

Ocular manifestations in fetal alcohol syndrome

T Chan, R Bowell, M O'Keefe, B Lanigan

Abstract

Eight children with the fetal alcohol syndrome are described with ocular anomalies. They all had a strong history of maternal alcohol abuse throughout pregnancy, especially in the first trimester. All the children had eye abnormalities. These included external eye lesions, Peters' anomaly, lens opacification, ocular motility disorders, and optic nerve hypoplasia.

Fetal alcohol syndrome is characterised by at least three of the following findings: (1) marked pre- and postnatal growth deficiency with generalised dystrophy (weight, length, and/or head circumference below the 10th percentile when corrected for gestational age); (2) involvement of central nervous system (signs of neurological abnormality, intellectual impairment, or developmental delay); (3) typical facies with at least two of the following signs: microcephaly (head circumference below the third percentile), microphthalmia and/or short palpebral fissures, long philtrum, thin upper lip, and flattening of the maxillary area.² Supplementary findings such as skeletal, cardiac, or genitourinary anomalies are also common. A wide variety of abnormalities during embryogenesis may result in a spectrum of change from minor alteration to the full blown syndrome.

We describe eight children, four males and four females, presenting at age 1 month to 6 years. All had a strong maternal history of alcohol abuse during pregnancy.

Case reports

CASE 1

A 1-month-old boy presented with a history of severe maternal alcohol abuse and the dysmorphic features of fetal alcohol syndrome. Chromosomal analysis and screening for intrauterine infection gave negative results. Ophthalmic examination revealed bilateral ptosis, short palpebral fissures, telecanthus, microphthalmia, bilateral Peters' anomalies (left more severe than right), nystagmoid eye movements, bilateral peripheral anterior synechiae, and partial obliteration of anterior chambers. The intraocular pressures and corneal diameters were normal. An ultrasound B scan showed normal posterior segments; the visual evoked response and binocular electroretinogram were normal.

A 7 mm full-thickness corneal graft was performed at the age of 4 months on the right eye. Follow-up showed slight anterior subcapsular cataract inferiorly in the right eye at 9 months. The corneal graft remains clear to date with a myopic fundus. Microscopic examination of the corneal button showed epithelial oedema with

extensive destruction of Bowman's layer and superficial stromal fibrosis. Descemet's membrane and endothelial cells were distinguished only at the edges of the specimen. Posterior corneal surface elsewhere showed keratocyte proliferation and absence of Descemet's membrane associated with fibrous strands with corneal adhesions.

CASE 2

A 1-year-old girl presented with failure to thrive since birth and a history of maternal alcohol abuse. Investigations for intrauterine infection and chromosomal studies gave normal results. Examination showed growth and developmental delay, and on ophthalmic examination she had central steady fixation bilaterally, a left ptosis (2 mm), and a small esotropia. Cycloplegic refraction was +3.0 dioptres sphere (DS) in both eyes and the fundi were normal.

CASE 3

A 4-month-old boy with a history of maternal alcohol abuse was born at 35 weeks gestation with a birth weight of 1.6 kg. He had developmental delay.

Ophthalmic examination revealed fixation bilaterally. He also had a horizontal jerk type of nystagmus of moderate amplitude and frequency in all directions of gaze. Funduscopy examination showed bilateral optic nerve hypoplasia, marked peripapillary depigmentation and peripheral pigmentary clumping, with surrounding chorioretinal atrophy. The electroretinogram was normal, but the visual evoked response was abnormal. At the age of 2 years he fixed and followed but developed an abnormal head posture. Cycloplegic refraction was +3.5 DS bilaterally.

CASE 4

A 2-month-old baby girl with a history of maternal alcohol abuse was referred after her recovery from a hypoxic episode and treated with anticonvulsants for posthypoxic seizures. She had a history of developmental delay, a duplex collecting system, and hydronephrosis of the left renal system.

Ophthalmic examination showed broad epicanthus, short palpebral fissures, and central steady fixation. Funduscopy examination showed bilateral optic nerve hypoplasia.

CASE 5

A 6-month-old boy was born at 41 weeks gestation with meconium grade 3. He had a marked bradycephaly, developmental delay, a right congenital dislocation of hip, and an inguinal

Department of Paediatric Ophthalmology, Children's Hospital, Temple Street, University College, Dublin 1, Ireland
T Chan
R Bowell
M O'Keefe
B Lanigan

Correspondence to:
Dr Tin Chan, Hinchingsbrooke Hospital, Hinchingsbrooke Park, Huntingdon, Cambs PE18 8NT.

Address for reprints:
Mr R Bowell, FRCS.

Accepted for publication
5 February 1991

Table 1 Systemic features of patients with fetal alcohol syndrome

Case	History of alcohol	Typical FAS features	Growth delay	Mental retardation	Skeletal deformities	Other
1	+	+	+	+	+	ASD, undescended testes, gastroesophageal and vesicoureteric reflux
2	+	+	+	+	0	
3	+	+	+	+	0	
4	+	+	+	+	0	Duplex collecting system and hydronephrosis; neonatal irritability; posthypoxic seizures
5	+	+	+	+	+	Inguinal hernia; partial absence of corpus callosum
6	+	+	+	+	+	
7	+	+	+	+	0	Cerebral palsy; neonatal jaundice; cerebral atrophy; ventricular dilatation
8	+	+	+	0	+	

Present +; Absent 0; Unknown -. ASD=atrial Septal defect.

hernia. Ultrasound examination showed a partial absence of the corpus callosum. Ophthalmic examination showed antimongoloid slants and short palpebral fissures, with a 2 mm left ptosis. He had a long philtrum and thin upper lip. Funduscopy showed bilateral optic nerve hypoplasia, and cycloplegic refraction was +4.0 DS both sides. Electrodiagnostic tests were carried out, including visual evoked response, which showed small amplitudes; the electroretinogram was normal.

CASE 6

A 6-year-old girl presented with a history of developmental delay, recurrent respiratory infections, and dysmorphic facies.

She had a left esotropia, and at follow-up at one year after strabismus surgery she still had a small residual left esotropia. Cycloplegic refraction showed +4.50/+1.0 cylinder at 80° in the right eye and +4.5 DS in the left. Funduscopy examination showed normal appearances.

CASE 7

A 9-month-old baby girl was born at 34 weeks gestation with a history of maternal alcohol abuse after spontaneous rupture of membranes and a

birth weight of 1.8 kg. On physical examination she had signs of a mixed dystonic and spastic type of cerebral palsy. Ultrasound scan of the brain showed cerebral atrophy and lateral ventricular dilatation. Computerised tomography showed diffuse atrophic changes of the brain, ventricular enlargement, and small brainstem.

She had wandering eye movements, and funduscopy showed bilateral optic nerve hypoplasia. The visual evoked response showed low amplitude and prolonged latency; the electroretinogram was normal.

CASE 8

A 2-year-old boy with a history of maternal alcohol abuse during pregnancy presented with bilateral partial ptosis (moderate levator function) and bilateral antimongoloid slant. Funduscopy showed bilateral tortuosity of retinal vessels. Cycloplegic refraction showed +0.5 DS/+1.0 dioptre cylinder (DC) at 110° of the right eye and +2.5 DC at 60° of the left eye. He then had the Fansanella Servat procedure for the correction of the left ptosis.

Discussion

The incidence of the fetal alcohol syndrome is 1:750 in the USA³ and 1:600 in Sweden.⁴ Affected children are usually mentally retarded and prone to frequent infections, failure to thrive, and may need operative correction for various skeletal, cardiac, or genitourinary defects.

The teratogenic effects of alcohol on ocular embryogenesis are multiple. Although the exact mechanism is unknown, it could be directly related to ethyl alcohol or its metabolite, acetaldehyde, or to secondary deficiencies. The developmental anomalies present a wide spectrum of severity involving the external eye, anterior segment, and posterior pole. Miller *et al*⁵ reported eight cases of anterior segment anomalies associated with the syndrome. Seven of them had Peters' anomaly and one had Axenfeld's

Table 2 Ocular anomalies in patients with fetal alcohol syndrome

Case	External eye	Anterior segment abnormality	Motility	Fundus	Refraction	Visual acuity
1	Short palpebral fissure, telecanthus, ptosis	Peters' anomaly, peripheral anterior synechiae	Exotropia OS	Myopic OD	OD -3.0	6/36 to 6/60
2	Ptosis	0	Esotropia OS	0	OD +3.0	Fix +
3	0	0	Horizontal type nystagmus	Optic nerve hypoplasia, chorioretinal atrophy	OD -3.5 OS -3.5	Fix + Fix + Fix +
4	Epicanthus, short palpebral fissure	0	0	Optic nerve hypoplasia	-	Fix +
5	Antimongoloid slants, ptosis, short palpebral fissure	0	0	Optic nerve hypoplasia	OD +4.0 OS +4.0	Fix + Fix +
6	0	0	Esotropia OS	0	OD +4.5/+1.0 DC at 80° OS +4.5	OD 6/6 OS 6/9
7	0	0	Wandering eye movement	Optic nerve hypoplasia	-	-
8	Ptosis	0	0	0	OD +0.5/+1.0 DC at 110° OS +2.5 DC at 60°	OD 6/9 OS 6/12

Present +. Absent 0. Unknown -. Fix + = fixation is present.

anomaly. There was one case with tortuosity of retinal vessels.

Embryologically a normal endothelium is essential for the secretion of Descemet's membrane, which begins at about 12–14 weeks gestation. If the teratogenic effect of alcohol occurs before the initial mesenchyme migration to form the corneal endothelium, keratocytes and iris stromal cells (about six weeks gestation), the endothelium, and Descemet's membrane might reach only the peripheral cornea.⁵

Stromland⁶ in a review of ocular abnormalities in 30 cases reported that 48% of the eyes showed hypoplasia of the optic nerve head and 49% had abnormal tortuosity of the retinal arteries. However, only 10% had anterior segment and media abnormalities (microcornea, cataract, iris defects, and persistent hyaloid artery), and none of them had either Peters' or Axenfeld's anomaly. He concluded that the teratogenic effects of alcohol on the developing optic nerve is from the appearance of the first retinal ganglion cell in the sixth gestational week until after birth. Retinal vascularisation takes place from the 16th gestational week until delivery at term. He suggested that the combination of tortuosity of retinal vessels and optic nerve hypoplasia are helpful signs for the diagnosis of the fetal alcohol syndrome.⁶⁻⁸ This is supported from the findings of Provis *et al*⁹ who reported that the development of mature ganglion cells appears to coincide with retinal vascularisation.

The degree of teratogenicity of an agent suggested by Wilson¹⁰ depends mainly on three factors. First is the genotype of the embryo and its interaction with environmental factors. This could explain the wide variety of lesions in this syndrome shown in the studies reported by Miller *et al*,⁵ Stromland,⁶ and ourselves. All the cases reported by Miller *et al*⁵ had mainly anterior segment anomalies, and the majority of the patients were from the black population. Stromland⁶ reported chiefly posterior segment anomalies, and most of the children reported were Caucasian (Swedish) in origin. In our study the findings are more comparable with those of Stromland, with four (50%) cases of hypoplasia of the optic nerve, one with Peters', anomaly and one case of tortuosity of retinal vessels. A genetic factor may cause a different degree of susceptibility to ocular embryogenesis.

Secondly, a factor to consider is the susceptibility of toxic agents, which depends on the timing of insult during embryogenesis. This would partly explain the various abnormalities mentioned earlier in the anterior segment and posterior pole. A 'critical period' in gestation when alcohol would have its most pronounced teratogenic effects on different parts of the growing eye could not be identified, but the eye

seems to be equally susceptible from the time when each individual structure begins to develop from one particular gestational stage until birth. However, it is established that craniofacial abnormalities are definitely related to prenatal alcohol exposure in a dose response manner in man, and the critical period for alcohol teratogenicity has been confirmed as being early in the first trimester.¹¹ It is further supported by the eye malformations in mouse experiments.¹²

Thirdly, the dose response factor is important during different stages of embryogenesis. The dosage of the teratogens may determine the severity of damage during the development of different structures of the eye.

It is difficult to determine the exact amount of maternal alcohol ingestion during pregnancy. Binge drinking is particularly common in alcoholic women, and periodical high blood alcohol levels may occur throughout pregnancy. All of our cases have a strong history of maternal alcohol abuse, especially during the first trimester. Half of them are children of single parent with poor social background and frequently failed to attend clinic for follow-up. Apart from ocular anomalies the systemic side effects of alcohol are detrimental to the physical and mental development of the child. These side effects include an increased risk of frequent infections, failure to thrive, multiple operations for various structural deformities, mental retardation, and visual deficit. Therefore preventive measures and education are imperative for women with chronic alcohol addiction. It is important to highlight the damage caused by alcohol in the period before pregnancy is recognised.

- 1 Loffe S, Childeeva MD, Chernick V. Prolonged effects of maternal alcohol ingestion on the neonatal electroencephalogram. *Pediatrics* 1984; 74: 330–5.
- 2 Clarren SK, Smith DW. Medical progress: The fetal alcohol syndrome. *N Engl J Med* 1978; 298: 1063–7.
- 3 Hanson JW, Streissguth AP, Smith DW. The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. *J Pediatr* 1978; 92: 457–60.
- 4 Olegard R, Sabel KG, Aronsson M, Sandin B, Johansson PR, Carlsson C, *et al*. Effects on the child of alcohol abuse during pregnancy – retrospective and prospective studies. *Acta Paediatr Scand* 1979; 275 (suppl): 112–21.
- 5 Miller MT, Epstein RJ, Sukar RJ, Pinchoff BS, Supar A, Allen G, *et al*. Anterior segment anomalies associated with the fetal alcohol syndrome. *J Pediatr Ophthalmol Strabismus* 1984; 21: 8–18.
- 6 Stromland K. Ocular abnormalities in fetal alcohol syndrome. *Acta Ophthalmol (Kbl)* 1985; 63 (suppl): 171.
- 7 Stromland K. Eye ground malformations in fetal alcohol syndrome. *Birth Defects* 1982; 18: 651–5.
- 8 Stromland K. Ocular involvement in fetal alcohol syndrome. *Surv Ophthalmol* 1987; 31: 277–84.
- 9 Provis M, Billson F, Russell P. Ganglion cell topography in human fetal retinae. *Dev Brain Res* 1982; 3: 481–6.
- 10 Wilson JC. Current status of teratology. In: Wilson J, Fraser FC, eds. *Handbook of teratology*. New York: Plenum, 1977.
- 11 Ernhart CB, Sokol RJ, Martier S. Alcohol teratogenicity in the human: a detailed assessment of specificity critical period, and threshold. *Am J Obstet Gynecol* 1987; 156: 33–9.
- 12 Cynthia SC, Nowotny AZ, Sulik KK. Fetal alcohol syndrome: eye malformations in a mouse model. *Arch Ophthalmol* 1987; 105: 1576–81.