LETTER TO THE EDITOR

The full spectrum of persistent fetal vasculature in Aicardi syndrome: an integrated interpretation of ocular malformations

Editor,—Aicardi syndrome (OMIM 304050), a rare genetic disorder of cerebro-ocular development, is characterised by infantile spasms, psychomotor retardation, agenesis of corpus callosum, and lacunar chorioretinopathy. We present an infant girl with Aicardi syndrome. In addition to chorioretinal lacunae, ophthalmic examination revealed microphthalmos, persistent pupillary membrane, posterior synechiae, posterior polar cataract, optic nerve malformation, and epipapillary and epiretinal gliosis. We believe that all these ocular anomalies other than the chorioretinal lacunae, are manifestations of persisting fetal blood vessels and should, therefore, be referred to as “persistent fetal vasculature.”

We discuss the ocular manifestations of Aicardi syndrome and their embryogenesis. We also attempt to link the ocular malformations with those of the brain.

CASE REPORT
A 22 day old baby girl was referred for evaluation of microphthalmos. She was the eighth child born to non-consanguineous parents and was delivered at term by caesarean section. There was no family history of neurological or eye disease.

The baby was microcephalic (head circumference 30 cm), but did not have any facial dysmorphism. Neurological examination was unremarkable. On ophthalmic examination, the right eye was found to be microphthalmic with a horizontal corneal diameter of 8 mm. The pupil was irregular with posterior synechiae and was delivered at term by caesarean section. There was no family history of neurological or eye disease.

Two disc diameters (Fig 2). The retina was attached and vitreous was clear. The left eye had a few lacunae around the disc. Axial length of the right eye measured by A-scan ultrasound was 15 mm, and of the left eye was 17.5 mm. Computed tomography scan of the brain showed agenesis of corpus callosum, a cyst in the posterior fossa (Dandy-Walker variant), and a second cyst in the right cerebral hemisphere near the midline (Fig 3). There was no radiological evidence of skeletal malformations and differentation take place during the ninth to twentieth week of gestation.14

The salient ocular malformations associated with Aicardi syndrome are listed in Table 1. Traditionally described in isolation and as unrelated physical findings, we postulate that these result from persistence of fetal intraocular vessels and, therefore, ought to be grouped under the term "persistent fetal vasculature" (PFV). PFV includes anomalies involving the entire globe, like persistent pupillary membrane, retrolental fibrovascular tissue, epiretinal and epiapillary glial tissue, retinal dysplasia, optic nerve malformations, abnormalities of the macula, and the size and shape of the eye and orbital cysts.15 Incidentally, our patient exhibited all the major components of PFV.

PFV has been described as an integral part of systemic conditions like Norrie’s disease, trisomy 13 and Warburg syndrome. A literature search revealed a report of anterior at the age of 3 months, the baby started developing seizures. Neurological re-evaluation demonstrated significant developmental delay, generalised hypotonia, and left hemiparesis. She did not give any visual contact with the right eye, but could fixate and follow light with the left eye. Visual evoked response was absent in the right eye and normal in the left eye. Electroencephalography showed hypersrrhythmia over the right cerebral hemisphere. The child was commenced on vigabatrin and a reduction in frequency of seizures was noted.

COMMENT
Aicardi syndrome was first described by Professor Jean Aicardi in 1965.1 The salient features of this syndrome are infantile spasms, mental retardation, callosal agenesis, and chorioretinal lacunae. Skeletal malformations, especially costovertebral anomalies, are often present in patients with this disorder.

Ocular anomalies, a cardinal feature of Aicardi syndrome, are usually bilateral but often asymmetric (Table 1). The pathognomonic chorioretinal lacunae are well defined, multiple, pale areas with minimally pigmented borders, and are usually clustered around the optic disc. The fundus picture resembles that of congenital toxoplasmosis and has often been referred to as “pseudotoxoplasmosis.”16 Histologically, the lacunae are characterised by defects in the choroid and retinal pigment epithelium (RPE). Although the overlying retina remains intact, disturbances in retinal architecture have been reported.

Embryologically, aberrations in development of the choroid and RPE explain the chorioretinal lacunae. Choroid is derived from mesoderm and neural crest cells, and RPE from neuroectoderm. While precursors of the choroid and RPE are detectable as early as the sixth week of gestation, major development and differentiation take place during the ninth to twentieth week of gestation.16

Ocular malformations are frequently encountered in Aicardi syndrome. The salient ocular malformations of Aicardi syndrome are characterised by defects in the choroid and RPE and, therefore, ought to be grouped under the term “persistent fetal vasculature” (PFV). PFV includes anomalies involving the entire globe, like persistent pupillary membrane, retrolental fibrovascular tissue, epiretinal and epiapillary glial tissue, retinal dysplasia, optic nerve malformations, abnormalities of the macula, and the size and shape of the eye and orbital cysts. Incidentally, our patient exhibited all the major components of PFV.

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Table 1. Ocular and cerebral malformations of Aicardi syndrome

<table>
<thead>
<tr>
<th>Ocular malformations</th>
<th>Cerebral malformations</th>
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<tbody>
<tr>
<td>Chorioretinal lacunae*</td>
<td>Agenesis of corpus callosum*</td>
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<tr>
<td>Microphthalmos*</td>
<td>Cerebral cortical heterotopias (pachygyria, polymicrogyria)</td>
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<tr>
<td>Persistent pupillary membrane*</td>
<td>Lissencephaly, pachygyria</td>
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<td>Iris synchiae*</td>
<td>Ventricular dilation*</td>
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<tr>
<td>Cataract, pseudoglioma</td>
<td>Posterior fossa cyst*</td>
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<tr>
<td>Coloboma disc,* morning glory disc anomaly</td>
<td>Cerebellar hypoplasia*</td>
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<td>Optic nerve hypoplasia</td>
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<td>Peripapillary and epipapillary glionic tufts*</td>
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<td>Retinal detachment and dysplasia</td>
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<tr>
<td>Iris and choroidal coloboma</td>
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<td>Scleral ectasia, retrolubar cyst</td>
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persistent hyperplastic primary vitreous with Aicardi syndrome. 9,10 Although microphthalmos, persistent pupillary membrane, vascular loops on the optic disc, scleral ectasia, epiretinal glial tissue, and many other ocular abnormalities have been reported in Aicardi syndrome, 7,9 these have not been linked with PFV.

Fetal intraocular blood vessels begin to develop around the third week of gestation and reach their maximal evolution by the eighth week. Regressive events then commence at about the ninth week and continue to term, by which time nearly all vestiges of fetal vessels disappear. 11

We believe that unifying the different ocular manifestations of Aicardi syndrome under the encompassing term PFV provides an integrated interpretation of seemingly disparate clinical findings. Furthermore, these malformations, like PFV, can be explained by arrest of intrauterine development during the ninth to twentieth week of gestation. 9

In the brain, multiple midline and cerebral hemispheric malformations are observed in Aicardi syndrome (Table 1). Callosal agenesis results from abnormal persistence of fetal glial cells of the lamina terminalis that interfere with the passage of callosal fibres across the midline. All other anomalies are neuronal migration defects. Both callosal development and neuronal migration occur concurrently during ninth to twentieth week of gestation. 12 Buchino et al reported degenerative changes in the brain of a 13 year old girl with Aicardi syndrome. However, these were most likely secondary phenomena, and would not explain the anomalies seen in our patient. 12

Aicardi syndrome is an X linked dominant disorder, with early embryonic lethality in hemizygous males. 12 All undisputed cases have been females and are thought to represent new mutations. 1 Chromosomal abnormality (microdeletion) involving Xp22.3 has been reported. 13 While no teratogenic agent or congenital infection has been consistently associated with this syndrome, 14 genetic factors might play a part. Failure of apoptosis (programmed cell death involved in normal developmental involution) 13 as well as abnormal synthesis of specific peptide growth factors (directing the migration, differentiation, and proliferation of embryonic cells) 7 have a genetic basis and can lead to the malformations.

In conclusion, we have referred to choroidal lacunae and other ocular malformations of Aicardi syndrome and have unified the latter anomalies as PFV. Clinical integration of apparently unrelated malformations prompts the clinician to look for different components of a disorder when one of them is discovered. Integration also facilitates an understanding of the embryological basis of the defects. In this article, we have linked the ocular and cerebral malformations by tracing their origins to similar periods (ninth to twentieth week) of intrauterine life.

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ANURADHA GANESH
SANDIP MITRA
Department of Ophthalmology, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman

ROSHAN L KOUL
POOTHIRIKOVIL VENUGOPALAN
Department of Child Health

Correspondence to: Dr Anuradha Ganesh, Department of Ophthalmology, Sultan Qaboos University Hospital, PO Box 38, Muscat, PC-123, Sultanate of Oman

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