European Journal of Ophthalmology / Vol. 17 no. 1, 2007 / pp. 104-109

Ocular manifestations in fetal alcohol syndrome

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PURPOSE. *To report the prevalence of ocular abnormalities in a group of Portuguese children with a complete fetal alcohol syndrome (FAS).*
METHODS. *Complete ophthalmologic examination in a sample of consecutive children with FAS. Ocular fundus photography was carried out on the cooperative FAS children and on 25 reference children. Ocular fundus anomalies were recorded by the observation of ocular fundus photography. The ratio between the distance of the center of the disc to the fovea and optic disc diameter (DM/DD) was determined. Small optic disc was defined as a DM/DD ratio above mean control group +1 SD.*
RESULTS. *The authors studied 32 children with FAS (mean age: 9 ± 5 years; 72% boys). The mean corrected visual acuity (VA) was 0.8 ± 0.2. Refraction ranged from –23.00 to +6.50 spherical equivalent. Ocular findings included short horizontal palpebral fissure (81% of children), strabismus (28% of children), epicanthus (27% of eyes), blepharoptosis (16% of eyes), telecanthus (13% of children), nystagmus (1 child), and cataract (1 eye). Ocular fundus photography analysis showed retinal vessel tortuosity in 30% of the eyes and optic disc hypoplasia in 25%. The mean DM/DD for the control and FAS groups was 2.72 ± 0.20 and 2.89 ± 0.25 (p=0.001). Forty percent of the eyes of FAS children had small optic discs.*
CONCLUSIONS. *The most common ocular findings were anomalies of retinal fundus and minor changes in the outer region of the eyes. The authors noted better VA and less severity of disease than others, which might be due to a different selection of patients, different pattern of alcohol consumption, or genetic differences. (Eur J Ophthalmol 2007; 17: 104-9)*

KEY WORDS. *Alcoholism, Children, Congenital defects, Eye, Fetal alcohol syndrome, Optic nerve hypoplasia*

Accepted: July 24, 2006

INTRODUCTION

Maternal alcohol abuse during pregnancy may cause severe damage to the offspring, manifested by fetal alcohol syndrome (FAS). The anomalies range from a less pronounced disease, fetal alcohol effects, to complete FAS. The criteria for establishing the diagnosis of a complete FAS were defined by Sokol and Clarren (1) in 1989 and include a history of maternal alcohol abuse during pregnancy together with neurodevelopment and growth delay and characteristic facial dysmorphism.
Previous reports showed that up to 90% of children with FAS may have an ophthalmologic abnormality (2). The prevalence of ocular lesions was noted to be different in children of various origins. While the cases of Miller et al (3), from the black population of the United States, had frequent anterior segment anomalies, Strömland (2) (Swedish) and Chan et al (4) (Ireland) reported mainly posterior segment anomalies, including a high prevalence of optic disc hypoplasia and retinal vessel tortuosity. These differences can be related to genetic differences between the populations.
To our knowledge, the prevalence of ocular anomalies in FAS in children of Mediterranean origin is not de-

1120-6721/104-06$15.00/0

This case series was presented at the 15th European Society of Ophthalmology Congress; Berlin; September 2005

termined. Our purpose is to report the prevalence of ocular abnormalities in a group of Portuguese children with complete FAS, and to compare the results with the previous studies.

METHODS

Patients

A retrospective review was performed on the records of 32 children with the diagnosis of FAS. The children were diagnosed with complete FAS by the neurodevelopment pediatric department of the hospital, using the criteria defined by Sokol and Clarren (1). After diagnosis was made, they were referred to ophthalmologic examination.
All of them had a strong history of maternal alcohol abuse during the pregnancy. In one case the mother also had abuse of cocaine during periods of the pregnancy. It was not possible to exclude history of psychotropic drug abuse during pregnancy in most children because they were institutionalized or in adoptive families who were unaware of the mother's behaviour. It was not also possible to get reliable, detailed data of drinking habits.

Ophthalmologic examination

All patients were evaluated by two of the authors (I.R. and P.V.). The ophthalmologic examination included assessment of best-corrected visual acuity (VA), ocular motility, slit-lamp examination, fundus examination with direct and indirect ophthalmoscopy, and refraction under cycloplegia. VA was tested with methods suitable for the age and mental condition of the children and was recorded in decimal form.
Checklist for ophthalmologic manifestations included presence or absence of short horizontal palpebral fissures, blepharoptosis, epicanthus, telecanthus, hypertelorism, strabismus, anterior segment abnormalities (including cataract), nystagmus, blepharophimosis, microphthalmia, optic nerve head hypoplasia, retinal vessel tortuosity, and other fundus abnormalities. In order to determine the presence of short horizontal palpebral fissures, telecanthus, and hypertelorism, the horizontal palpebral fissure length, inner intercanthal distance, and interpupillary distance were measured and the results were compared with percentile scales adjusted to the age (5).

Evaluation of ocular fundus abnormalities

Colour fundus photography, centered on the papillomacular bundle, was carried out on the cooperative children. Only well-focused photographs were accepted. Fundus photographs were evaluated by two of the authors (I.R. and P.R.), in two occasions separated by at least 1 week (total of four observations). The observers recorded the presence of optic disc hypoplasia, double ring sign, retinal vessel tortuosity, and other ocular fundus abnormalities. These anomalies were diagnosed when recorded in at least three of the four observations.
In order to better determine the presence of optic disc hypoplasia, we also calculated in all observations the ratio of the distance from the disc's center to the fovea to the disc diameter (DM/DD) of ocular fundus of the children. The horizontal and vertical diameter of the disc and the distance between the fovea and optic disc temporal border were measured using a cursor and the measures were calculated by the computer. The distance between the center of the disc to the fovea (DM) was calculated as the sum of the distance between the fovea and optic disc temporal border and half of optic disc horizontal diameter. Optic disc diameter (DD) was calculated as the mean of horizontal and vertical diameters of optic disc. The final DM/DD ratio for each fundus was the average of the four observations.
The results were compared with a reference group of Portuguese children that included 25 children referred to the ophthalmologic department because of various nonspecific complains, but without a history of maternal alcohol abuse, without systemic or ophthalmologic pathology and with a normal ophthalmologic examination and uncorrected VA of 1.0 in both eyes. The DM/DD ratio of ocular fundus of reference group children was determined using the same method described above. Small optic disc was defined as a DM/DD ratio above mean control group +1 SD.

Statistical analysis

Results were analyzed using the statistical methods analysis of variance (ANOVA), chi square test, and-Pearson correlation coefficient.

RESULTS

Patients

Thirty-two children with FAS were included in the study. Their mean age was 9.6 ± 5 years (range 1–17 years) and 72% were boys. All children had neurodevelopment and growth delay, learning difficulties, and the facial features that characterize a complete FAS.

Visual acuity and refraction

Corrected VA ranged from 0.1 to 1.0 (mean 0.8 ± 0.2) (52 eyes). Almost all children had good VA (Tab. I).

TABLE I - CORRECTED VISUAL ACUITY (decimal) OF OUR SERIES COMPARED WITH STRÖMLAND (2)

Visual acuity	Ribeiro et al (n=52)	Strömland (2) (n=48)
≤0.2	3.8	19
0.3–0.6	13.5	46
0.7–1.0	82.7	35

Values are percentages

TABLE II - REFRACTION DETERMINED UNDER CYCLOPLEGIA OF OUR SERIES COMPARED WITH STRÖMLAND (2) (SPHERICAL EQUIVALENTS)

Diopters	Ribeiro et al (n=62)	Strömland (2) (n=57)
≥–2.0	1.3	1.2
–2.0 to + 3.5	83.8	84.2
≥+3.5	3.2	3.5

Values are percentages

The best-corrected VA of 12 eyes was not determined because the children were too young or had severe mental deficits. Their fixation behavior was normal. Refraction determined under cycloplegia ranged from –23.00 to +6.50 (spherical equivalent) in 62 eyes (mean –0.75 ± 5.00) (Tab. II). Myopia above –5.0 diopters was present in 9.6% of the eyes (6 eyes), astigmatism above 1.5 diopters in 37.5% of the eyes, and anisometropia above 2 diopters in 22.5% of the children. Only two eyes had hypermetropia.

Outer region of the eyes, motility, and anterior segment

The examination of the outer region of the eyes, motility, and anterior segment showed short horizontal palpebral fissure in 81% of children, strabismus in 28% of children, epicanthus in 27% of the eyes, blepharoptosis in 16% of the eyes, telecanthus in 13% of the children, a nystagmus in one child, and a unilateral anterior polar cataract that did not affect the vision in one eye of one child (Tab. III).

Strabismus was present in nine children, from which four had esotropia and four had an intermittent exotropia. One child had an exophoria. In all except one child, esotropia was of small and variable angle, with an alternate pattern. Only one child had an esotropia with a preference fixation pattern and amblyopia.

Blepharoptosis was present in six children and it was unilateral in two children and bilateral in four cases.

We found no other abnormalities of anterior segment described in literature, like posterior embryotoxon, Axenfeld-Rieger anomaly, Peters anomaly, or corneal opacities.

TABLE III - OPHTHALMOLOGIC ABNORMALITIES OF OUR SERIES COMPARED WITH STRÖMLAND (2)

Abnormalities	Ribeiro et al (n=32)	Strömland (2) (n=30)
Minor changes in the outer region of the eyes*	90.6 (29/32 children)	70 (21/30 children)
Strabismus	28.1 (9/32 children)	43 (13/30 children)
Blepharoptosis	15.6 (10/64 eyes)	20 (10/60 eyes)
Nystagmus	3.1 (1/32 children)	6.6 (2/30 children)
Anterior segment anomalies†	1.6 (1/64 eyes)	10 (6/60 eyes)
Blepharophimosis	0	1.6 (1/60 eyes)
Microphthalmia	0	1.6 (1/60 eyes)
Asymmetry of the midfacial structures	3.1 (1/32 children)	6.6 (2/30 children)

Values are percentages. *As defined by Strömland (2), including short palpebral horizontal fissures, telecanthus, flat broad nose bridge, flattening of the maxilla, ptosis, and strabismus. †Including microcornea, shallow anterior chamber and congenital glaucoma, cataract, and persistent hyaloid

Ocular fundus abnormalities

Fundus photography was carried out on 22 children with FAS. The fundus of two children was not quantitatively evaluated because of indistinct borders of the disc. The main reason to not perform ocular photography was young age. Three children could not cooperate in photography because of moderate to severe mental deficits.

Thirty percent of the photographed eyes had retinal vessel tortuosity, 25% had clinical signs of optic disc hypoplasia, and 12.5% had the double ring sign (Tab. IV). Optic disc hypoplasia was diagnosed in seven eyes without the double ring sign because of small and pallid optic discs, with sharply defined margins. One child had myopic choroidosis in both eyes. We did not observe macular ectopia or other severe ocular abnormalities.

The DM/DD ratio

There was a good reproducibility of the DM/DD measures for the observations (R = 0.93, 0.94 for the two observers; R = 0.90 between observers).

The mean DM/DD for the control group and for the FAS group were respectively 2.72 ± 0.20 and 2.89 ± 0.25 (p=0.001). There was a significant difference between the two groups (p=0.001, ANOVA), meaning that the children with FAS had smaller discs than the controls. Small optic discs, as defined, were found in 40% of the eyes of FAS children. All eyes that were considered to have clinical signs of optic disc hypoplasia on observation of ocular fundus photography had high DM/DD ratios (Tab. IV).

There was no significant statistical difference between the mean DM/DD ratio for males and females (mean DM/DD = 2.93 and 2.83, respectively, p=0.24), and between the right and left eyes (mean DM/DD = 2.91 and 2.87, respectively, p=0.64).

Visual acuity and ocular fundus abnormalities

The mean VA of the eyes with and without small optic discs was respectively 0.83 and 0.84 (p=0.98). Six eyes with abnormally small optic discs (including one eye with double ring sign) had VA of 1.0. Four chil-

TABLE IV - VISUAL ACUITY (decimal), REFRACTION DETERMINED UNDER CYCLOPLEGIA, OCULAR FUNDUS ABNORMALITIES, AND DM/DD RATIO ON THE PHOTOGRAPHED EYES OF CHILDREN WITH FAS

Age	Sex	R-RE	R-LE	VA RE	VA LE	OF	DM/DD RE	DM/DD LE
3	M	–1.50+5.00x90°	–1.50+4.50x90°	NC	NC	RLE: RVT; ODH	3.54	3.44
6	M	–0.75x0°	–0.25–1.50x150°	1.0	0.8	RLE: ODH	3.14	3.08
6	M	0	0	0.5	0.6		2.78	2.84
7	F	+0.75+0.75x90°	+0.75+0.75x65°	0.9	0.9		2.87	2.78
7	M	+0.50+0.75x90°	+0.50	1.0	1.0	RE: ODH; DRS	3.13	2.75
7	F	0	0	0.9	1.0	RLE: RVT	2.76	2.63
9	M	+1.50x100°	–0.50+1.25x90°	0.6	0.6	RLE: RVT RE: ODH	3.30	2.83
9	M	+0.75x135°	+0.75x45°	0.8	0.8		2.74	2.79
11	M	–0.25 x 0°	–0.25 x 0°	1.0	1.0	RLE: RVT	2.61	2.73
11	M	+1.00	+1.00	1.0	1.0	LE: ODH	3.20	3.35
12	F	+0.75–4.50x170°	+4.00x90°	0.5	0.4		2.48	2.77
12	M	–0.75	–1.00x180°	1.0	0.7		2.77	2.73
14	F	+0.50+0.50x90°	+0.50	1.0	1.0		2.78	2.99
14	F	0	0	1.0	1.0	RLE: RVT	2.53	2.80
15	F	–5.50–3.25x5°	–11.50–3.00x160°	0.5	0.5	RLE: ODH; DRS; MC	3.25	3.02
15	M	–1.75+4.00x95°	+0.50+4.00x70°	0.8	0.9		3.04	2.66
15	M	+1.50+1.50x90°	–0.25+2.00x70°	1.0	0.8	RLE: RVT	2.63	2.55
15	M	+0.50x60°	0	0.8	1.0		3.09	3.02
16	F	– 0.75x85°	–1.00x95°	0.8	0.8	LE: ODH	2.71	3.05
17	M	–0.25+0.50x180°	–0.25	0.8	0.8	LE: DRS	2.76	3.00

DM/DD = Ratio between the distance of the center of the disc to the fovea and the mean optic disc diameter; FAS = Fetal alcohol syndrome; R-RE = Refraction of the right eye; R-LE = Refraction of the left eye; VA = Visual acuity; OF = Ocular fundus; NC = Did not cooperate for evaluation of visual acuity; RLE = Right and left eyes; RVT = Retinal vessel tortuosity; ODH = Optic disc hypoplasia; DRS = Double ring sign; MC = Myopic choroidosis

dren had the same VA in both eyes despite a great difference in optic disc size (Tab. IV).

DISCUSSION

We determined the prevalence of ocular abnormalities in a group of Portuguese children with FAS. Because all observations were performed by at least two of the authors, observational bias is less likely to occur.

The prevalence of ocular fundus anomalies was determined by observation of ocular fundus photography. Because not all children cooperate in photography, the ocular fundus findings cannot be representative of the real prevalence of these anomalies in children with FAS, and because the more affected children are less able to cooperate, we can fail to diagnose the more severe abnormalities. However, the main reason children did not cooperate in photography was young age. VA and refraction were similar in the groups of children that performed and did not perform photography. On the other hand, ocular fundus of children who did not cooperate in photography was evaluated by ophthalmoscopy and we did not find gross abnormalities.

To help the diagnosis of optic disc hypoplasia, we used a relative measure of optic disc diameter, the DM/DD ratio. It was described for the first time for the diagnosis of optic disc hypoplasia by Awan in 1976 (6), as the ratio of the distance from the disc's center to the fovea to the horizontal disc diameter. Like Wakakura and Alvarez in 1987 (7), we used a modified DM/DD ratio, in which the horizontal optic disc diameter was replaced by the mean optic disc diameter. Because optic disc is oval, the purpose of the modification is to increase the precision of the measure.

To determine a cutoff limit for the size of optic disc, we selected a reference group of healthy children. In opposition to children with FAS, all of the control group children were emmetropic, with uncorrected VA of 1.0 in both eyes. If an absolute measure of optic disc were used, the differences in refraction could influence it. However, because a relative measure was used, it is unlikely that refraction had influence in the results.

As in other studies (7-9), DM/DD ratio showed to be a simple and reproducible measure of the relative optic disc diameter in the children. Because severe optic disc hypoplasia is commonly easily clinically detected, we think it can be helpful for the diagnosis of optic disc hypoplasia with low severity. We calculated the cutoff limit as 1 standard deviation (SD) of the mean of the control group, and in our population it was 2.92.

The most common eye findings were minor changes of the outer region of the eyes, described above, and anomalies of retinal fundus, particularly hypoplasia of the optic nerve and increased tortuosity of the retinal vessels.

Like in other series, strabismus was a frequent finding. However, in opposition to others, we found a significant prevalence of intermittent exotropia and, in all except one case, the presence of strabismus did not cause amblyopia.

Like Strömland (2), and in opposition to Miller et al (3), we did not find a high prevalence of anterior segment abnormalities in our group of children. The prevalence of anterior segment abnormalities in our series was even smaller than that of Strömland (2).

Although the prevalence of small optic discs was only slightly less frequent than that found in the series of Strömland (2), there was a big difference in the prevalence of clinically evident optic disc hypoplasia. On the other hand, in opposition to the study of Strömland (all small optic discs had the double ring sign), in our series, most of them did not have the double ring sign and we did not consider the double ring sign as a criterion for the diagnosis of optic disc hypoplasia. We think that, because the double ring sign is present only in severe cases of optic disc hypoplasia (10), the small optic discs without double ring sign that were found in our study can represent a spectrum of optic disc hypoplasia of less severity, that is not easily clinically diagnosed.

In our series most children did not have severe visual impairment (Tab. I). There was not a significant difference between the refraction of the children compared with that of Strömland (2) that can explain this difference (Tab. II). We believe that our children's better VA are due to the lower severity of the disease, including optic disc hypoplasia. Most children did not have severe ocular abnormalities and, as mentioned above, optic disc hypoplasia appears to be of lesser severity. Possible explanations for the lessened severity of disease in our series are a different se-

lection of patients (while Strömland's study took place in a referral center for severe ocular disorders, we studied children from a general hospital that is not such a referral center), genetic differences between the populations, or a different pattern of alcohol consumption.

There was no correlation between small optic discs/optic disc hypoplasia and VA. This finding suggests that the papillomacular bundle was not affected in most of the children of our study. Most children with low VA had high refractive errors, including moderate myopia, astigmatism, and anisometropia (Tab. IV). Amblyopia as a result of high refractive errors and anisometropia was the main cause of reduced VA. Because of the intermittent or alternate patterns, most of the cases of strabismus were not associated with a decrease in VA.

In conclusion, like the series of Strömland (2) and Chan et al (4), we found mainly posterior segment anomalies, including a high prevalence of optic disc hypoplasia and retinal vessel tortuosity. We noted better VA and less severity of disease than others, which might be due to a different selection of patients, different pattern of alcohol consumption, or genetic differences.

The authors have no proprietary interest in any aspect of this article. There were no grants or funds in support of this work.

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REFERENCES

1. Sokol RJ, Clarren SK. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. Alcohol Clin Exp Res 1989; 13: 597-8.
2. Strömland K. Ocular abnormalities in the fetal alcohol syndrome. Acta Ophthalmol 1985; 63 (Suppl): S1-50.
3. Miller M, Israel J, Cuttone J. Fetal alcohol syndrome. J Pediatr Ophthalmol Strabismus 1981; 18: 6-15.
4. Chan T, Bowell R, O'Keefe M, Lanigan B. Ocular manifestations in fetal alcohol syndrome. Br J Ophthalmol 1991; 75: 524-6.
5. Hall JG, Froster-Iskenius UG, Allanson JE. Handbook of normal physical measurements. Oxford; New York: Oxford University Press, 1989; 132-50.
6. Awan KJ. Ganglionic neuroretinal aplasia and hypoplasia: aplasia and hypoplasia of optic nerve. Ann Ophthalmol 1976; 8: 1193-202.
7. Wakakura M, Alvarez E. A simple clinical method of assessing patients with optic nerve hypoplasia. The disc-macula distance to disc diameter ratio (DM/DD). Acta Ophthalmol 1987; 85: 612-7.
8. Borchert M, McCulloch D, Rother C, Stout AU. Clinical assessment, optic disk measurements and visual-evoked potential in optic nerve hypoplasia. Am J Ophthalmol 1995; 120: 605-12.
9. Zeki SM, Dudgeon J, Dutton GN. Reappraisal of the ratio of disc to macula/disc diameter in optic nerve hypoplasia. Br J Ophthalmol 1991; 75: 538-41.
10. Frisen L, Holmegaard L. Spectrum of optic nerve hypoplasia. Br J Ophthalmol 1978; 62: 7-15.