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CLINICAL STUDY

Ocular pathology in congenital heart disease

AM Mansour[1,2,3,4], FF Bitar[1,2,3,4], EI Traboulsi[5], KM Kassak[1,2,3,4], MY Obeid[1,2,3,4], A Megarbane[6] and HI Salti[1,2,3,4]

Abstract

Purpose **To describe the ocular findings in subjects with congenital heart disease (CHD).**
Methods **In a prospective study, the same observer examined 240 consecutive patients with CHD admitted to the medical centre. Two independent geneticists performed identification of syndromes.**
Results **The commonest anatomic cardiac anomalies were ventricular or atrial septal defects (62), tetralogy of Fallot (39), pulmonary stenosis (25), and transposition of the great arteries (24). The heart lesions were divided physiologically into volume overload (90), cyanotic (87), and obstructive (63). In all, 105 syndromic subjects included the velocardiofacial syndrome (18), Down's syndrome (17), CHARGE association (6), DiGeorge syndrome (5), Williams syndrome (3), Edwards syndrome (3), Noonan syndrome (3), VACTERL association (2), and Patau syndrome (trisomy 13) (2). The paediatric team recognized 51 patients as syndromic. Two independent geneticists recognized additional 54 patients as syndromic. Positive eye findings were present in 55% (132) and included retinal vascular tortuosity (46), optic disc hypoplasia (30), trichomegaly (15), congenital ptosis (12), strabismus (11), retinal haemorrhages (8), prominent eyes (7), and congenital cataract (6). There was a strong correlation between the retinal vascular tortuosity and both a low haematocrit ($P = 0.000$) and a low arterial oxygen saturation ($P = 0.002$).**
Conclusions **Patients with CHD are at a high risk for ocular pathology and need screening for various ocular abnormalities.**

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Introduction

Congenital heart disease (CHD) is one of the most common birth defects, affecting around 1% of live births.[1,2] Both environmental factors and genetic factors have been implicated.[1,2] Ocular studies in CHD are few and have concentrated on one cardiac anomaly,[3–8] one syndrome with cardiac anomaly,[9–25] small series, single case reports,[26–28] or literature review.[29] Ocular findings in CHD were not revisited for the past 25 years. In 1967,[3] 1968,[4] and 1972,[5] three papers detailed, respectively, the ocular findings in 12, 85, and 83 patients with CHD. A prospective study of the ocular findings in a large series of CHD was undertaken to further define the ocular findings.

Materials and methods

In a prospective study, consecutive patients with CHD admitted to the medical centre were examined between December 1997 and July 2002. The diagnosis of CHD was established by echocardiography or cardiac catheterization by one of the researchers (FB). The Institutional Review Board approved the study protocol, and parents signed a consent form as part of the enrollment in the paediatric cardiology registry.

One observer (AMM) carried the eye examination. This included cycloplegic refraction (four instillations at 15 min interval of tropicamide 1%),[30] indirect ophthalmoscopy, and assessment of ptosis. Identification of associated syndromes was based on review of the clinical findings, karyotyping results (done in 27 patients), and review of external photographs of the face, and of accompanying systemic anomalies. Two independent geneticists (EIT, AM) characterized the associated syndromes.

The cardiac lesions were divided physiologically into three categories: volume overload, cyanotic, and obstructive. The category of volume overload included various defects producing left-to-right shunts, resulting in right-sided dilatation (atrial septal defect) or

[1]Department of Ophthalmology American University of Beirut, Beirut, Lebanon

[2]Department of Pediatrics American University of Beirut, Beirut, Lebanon

[3]Department of Surgery American University of Beirut, Beirut, Lebanon

[4]Faculty of Health Sciences American University of Beirut, Beirut, Lebanon

[5]Cole Eye Institute Cleveland OH, USA

[6]Department of Medical Genetics Saint Joseph University Beirut, Lebanon

Correspondence:
A Mansour
Department of Ophthalmology
American University of Beirut
Beirut, Lebanon
Tel: 9611-374625
Fax: 9611-744464
E-mail: dr.ahmad@cyberia.net.lb

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left sided-dilatation (ventricular septal defect, patent ductus arteriosus). The cyanotic category included lesions with right-to-left shunts or mixing abnormalities (transposition of the great vessels, persistent truncus arteriosus, tetralogy of Fallot). The obstructive category included pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta.

The haematocrit was divided into three levels: below 31 ('anaemia'), 31–49 ('normal'), and above 49 ('polycythaemia'). The oxygen saturation was divided into two levels: 'normal' (90 and above), and 'hypoxia' (below 90). Statistical analysis was performed by one of us (KMK) using SPSS for Windows (SPSS Inc., Chicago, IL, USA) and the Pearson χ^2 test.

Results

In all, 240 subjects were examined. Gender distribution was 53.3% male, racial composition was 100% white, and the median age was 1.0 year (mean = 2.9 years; SD = 4.2 years). Physiologically, the cardiac categories included volume overload in 90 (37.5%), cyanotic in 87 (36.3%), and obstructive in 63 (26.3%). The most common anatomic cardiac anomalies were ventricular or atrial septal defects (62), tetralogy of Fallot (39), pulmonary stenosis (25), and transposition of the great arteries (24). Other lesions included patent ductus arteriosus (13), double-outlet right ventricle (11), aortic stenosis (10), pulmonary atresia (10), coarctation of aorta (9), single ventricle (6), and atrio-ventricular canal (6). The mean oxygen saturation was 88% (SD = 10), and the mean haematocrit was 39 (SD = 8). A majority of patients with the cyanotic lesions tended to have polycythaemia, while a majority of subjects with volume overload tended to have anaemia ($P = 0.008$). Hypoxia occurred in 22.4% of subjects with volume overload (some patients had pneumonia, endocarditis, high fever, or had already undergone cardiac surgery at the time of the eye exam), 43.5% of subjects with obstructive lesions, and 74.7% of subjects with cyanotic lesions (some cyanotic lesions had partial correction prior to admission) ($P = 0.000$). A total of 81 subjects had undergone some type of surgical intervention prior to the eye exam.

In all, 105 subjects (43.7%) were syndromic, and these included velocardiofacial syndrome (18), Down's syndrome (17), CHARGE (coloboma, heart defect, atresia of choanae, retarded growth, genital hypoplasia, ear anomaly) association (6), DiGeorge syndrome (5), Williams syndrome, Edwards syndrome (trisomy 18), Noonan syndrome (3 each), VACTERL (vertebral, anal, cardiovascular, tracheo-oesophageal, renal, and limb defects) association, and Patau syndrome (trisomy 13) (2 each) (Table 1). The paediatric team recognized 51 syndromic patients, and the two geneticists identified the additional 54 syndromic patients.

Positive eye findings were present in 55% (132), and included retinal vascular tortuosity (46), optic nerve hypoplasia (30), trichomegaly (15), congenital ptosis (12) (bilateral in 7), squint (11), retinal haemorrhages (8), prominent eyes (7), cataract (6), nystagmus (4), megalopapilla (4), coloboma of optic disc or choroid (4), nasolacrimal duct obstruction (3), periorbital cyanosis (3), congenital glaucoma (2), and lens subluxation (2) (Tables 1 and 2). Cataract, ptosis, and strabismus occurred mainly in the syndromic population: eleven of twelve patients with ptosis, nine of eleven patients with strabismus, and five of six patients with cataract were syndromic (Table 1). High myopia (more than eight), high hyperopia (more than 6), and high astigmatism (more than 2) were present in four, six and 11 subjects, respectively. The mean spherical equivalent was $+0.95$ in the right eye (SD = 3.2), and $+0.97$ in the left eye (SD = 3.3). The mean astigmatism was 0.29 in the right eye (SD = 0.60), and 0.31 in the left eye (SD = 0.66).

There was a strong correlation between retinal vascular tortuosity and low haematocrit ($P = 0.000$), and low arterial oxygen saturation ($P = 0.002$). Cross-tabulation of the normal haematocrit group showed that retinal vascular tortuosity in that group was related to low oxygen saturation (Fisher's exact test $P = 0.028$). Retinal vascular tortuosity was present in 11 subjects with the velocardiofacial syndrome: five of 11 had normal hematocrit and oxygen saturation. There was no relation between hyperopia and either retinal vascular tortuosity or optic nerve hypoplasia. In all, 10 subjects had both retinal vascular tortuosity and optic nerve hypoplasia (See Figures 1 and 2).

There was a correlation between the CHD anatomic types and syndromes. Syndromes were identified in 49% of those with tetralogy of Fallot (19/39) *vs* 28% of those with pulmonic stenosis (7/25), and 13% of those with transposition of great arteries (3/24) ($P = 0.008$). There was no correlation between the CHD anatomic types and eye findings.

As a background, we present some epidemiological data on CHD in Lebanon (FFB, Children Cardiac Registry Center, AUB, Beirut, Lebanon; unpublished data collected prospectively from March 1997 till January 1999). The consanguinity among the parents was 32%. In all, 16% of patients had a family history of CHD. Maternal smoking was 35%, while paternal smoking was 54%. Maternal age distribution was as follows: In all, 11% were between 14–20 years, 68% between 21–30 years, and 21% between 31-42 years. The incidence of CHD in the medical centre was retrospectively 1.2% (27 CHD patients among 2345 live births at AUB medical centre during the year 1996).

Table 1 All syndrome types and major ocular findings

All syndrome types and major ocular findings	*Total N.*	*Ptosis*	*Squint*	*Cataract*	*Disc hypoplasia*	*Vascular tortuosity*	*Retinal haemorrhage*
Velo-cardio-facial/DiGeorge syndromes[a]	24	3	1	0	6	11	0
Down syndrome	17	0	1	2	2	5	0
Mild Dysmorphic features	8	1	1	0	0	3	0
CHARGE association	6	1	3	0	0	0	0
Williams syndrome	3	0	0	0	1	0	0
Noonan syndrome	3	2	0	0	1	0	0
Edward syndrome	3	0	0	0	0	0	0
Patau syndrome	2	0	0	2	0	0	0
VACTERL association	2	0	1	0	0	1	0
PHACE syndrome	1	0	0	0	0	0	0
Holt–Oram syndrome	1	0	0	0	0	0	0
Allagille syndrome	1	0	0	0	0	0	0
Trisomy 9p	1	0	0	0	0	0	0
Goldenhar syndrome	1	0	0	0	0	0	0
Pierre–Robin syndrome	1	0	0	0	0	0	0
Dubowitz syndrome	1	1	1	0	0	0	0
Eisenmenger syndrome	1	0	0	0	1	0	0
Marfan syndrome	1	0	0	1	0	0	0
Ohdo syndrome	1	1	0	0	0	0	0
Weil–Marchesani syndrome	1	0	0	0	0	1	0
Blepharophimosis-ptosis-epicanthus inversus	1	1	1	0	0	0	0
4p trisomy 4q deletion	1	0	0	0	0	1	1
47XYY	1	0	0	0	0	0	0
Carnithine deficiency	1	0	0	0	0	0	0
Sandhoff disease	1	0	0	0	0	0	0
Mucopolysaccharidosis	1	0	0	0	0	1	0
Other syndromic patients[b]	20	1	0	0	6	2	1
All syndromic patients	105	11	9	5	17	25	2
Nonsyndromic patients	135	1	2	1	13	21	6
Total	240	12	11	6	30	46	8

[a]18 patients had velocardiofacial syndrome, five had DiGeorge syndrome and one shared both features.
[b]Unclassified syndromes.

Discussion

There is a high prevalence of associated syndromes with CHD in Lebanon (possibly from referral bias and high consanguinity) and around 50% of the involved syndromes can be missed without formal genetic consultation. There are several studies on the prevalence of individual chromosomal abnormalities, like 22q11.2 deletions[31–33] (velocardiofacial and DiGeorge syndromes are due to 22q11.2 deletions). Borgmann *et al*[31] found that routine screening for 22q11.2 deletions in nonsyndromic CHD subjects gave no yield. The morphological identification by geneticists is thereby emphasized.

The large percentage of ocular findings in CHD could be related to the high incidence of associated syndromes (Tables 1 and 2), to the possible embryologic link between the ocular and cardiac defect, or to the high incidence of consanguinity.

The present cross-sectional study underestimates the incidence of strabismus as half of the subjects were examined below age one. Gardiner and Joseph[4] found strabismus in 14% of a total of 85 children with CHD, and amblyopia in 50% of patients with the tetralogy of Fallot. The present study did not measure intraocular pressure that can be elevated in some subjects with congestive heart failure.[34,35]

Retinal vascular tortuosity is related to oxygen saturation and to certain syndromes (velocardiofacial syndrome). Pulsatile three-dimensional retinal arteriolar tortuosity has been previously reported in about 50% of patients with coarctation of the aorta.[6] More recently, subjects with coarctation of the aorta have been found not to display these findings because of early surgical correction of the cardiac lesion, implying haemodynamic aetiology of vascular tortuosity.[6] Similarly Crowe *et al*[3,8] showed that retinal vascular dilation and tortuosity in 14 subjects with cyanotic CHD decreased after surgical correction and seems related to the combination of polycythaemia and hypoxia. Petersen and Rosenthal[5] found dilation and tortuosity of retinal vessels to be related to hypoxia and polycythaemia and to be present in nearly half of the patients (42 of 83) with cyanotic

Table 2 Complete ocular findings in major syndromes

Complete ocular findings in major syndromes	*Velocardiofacial-DiGeorge*	*Down's*	*Charge*	*Mild dysmorphic feature*
Total number of patients	24	17	6	8
Positive eye findings	15	15	5	4
Negative eye findings	9	2	1	4
Retinal vascular tortuosity	11	5	0	3
Optic disc hypoplasia	6	2	0	0
Coloboma of optic nerve or uvea	0	0	4	0
Ptosis	3	0	1	1
Cataract	0	2	0	0
Microphthalmos	0	0	2	0
Esotropia	0	1	2	1
Trichomegaly	0	2	0	1
Megalopapilla	0	2	0	0
Duane retraction syndrome	1	0	0	0
Trochlear palsy	0	0	1	0
Sclerocornea	0	0	1	0
Floppy eyelid	0	1	0	0
Congenital nystagmus	0	1	0	0
Disc drusen	1	1	0	0
Iris dysgenesis	0	1	0	0
Atresia of lacrimal puncta	0	0	1	0
Nasolacrimal duct obstruction	0	1	1	0

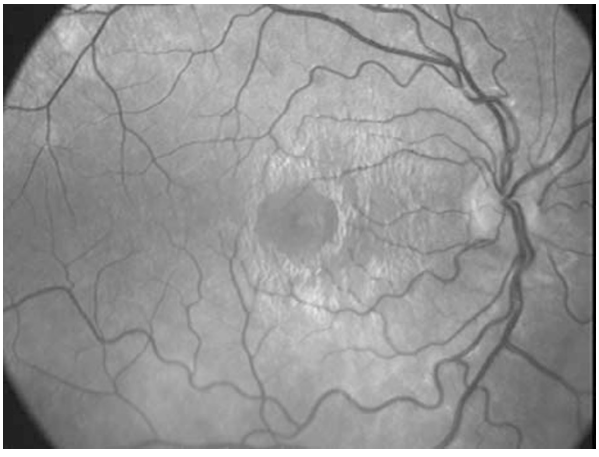

Figure 1 Posterior pole of right eye. Retinal artery tortuosity and optic nerve hypoplasia in a 13-year-old male subject with pulmonic stenosis, aortic stenosis, and Williams syndrome.

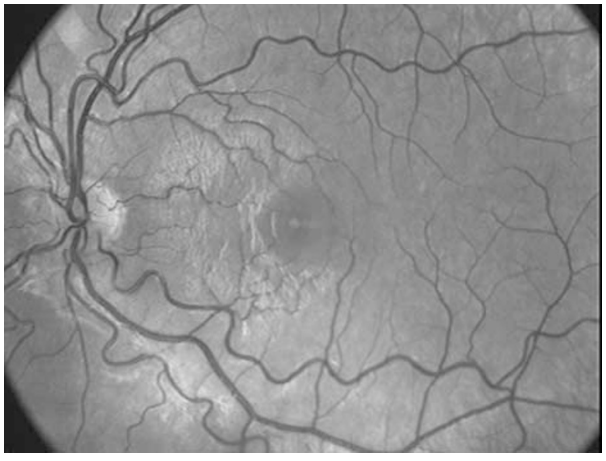

Figure 2 Posterior pole of left eye. Retinal artery tortuosity and optic nerve hypoplasia in a 13-year-old male subject with pulmonic stenosis, aortic stenosis, and Williams syndrome.

CHD. Analysis of our data suggests that subjects with high or low haematocrit develop tortuosity. In patients with normal haematocrit, low oxygen saturation or the presence of the velocardiofacial syndrome may account for the tortuosity.

Since there is a very high incidence of smoking in Lebanon,[36] and a large number of patients were examined soon after birth, the effect of smoking mothers on the high incidence of retinal vascular tortuosity in neonates is to be considered. Beratis *et al*[37] examined the retina of 162 neonates of smoking mothers and 162 matched neonates of nonsmoking mothers. Retinal venous dilatation and tortuosity was found in 100 and 36 eyes of neonates of smoking and nonsmoking mothers. Also, intraretinal haemorrhages were found in 61 and 31 eyes of neonates of smoking and nonsmoking mothers. All retinal abnormalities resolved by 6 months. Retinal vascular tortuosity may also be due congestive heart failure or rarely central retinal vein occlusion from cyanotic heart disease,[28] or may be related to high hyperopia or an associated optic nerve hypoplasia.

Optic nerve hypoplasia[38] is a congenital abnormality characterized by reduced number of axons in the optic nerve manifesting clinically as a small disc, often

surrounded by a peripapillary halo (double-ring sign), and often accompanied by retinal vascular tortuosity. One-third of subjects (10 of 30) with optic nerve hypoplasia had retinal vascular tortuosity in the present study. Optic nerve hypoplasia was found to be associated with general disturbance in foetal development, young maternal age, first parity, maternal smoking, and preterm birth.[38] The association of optic nerve hypoplasia with CHD is probably the result of a disturbance in early foetal development.

Coloboma is seen in many syndromes (trisomy 13 and 18, 4p-, cat's eye), in the CHARGE association, or in subjects with a normal karyotype. The highest incidence of coloboma among syndromes occurs in the CHARGE association (82%).[39] Only 11% of patients with colobomas have the CHARGE association.[15]

The association of ptosis with CHD[26] was first noted in 1986. Larned *et al*[26] reviewed 156 cases of congenital ptosis and found seven nonsyndromic cases with CHD divided into pulmonic stenosis (three), ventricular septal defect (three), and patent ductus arteriosus (one). The authors noted that the frequency of CHD in the congenital ptosis study group was five times the expected frequency, and suggested an association between congenital ptosis and CHD. In the present study, congenital ptosis was present in 12 of 240 subjects, or 5%: three with velocardiofacial syndrome, two with Noonan syndrome, six cases with various syndromes, and one nonsyndromic. The present study confirmed the association of congenital ptosis with CHF in general, as the prevalence of congenital ptosis in the general population (0.18%)[40] was 30 times lower than that the present series (5%).

Congenital cataract was present in six cases (2.5%): two with Down's syndrome, two with trisomy 13, one with Marfan syndrome, and one in a nonsyndromic patient. Wirth[41] found Down's syndrome in 62% of a series of 29 syndromic congenital cataract cases. The prevalence of congenital cataract was 0.037% in the general population,[41] 68 times less than that in the present series (2.5%).

The distribution of refractive errors in CHD was quite similar to the normal distribution in healthy children from several continents.[42–45]

Trichomegaly could be related to the high degree of consanguinity between the parents as suggested by Harrison and Mullaney[46] and not part of a syndrome.

We had no case of bleeding tendency or venous stasis, and the instances of retinal haemorrhages could be related to sequelae of birth trauma, or severe cyanosis. Intraretinal haemorrhage was present in 34% of newborns, resolved within 4 weeks,[47] and was more common in babies of smoking mothers.[37]

With modern interventional cardiac procedures, a large number of CHD subjects are expected to have a longer lifespan. Ophthalmologists will play an increasing role in the management of ocular diseases in this growing population, with emphasis on a multidisciplinary approach to the management of subjects with CHD.

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