23-25]. (see Table 1) Fifty-three percent (10/19) of subjects with measurable motor or language impairment scores had severe or profound impairment in one or both categories. An age dependent scale was used in the present study, which is likely more accurate than other scales in determining language and motor impairment among widely disparate ages. Interestingly, severity of MRI findings did not always correlate with severity of phenotypic outcomes, as best illustrated by subject number 7 and subject number 9, both of whom had MRI severity scores that did not match the severity of language and motor findings. Such findings suggest that other factors may

contribute to functional outcomes, which are not detectable by MRI, such as possible deficits in interneuron development.

Although a purported gene has not been identified to date, a genetic origin for Aicardi syndrome is suspected. An X-linked genetic mutation is strongly implicated in the pathogenesis due to the appearance of disease exclusively in females, with the few male cases found to have a 47, XXY genotype [2-6] although reported exceptions exist with an XY genotype [26-28]. Some authors have suggested that X chromosome inactivation may explain the variability and asymmetry seen in the phenotype of this disease, supported by a higher than normal prevalence of skewed X chromosome inactivation in peripheral lymphocytes among Aicardi patients, particularly those with worse neurological status [24, 29]. Known to occur at 5 weeks gestation, X chromosome inactivation would not be expected to lead to developmentally shared lesions in the eye and brain, as these structures have already differentiated from one another by 4 weeks gestation. In this study, microphthalmos was associated with sidedness of Aicardi associated brain lesions, however X chromosome inactivation may still play a role in other Aicardi associated ocular and brain anomalies. We hypothesize that the developmental process that is disrupted in Aicardi syndrome is occurring broadly within the developing neuraxis primarily at 3-4 weeks gestation. At this time, the optic cup is forming from what will become the diencephalon, and the prosencephalon is forming more generally from the anterior neuraxis. It is possible that inducing structures like the anterior visceral endoderm (AVE) and signaling molecule families like Wnt's, retinoids and fibroblast growth factors (FGF) may play a role [30]. Thus, microphthalmos and colobomata likely relate to this early disruption of development. In contrast, the variable pattern and location of chorioretinal lacunae and other Aicardi associated lesions may occur at a later time because of X chromosome inactivation.

There were some limitations to this study. Patients were selected for this study based on a clinical definition of Aicardi syndrome, rather than a molecular definition, therefore we have no certainty that all children in our series had the same pathogenesis of disease. In addition, Aicardi syndrome may be caused by a mutation in more than one gene or variable isolated mutations of the same gene, therefore heterogeneous genotypes and phenotypes may confuse the outcomes of this study. Subjects recruited from the Aicardi Syndrome conferences may introduce selection bias if, for example, families who choose to participate tend to have children with more severe disease. Prior studies with other recruitment methods had similar rates of ocular and brain MRI findings, suggesting that selection bias is less significant. Finally, although Aicardi associated lesions are thought to be static with time, at least one previous study documents changes in the size of fundus lesions over time with disappearance of a lacunae and development of a new retinal coloboma in one patient [31]. Colobomas are known to represent failed embryonic optic fissure closure, calling into question the validity of an observed acquired coloboma later in life. Nonetheless, without longitudinal follow up, it is not known if some of the subjects in the present study would have growing or shrinking lesions as they age which may alter asymmetry over time.

In conclusion, this study is the largest series to our knowledge of Aicardi syndrome patients with both ophthalmologic and brain MRI findings reported [22, 25, 31, 32]. These results substantiate prior smaller case series looking at ophthalmologic and brain MRI Aicardi associated lesions. A correlation between brain disease and microphthalmos sidedness was seen in this case series. This work expands our understanding of phenotypic variance in other X linked disorders. Knowledge gained from this study may assist future work in gene discovery in other disorders as well as in Aicardi syndrome. Identifying the responsible gene in Aicardi syndrome is important for prenatal diagnosis, prognosis, and future development of medical therapies.

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Table 1

Ocular and brain MRI severity scores for Aicardi syndrome associated findings with motor impairment and language impairment levels.

N	Age	Side	Ocular					Brain MRI					Motor††	Language‡‡
			C*	M†	L‡	IC§	Total Ocular Score	PMG//	PVH¶	SCH#	Dysplasia NOS**	Total brain MRI score		
1	6yr	R	1	2	3	0	**6**	5	2	5	0	**12**	Mod	Severe
		L	1	0	3	0	**4**	3	2	2.5	0	**7.5**		
2	3yr	R	0	0	2	0	**2**	0	0	0	0	**0**	Mod	Mild/Mod
		L	0	0	2	0	**2**	0	0	0	3	**3**		
3	7mo	R	0	0	3	1	**4**	5	1	5	0	**11**	NA	NA
		L	0	0	3	0	**3**	1	2	0	0	**3**		
4	10yr	R	0	0	2	0	**2**	5	0	0	0	**5**	Severe	Profound
		L	NA	2	NA	0	**NA**	5	0	0	0	**5**		
5	14yr	R	0	0	2	0	**2**	1	0	0	0	**1**	Mild	Mild
		L	0	0	2	0	**2**	1	0	0	0	**1**		
6	4yr	R	0	0	2	0	**2**	0	0	0	3	**3**	Mild	Mild/Mod
		L	0	0	2	0	**2**	0	0	0	0	**0**		
7	6mo	R	0	0	2	0	**2**	5	2	5	0	**12**	Mild/Mod	NA
		L	1	0	2	0	**3**	1	0	0	0	**1**		
8	3yr	R	0	0	1	0	**1**	5	2	0	0	**7**	Mild/Mod	NA
		L	0	0	1	0	**1**	5	2	0	0	**7**		
9	6mo	R	1	0	1	0	**2**	1	2	0	0	**3**	Mod	Profound
		L	1	0	3	0	**4**	1	2	0	0	**3**		
10	1yr	R	0	0	2	0	**2**	5	2	0	0	**7**	NA	NA
		L	0	0	2	0	**2**	3	2	0	0	**5**		
11	6mo	R	0	0	1	0	**1**	0	0.5	0	0	**0.5**	Mod	NA
		L	0	0	2	0	**2**	0	1	0	3	**4**		
12	8yr	R	1	0	1	0	**2**	0	1	2.5	0	**3.5**	Mod	Mild
		L	0	0	1	0	**1**	0	1	5	0	**6**		
13	4yr	R	0	0	0	0	**0**	3	2	0	0	**5**	Mild/Mod	Mild/Mod
		L	0	0	2	0	**2**	3	0	0	0	**3**		
14	15yr	R	0	0	2	0	**2**	0	2	0	3	**5**	Mild	Mod
		L	0	0	2	0	**2**	0	2	0	3	**5**		

N	Age	Side	Ocular					Brain MRI					Motor††	Language‡‡
			C*	M†	L‡	IC§	Total Ocular Score	PMG‖	PVH¶	SCH#	Dysplasia NOS**	Total brain MRI score		
15	8yr	R	0	0	1	0	**1**	0	2	5	0	**7**	Mild	Mild
		L	0	0	1	0	**1**	0	1	0	0	**1**		
16	9yr	R	0	0	1	0	**1**	1	0.5	5	0	**6.5**	Mod	Severe
		L	0	0	1	0	**1**	5	2	5	0	**12**		
17	3yr	R	0	0	2	0	**2**	0	1	0	0	**1**	Mod	NA
		L	0	0	2	0	**2**	0	2	0	0	**2**		
18	9yr	R	NA	2	NA	0	**NA**	5	2	5	0	**12**	Severe	Profound
		L	1	0	1	0	**2**	1	1	0	0	**2**		
19	19yr	R	0	0	0	0	**0**	0	2	2.5	0	**4.5**	Mild	Mild
		L	0	0	1	0	**1**	0	2	5	0	**7**		
20	3yr	R	NA	2	NA	0	**NA**	0	2	5	3	**10**	Severe	Profound
		L	1	0	2	0	**3**	0	1	0	0	**1**		
21	2yr	R	NA	0	NA	0	**NA**	0	1	5	0	**6**	Mild	Severe
		L	NA	0	NA	0	**NA**	0	1	5	3	**9**		
22	6yr	R	1	0	2	0	**3**	5	2	5	0	**12**	Severe	Profound
		L	1	2	3	0	**6**	5	2	0	0	**7**		
23	11yr	R	1	2	3	1	**7**	0	2	0	0	**2**	Mild	Mild
		L	0	0	1	0	**1**	0	0.5	0	0	**0.5**		
24	7yr	R	1	0	3	0	**4**	0	0	5	3	**8**	Mild	Severe
		L	0	0	1	0	**1**	0	0	2.5	0	**2.5**		
25	4yr	R	0	2	3	0	**5**	5	2	5	0	**12**	Severe	NA
		L	0	0	3	0	**3**	3	1	0	0	**4**		
26	3mo	R	1	0	3	0	**4**	5	2	0	0	**7**	NA	NA
		L	0	0	0	0	**0**	1	0.5	0	0	**1.5**		

N = subject number
C = optic nerve coloboma
M = microphthalmos
L = retinal lacunae
IC = iris coloboma
PMG = polymicrogyria
PVH = periventricular heterotopia
SCH = subcortical heterotopia
Dysplasia NOS = Dysplasia not otherwise specified

NA = not available; for ocular findings, fundus examination could not be obtained, for motor or language impairment subject was too young for categorization

[*] Presence or absence of optic nerve coloboma (1 point)

[†] Presence or absence of microphthalmos (2 points)

[‡] Severity of retinal lacunae - none (0 points), all lacunae less than 1 disk diameter in size and ≤4 in number (1 point), largest lacunae 2-3 disk diameters in size or 4-7 in number (2 points), largest lacunae >3 disk diameters in size or >7 in number (3 points) regardless of location

[§] Presence or absence of iris coloboma (1 point)

[//] Polymicrogyria (<1 lobe involvement 1 point, full lobe involvement 3 points, ≥2 lobe involvement 5 points)

[¶] Periventricular heterotopias (1-2 nodules 0.5 point, 3-5 nodules 1 point, >6 nodules 2 points)

[#] Presence or absence of subcortical heterotopias (5 points)

[**] Presence of Dysplasia NOS (3 points)

[††] Motor impairment: NA = too young, potential to achieve motor milestones (<11 months); Mild = walks; Mild/Mod = rolls, potential to walk (<4 years and rolled by 11 months); Mod = rolls, no potential to walk (<4 years or did not roll by 11 months); Severe = does not walk or roll.

[‡‡] Language impairment: NA = too young, potential to have words (<16 months or <4.5 years and cooed by 16 months); Mild = puts words together; Mild/Mod = has words, potential to put words together (<6.5 years); Mod = has words, no potential to put them together (>6.5 years); Severe = no words (>4.5 years); Profound = no cooing or words (>16 months)

Table 2

Results of ocular findings in the present case series compared to a previous case series by Menezes et al. Number of patients with finding/Total number of patients with that finding detectable (%)

	Present study	Menezes et al [2006]
Total number of patients	26	14
Optic nerve coloboma	10/24 (42)	3/14 (21)
Microphthalmos	7/26 (27)	4/14 (29)
Severe lacunae	8/22 (36)	6/14 (43)
Asymmetric lacunae*	5/22 (23)	4/14 (29)
Iris coloboma	2/26 (8)	None reported

*Defined as 2 or more point difference between the two eyes