

Analyzing Ocular and Systemic Findings of Patients with Down Syndrome

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ABSTRACT

Objective: The aim of this study was to analyze the ocular and clinical findings of patients with Down syndrome.

Methods: A total of 72 patients, aged between 4 months and 22 years (mean: 5.5±5.1 years), were included in the study. All of the patients had been genetically analyzed and diagnosed with Down syndrome. The results of eye examinations and the accompanying systemic findings of the patients were obtained from computer records and the families. A visual acuity assessment, biomicroscopy, fundus examination, cycloplegic refraction, and in required cases, a fluorescein dye disappearance test, were performed.

Results: Of the 72 patients, 48 (67%) were male and 24 (33%) were female. Chromosome analysis revealed regular trisomy in 69 patients (96%), a genetic mosaic in 2 patients (3%), and a translocation pattern in 1 patient (1.4%). The results of the eye examination of patients revealed refractive errors (85%), upward slanting of the palpebral fissures (68%), epicanthus (63%), strabismus (33%), blepharitis (22%), retinal pathologies (19%), cataract (19%), nasolacrimal duct obstruction (17%), Brushfield spots (17%), eyelid laxity (11%), nystagmus (4%), and keratoconus (3%). The systemic findings identified were congenital heart disease (36%), hypothyroidism (31%), growth retardation (7%), hearing loss (6%), undescended testis (4%), asthma (4%), Hirschsprung's disease (1.4%), and autism (1.4%). No refractive error was observed in 11 patients (15%), and no systemic disease was seen in 13 patients (19%). Astigmatism was the most frequent finding (68%), followed by hyperopia (47%) and myopia (19%). The most common congenital heart disease was a septum defect (33%).

Conclusion: Ocular problems and systemic diseases are more common in patients with Down syndrome. Early diagnosis and treatment will make it easier for patients to adapt to all aspects of life.

INTRODUCTION

Trisomy 21, also known as Down syndrome, was first described by Edouard Onesimus Seguin in 1846, but was first introduced to the literature with written data in 1866 by John Langdon.^[1] The incidence is 1:750–1000 in neonates, and it is the most common chromosomal disease in humans.^[2] Its main features include typical facial and head appearance (cranio-facial dysmorphism), varying degrees of mental retardation, hypothyroidism, congenital heart defects, gastrointestinal (GIS) problems, ocular anomalies, hearing impairment, and immunodeficiency.

Chromosome analysis of Down syndrome cases revealed complete trisomy 21 resulting from meiotic “non-disjunction” with a rate of 95%, 4% translocation and 1% mosaicism.^[3] While the somatic cell chromosome structure of the parents of the patients with complete trisomy 21

was found to be normal and 47 chromosomes were detected due to “non-disjunction” during gametogenesis, in translocation Down syndrome, in addition to two copies Chromosome 21 that are free, there is a third copy of chromosome 21 that is translocated to chromosome 14, 21 and rarely 22. In the mosaic type, normal and trisomic cell lines coexist as a result of post-zygotic division error, but the clinical picture is usually similar.^[4]

Ocular findings of patients with Down syndrome are diverse and these findings are not diagnostic. They can be also seen rarely in normal individuals or in patients with other mental and physical defects. Pathologies such as epicanthus, upward slanting palpebral fissures, eyelid laxity, iris and retinal anomalies can be seen in these cases, as well as refractive errors, cataract, strabismus, lacrimal drainage problems, keratoconus, nystagmus and amblyopia that may cause serious problems. The nature of the anom-

alies in Down syndrome cases indicates that the globe is affected in the late stage of embryological development. While some of the findings are present at birth, some of them appear as the child grows up.^[5]

Although congenital heart defects are the most common systemic diseases, hypothyroidism, GIS anomalies, hearing problems, neuromuscular disorders, musculoskeletal disorders and immunological disorders are also common.

Although Down Syndrome cases can be easily recognized by their phenotypic features, related systemic diseases and ocular findings, there are various clinical variations among patients. Therefore, we aimed to investigate the ocular and associated systemic findings of patients with Down syndrome admitted to our clinic.

MATERIALS AND METHODS

A total of 72 patients with Down syndrome who were examined in the outpatient clinic between January 2016 and March 2018 were included in the study. Chromosomal analysis of all cases was obtained by short-term cell cultures of lymphocytes in genetic diagnosis centers and patients had definitive diagnosis as Down syndrome. In addition to eye examinations, the systemic findings of the patients were obtained from computer records and, if necessary, from their families, and by requesting a pediatric and cardiology consultation. Visual acuity examination, cycloplegic refraction, biomicroscopy and fundus examination were performed, and when necessary, fluorescein dye disappearance test was performed in all patients.

Visual acuity was measured with Snellen chart according to age and compliance of the cases. Refractive errors were calculated by taking cycloplegic spherical equivalent into account. The difference between refractive error of 1.0 diopters (D) and above between the two eyes was considered as anisometropia, and values out of -1.0 D and +2.0 D range were considered as ametropia. Cylindrical values of one diopter and above were accepted as astigmatism.

The features of palpebral fissure, presence of eyelid pathologies such as epicanthus and eyelid laxity were investigated. 2 mm or more upward and outward inclination of lateral canthal angle from the medial canthal angle; was considered as 'upward slanting palpebral fissure'. The term eyelid laxity is used for eyelids that spontaneously show eversion backward when the child cries or when the lid is opened for examination.

Eyelids, conjunctiva, cornea, iris and lens examinations were performed by biomicroscopy in compatible patients. Incompatible patients were examined macroscopically with the aid of light source or indirect ophthalmoscope. The presence of strabismus was examined in primary position with Hirschberg and/or cover-uncover test, and the angle of deviation, if any, was determined by Krimsky or prism cover test. Eye movements were evaluated and presence of limitation and excessive functions and nystagmus were recorded.

All cases received 1% cycloplegine drop (1% cyclopentolate hydrochloride) for refraction and fundus examination. A history of epiphora and/or fluorescein dye disappearance test revealed nasolacrimal duct obstruction.

RESULTS

A total of 72 Down syndrome patients (48 male and 24 female), aged between 4 months and 22 years (mean 5.5±5.1 years) were included in the study. Chromosome analysis revealed trisomy 21 in 69 patients (96%), mosaic in 2 patients (3%) and translocation pattern in 1 patient (1.4%) (Table 1).

The most common ocular problem was refractive error (85%). Forty-nine patients (68%) had astigmatism, 34 patients (47%) had hyperopia, 14 patients (19%) had myopia, while 13 patients (18%) had anisometropia. Eleven (15%) cases had no refractive errors.

When the eyelid problems were evaluated; upward eyelid slanting was found in 49 cases in 45 (63%), blepharitis in 16 (22%), eyelid laxity in 8 (11%) and bilateral upper eyelid ectropion in 1 case. Nasolacrimal duct obstruction was present in 12 cases (17%).

Strabismus was detected in 24 (33%) patients, 20 (83%) of them had esotropia and 4 (17%) had exotropia. No vertical deviation was detected in any of our patients. Nystagmus was detected in 3 cases (4%), all of whom were operated for bilateral white cataracts. Nystagmus was horizontal in 2 cases and rotary in 1 case.

Cataract was detected in 14 cases (19%). Four cases (29%) had sutural cataract, 4 cases (29%) had blue dot cataract, 3 cases (21%) had bilateral white mature cataract and 3 cases (21%) had posterior polar cataract.

Iris anomalies was present in 17 cases (24%). Of these, 12 (71%) had Brushfield spots, 4 (23%) had stromal hypoplasia, and 1 (6%) had iris coloboma. Only 2 patients (3%) had keratoconus as a corneal pathology.

Retinal and optic nerve changes were detected in 14 cases (19%). Increased retinal pigmentation was present in 7 cases (50%), peripapillary atrophy in 2 cases (14%), blurring of the optic nerve margins and increased vascular tortuosity in 2 cases (14%), car wheel image made by the vessels originating from the optic nerve in 1 case (7%), degenerative myopia findings in 1 case (7%) and choroid coloboma in 1 case (7%) (Table 2).

Table 1. Characteristics of Down syndrome cases

Gender	Total	%
Female	48	67
Male	24	33
Karyotyp		
Regular Type	69	96
Mosaic	2	3
Translocation	1	1.4

Table 2. Ocular findings of Down syndrome cases

Ocular findings	Total	%
Refractive error		
Astigmatism	49	68
Hyperopia	34	47
Myopia	14	19
Eyelid disorder		
Upward slanting palpebral fissure	49	68
Epicanthus	45	63
Blepharitis	16	22
NLD occlusion	12	17
Eyelid laxity	8	11
Ectropion	1	1.4
Strabismus	24	33
Cataract	14	19
Iris pathology	17	24
Brushfield spot	12	71
Iris hypoplasia	4	23
Iris coloboma	1	6
Optic nerve-retina pathology	14	19
Nystagmus	3	4
Keratoconus	2	3

Table 3. Systemic findings of Down syndrome cases

Systemic findings	Total	%
Congenital heart diseases	26	36
VSD	19	73
ASD	5	19
PDA	1	4
Tetralogy of Fallot	1	4
Hypothyroidism	22	31
Developmental retardation	5	7
Hearing loss	4	6
Undescended testis	3	4
Asthma	3	4
Inguinal-umbilical hernia	3	4
Torticollis	2	3
Hirschsprung's disease	1	1.4
Duodenal atresia	1	1.4
Laryngomalacia	1	1.4
Autism	1	1.4

The most common systemic disease was congenital heart defects (36%). Of these, 19 (73%) had ventricular septal defect, 5 (19%) had atrial septal defect, 1 (4%) had patent ductus arteriosus and 1 (4%) had tetralogy of Fallot. In addition, when accompanying systemic diseases are examined; congenital hypothyroidism was seen in 22 cases (31%), developmental delay in 5 cases (7%), GIS anomalies in 5 cases (7%), hearing loss in 4 cases (6%), undescended testicle in 3 cases (4%), asthma in 3 cases (4%), torticol-

lis in 2 cases (3%), laryngomalacia in 1 case (1.4%) and autism in 1 case (1.4%). Of cases with GIS anomaly, three cases (4%) had inguinal-umbilical hernia, 1 case (1.4%) had Hirschsprung's disease, and 1 case (1.4%) had duodenal atresia. In 14 cases (19%), no accompanying systemic diseases were detected (Table 3).

DISCUSSION

In addition to the intelligence levels and general appearance of Down syndrome patients, systemic and ocular findings are of great importance in the follow-up of the patients.

Eyelid pathologies were the most frequently encountered ocular findings in patients with Down syndrome. Epichantal fold has been reported in the literature at variable rates between 9–100%, while the slanting of the lid has been reported as high as 43–94%.^[6,7] In our study, the incidence of epichantal was 63% and of the slanting lids, it was 68%. It has been suggested that different rates in the literature may be related to age, racial factors and measurement techniques.^[8] Blepharitis was detected at a rate of 22% in our study, while the incidence of blepharitis was found between 10-30% in the meta-analysis of 11 articles by Creavin et al.^[9] There are studies that link the high incidence of blepharitis in Down syndrome to disorders of the immune system, as well as these patients being more susceptible to infection due to abnormal structure of the eyelid.^[10,11] The loose eyelids and the lids rotating out easily can be considered to cause the conjunctiva to be exposed to external factors and providing the ground for infection. While the rate of nasolacrimal duct obstruction in Down syndrome patients varied between 5-30% in various studies, this rate was found to be 17% in our study.^[7,8,12] Catalano et al. reported that nasolacrimal duct obstruction was not associated with Down syndrome and decreased with age as in the normal population.^[10] Slanting eyelids was detected in 11% of our cases. In the literature, there are no reports on the rate of loose eyelids, while there are case reports of eversion of both upper eyelids.^[8]

Compared with the normal population, refractive errors are more common in Down's syndrome cases.^[13–19] Since different criteria are used for the definition of refractive error, ametropia has been reported in variable rates in the studies. While the frequency of hyperopia, which has been calculated using spherical equivalent varies between 20-40% in the studies, hyperopia was found to be higher than myopia.^[20–25] In the studies related to accommodation, it was observed that accommodation ranges were significantly lower in Down syndrome cases compared with similar age groups.^[26–28] Jaeger reported 46% myopia, 28% hyperopia and 26% astigmatism in his study with Down syndrome patients, while Shapiro and France reported 27% myopia and 25% astigmatism.^[6,29] In a study by Watt et al., hyperopia was reported as 56%, myopia as 25%, and astigmatism as 74%.^[30] In our study, the most common error was astigmatism (68%), followed by hyperopia (47%) and myopia (19%). In contrast to the control group, it was observed that re-

fractive errors gradually increased in preschool period in Down syndrome cases. They attributed this to an insufficiency of infant emmetropization process in cases with Down syndrome. Although it is not fully understood why emmetropization does not proceed properly, it has been suggested that accommodative insufficiency, the lack of close activity in contrast to the high rate of outdoor activity, and the changes in the visual cortex were cited as the causes.^[30] Also, delayed correction of refractive errors due to difficulties in visual examination of these cases and other systemic disorders may slow down the emmetropization process.

The presence of nystagmus in Down syndrome cases has been reported in various studies as 4–30%.^[12–14,31,32] Shapiro and France reported that the nystagmus detected in 9% of their cases was horizontal and not related to ocular anomalies.^[29] These authors suggest that nystagmus in Down syndrome may be due to an undetectable central nervous system defect or an unidentified retinal pathology. In our study, congenital bilateral cataract was present in 3 cases (4%) with nystagmus. Esotropia was also present in these patients who underwent cataract surgery. Nystagmus was horizontal in two patients and rotatory in one patient. Nystagmus was detected in 23% of patients with esotropia in the study of Heller et al.,^[33] while Jaeger reported nystagmus rate as 8%.^[6]

Strabismus rate is higher in Down syndrome cases than in general population.^[5,34–37] In their study, Haugen and Hovdig reported that accommodative strabismus was more frequent (46%) in Down syndrome, especially due to high hyperopia.^[16] Yurdakul et al. also reported the frequency of esotropia as 18% in Down syndrome cases.^[38] While the incidence of strabismus was 33% in our patients, 83% were esotropia and 17% were exotropia. No vertical deviation was detected in any of our patients.

Various authors have reported the incidence of cataracts in patients with Down syndrome ranging from 5% to 37%.^[30] In a Danish study, the incidence of cataracts at birth was found as 1.4% in Down syndrome cases and as 0.06% in the normal population.^[39] The incidence of cataract was 19% in our cases. Four patients (5.5%) had sutural cataract, four patients (5.5%) had blue dot cataract, three patients (4%) had white mature cataract, and three patients (4%) had posterior polar cataract. In studies, while the most common in Down syndrome cases were blue dot or punctate opacities, it is mentioned that the incidence of opacities increases with age.^[40]

Although Brushfield spots are not pathognomonic signs of Down syndrome, its presence is considered as a complementary parameter. Its incidence was reported to be between 10–90% in the literature, while in our study, it was 17%.^[5,13,41] These spots are yellow-white, ring-shaped structures seen in the iris stroma, but are less likely to occur in dark iris. It was seen that all of our patients who had Brushfield spots had light iris color. This can be explained by the fact that the darker iris is more common in regards to race and the rare occurrence of spots with dark iris. Bişkin et al. found Brushfield spots in 22% of Down syn-

drome cases, Yurdakul et al. found in 27%, and Da Cunha et al. found in 52%.^[5,12,38]

Iris hypoplasia is seen in 8–17% of normal population, while it was reported as 34–48% in Down syndrome cases.^[7,42,43] In addition, there are several publications about both Brushfield spots and iris hypoplasia are not seen at all in Down syndrome patients.^[22,44–47] In these studies it is mentioned that it may not be seen especially in races with dark iris. While the rate of iris hypoplasia was 5.5% in our cases, Yurdakul et al. reported it as 4% and Bişkin et al. reported as 30%.^[5,38]

The most commonly reported changes in the posterior segment of the eyes in patients with Down syndrome are the car wheel image originating from increased vessels, hyperemia of the optic nerve, degenerative fundus appearance, peripapillary choroidal atrophy, retinal pigmentation changes, retinoblastoma and retinal detachment.^[5,39,45,47] In our study, retinal anomalies were found in 19%. The most common fundus findings were increased retinal pigmentation (10%), while peripapillary atrophy (2.8%), blurring of the optic nerve margins and increased vascular tortuosity (2.8%), car wheel image (1.4%), degenerative fundus changes (1.4%) and choroid coloboma (1.4%) were other findings.

The most common systemic disease in Down syndrome cases is reported as congenital heart defects in the literature. Several studies have reported that the most common congenital heart defects are atrioventricular septal defect, ventricular septal defect, isolated secundum type atrial septal defect, isolated persistent patent ductus arteriosus and isolated tetralogy of Fallot.^[48–50] In our study, congenital heart defects were seen in 36%, and 73% of them were ventricular septal defect, 19% were atrial septal defect, 4% were patent ductus arteriosus and 4% were tetralogy of Fallot. Congenital heart defects were reported in 40% in a study in Egypt, 44% in a US study, 46% in a prospective study in Europe, and 18% in another retrospective study in India.^[44,51,52] As seen from the results, approximately half of the patients with Down syndrome are born with congenital heart defects. Therefore, routine echocardiography in the neonatal period is recommended in these patients.

While the incidence of hypothyroidism in the normal population is 1 in 4000 live births, this rate is approximately 28 times higher in newborns with Down syndrome and occurs in a rate of 1 in 141.^[53] In a large series study in the USA, the incidence of thyroid dysfunction in newborns with Down syndrome was reported as 0.1%, and in a study in Kuwait, as 52%.^[53,54] In our cases, congenital hypothyroidism was found in 31%. The fact that hypothyroidism between races was seen at different rates is explained by geographical differences, nutrition and genetic predisposition.^[44] Periodic evaluation of thyroid functions in patients with Down syndrome is important both for the persistence of normal development and to prevent further worsening of existing mental retardation.

It is reported that the incidence of GIS pathologies in Down syndrome cases is 20 times higher than the nor-

mal population.^[55] GIS anomalies include duodenal atresia, Hirschsprung's disease, omphalocele, duodenal bands, ileal and jejunal atresia and diaphragmatic hernias. In their study, Abbag et al. found that GIS anomalies as 22.4%, and duodenal atresia was the most common anomaly, while Kallen et al. reported that the frequency of annular pancreas and duodenal atresia increased 300-fold.^[56,57] In our study, the incidence of GIS anomalies was 7% and inguinal-umbilical hernia was the most common (4%).

Head circumference, weight and height are low in newborns with Down syndrome and growth retardation is common compared to the normal population.^[55] It has been reported that patients with congenital heart disease have more frequent growth retardation than those without.^[58] There was developmental retardation in our 5 patients (7%), all of which were operated due to cardiac problems.

Evaluation of hearing loss in patients with Down syndrome is crucial because it affects the intellectual development. 38–78% of patients with Down syndrome have hearing loss.^[46,48] It has been reported that ear infections are common due to weak immune system, flattened face, variety in head bones and narrow sinuses, and hearing loss develops in 5% of the cases within 1 year after infection.^[55] In our study, there were 4 patients (6%) with hearing loss.

Apart from the aforementioned systemic diseases, various hypotonia, speech disorders, microcephaly, holoprosencephaly, convulsions, spinal cord compression, Alzheimer's disease, dementia, autism, undescended testes, asthma and torticollis are also seen in varying rates in patients with Down syndrome.^[55] Also in our study, there were cases with undescended testes (4%), asthma (4%) and autism (1.4%).

Down syndrome is easily recognizable by its characteristic features and associated systemic malformations. Early clinical diagnosis is very important to combat the problems related to the syndrome. Early intervention to the problems that may adversely affect somatic and intellectual development such as hypothyroidism, congenital heart defects, ophthalmologic and otological problems will provide more positive responses in the treatment of patients. The support and education is essential and necessary for this families.

Ethics Committee Approval

Approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.T.K., N.Z.K.; Design: A.T.K., A.Y.O.; Supervision: A.T.K., N.Z.K. M.C.Ö.; Fundings: A.T.K., M.C.Ö.; Materials: N.Z.K., M.C.Ö.; Data: A.T.K., N.Z.K., A.Y.O.; Analysis: A.T.K., A.Y.O., Ş.Ş.; Literature search: A.T.K., A.Y.O., Ş.Ş.; Writing: A.T.K., A.Y.O.; Critical revision: A.Y.O., Ş.Ş.

Conflict of Interest

None declared.

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Down Sendromlu Hastaların Göz ve Eşlik Eden Sistemik Bulgularının İncelenmesi

Amaç: Kliniğimize başvuran Down sendromlu hastaların göz ve eşlik eden diğer klinik bulgularını incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmamıza, yaşları 4 ay ile 22 yaş (ort. 5.5±5.1) arasında değişen 72 olgu dahil edildi. Tüm olguların genetik analizi yapılmış olup Down sendromu tanısı almışlardı. Göz muayeneleri dışında olguların eşlik eden sistemik bulguları da bilgisayar kayıtlarından ve gerekli hallerde ailelerinden bilgi alınarak elde edildi. Olgulara görme keskinliği ölçümü, biyomikroskopi, fundus muayenesi, sikloplejik refraksiyon muayenesi ve gereken olgularda floressein boya kaybolma testi yapıldı.

Bulgular: Çalışmaya dahil edilen 72 olgunun 48'i (%67) erkek, 24'ü (%33) kız idi. Kromozom analizlerinde, 69 olguda (%96) regüler trizomi, 2 olguda (%3) mozaik, 1 olguda (%1.4) ise translokasyon paterni tespit edildi. Olguların göz muayenelerinde; refraksiyon kusuru (%85), yukarı kapak eğimi (%68), epikantus (%63), şaşılık (%33), blefarit (%22), retina anomalileri (%19), katarakt (%19), nazolakrimal kanal tıkanıklığı (%17), Brushfield lekesi (%17), kapak gevşekliliği (%11), nistagmus (%4) ve keratokonus (%3) tespit edilirken; sistemik hastalık olarak konjenital kalp hastalığı (%36), hipotroidizm (%31), gelişme geriliği (%7), işitme azlığı (%6), inmemiş testis (%4), astım (%4), Hirschsprung hastalığı (%1.4) ve otizm (%1.4) saptandı. Olguların 11'inde (%15) hiçbir göz patolojisine rastlanılmadığı gibi, 13 olguda (%19) sistemik hastalığa rastlanmadı. En sık astigmatizma (%68) tespit edilirken bunu sırasıyla hipermetropi (%47) ve miyopi (%19) izledi. Konjenital kalp hastalıklarından ise en sık septum defektleri (%33) tespit edildi.

Sonuç: Down sendromlu olgularda göz problemleri ve sistemik hastalıklar sık görülmektedir. Erken dönemde yapılacak doğru tanı ve tedavi ile hastaların eğitim hayatına ve sosyal hayata uyumu daha kolay olacaktır.

Anahtar Sözcükler: Brushfield lekesi; Down sendromu; göz bulguları.