Ocular Findings and Management in Egyptian Children with Down Syndrome

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Abstract: Background: Ocular disorders in Down syndrome (DS) are not uncommon. However their frequency in Egyptian population is not well defined. Methods: Ninety Egyptian children with Down syndrome (3 months to 10 years old) were diagnosed both clinically and cytogenetically and followed up for three years. The ophthalmic examination included, evaluation of ocular motility, assessment of eye alignment, using Hirschberg test, portable slit lamp biomicroscopy, cycloplegic retinoscopy, ophthalmoscopy and ultrasound if needed. Results: Fifty two patients (57.8%) with one or more ophthalmological findings were diagnosed in the first visit. Refractive errors (41%) were the most common, with hypermetropia being the most frequent. Strabismus (14.4%) was the next common ocular disorder, followed by nasolacrimal duct obstruction (10%), conjunctivitis and congenital cataract each of them represented (5.6%), blepharoconjuctivitis (4.4%), nystagmus (3.3%) and tilted optic disc (2.2%). However, Brushfield spots were not observed among these patients. There were 12 more ocular disorders detected on follow up. Thirty six patients (40%) had congenital heart defects and 86.1% of them had associated ocular disorders. Conclusions: More than half of patients with Down syndrome had ophthalmic abnormalities. Patients with congenital heart defects had possible association with ophthalmic disorders especially myopia. Ocular examination and management for patients with DS are essential to improve their quality of life.
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1. Introduction:

Down syndrome (MIM, 190685) [(1)] is the most common cause of mental retardation with an incidence of about 1.5/1000 live births. Life expectancy and quality of life have improved substantially for this group over the last few decades [(2)]. Down syndrome was first described by Langdon Down in 1866 [(3)], who had observed that the eyes of patients were obliquely placed, the internal canthi were more than the normal distance from one another, and the palpebral fissure was very narrow. In addition to the external ocular features, there were other ocular manifestations occurring at higher frequency in individuals with Down syndrome [(4)]. Investigators demonstrated that children with Down syndrome are at risk for developing refractive errors[(5)], strabismus, nystagmus, and blepharitis. Cataract and glaucoma were less common, but had potentially serious implications for future vision [(6)].

Normal vision is important for any child. However, if the child is mentally retarded, as individuals with Down syndrome, an additional handicap or sensory impairment may further limit the child's overall functioning and may prevent the child from participating in different learning activities [(7)].

We aimed to identify the ocular disorders in a pediatric group with Down syndrome and follow them up for three years to determine various ocular and clinical changes. We also evaluated whether these ocular anomalies were associated with cardiac anomalies, or cytogenetic findings.

2. Patients and Methods:

A random prospective study included infants and children with DS attending the Clinical Genetics Clinic, in both National Research Centre and Research Institute of Ophthalmology (RIO), during 2006 and 2007, were offered the chance to participate willingly in the study. Inclusion criteria were: clinical examination, required investigations, ophthalmic examination and commitment to regular follow up visits over a period of three years.

Ninety children with Down syndrome were included in the study. They were 47 males and 43 females and their ages ranged between 3 months and 10 years (mean age 2±2.1 years), at the first examination visit. The recruitment and experimental protocols for the study were conducted in compliance with the Declaration of Helsinki, and approved by NRC Ethical Research Committee. Each patient was subjected to complete personal, medical and developmental history taking, family pedigree

construction and analysis with special emphasis on similarly affected family member(s), and meticulous systemic clinical examination to detect any abnormality. The diagnosis of Down syndrome was provisionally based on clinical findings, and confirmed by the G-banding chromosomal analysis. Echocardiography and thyroid profile were done for all patients. Then patients were referred to the Research Institute of Ophthalmology (RIO) for ocular examination by two expert ophthalmologists.

The ophthalmic evaluation included evaluation of ocular motility, portable slit lamp biomicroscopy, cycloplegic retinoscopy, ophthalmoscopy and ultrasound if needed. The presence of nystagmus was noted and eye alignment was assessed using Hirschberg test, and when possible using the prism and cover test. Refraction errors were measured using cycloplegic retinoscopy. Myopia was defined as a refractive error ≥ -1/5.0 spherical equivalent, hypermetropia as ≥ +1.0 spherical equivalent, and astigmatism as > 1.0 dioptre (D) of cylinder. Uncooperative children were examined under anesthesia.

Patients were followed up by regular clinical and ophthalmic examinations every 3 months. The follow-up period ranged from 31 to 36 months with mean period of 33± 2.5 months.

Enrollment in early stimulation/intervention program was offered as a service for the patients, but was not one of the inclusion criteria. Seventy one Down syndrome cases (78.9%) were enrolled in an early stimulation/intervention program using Portage program to improve their developmental milestones. This was performed in the motor-mental skills development unit at the Clinical Genetics Department, National Research Centre.

Statistical analysis was conducted using SPSS program (version 10). Differences in frequency of ophthalmic disorders in different age groups, type of refractive errors in relation to age groups and the frequency of heart defects in Down syndrome children with ocular anomalies were calculated using Chi-Square test. The association of heart defects in Down syndrome children with ocular anomalies was tested using Chi-Square, and Fisher's exact test.

3. Results:

At the first examination visit, only two children had a positive family history of Down syndrome and fifty two patients (57.8%) had ophthalmic disorders; some of them had more than one ocular manifestation. Refractive errors (41%) were the most common followed by strabismus, nasolacrimal duct obstruction, conjunctivitis, congenital cataract, blepharoconjunctivitis, nystagmus and tilted optic disc (Table 1). Twelve other ocular disorders (2 esotropia and 10 conjunctivitis cases) developed in the patients along the course of follow up. Although all patients had hypertelorism, epicanthic folds and upward slanting of palperbral fissures, none of them showed Brushfield spots.

Table (2) showed that most of our patients were 3 months to 5 years old and the percentage of most of ophthalmic disorders significantly increased with age (X^2 = 66.94; P<0.001). Table (3) showed that hypermetropia was the most common type of refractive errors. In spite of increasing the percentage of total refractive errors with age, the difference between individual errors was not statistically significant in relation to age (X^2 = 0.53; P = 0.97).

Table (4) showed congenital heart, cytogenetic and thyroid findings in children with Down syndrome. Thirty six (40%) patients had congenital heart defects (CHD). The most common defects were isolated ASD or VSD. Karyotype analysis revealed non-disjunction trisomy 21 in 85 patients (94.5%). Thyroid profile assessment revealed that most of the patients were normal (94.5%). A total of 31 children (86.1%) out of 36 cases with CHD had associated ocular disorders.

Table 5 shows the frequency of heart defects in children with ocular anomalies. The children with CHD were more likely to have myopia (P = 0.027), and were less likely to have astigmatism (P = 0.045) using Fisher exact test. No statistical correlation could be detected between ocular anomalies and cytogenetic or thyroid findings, probably due to the small number of cases with translocation or thyroid dysfunction.

4. Discussion:

The incidence and severity of ophthalmic disorders varies among individuals with Down syndrome. It is not known why some individuals develop ocular problems and others do not, given that the underlying chromosomal abnormality is almost identical [(8)]. Some authors suggested that the extra chromosomal material causes a generalized disruption in the genetic balance of cells. Accordingly, non-specific developmental instability following aneuploidy may account for ophthalmic anomalies in Down syndrome [(9)].

In this study 52 Down syndrome cases (57.8%) had ophthalmic abnormalities. Thirty seven cases (41% of all Down syndrome cases) had refractive errors, with hypermetropia being the most frequent, followed by astigmatism then myopia, representing 16.6%, 14.4% and 10% of all cases respectively. The percentage of refractive errors increased with age (Table 3).

Table (1): Frequency of ophthalmic disorders in children with Down syndrome at the first examination and during follow up visits

Ophthalmic disorders	Number and % In the first visit	Management	Follow up results
Refractive errors (hypermetropia, astigmatism and myopia)	37 (41%)	- 25 cases were prescribed spectacle correction, - 12 cases just observed for mild refractive error.	- 25 cases with glasses were followed up - 12 cases with no glasses were followed up. - one of 37 patients developed esotropia
Strabismus Esotropia 9 Exotropia 4	13 (14.4%)	- 6 cases (46%) needed glasses - 1case (8%) required occlusion - 2 cases (15%) required both - 4 (31%) cases had surgical correction of strabismus	- treated cases were improved -one DS patient developed esotropia.
Nasolacrimal duct obstruction	9 (10%)	massage of the nasolacrimal duct for 2 months maximum	-7 cases improved with digital massage - 2 cases were treated by probing
Conjunctivitis	5 (5.6%)	- treated with antibiotic eye drops - swabs were taken from resistant cases for culture	- all 5 cases improved with treatment & conjunctivitis resolved - 10 cases had conjunctivitis during follow up visits & were similarly treated
Congenital cataract	5 (5.6%)	cataract extraction and implantation of intraocular lens	- improved visual functions
Blepharoconjunctivitis	4 (4.4%)	sodium bicarbonate 3% lotion & antibiotic eye drops	- improved
Nystagmus	3 (3.3%)	1 case had associated congenital cataract.	- case improved after cataract extraction and intraocular lens implantation -the other 2 cases had congenital heart & were unfit for examination under anesthesia
Tilted optic disc	2 (2.2%)	- associated astigmatism was corrected by eye glasses	- improved visual functions

Table (2): Ophthalmic disorders in different age groups during follow up

Ophthalmic disorders	**≤ 1 year** n=35	**1-5 years** n= 46	**5-10 years** n = 9
Refractive errors	10 (28.6%)	21 (45.7%)	6 (66.7%)
Strabismus	4(11.4%)	7 (15.2%)	4 (44.4%)
Nasolacrimal duct obstruction	6 (17.1%)	3 (6.5%)	0 .0
Conjunctivitis	4 (11.4%)	7(15.2%)	4(44.4%)
Cataract	0.0	4(8.7%)	1 (11.1%)
Blepharoconjunctivitis	1 (2.9%)	2(4.3%)	1 (11.1%)
Nystagmus	1 (2.9%)	2 (4.3%)	0.0
Tilted optic disc	1(2.9%)	0.0	1 (11.1%)

Table (3): Type of refractive errors in age groups of children with Down syndrome

Age (years) and patients number	**Hypermetropia** (sphere range in diopters)	**Myopia** (sphere range in diopters)	**Astigmatism** (sphere range in diopters)	**Total (%)**
≤ 1 year n =35	6 (3.0-4.5 D)	2 (5.0 D)	2 (1-4 D)	10 (28.6)
1-5 years n =46	8 (3.0-6.0 D)	5 (2.0 – 20 D)	8 (1-2 D)	21 (45.7)
5- 10 years n =9	1 (3.0 D)	2 (5.0 – 8.0 D)	3 (2-6.8 D)	6 (66.7)
Total n =90 (%)	15 (16.6)	9 (10)	13 (14.4)	37 (41)

Table (4): Frequency of congenital heart defects (CHD), cytogenetic and thyroid findings in children with Down syndrome

Findings	n(%)
Type of congenital heart disease	
Atrial septal defect (ASD)	8 (8.9%)
Ventricular septal defect (VSD)	8 (8.9%)
Patent foramen ovale (PFO)	3 (3.3%)
Atrio-Ventricular canal (A-V canal)	2 (2.2%)
ASD + Patent ductus arteriosus (PDA)	4 (4.4%)
ASD +VSD	3 (3.3%)
Other combinations of CHD	8 (8.9%)
Total patients	
with CHD	36 (40%)
without CHD	54 (60%)
Cytogenetic findings	
Non-disjunction trisomy 21	85 (94.5%)
Translocations trisomy 21	4 (4.5%)
Mosaic trisomy 21	1 (1%)
Thyroid profile	
Normal	85 (94.5%)
Hypothyroidism	3 (3.3%)
Hyperthyroidism	2 (2.2%)

Table (5): Frequency of heart defects in Down syndrome children with ocular anomalies

Ocular anomaly	Heart defects		Total
	Yes	No	
Refractive errors	15 (40.5%)	22 (59.5%)	37
Hypermetropia	6 (40.0%)	9 (60.0%)	15
Myopia	* 7 (77.8%)	2 (22.2%)	9
Astigmatism	2 (15.4%)	*11 (84.6%)	13
Strabismus	5 (33.3%)	10 (66.7%)	15
Nasolacrimal duct obstruction	4 (44.4%)	5 (55.6%)	9
Conjunctivitis	5 (33.3%)	10 (66.7%)	15
Congenital cataract	2 (40.0%)	3 (60.0%)	5
Nystagmus	2 (66.7%)	1 (33.3%)	3

* $P \leq 0.05$ is significant

Previous studies reported that refractive errors, especially hypermetropia, were the most frequent ophthalmic anomaly among young patients with Down syndrome. Stephen et al. [10], studied ocular disorders in 81 children with Down syndrome at school age, where they documented refractive errors in 43% of cases, with hypermetropia as the most frequent disorder (27%). Another study by Fimiani et al. [11] identified the incidence of primary ocular pathologies among 157 Italian children with Down syndrome (1 month to 18 years old) as follows: hypermetropia 59% of patients, astigmatism 28% and myopia 9%. Analysis of our data revealed that the refraction errors did not improve with age. Similarly,
Stephen et al. [10] reported an increase of refractive errors with age in Down syndrome patients. This finding is in contrast to healthy developing children, who become more emmetropic with age.

The prevalence of strabismus among the individuals with Down syndrome at the first visit was 14.4%, (another 2 cases developed esotropia during follow up, and accordingly the percentage reached 16.6%). A study conducted in Nigeria [12] reported

similar results (18.1%). Other studies in Malaysia and United Kingdom documented higher incidence of strabismus among DS patients, presenting 26.7% and 47%, respectively [10; 13]. However, the patients' age groups of these two studies were older than our cases. It has also been documented that the incidence of strabismus among general population ranged from 1-5% [14], which is much lower than the that reported by various studies among children with Down syndrome [10; 12; 13], including our study. Esotropia was more common (12.2%) than exotropia (4.4%) among our cases. Merrick and Koslowe [15] found that the majority of Down syndrome children with strabismus had an acquired esotropia. They also suggested that hypermetropia and accommodation weakness were important factors of esotropia in Down syndrome patients.

Nasolacrimal duct (NLD) obstruction was diagnosed in 10% of cases (9 patients), and was more common in younger children (3-12 months, 17.1%) than in older age groups (6.5% and 0% respectively). In the current study, lacrimation problem improved by time with regular digital massaging technique in 7 patients, while 2 cases needed probing of the NLD. Nasolacrimal outflow obstruction is common and is believed to be a difficult problem to treat in Down syndrome patients [16]. Some studies have suggested that simple nasolacrimal duct (NLD) probing can be an effective primary surgery for congenital NLD obstruction and age does not appear to have an impact on success of probing [13; 17].

At the first visit, 5 Down syndrome cases had conjunctivitis, and 4 had blepharoconjunctivitis. Another 10 patients developed conjunctivitis during follow up. Conjunctivitis was treated by antibiotic eye drops, and swabs were taken from resistant cases for culture and sensitivity. Patients with blepharoconjunctivitis were given sodium bicarbonate 3% lotion and antibiotic eye drops. Previous studies indicated that Down syndrome is associated with disturbance of tear function and impaired immunity. These anomalies could be responsible for the frequent infectious pathologies found in the anterior eye segment [18; 19].

The frequency of congenital cataract in this study was 5.6 %, which was more or less similar to other publications [10; 12]. Most of our cases were 1- 5 years old, except one case, which developed cataract at the age of 9 years. Some authors reported that cataract was more common in Down syndrome children above the age of 12 years [20]. Early detection and management is essential to prevent amblyopia[21].

In this study three children had nystagmus (3.3% of patients) and one of them was diagnosed as congenital cataract with nystagmus. The other two patients had complicated congenital heart disease and were unfit for examination under anesthesia. Wagner et al. [22] observed that nystagmus in Down syndrome patients, was not always associated with significant decrease in visual acuity and not indicative of severe ocular abnormalities.

Funduscopic examination showed tilted optic disc in two Down syndrome patients with astigmatism. Vongphanit et al. [23] documented that a tilted disc appearance was strongly associated with astigmatism and higher levels of spherical refractive error, particularly myopia. No notable Brushfield spots were detected in our Egyptian patients. This finding was reported before in an Asian study, although most Caucasian studies reported Brushfield spots in children with Down syndrome [24]. A study of a larger Egyptian sample of Down syndrome patients is needed to establish the significance of this finding.

Congenital heart diseases were diagnosed in (40%) of patients. A previous Egyptian study of another 23 Down syndrome cases reported a nearly similar percentage of congenital heart defects (39.1%) [25]. Published molecular studies suggested that the 21q22.1-q22.3 region, or Down syndrome critical region (DSCR), might contain the genes responsible for the congenital heart disease [5, 26].

In this study, congenital heart defects were significantly associated with myopia (P = 0.027), while astigmatism was associated with absence of congenital heart defects in children with Down syndrome (P = 0.045). Bromham et al. [8] found that Down syndrome children with heart defects were associated with both myopia and nystagmus. Davies *et al.* [27] reported an association between variation in the COL6A1 gene region and congenital heart defects in Down syndrome. COL6A1 codes for a part of collagen VI, a component of many ocular tissues [28]. Down syndrome cell adhesion molecule (DSCAM) has also been considered as a candidate gene for heart and visual pathway defects in Down syndrome [29]. These findings may explain the association between some ocular disorders and congenital heart defects in Down syndrome patients. The interesting finding of negative association between CHD and astigmatism needs further study.

Karyotype analysis revealed that 94.5% of patients had non-disjunction trisomy 21 and 4.5% of them had translocations. This result agrees with previous cytogenetic investigations carried out on 1021 Indian cases of Down syndrome [30]. Also, thyroid profile assessment revealed that most of the patients were normal (94.5%), while three patients had hypothyroidism, and two had hyperthyroidism. Similar results have been previously documented with Down syndrome [31]. Murphy et al. [32], documented that thyroid dysfunction was detected in 4.6% of children with Down syndrome screened for

hypothyroidism by capillary whole blood TSH sample.

In conclusion, young Egyptian patients with Down syndrome demonstrated a high frequency of ophthalmic disorders, and no notable Brushfield spots. Follow up of Down syndrome children showed that refractive errors do not improve with age, and the percentage of ophthalmic disorders as strabismus increased. There was a variable association between congenital heart defects and ophthalmic disorders. Therefore, we suggest implementation of an ophthalmic program for Down syndrome individuals, which necessitates a regular check-up of patients every 3 months, starting since birth. Such a program will lead to early diagnosis and treatment of ocular conditions in patients with Down syndrome to alleviate future health problems. The overall aim for patients with Down syndrome should be to improve their quality of life, not just their life expectancy.

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