Ocular Alterations Associated with Primary Congenital Heart Disease – A Cross-sectional Study

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Abstract:

OBJECTIVE: The objective of the study was to assess ocular findings’ prevalence in children with primary congenital heart disease (CHD).

PATIENTS AND METHODS: This is a prospective cross-sectional study of children with CHD treated at a specialized center in the South of Brazil between 2013 and 2015. They underwent a complete ocular examination, including measurement of visual acuity, refraction test, external motility, anterior and posterior biomicroscopy, and binocular indirect fundoscopy with retinal photographs. Two experienced examiners independently assessed fundus findings: one at the time of examination and image capture, while the other assessed only the captured images.

RESULTS: Of a total of 146 children examined, 124 were included in this analysis (16% loss). Seventy children were male (55.5%). The average age was 9.3 years (minimum 1 month and maximum 15 years). Caucasians race were 81.2%, African Descendants race were 11.1%, and others were 7.7%. About 57.1% had already had heart surgery. About 14.8% had visual acuity below 0.6 and 2.8% below 0.1. Strabismus was found in 7.4% and cataracts in 1.7%. Retinal alterations were recognized in 13.5%, of which 4.8% were related to vascular narrowing or dilation and/or abnormal arteriovenous crossing; 7.14% were related to increased vascular tortuosity, while 1.6% were related to active toxoplasmic chorioretinitis lesions. Concomitant abnormalities in ocular motility, biomicroscopy, or ophthalmoscopy were detected in 24% of the cases.

CONCLUSION: Children under the age of 15 years old with primary CHD have a high prevalence of ocular alterations, with external ocular and retinal manifestations, with higher occurrence rate among cyanotic cases. This leads us to strongly recommend the performance of a complete ophthalmological examination in such cases.

Keywords:
Cataract, congenital heart disease, retina

Introduction

Congenital heart disease (CHD) occurs in 8:1000 births, 25% of which consist of severe forms.¹ CHD association with ocular problems has received limited attention, with prevalence varying widely in the literature, from 6.3% to 65%.²⁻⁴

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The majority of studies of CHD present small case series or reviews, associated syndromes, or case reports, with very few with relevant samples.\textsuperscript{[14–22]} The largest study is that of the 500 cases described by Alfano, which detected ocular abnormalities in 10.4% of primary or idiopathic CHD cases, i.e., not associated with genetic diseases or syndromes.\textsuperscript{[14]} The next most relevant study in terms of sample size is by Mansour et al. who adequately described the different types of CHD and found associated ophthalmological changes in 32.6% of cases with primary CHD.\textsuperscript{[19]}

Thus, the purpose of this study is to describe the prevalence and ophthalmological findings in a larger sample of cases with primary CHD attending a specialized outpatient clinic at a cardiology referral center, seeking to identify associated variables and repercussions.

**Patients and Methods**

Between January 2013 and December 2015, a cross-sectional study was conducted with children up to 15 years of age attending the weekly specialized outpatient clinic at our institution. The study included children with CHD not associated with systemic syndromes, who already had clinical, echographic, and hemodynamic diagnosis, and who either had never been treated or were already having clinical, pharmacological, or surgical follow-up. We excluded cases still in diagnostic investigation, incomplete data, with the previous diagnosis or treated by retinopathy of prematurity, or with acquired heart disease.

Participants were presented to complete ophthalmological examination, including measurement of visual acuity (Snellen E-Chart), ocular motility, color vision testing (Ishihara plates), and anterior segment biomicroscopy and followed mydriasis, retinoscopy, and binocular indirect fundoscopy. Mydriasis and cyclogogia were obtained using three drops of 1% cyclopentolate solution at 10-min intervals between each drop. The indirect fundoscopic findings (20 D or 28 D lenses, Nikon\textsuperscript{®}) were recorded using a video system (EyeTec model ODS 6.0, Brazil) for later reanalysis. Two experienced examiners independently assessed (CGC, MAPV) fundus findings: one at the time of examination and image capture, while the other assessed only the captured images.

The demographic variables studied were age, sex, and race. Heart disease was categorized into four subgroups [Table 1]. Refractive state was categorized into emmetropia, hypermetropia (> +0.50 D), myopia (> −0.50 D), astigmatism (>0.75 D), and anisometropia (difference > 1.0 D).

The analysis was performed using StataCorp. 2013. Stata Statistical Software: Release 13. (College Station, TX: StataCorp LP). Variable category proportions were estimated. The outcomes were calculated according to the independent variables using the Chi-square test. Poisson regression with robust variance according to the hierarchical model was used to analyze associated factors. Variables having $P < 0.2$ were kept in the model. Demographic variables comprised the first level; the second level comprised heart diseases and ophthalmological examination findings, while ocular alterations of any nature or just fundoscopic alterations were included in the third level. The agreement between examiners was assessed using the kappa test. A level of significance of $< 0.05$ was chosen.

The study was approved by our Institution’s Research Ethics Committee, and in all cases, a free and informed consent form was signed by a parent. The study complied with the Helsinki Declaration requirements.\textsuperscript{[23]}

**Results**

Of a total of 146 children examined, 124 were included in this analysis (16% loss due to incomplete data). Seventy children were male (55.5%). The average age was 9.3 years (minimum 1 month and maximum 15 years). About 58.5% of children were <10 years of age. Prematurity was reported by family members (8%). White race was 81.2%, black race was 11.1%, and others were 7.7%. With regard to the type of heart disease, 14.3%, 30.9%, 34.9%, and 19.9% corresponded to types 1, 2, 3, and 4, respectively. Nearly 75.4% were not taking medication. About 57.1% had already had heart surgery.

| Table 1: Congenital heart disease categories |
|--------------------------------------------|
| Minimal lesions                            |
| Patent foramen ovale                       |
| Minimal stenosis and pulmonary valve insufficiency |
| Arrhythmias                                |
| Minimal pulmonary valve insufficiency      |
| Mitral valve prolapse                      |
| Acyanotic and no repercussion              |
| Small IAC                                  |
| Small IVC                                  |
| Mild PVS                                   |
| Mild AoS                                   |
| Mild AoI                                   |
| Mild DPL                                   |
| Acyanotic with repercussion (need for surgery) |
| Moderate or large IAC and IVC with pulmonary hypertension |
| Moderate to severe PVS                     |
| Moderate to severe AoS or AoI              |
| Moderate to severe DPL                     |
| Cyanotic with and without repercussion     |

IAC: Interaatrial communication, IVC: Interventricular communication, PVS: Pulmonary valve stenosis, AoS: Aortic stenosis, AoI: Aortic insufficiency, DPL: Double pulmonary lesion
The mean visual acuity was 0.86 (0.01–1.5). In 12 children younger than 4 years, we could not measure the visual acuity (9.6%). About 14.8% had visual acuity below 0.6 and 2.8% below 0.1. Emmetropia was 52.0%, hypermetropia was 32.0%, astigmatic was 10%, myopic was 4%, and anisometropia was 2%. Strabismus was found in 7.4% and cataracts in 1.7%. Retinal alterations were recognized in 13.5%, of which 4.8% were related to vascular narrowing or dilation and/or diseases arteriovenous cros: 7.14% were related to increased vascular tortuosity, while 1.6% were related to active toxoplasmic chorioretinitis lesions. Joint alterations to motor function or biomicroscopy or fundoscopy were detected in 24% [Table 2].

In the multivariate analysis, the outcome “any ocular alteration” was found to significantly relate to low levels of acuity (P = 0.02). No relationships were noted between demographic data and treatment with pharmaceutical drugs. Type of heart disease or surgical treatment showed borderline significance when analyzed in isolation [Table 3].

With regard to the fundoscopic alterations, no relationship was found in the multivariate analysis with demographic data or forms of treatment. In isolation, the presence of retinal alterations was significantly related to some kind of heart disease (P = 0.04), being more prevalent in relation to type 4 (28.0%) where relative risk = 1.2. However, when controlled by race, type of heart disease, and surgical treatment, only low visual acuity (under 0.02) showed a significant relationship with the fundus outcome findings [P = 0.02, confidence interval Table 3]. There was 95% agreement between examiners.

Discussion

In this study, the prevalence of ocular abnormalities in children with CHD not associated with genetic syndromes was (1) 20.4% with acuity lower than 0.6; (2) 13.5% with fundus alterations; and (3) 7.4% with isolated strabismus. Combined alterations of the motor function and anterior or posterior segments were found in 30 patients (24%). The lower visual acuity was related to refractive problems, strabismus, and cataract. Cyanotic heart disease showed a significant relationship with retinal findings only in the univariate analysis.

The only systematic review available on this subject brings together information on 1061 children, 32.5% of whom showed some ocular abnormality. The most common findings described in relation to nonsyndrome-associated CHD are cataract (0.5%–2.3%), strabismus (1.5%–14%), retinal vascular tortuosity (15.5%–35%), retinal vascular dilation (6.3%–40%), retinal vascular narrowing (20%), and hemorrhages (4.4%). However, there was high heterogeneity or any kind of variability among the studies reviewed (I² = 85%). I² describes the percentage of variability not caused by chance.[24]

Strabismus has shown itself to be more frequent among children with CHD. The prevalence we found was equally higher than that described in relation to strabismic people without heart disease, even though a mechanism has not been proposed thus far (2.1%–3.3%).[25,26] Cataract prevalence was not different from that found in people without heart disease.[27]

Described fundoscopic alterations include vascular narrowing or dilation, increased dorsal reflex, abnormal vascular tortuosity, arteriovenous crossings, retinal neovascularization, hemorrhages, and tractional retinal detachment. The prevalence of tortuosity in the retinal vessels of children unlinked to systemic or ocular diseases has not yet been completely established. It has been described among 13% (218 cases) of monzygotic or dizygotic twins, the vast majority of which were proven to be of genetic origin.[28] The CHASE study did not find differences between races in relation to geometric arteriolar mean values, and tortuosity was positively associated with triglycerides, total and low-density lipoprotein cholesterol levels, and systolic and diastolic pressures.[29] However, this was a school-based survey of children with 11 years and older, with semi-automated measures. Our sample included only cases with CHD and 58.8% were under 10 years of age.

It is accepted that age, transmural pressure, hypoxemia and VEGF release, increased blood viscosity, and endothelial dysfunction are some of the factors most commonly associated with tortuosity.[30–32] On the other hand, arteriolar narrowing in childhood may also be related to age, weight at birth, and growth rate during the first 24 months of life.[33] What is most evident is that among children with CHDs (20% greater risk in our series), particularly diseases associated with prematurity, low weight, or very rapid growth in the 1st month of life, the number of fundoscopic findings is more prevalent, although a more definitive cause–effect definition is lacking, given that all the existing studies are cross-sectional.[33–35]

There is clinical evidence that more than half of these children with CHD have neurological abnormalities which can influence posterior neural development.[34–37] The retina and the optic nerve have the same central nervous system (CNS) embryological origin. As such, analysis of these repercussions is mandatory, besides evaluating other disabling functional losses. In our records, little information was found on neurological status. Thus, it was not possible for us to analyze this point.
Table 2: Sample description by demographic and ophthalmic examination. Any ocular finding in children with congenital heart disease according to the following independent variables: crude prevalence and association (n=124)

| Variable                              | n (%) | Percentage (95% CI) | P               |
|---------------------------------------|-------|---------------------|-----------------|
|                                       |       | Prevalence          | Poisson regression |
| Age (years)                           |       |                     |                 |
| <4                                    | 19 (15.3) | 15.3 (7.3-38.0) | 1               |
| 5-10                                  | 54 (43.5) | 21.6 (9.8-33.2) | 1.05 (0.87-1.27) | 0.8 |
| >10                                   | 51 (41.2) | 20.0 (8.5-31.4) | 1.15 (0.97-1.36) |
| Sex                                   |       |                     |                 |
| Male                                  | 70 (55.5) | 21.5 (11.2-31.8) | 1               |
| Female                                | 56 (44.5) | 19.6 (8.3-30.8) | 0.98 (0.86-1.13) | 0.79 |
| Race                                  |       |                     |                 |
| White                                 | 95 (81.2) | 46.1 (14.9-33.3) | 1               |
| Black                                 | 13 (11.1) | 7.7 (~9.0-24.4) | 0.86 (0.74-1.01) | 0.10 |
| Others                                | 9 (7.7) | 11.1 (~14.4-36.7) | 0.89 (0.73-1.09) |
| Cardiopathy                           |       |                     |                 |
| Minimal lesion                        | 18 (14.3) | 12.5 (~5.7-30.7) | 1               |
| Acyanotic and no repercussion         | 39 (30.9) | 16.2 (3.7-28.6) | 1.03 (0.86-1.23) | 0.056 |
| Acyanotic with repercussion           | 44 (34.9) | 19.0 (6.6-31.4) | 1.05 (0.88-1.26) |
| Cyanotic                              | 25 (19.9) | 38.0 (15.4-60.7) | 1.22 (0.97-1.30) |
| Clinical treatment                    |       |                     |                 |
| No                                    | 86 (75.4) | 20.9 (6.9-88.0) | 1               |
| Yes                                   | 28 (24.6) | 20.0 (3.1-36.8) | 0.99 (0.85-1.15) | 0.91 |
| Surgery                               |       |                     |                 |
| No                                    | 51 (42.9) | 14.0 (7.6-95.9) | 1               |
| Yes                                   | 68 (57.1) | 27.8 (16.2-39.4) | 1.12 (1.04-1.24) | 0.06 |
| Visual acuity right eye               |       |                     |                 |
| <0.2                                  | 4 (3.7) | 75.0 (~4.5-154.5) | 1               |
| 0.3-0.6                               | 18 (16.7) | 44.4 (19.0-69.8) | 0.82 (0.61-1.10) | <0.001 |
| >0.61                                 | 86 (79.6) | 13.2 (5.8-20.7) | 0.64 (0.50-0.83) |
| Visual acuity left eye                |       |                     |                 |
| <0.2                                  | 3 (2.8) | 66.6 (~11.0-175.7) | 1               |
| 0.3-0.6                               | 13 (12.0) | 42.8 (13.2-72.5) | 0.85 (0.59-1.24) | 0.003 |
| >0.61                                 | 92 (85.2) | 15.9 (8.1-23.7) | 0.69 (0.50-0.96) |
| Refraction                            |       |                     |                 |
| Emmetropic                            | 52 (52) | 14.0 (4.0-23.9) | 1               |
| Hyperopic                             | 32 (32) | 20.6 (5.0-36.3) | 1.05 (0.91-1.22) | 0.01 |
| Astigmatism                           | 10 (10) | 60.0 (23.0-96.9) | 1.40 (1.13-1.72) |
| Myopic                                | 4 (4) | 25 (~5.4-104.5) | 1.09 (0.77-1.58) |
| Anisometropic                         | 2 (2) | 50 (~5.8-685.3) | 1.31 (0.82-2.10) |
| External motricity                    |       |                     |                 |
| Normal                                | 113 (92.6) | 14.0 (7.3-20.7) | 1               |
| Strabismus                            | 9 (7.4) |                     |                 |
| Biomicroscopy                         |       |                     |                 |
| Normal                                | 113 (96.5) | 18.5 (11.3-25.8) | 1               |
| Cataract                              | 2 (1.7) |                     |                 |
| Nevus of Ota                          | 1 (0.9) |                     |                 |
| Nevus iris                            | 1 (0.9) |                     |                 |
| Fundoscopy                            |       |                     |                 |
| Normal                                | 109 (86.5) | 8.0 (2.5-13.4) | 1               |
| Abnormal vessels caliber              | 6 (4.8) |                     |                 |
| Abnormal vascular tortuosity          | 9 (7.1) |                     |                 |
| Others                                | 4 (1.6) |                     |                 |

CI: Confidence interval

More recently, the use of optical coherence tomography (OCT) has corroborated previous impressions regarding damage in the neuronal context. Evidence of delayed myelinization, functional and
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Table 3: Any ocular-associated findings following adjusted analysis (n=124)

| Variable | PR (95% CI) | P  |
|----------|-------------|----|
| First level | | |
| Race | | |
| White | 1 | |
| Black | 0.97 (0.78-1.19) | 0.12* |
| Others | 0.80 (0.64-1.00) | |
| Second level | | |
| Cardiopathy | | |
| Minimal lesion | 1 | |
| Acyanotic and no repercussion | 1.10 (0.85-1.42) | 0.88 |
| Acyanotic with repercussion | 1.07 (0.84-1.37) | |
| Cyanotic | 1.09 (0.80-1.40) | |
| Surgery | | |
| No | 1 | |
| Yes | 1.09 (0.95-1.25) | 0.33* |
| Visual acuity | | |
| <0.2 | 1 | |
| 0.3-0.6 | 0.91 (0.54-1.52) | 0.02* |
| >0.6 | 0.87 (0.56-1.35) | |
| Refraction | | |
| Emmetropic | 1 | |
| Hyperopic | 1.07 (0.90-1.26) | 0.08* |
| Astigmatism | 1.32 (1.04-1.68) | |
| Myopic | 0.92 (0.61-1.39) | |
| Anisometropic | 1.40 (0.86-2.26) | |

*Wald’s linear trend test, †Wald’s heterogeneity test. PR: Prevalence ratio, CI: Confidence interval

Volumetric development, glial band formations, and CNS convolutions is described in 20% of children with CHD. OCT provides evidence, in small series, of decreased macular thickness atrophy and loss of nerve fiber layer, and the field of vision shows corresponding alterations in mean deviation in children with CHD.[31,32]

One limitation of this study is related to its design (cross-sectional) which prevents direct proof of cause and effect. Another one is the population studied as it represented cases already having outpatient management and in a noncritical state, without data on ocular findings before surgery or at the beginning of pharmacological treatment in many cases, and only 20% of the sample were cyanotic. Moreover, retinal assessments were qualitative, and even though the agreement between examiners was high, estimates do not offer the same precision. There are several articles on the subjective agreement between observers in retinal evaluation.[5,34] Semi-automated or automated quantitative analysis using integrated equipment predominates in more recent studies. We do not know neither birth weight (only the prematurity reported by family members)nor growth rates in our patients and any role these variables may have had was not able to be analyzed. We decided to analyze the sample as a whole and in subgroups according to age. Premature babies may have ocular signs related to their gestational age. Although for the subgroup (<4 years) we did not measure Snellen visual acuity in many cases, the other tests were done. Moreover, in this sample, no retinopathy of prematurity was diagnosed. However, it is important to highlight this common association. Sometimes, the retinal signs can be mixed or simultaneous and we have to take care to distinguish from those associated with CHD.

However, as yet, there are neither data standardization in relation to ways of acquiring images nor of logarithms and places used to take measurements. Given the different formulas used, comparison of vascular tortuosity is impractical. Furthermore, the software used for these measurements and software relating to retinal vessel caliber are very expensive and not publicly available. More subtle findings related to differences between calibers may not be perceptible through traditional clinical examination, even when performed by experienced examiners. All these aspects result in these systems being little used in clinical practice. On the other hand, our study provides the largest known series with captured images, and in terms of the absolute number, it is only surpassed by the study conducted by Mansour et al.[19] (138 nonsyndrome-associated cases).

Conclusion

Children aged up to 15 years of age with primary CHD attending outpatient services have a relevant prevalence of ocular abnormalities. This prompts us to recommend the performance of complete ophthalmological examinations in all cases of CHD. Longitudinal studies in this population using quantitative (OCT) or functional (visual fields or electrophysiological) resources should provide more information.

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Conflicts of interest

There are no conflicts of interest.

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