

# Is There an Association between Ocular Pathology and Congenital Heart Defects in Patients with Down Syndrome?

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## Abstract

**Background:** Additional chromosomal material dictates the severity of craniofacial dysmorphism, intellectual disability and associated pathologies, mostly Congenital Heart Defects (CHD). High geographical and seasonal fluctuation in CHD has been reported. The presence of type VI collagen both in ocular and cardiac tissue may be the reason for an association between ocular and cardiac disease. **Methods & Materials:** We conducted a prospective study on 54 patients with Down syndrome. Patients were recruited from Genetics Department, between December 2018 and January 2020. All patients underwent a complete eye examination by a general ophthalmologist and a cardiologic evaluation. Results: Congenital heart defects were present in 57% of the DS patients. The most common defect was the interatrial communication present in 7 (14%) of the patients followed by the Fallot tetralogy and a defect in the atrioventricular sept in 6 patients (12%). Astigmatism was the most frequent cause of decreased visual acuity in DS patients with congenital heart. Conclusion: The results of our study did not identify specific associations, with statistical significance, between ophthalmic and cardiac pathology in patients with DS

## Keywords:

Congenital heart defects; Ocular disease; Astigmatism

## Introduction

Minor congenital ocular anomalies are most common in patients with Down Syndrome (DS).<sup>[1]</sup>

Due to the presence of extra genetic material, children with 21 trisomy have associated systemic pathologies.

The amount of additional genetic burden dictates the severity of craniofacial dysmorphism, intellectual disability and associated pathologies.<sup>[2]</sup>

The diagnosis of DS consists of a constellation of more than 80 major or minor markers.<sup>[3]</sup>

The most commonly encountered pathologies are cardiovascular (40%-50%), gastrointestinal (4%-10%) and childhood leukemia.<sup>[4]</sup>

Congenital Heart Disease (CHD) is the most important cause of morbidity and death in patients with DS in the first 2 years of life worldwide.<sup>[5-7]</sup>

High geographical and seasonal fluctuations in the incidence of CHD have been reported.<sup>[8]</sup> In Europe, by far the most frequent CHDs in DS patients are atrioventricular septal defects. [9-10]

A high incidence of ocular abnormalities has prevailed in all studies that describe the prototype of the patient with SD. [11-13]

Eyelid malformations and refractive errors were most often described in these patients. [14-15]

Even if most of the ocular markers present in DS patients are minor or without significant importance, their presence alone or in association with other malformations can offer important clues. Typically, in DS all ocular contents and their adnexa can present anomalies. [16]

The presence of type VI collagen in cardiac tissue (COL6A1) could also be the cause of a certain association between ocular and cardiac anomalies in patients with DS. [17]

The aim of the study was to analyze the ocular profile of DS patients that suffer from a congenital heart anomaly.

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**How to cite this article:** Nemes-Dragan IA, et al. Is There an Association between Ocular Pathology and Congenital Heart Defects in Patients with Down Syndrome? Ann Med Health Sci Res.2021;11:412-415

## Materials and Methods

This prospective study was based on the DS patient’s registry from a Genetics Department between December 2018 and January 2020. The diagnosis of DS was established after clinical examination and was confirmed in all cases through a cytogenetic exam (karyotype and/or fluorescence *in situ* hybridization). All data regarding the patient’s cardiac anomalies was obtained from their medical history.

Study inclusion criteria were: DS patients between 1 and 18 years old on whom a complete ophthalmological assessment could be performed.

Exclusion criteria were: patients for whom we did not have a complete cardiac history.

### Ethical consideration

The study was approved by the Ethical Council of the Hospital. Informed parental consent was required for each assessed patient.

The first step of the clinical examination of the eye included: visual assessment, refraction and assessment of the ocular motility.

The visual acuity and refraction (with and without cycloplegia) were measured according to patient age and intellectual disability. In a nonverbal patient, vision was evaluated in terms of fixation (eccentric or central fixation) and duration. In verbal patients it was tested using optotypes (Snellen chart, tumbling E chart). Cycloplegia was carried out in all patients through instillation of 3 drops of Tropicamide 1%. According to age and compliance, refraction was measured with an auto refractometer (Tomey RC-800 Auto Ref/K) or PlusOptix A12C or streak retinoscopy in non-compliant patients.

The ophthalmic assessment included the inspection and slit lamp examination of the ocular adnexa. The ruler was used to

measure the intercanthal and interpupillary distance, necessary parameters for establishing the proper diagnosis of hypertelorism or of telecanthus. The vertical palpebral fissure was measured using the cornea superior eyelid index or the pupil superior eyelid margin index. The eyelash line and Meibomian glands line were assessed using the slit lamp. A gross examination of the conjunctiva and the lacrimal system was made in a well-lighted room and after that through magnification by means of a slit lamp.

The eyeball assessment was performed from anterior to posterior, first time in miosis and after that in mydriasis (Tropicamide 1%). The fundus exam was performed using indirect ophthalmoscopy when we had good compliance or the ophthalmoscope for less compliant patients (Welch Allyn Panoptic). The optic nerve head and disc, macula with fovea, the periphery of the macula and retinal vessels were followed from the emergence to the periphery.

All patients in the study benefited from a detailed systemic clinical examination and those older than 3 also had an IQ test.

## Results

We examined a total of 54 patients, 25 female (46%) and 29 males (54%). The mean age of the study participants was 8.78 years.

Congenital heart disease was present in 31 (57%) of the DS patients. The most common defect was the Atrial Sept Defect (ASD) present in 7 (14%) of the patients followed by the Fallot tetralogy and the Atrioventricular Sept Defect (AVSD) in 6 patients (12%), tricuspid insufficiency in 5 (10%) patients, interatrial and intraventricular communication in 4 (8%) patients and 3 patients presented with other birth defects. The category of other birth defects includes arterial canal patency, pulmonary stenosis and heart failure of other causes [Table 1].

Table 1: Prevalence of the congenital heart disease

Congenital cardiac disease	Nr.	% Patients
Atrial sept defect	7	14
Fallot tetralogy	6	12
AtrioVentricular Sept Defect (AVSD)	6	12
Tricuspid insufficiency	5	10
Interatrial and Intra Aventricular Communication (IAC)	4	8
Other birth defects	3	6
Total	31	58.49

The most frequent cause of decreased visual acuity in DS patients with congenital heart disease was astigmatism (35 eyes) [Table 2]. Because there have been many cases of anisometropia, the total number of eyes with a refractive error

has been taken into account. Astigmatism was equally well represented (34 eyes) among patients with DS but without congenital heart disease.

**Table 2: Ocular pathology in DS patients**

Ocular pathology	Nr of affected eyes in patients with CHD	Nr of affected eyes in patients without CHD
Astigmatism	35	34
Hyperopia	30	28
Myopia	27	11
Esotropia	10	6
Blepharitis	7	3
Lens opacities	6	4
Brushfield spots	5	6
Nystagmus	4	2

The same number of eyes were diagnosed with hyperopia in both those who suffer from CHD and those without CHD. Myopia had a higher prevalence among those with CHD, 27 eyes versus 11 eyes in those without CHD.

Esotropia was the only ocular deviation detected in patients in our group. 10 DS patients with CHD were diagnosed with an ocular deviation and also 6 DS patients without CHD [Table 2].

Inflammation of the eyelid margin (blepharitis) was present more often in patients with CHD, 7 vs. 3 patients without CHD.

Ocular examination revealed 6 patients with CHD and lens opacities and 4 patients without CHD and lens opacities. Brushfield spots were present in 6 patients with DS and without CHD and in 5 patients with CHD [Table 3].

**Table 3: Distribution of astigmatism in patients with CHD**

Cardiac malformations	Nr patients with myopic astigmatism	Nr patients with hyperopic astigmatism
Atrial sept defect	7	0
Tricuspid insufficiency	5	3
Fallot tetralogy	5	2
Atrioventricular Sept Defect(AVSD)	1	2
Interatrial communication	1	3
Other birth defects	1	3
Total	17	13

Nystagmus was present in 4 patients with CHD and 2 patients without CHD.

Regarding the type of astigmatism in patients with CHD, the myopic type prevails over the hyperopic one. Most often the myopic type has been associated with IAC, 7 patients out of a total of 17.

All refractive errors and ocular pathology were correlated with each cardiac malformation using Fischer's exact test, but the results were without statistical significance ( $p > 0,05$ ).

Except for the Brushfield spots, any ocular pathology found in patients with DS was more common in those with CHD.

## Discussion

It has been shown by other authors that there is a correlation between certain refractive errors, most often myopia or astigmatism, and some cardiac anomalies.<sup>[18-20]</sup>

The data obtained in our study showed that there is no correlation with statistical significance ( $p > 0,05$  calculated with exact Fischer test) between a cardiac malformation and a certain refractive error, ocular deviation (esotropia was the only ocular deviation present in our patients) or other ocular pathology which could cause decreased visual acuity or a decrease in the quality of life of these patients.

Atrial sept defect, Fallot tetralogy and atrioventricular sept defect were the most common CHD found in our patients results, in concordance with other studies from Europe and Africa.<sup>[21,22]</sup>

In contrast with the results of our study, the group of DS studied by Afifi et al. revealed a correlation between CHD and myopia in subjects with DS. The results were interpreted by the author as a genetic feature found in the inhabitants of the Nile region river and the city of Cairo.<sup>[20]</sup>

Similar with Bromham, Morreale-Bubella et al. and Afifi studies<sup>[19,20,23]</sup> myopia was more common in patients with CHD than in those without CHD. Al-Jarallah et al. mention the role of consanguinity in DS population from Saudi Arabia and Egypt.<sup>[24,20]</sup> The explanation would be the presence of a copy of chromosome 21 in cells that could increase the expression of some genes. Other hypothesis launched by Bromham would be that genes located on chromosome 21 participate in the development of the cardiac system.<sup>[23]</sup>

The genetic polymorphism involved in cardiac pathology could explain a certain association with myopia.

Ljubic et al. found no statistical significance between any refractive error, strabismus or nystagmus with certain CHD. The explanation for these results may be the small number of subjects studied with DS and CHD. The authors also described an association of statistical significance that has not been cited in other studies, the combination of Brushfield spots and epiblepharon with CHD. In contrast, in our study, Brushfield spots were the only DS ocular marker less common in patients with DS and CHD.<sup>[25]</sup>

## Conclusion

The results of our study did not identify specific associations, with statistical significance, between ophthalmic and cardiac pathology in patients with DS. However, it is important to perform an early ophthalmic screening in patients with DS with or without CHD.

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