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ORIGINAL ARTICLE

Ophthalmic Manifestations in Children and Young Adults with Down Syndrome and Congenital Heart Defects

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ABSTRACT

Purpose: To investigate whether different types of ocular manifestations are associated with congenital heart disease (CHD) in a large Caucasian population of children and young adults with Down syndrome (DS).

Methods: Population-based, case-control study which included 185 subjects with DS (mean age 13.2 ± 7.9 years), who reported presence or absence of CHD; DS with CHD group (51 subjects, mean age 10.6 ± 5.6 years) and DS without CHD (134 subjects, mean age 14.2 ± 8.4 years).

Results: In our sample with DS and CHD, strabismus was found in 15 subjects (29.4%), nystagmus in 1 (2.0%), epiblepharon in 21 (41.2%) and Brushfield spots in 15 (31.3%). In the DS without CHD group, strabismus was found in 38 participants (28.4%), nystagmus in 13 (9.7%), epiblepharon in 31 (23.5%) and Brushfield spots in 21 (16.0%). Only the variables epiblepharon and presence of Brushfield spots differed significantly between the two groups ($p = 0.02$ and $p = 0.03$, respectively). Hyperopia was present in 26 participants (53.1%) in the DS with CHD group, and in 65 (57.0%) in the DS without CHD group. Oblique astigmatism was present in 25 (52.1%) in the DS with CHD group and in 61 (53.5%) in the DS without CHD group.

Conclusions: Frequencies of DS participants presenting with strabismus, nystagmus, hyperopia and oblique astigmatism were not statistically different between those with CHD and those without CHD in this sample. Further studies are needed to confirm if there are associations between the presence of Brushfield spots or epiblepharon and CHD in patients with DS.

Keywords: Brushfield spots, congenital heart defects, Down syndrome, epiblepharon, nystagmus, refractive errors, strabismus

INTRODUCTION

One of the best characterized chromosomal disorders is Down syndrome (DS), which results from an extra copy of part or all of chromosome 21. Congenital malformations are more common in individuals with DS than in the general population. Ophthalmic manifestations are present in a higher percentage of the DS population compared with the general population.[1–3]

Previous reports have rarely included and correlated systemic diseases with ophthalmic malformations in patients with DS. Congenital heart defects

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(CHD) are a common finding in DS, with a frequency of 18.3–40%.[4,5] Previous studies found that myopia[6–8] and nystagmus[7] were more frequent ocular findings in children with DS and CHD compared to those without such malformations, suggesting that CHD might be related to ocular malformations in these patients. The basis for the association of CHD and reported ocular manifestations in DS is not clear. Therefore, our aim was to investigate whether different types of ocular manifestations are associated with CHD in a large Caucasian population of children and young adults with DS, and to compare our findings with those described in other regions of the world.

MATERIALS AND METHODS

Sample and Population

A total of 185 non-selected Caucasian children and young adults with DS were enrolled in a population-based, case-controlled study. The study population included two groups of subjects: an examined group with DS and CHD (51 subjects, 10.6 ± 5.6 years) and a control group with DS without CHD (134 subjects, 14.2 ± 8.4 years). The study setting was clinical practice. Participants were seen in the private polyclinic ''Medika plus'' in the capital Skopje, Macedonia, in the private polyclinic ''Svjetlost'' in Zagreb, Croatia, as well as in local private offices in eight other towns in Macedonia and in one other town in Croatia, in the period from March 2007 until July 2009.

The study adhered to the tenets of the Declaration of Helsinki and the local ethics committee of the University Ss Cyril and Methodius, Skopje, Macedonia approved the study protocol. For every individual with DS, parental informed consent was obtained.

Measures

Protocols for general health and presence of CHD[9,10] (recorded from medical records), birth dates and ocular examination which included inspection, biomicroscopy, cycloplegic refraction, ocular alignment and motility were fulfilled. The cardiologist of this study group extracted all relevant cardiological data from the medical records. All patients were previously evaluated by pediatric cardiologists, which included echocardiographic examination as a part of the screening program for CHD in DS patients. According to echocardiographic examination, classification of different types of CHD was made on the presence of: (1) ventricular septal defect; (2) atrial septal defect; (3) atrioventricular septal defect; (4) ductus arteriosus; (5) mitral valve prolapse; and (6) Tetralogy of Fallot.

Objective Refraction

Cycloplegic refraction was performed after 3–5 installations of 1 drop of cyclopentolate 1% and assessed by retinoscopy and autorefractometry where feasible (Potec Auto-Ref-Keratometer PRK-5000, Daejeon, Korea). For each subject, spherical equivalent, power and axis of cylinder were recorded. Emmetropia was defined as refractive error between –0.75 diopter (D) and +0.75 D spherical equivalent. Myopia was defined as <–0.75 D spherical equivalent and hyperopia was defined as >+0.75 D spherical equivalent.

Clinically significant astigmatism was defined as refractive error ≥1.0 D of cylinder. In the evaluation of the astigmatism group, the minus form of the cylinder was used. The axis of astigmatism was classified as with the rule, against the rule and oblique astigmatism or axis between 100–170 and 10–80. Eyes with cylindrical power <1.0 D were excluded from the astigmatism group.

Eye Alignment and Ocular Motility

Alignment of the eyes was as standard evaluated for distance fixation using Hirschberg's corneal reflex method, and cover test. A cover test was also performed using an accommodative fixation target. Both distance and near ocular alignment were tested with optical correction, if prescribed. Deviation from the straight position was classified as esodeviation, exodeviation or vertical deviation. Classification of deviation was done according to The Royal College of Ophthalmologists (RCOPHTH)[11] guidelines on infantile esodeviations, acquired esodeviations, exodeviations and vertical deviations.

Infantile esodeviations were defined as constant esodeviations with an onset before 6 months of age reported by the parent. All other cases of esodeviations were classified as acquired esodeviations. Intermittent exotropia and manifest exotropia were designated as exodeviation.[12] The presence of nystagmus was noted (latent or manifest).

External Eye, Anterior and Medial Ocular Segment

The presence of epicanthic folds, epiblepharon and hypertelorismus was established by inspection of the external eye. The presence of any ocular manifestation on the palpebrae, conjunctiva, or cornea as well as iris and lens, was assessed by biomicroscopy. In this population, 90% of subjects had reliable slit lamp biomicroscopy for visualization of Brushfield spots.

Statistical Analysis

Data were categorized as ordinal and categorical. Descriptive statistics are presented with frequency

tables and graphics, and mean, percentage and corresponding standard deviation (SD) and standard error (SE) are reported. The 2-tailed χ^2 test of independence was applied to corresponding contingency tables and when low subject numbers precluded its use, Fisher's exact test was applied. We report odds ratios (ORs), 95% confidence intervals (CIs) and p values. For testing equality of means (age of parents, spherical equivalent and astigmatism), Levene's test for equality of variances was used and based on its results the corresponding t test for equality of means was applied. Here we report p values with 95% CIs for the differences of means. All tests are 2-sided with alpha level of statistical significance set at 0.05, unless otherwise specified. Data was processed in Microsoft Office Excel 2007 and using the statistical software package R (version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic data of the DS patients with or without CHD are presented in Table 1. In our study population, 108 subjects (58%) were male, of whom 22 had CHD (43.1%), while 77 (42%) were female, of whom 29 had CHD (56.9%). A statistically significant association of sex was detected between DS groups with or without CHD ($p = 0.01$, OR 0.42 95% CI 0.22–0.82 for male compared to female). Cytogenetic confirmation of the DS diagnosis in the DS with CHD group was confirmed in 29.4% ($n = 15$) and in the DS without CHD group in 26.9% ($n = 36$). Different types of CHD in the DS with CHD group are presented in Figure 1. In our study the most frequent CHD type was atrial septal defect, following by ductus arteriosus and atrioventricular septal defect.

In Table 2, different ocular findings in the DS groups with and without CHD are presented. Only variable epiblepharon and presence of Brushfield spots differed significantly between the two groups of DS with and without CHD ($n = 21$, 41.2% vs $n = 31$, 23.5%, $p = 0.02$ for epiblepharon; $n = 15$, 31.3% vs $n = 21$, 16.0%, $p = 0.03$, for Brushfield spots). Presence of strabismus and nystagmus did not differ significantly between these groups. The most common refractive error in both groups was hyperopia, at 53.1% (26 patients) in the DS with CHD group and 57% (65 patients) in the DS without CHD group. Mean numeric values of spherical equivalent in each subgroup of refractive error were examined. In the DS with CHD group, mean spherical equivalent for myopia was −5.2 D (SD 3.8 D), for emmetropia −0.1 D (SD 0.4 D) and for hyperopia 2.9 D (SD 2.1 D), while in the DS without CHD group, mean spherical equivalent for myopia was −8.8 D (SD 5 D), for emmetropia 0 D (SD 0.4 D) and for hyperopia 3.2 D (SD 2.0 D). Statistical significance was present only when comparing the difference of mean spherical equivalents in myopic groups between DS with CHD and DS without CHD ($p = 0.04$, mean difference 3.6 D, 95% CI 0.09–7.12 D). The most common type of astigmatism in both groups was oblique astigmatism,

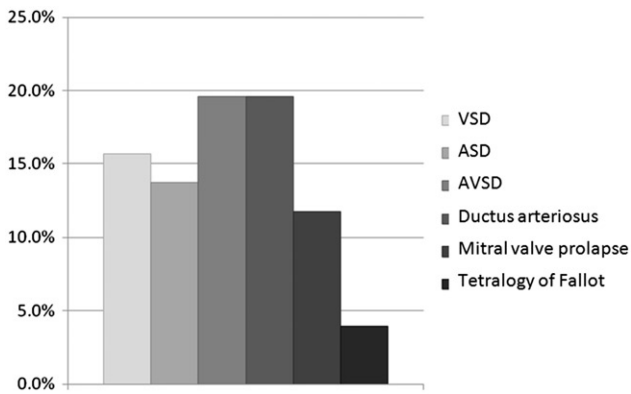

FIGURE 1. Distribution of different congenital heart defects in a population of children and young adults with Down syndrome in Macedonia and Croatia (VSD, ventricular septal defect; ASD, atrial septal defect; AVSD, atrioventricular septal defect).

TABLE 1. Demographic characteristics of children and young adults with Down syndrome with and without congenital heart disease, Macedonia and Croatia.

Characteristic	DS with CHD ($n = 51$)	DS without CHD ($n = 134$)	Mean difference/OR (95% CI)	p Value
Age, mean years (SD)	10.6 (5.6)	14.2 (8.4)	−3.6 (−5.70 to −1.48)	**<0.01**[a]
Maternal age, mean years (SD)	27.9 (5.6)	29.7 (6.4)	−1.8 (−3.81 to 0.24)	0.08[b]
Paternal age, mean years (SD)	31.5 (6.4)	33.3 (7.0)	−1.8 (−3.96 to 0.52)	0.13[b]
Male sex, % (SE)	43.1 (9.2)	64.2 (4.1)	0.42 (0.22 to 0.82)	**0.01**[c]

[a]Welch two-sided t test.
[b]Two-tailed Student's t-test.
[c]χ^2 test of independence for 2×2 contingency table (df = 1).
DS, Down syndrome; CHD, congenital heart disease; SE, Standard error; SD, standard deviation; CI, confidence interval; OR, odds ratio (DS with CHD compared to DS without CHD). All bold p values are statistically significant.

TABLE 2. Ocular findings in children and young adults with Down syndrome with and without congenital heart disease, Macedonia and Croatia.

	DS with CHD ($n=51$) % (SE)	DS without CHD ($n=134$) % (SE)	OR (95% CI)	p Value
Ocular alignment				
Strabismus	29.4 (6.4)	28.4 (3.9)	1.05 (0.52 to 2.14)	0.89[b]
Nystagmus	2.0 (1.9)	9.7 (2.6)	0.19 (0 to 1.31)	0.12[c]
Refractive errors				
Myopia	20.4 (5.8)	23.7 (4.0)	0.83 (0.36 to 1.87)	0.65[b]
Hyperopia	53.1 (7.1)	57.0 (4.6)	0.85 (0.43 to 1.67)	0.64[b]
Emmetropia	26.5 (6.3)	19.3 (3.7)	1.51 (0.69 to 3.32)	0.30[b]
Astigmatism	68.8 (6.7)	65.8 (4.4)	1.14 (0.56 to 2.36)	0.72[c]
Oblique	52.1 (7.2)	53.5 (4.7)		
ATR	8.3 (4.0)	10.5 (2.9)		
WTR	8.3 (4.0)	1.8 (1.2)		
No astigmatism	31.3 (6.7)	34.2 (4.4)		
Anterior and medial segment				
Epiblepharon	41.2 (6.9)	23.5 (3.7)	2.28 (1.36 to 3.82)	**0.02**[b]
Epicanthus	31.4 (6.5)	19.5 (3.4)	1.88 (0.91 to 3.91)	0.12[b]
Hypertelorism	4.0 (2.8)	8.5 (2.4)	0.45 (0.05 to 2.19)	0.52[c]
Conjunctivitis	5.9 (3.3)	7.6 (2.3)	0.76 (0.13 to 3.11)	1.00[c]
Blepharitis	21.6 (5.8)	15.3 (3.1)	1.53 (0.67 to 3.46)	0.38[b]
Blepharoconjuctivitis	8.0 (3.8)	8.5 (2.5)	0.93 (0.21 to 3.36)	1.00[c]
Keratoconus grade IV	0.0 (0.0)	0.7 (0.7)	0 (0 to 13.98)	1.00[c]
Corneal changes	2.0 (1.9)	0.7 (0.7)	2.64 (0.03 to 209.98)	0.48[c]
Glaucoma	0.0 (0.0)	1.5 (1.0)	0 (0 to 13.78)	1.00[c]
Brushfield spots	31.3 (6.7)	16.0 (3.2)	2.38 (1.10 to 5.13)	**0.03**[b]
Iris stromal atrophy	28.6 (6.5)	25.4 (3.8)	1.18 (0.57 to 2.45)	0.71[b]
Lens opacities	8.0 (3.8)	7.7 (2.3)	1.04 (0.23 to 3.85)	1.00[c]
Dense cataract	2.0 (2.0)	1.5 (1.1)	1.30 (0.02 to 25.58)	1.00[c]
Congenital cataract	0.0 (0.0)	1.5 (1.1)	0 (0 to 13.9)	1.00[c]
Iris color				
Brown	52.9 (8.6)	64.7 (4.4)		0.45[d]
Blue	29.4 (7.8)	23.3 (3.9)		
Green	17.6 (6.5)	12.1 (3.0)		
Mean spherical equivalent, diopters (SD)			Mean difference (95% CI)	p Value
Myopia	−5.2 (3.8)	−8.8 (5.0)	3.6 (0.09 to 7.12)	**0.04**[a]
Hyperopia	2.9 (2.1)	3.2 (2.0)	−0.3 (−1.20 to 0.67)	0.57[a]
Emmetropia	−0.1 (0.4)	0 (0.4)	−0.1 (−0.35 to 0.23)	0.68[a]

[a]Two-tailed Student's t-test.
[b]χ^2 test of independence for 2×2 contingency table (df = 1).
[c]Fisher's exact test of independence for 2×2 contingency table.
[d]Fisher's exact test of independence for 2×3 contingency table.
DS, Down syndrome; CHD, congenital heart disease; ATR, against the rule; WTR, with the rule; SE, standard error; SD, standard deviation; CI, confidence interval; OR, odds ratio (DS with CHD compared to DS without CHD). All bold p values are statistically significant.

at 52.1% ($n=25$) in the DS with CHD sample and 53.5% ($n=61$) in the DS without CHD group. Mean numeric values of astigmatism in the DS with CHD group were −1.7 D (SD 0.8 D) of cylinder, and in the DS without CHD group −2.0 D (SD 1.0 D) of cylinder.

Different types of strabismus in the DS with CHD and DS without CHD groups are presented in Figure 2. The most common type of strabismus in both groups was acquired esotropia at 53.3% ($n=8$) in the DS with CHD sample, and 57.9% ($n=22$) in the DS without CHD group.

DISCUSSION

Many previous publications describe the rates of various ocular abnormalities in DS patients, without specific study of heart disease, as presented in Table 3. To the best of our knowledge this study has the largest reported group of patients comparing ocular findings in DS subjects with and without CHD. We found statistically significant associations between CHD and Brushfield spots and epiblepharon in our cohort of children and young adults with DS. We are unaware of previous reports examining associations of CHD

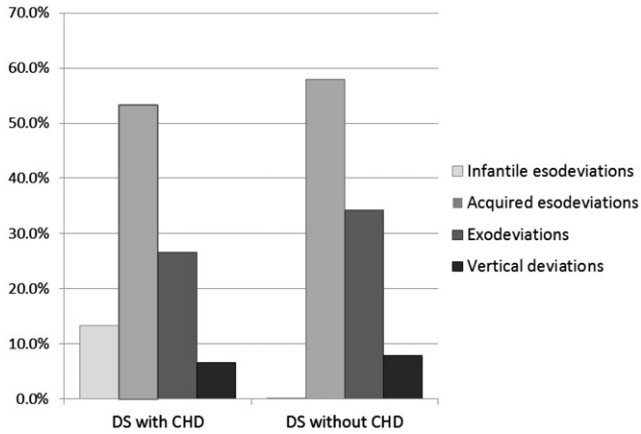

FIGURE 2. Distribution of different types of strabismus in a population of children and young adults with Down syndrome (DS), with and without congenital heart defects (CHDs), Macedonia and Croatia.

with Brushfield spots and epiblepharon in a population with DS and could not find reference to it in a search on the PubMed database. We did not find significant associations between CHD and strabismus, nystagmus or presence of refractive error in our cohort.

This study does not confirm previous findings, showing that in children DS and CHD were more strongly associated with myopia[6–8] or nystagmus.[7] Still, it is only speculation that overexpression of several characteristic genes, resulting either from trisomy or polymorphisms, might lead to the correlation between CHD and myopia, as a result of damage during development of heart and visual pathways.[7,8] Alternatively, another explanation from Afifi and colleagues is that mutations in genes that result in autosomal recessive myopia and cardiac malformations may be more common in the Egyptian population leading to significant correlation of myopia and CHD.[8]

The prevalence of hyperopia in the general DS population ranges from 4–59%.[13,14] Our study found that astigmatism and hyperopia were the most common refractive errors in children and young adults with DS and CHD and that there was no statistically significant association between both groups with any type of refractive error. Prevalence of myopia in different studies ranged from 8–41%,[13,15] and in our study was 22.7%. Our prevalence of myopia was higher compared to Brazilian[6] (12.5%), Egyptian[8] (10%) and British[7] (10.3%) cohorts where a relationship between CHD and myopia was found. The prevalence of clinically significant astigmatism (astigmatism $\geq$ 1.0 D of cylinder) in infants, young children and young adults with DS is between 26 and 53%.[3,16] Oblique astigmatism was the most common astigmatism in DS subjects both with and without CHD.

Strabismus is also a frequent finding in subjects with DS with occurrence between 22 and 57%.[1,6,17] There was no statistically significant relationship between CHD and strabismus in the DS population.

Exact causes of nystagmus is still unknown in DS populations.[8] Frequency of nystagmus in our cohort was 7.6%, while previous studies have ranged from 3–33%.[8,18,19] In our cohort of subjects with DS, there was no relationship between CHD and nystagmus, contrary to the previous results of Bromham and co-authors,[7] where DS children with CHD were more likely to have nystagmus than those without CHD.

The lack of a statistically significant relationship between nystagmus and CHD in our study might be due to an insufficient sample size of study subjects in the two groups.

Epicanthic folds are also common in DS, found in more than 60% of subjects in studies where this was assessed.[6,14,18–20] In our study, epicanthic folds were less reported compared to those studies due to the age of the population and already formed bridge of the nose. There was no significant difference in the frequency of epicanthus in the DS with CHD group compared to the DS without CHD group.

Brushfield spots are visible white or yellow, slightly raised, pinhead points of condensed collagenous tissue in the peripheral iris, usually in a concentric ring.[21] They are also found in about 10% of the general population with blue or green irises, and are infrequently reported in individuals with dark brown irises.[18] Although found in healthy individuals, Brushfield spots are a more common and pathognomonic feature of DS, but racial/ethnic prevalences of Brushfield spots exist. In cohorts with DS from Italy,[14] Malaysia,[19] Korea,[18] China[21] and Egypt,[8] presence of Brushfield spots was not detected. In an Indian cohort of children and young adults with DS, the prevalence of Brushfield spots was 3.2%,[4] in a Slovenian cohort the prevalence was 16.9%,[22] while in a Turkish cohort it was 36.3%.[1] It has also been suggested, based on inconsistencies of correlation with iris color and Brushfield spots in published data, that the wide variation in findings might be related to differences in genetic background.[8] We believe that one of the possible reasons for such differences in prevalence of Brushfield spots in different populations might be due to high prevalences of dark irises especially in eastern Asia populations compared to Caucasian populations. In the Malaysian cohort,[19] slit lamp biomicroscopy was performed in only 25% of children which may have resulted in underestimation of Brushfield spots. In our whole Caucasian cohort we had 36 subjects (20.1%) with Brushfield spots, which was a similar frequency to the Slovenian cohort (16.9%).[22] In our population of DS patients with CHD, the frequency of Brushfield spots differed significantly compared to those with DS without CHD. On the other hand, even though da Cunha

TABLE 3. Comparison of ophthalmic findings in Macedonian and Croatian children and young adults with Down syndrome with previous studies worldwide.

	Caputo et al.[17]	da Cunha and Moreira[6]	Wong and Ho[12]	Kim et al.[18]	Liza-Scharmini et al.[19]	Ljubic et al.[2]	Stirn Kranjc[22]	Afifi et al.[8]	Present study	
Year of publication	1989	1996	1997	2002	2006	2011	2012	2013	2014	
Country	US	Brazil	Hong Kong	Korea	Malaysia	Macedonia and Croatia	Slovenia	Egypt	Macedonia and Croatia	
									DS+CHD	Total
Subjects, *n*	187	152	140	123	60	170	65	90	51	185
Age range	0–26 years	0–18 years	0–13 years	0–14 years	1 month–17 years	1–34 years	2 months–13 years	3 months–10 years	2–23 years	2–34 years
Mean age, years	5.8	-	3.7	6.5	6.7	13.8	-	2.2	10.6	13.2
Hyperopia, %	20.9	25.7	30.0	28.5	25.0	55.2	36.9	16.7	53.1[a]	55.8[a]
Myopia, %	22.5	12.5	8.6	25.2	29.2	20.7	24.6	10.0	20.4[a]	22.7[a]
Astigmatism, %	21.9	60.0	5.7	30.9	8.3	72.4	29.2	14.4	68.8[a]	66.7[a]
Strabismus, %	57.0	38.0	20.0	25.0	26.7	26.5%	26.1[e]	16.7	29.4	28.6
Nystagmus, %	29.0	18.0	11.0	22.0	33.3	11.0	29.2	3.3	2.0	7.6
Upward slanting, %	-	-	100	63.0	-	-	-		-	-
Epicanthus, %	-	-	100	61.0	96.7	-	-	100	31.4	22.8
Epiblepharon, %	-	-	-	54.0	1.7	-	-	-	41.2	28.4
Hypertelorism, %	-	-	-	-	-	-	-	100	4.0	7.2
Conjunctivitis, %	-	-	-	-	6.7	-	-	-	5.9[a]	7.1[a]
Blepharitis, %	-	30.0	-	-	10.0	-	-	-	21.6[a]	17.0[a]
Blepharoconjunctivitis, %	-	-	7.0	16.0	-	-	-	20.0[c]	8.0[a]	8.4[a]
Corneal changes, %	-	-	-	0.8	-	-	-	-	2.0	1.1
Congenital cataract, %	-	-	-	-	13.3	-	-	-	0.0	1.1
Dense cataract, %	-	13.0[b]	-	-	-	-	-	-	2.0	1.7
Lens opacities, %	11.0	-	-	0.8	-	-	12.3	6.0[d]	8.0	7.8
Keratoconus, %	-	-	0.0	0.0	-	-	0.0	0.0	0.0	0.5
Glaucoma, %	5.0	-	0.7	0.8	6.7	-	0.0	0.0	0.0	1.1
Brushfield spots, %	-	52.0	0.0	0.0	-	-	16.9	0.0	31.3	20.1

[a]Percentages are calculated from a smaller sample size, due to missing data as a result of non-cooperation of some subjects.
[b]Total number of cataract findings (divided into three subgroups in our study).
[c]Because of clinical overlap, nasolacrimal duct obstruction, conjunctivitis and blepharoconjunctivitis, were combined and estimated as blepharoconjunctivitis.
[d]As no dense lens opacities were noted, infantile and juvenile cataract were estimated as lens opacities.
[e]Only esotropia.
DS, Down syndrome; CHD, congenital heart disease.

and co-workers[6] found 52% iris abnormalities including Brushfield spots in their population, they did not find any association with CHD.

The frequency of epiblepharon in DS subjects in Asian cohorts ranged from 2–54%.[18,19] We are unaware of previous reports of the prevalence of epiblepharon in patients with DS in Caucasian patients. It has been reported that the prevalence of epiblepharon typically seen in non-DS children and young adults of Asian descent is 9.1%,[23] as well as that natural remission of epiblepharon rarely occurs in the case of DS subjects, in contrast to that reported in the case of non-DS subjects.[18] A total of 52 subjects (28.4%) in our whole Caucasian group had epiblepharon, which was also related to CHD. Results of the first reported Asian cohort[19] contrast both with expected prevalences in non-DS Asian populations and also with the expected natural course. It is difficult to find a possible explanation for the greater association of Brushfield spots and epiblepharon in DS patients with CHD, and any speculation regarding the association as genetic background and/or sample size would probably be limited.

A limitation of the study is a lack of results of posterior ocular segment examination, since a significant number of patients did not cooperate sufficiently for reliable evaluation.

Strabismus, nystagmus, hyperopia and oblique astigmatism did not show statistically significant associations with CHD in this population. Although we found statistically significant associations between CHD and Brushfield spots and epiblepharon in this DS population, the data are not clinically convincing enough to conclude that presence of these ocular malformations suggest a high likelihood of CHD. Further studies are needed to confirm if there are associations between the presence of Brushfield spots or epiblepharon and CHD in patients with DS.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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