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RESEARCH REPORT

Strabismus, refractive errors and nystagmus in children and young adults with Down syndrome

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ABSTRACT

Purpose: The aims of the present population-based, cross-sectional study were to examine the frequency and type of strabismus, refractive errors and nystagmus in children and young adults with Down syndrome (DS) in Macedonia and Croatia.

Methods: A total of 170 unselected children and young adults with DS aged 1–34 years were examined for ocular findings. The ocular examination included: a visual acuity assessment, cycloplegic refraction, ocular alignment and ocular motility.

Results: Strabismus was found in 45 of 170 children (26.5%), and esodeviation was the most common type. Nine (20%) had exodeviation and 4 (8.9%) vertical deviation. In 27 of 32 esotropic patients, the strabismus was regarded as acquired esodeviations. The frequency of strabismus was lowest in the high-grade hyperopia group (5%). Concerning esodeviations, fewer cases (3%) were in the high-grade hyperopia group. Most of the cases with esodeviations were in correlation with low-grade hyperopia (31%), myopia (28 %) and emetropia (16%). Hyperopia was the most common refractive error and high myopia increased in prevalence in the over 20 age group. Astigmatism was present in 72.4% of patients. Nystagmus was observed in 18 patients. Ten of 18 patients with nystagmus were associated with the presence of strabismus (9 esodeviations, 1 exotropia).

Conclusion: In our study, the high prevalence of strabismus can not be attributed to the presence of hyperopia. Our data show no association between refraction and strabismus in children with DS. Oblique astigmatism has been found to be the most common type of astigmatism in our study group.

Keywords: Down syndrome, strabismus, refractive errors, nystagmus, amblyopia

INTRODUCTION

Strabismus and refractive errors are frequently encountered in Down syndrome (DS).[1–3] Various studies on non-selected populations of individuals with DS have reported a prevalence of strabismus of 20–42%.[1, 2,4–7] Two studies found the prevalence of strabismus to be less than 20%.[8,9]

There are several studies reporting refractive errors in 30–51% of DS patients.[2,3,10] Frequency of nystagmus in the Down population in different studies is 8–30%.[11–14] Concerning amblyopia, the reported frequency in different studies is 8.5–26%. [5,11,12,14,15] The aim of the present population-based, cross-sectional study was to examine the prevalence of strabismus, refractive errors, nystagmus and amblyopia in children and young adults with DS.

SUBJECTS AND METHODS

Non-selected home reared children and young adults with DS enrolled in this population-based, cross-sectional study, were recruited from the special educational system, social services as well as parental associations in the region of Macedonia and Croatia.

A total of 170 children and young adults with DS who were enrolled were seen in the private polyclinic "Medika plus" in the capital Skopje, Macedonia, in the private polyclinic "Svjetlost" in the capital Zagreb, Croatia, as well as in local private eye offices in eight other towns, in Macedonia and in one other town in Croatia. The study was performed in the period from March 2007 until July 2009.

The diagnosis of DS was made either on clinical characteristics or by cytogenetic analysis. All parents

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of Macedonian children originated from Macedonia, except two mothers from Bulgaria, and the Croatian children all originated from Croatia. Written informed consent was obtained from each subject's parent.

All subjects (98 male, 72 female) between 1 year and 34 years of age were examined for ocular findings by one of the authors (A.Lj.). Protocols for general health,[16,17] birth dates and ocular examination which included a visual acuity assessment, cycloplegic refraction, ocular alignment and motility were prepared.

Eye Alignment

The alignment of the eyes was a standard evaluated for distance fixation using Hirschberg's corneal reflex method, and cover test. The cover test was also performed using an accommodative fixation target. Both distance and near ocular alignment were tested with optical correction, if prescribed. Examination of the motility was done in subjects who were cooperating. Deviation from the straight position was classified as esodeviations, exodeviations or vertical deviations. In addition, the deviations were classified into unilateral or alternating strabismus, and it was noted whether the deviation was manifest or intermittent.

Infantile esodeviations were defined as a constant esodeviation with an onset before 6 months of age reported by the mother. All other cases of esodeviations were classified as acquired esodeviations. These were divided according to refractive error into hyperopic, myopic, and anisometropic groups. Microtropia was defined as a deviation of less than 10 prism diopters. Intermittent exotropia and manifest exotropia were designated as an exodeviation. The presence of nystagmus was noted (latent or manifest).

Visual Acuity and Refraction

In cooperative children and young adults, the best corrected visual acuity was tested with full line Snellen visual acuity charts in the better eye. In Macedonia and Croatia there is no use of charts for accurate assessment of children and adults with intellectual disability.

Amblyopia was defined as a difference in visual acuity between the two eyes of more than one line on the acuity chart.

Cycloplegic refraction was performed after three to five installations of one drop of Cyclopentolate 1%. In this study we used photorefraction (Auto-Ref-Keratometer Potec PRK-5000).

For each of the subjects, spherical equivalent and power and axis of cylinder were recorded. Emmetropia was defined as a refractive error between −0.75 diopter (D) and +0.75 D spherical equivalent. Myopia was defined as less than −0.75 D spherical equivalent and hyperopia was defined as more than +0.75 D spherical equivalent.

Low grade hyperopia was defined as +1.00 D to +2.75 D spherical equivalent, moderate hyperopia as +3.00 D to +5.75 D spherical equivalent and high-grade hyperopia as ≥ +6.00 D spherical equivalent. Respectively, myopia was divided into low-grade, moderate and high-grade myopia.

Anisometropia was defined as the difference between the right and the left eye > 1.0 spherical and/or >1.50 cylinder power

Clinically significant astigmatism was defined as refractive error ≥1.0 D of the cylinder. In the evaluation of astigmatism group, minus form of the cylinder was used.

The axis of astigmatism was classified as follows: WTR ("with the rule"), ATR ("against the rule") and OBL (oblique astigmatism or axis between 100–170 and 10–80). Eyes with a cylindrical power of < 1.0 D were excluded from the astigmatism group (Table 1).

Statistical Analysis

The data were analyzed statistically with the SPSS for Windows version 13.0, using χ^2 test and Fisher's exact test, and $P<0.05$ was chosen as the level of statistical significance.

RESULTS

The mean age of the patients was 13.8 years (range 1–34 years). The age distribution of all subjects is given in Fig. 1.The mean maternal age at birth of the children was 29.1 years. In our study population 98 (57.9%) of the examined children and young adults with DS were male, 42.1% female. All the DS patients were Caucasian.

Regarding ethnicity, 48.5% were Macedonians, 37.4% Croatians, 13.5% Albanians and 0.6% Roma.

TABLE 1 Astigmatism in children and young adults with DS.

Author	Year	Method of refraction	No of patients	Astigmatism ≥ 1.0 D	WTR	ATR	OBL
Woodhouse[2]	1997	Non-cycloplegic	24 (4y–12y)	37.5%	Axis not reported		
Haugen[3]	2001	Cycloplegic	60 (2.5y–11y)	57%	68%	6%	26%
Doyle[18]	1998	Cycloplegic	50 (15y–22y)	Not reported	22%	39%	38%
Present study	2010	Cycloplegic	145 (1y–34y)	72.4%	37%	11%	52%

WTR, with the rule; ATR, against the rule; OBL, oblique astigmatism.

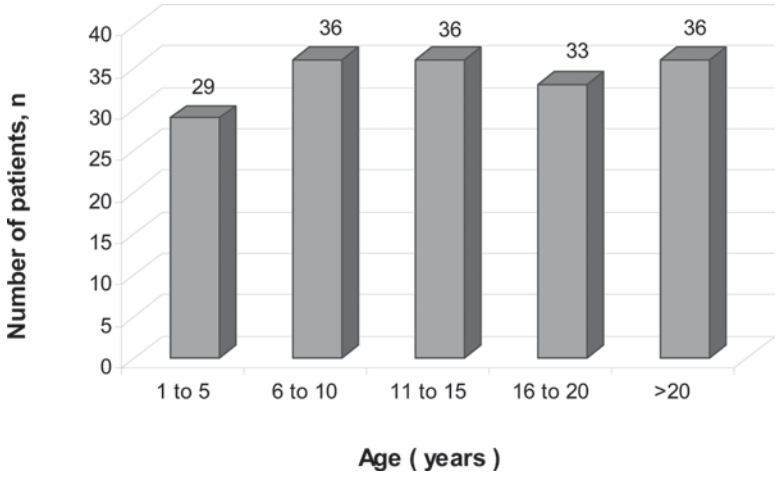

FIGURE 1 Age distribution of 170 subjects with DS.

TABLE 2 Prevalence of strabismus (all types) and specifically esodeviations (*Italic numbers in brackets*) in 170 children and young adults with DS, classified by refractive state in spherical equivalent.

	Prevalence of strabismus (esodeviations in italics in brackets)	
Refractive state	n	%
Group 1 Myopia	12(*9*)	26(*30*)
Group 2a Emmetropia	7(*5*)	16(*16*)
Group 2b Low grade hyperopia	10(*10*)	22(*31*)
Group 2c Moderate hyperopia	8(*2*)	17(*7*)
Group 2d High grade hyperopia	2(*1*)	5(*3*)
Group 3 Anisometropia	3(*3*)	7(*10*)
Group 4 No refractive state provided	3(*2*)	7(*3*)
Total	45(*32*)	100(*100*)

Strabismus

Strabismus was found in 45 of 170 children (26.5%), and esodeviation was the most common type (32 of 45 children, 71.1 %). Nine (20%) had exodeviation and four (8.9%) vertical deviation (hypertropia).

In 28 of 32 esotropic patients the strabismus was regarded as an acquired esodeviation, four were classified as an infantile esodeviation. In nine cases with exodeviation, two were found to have intermittent exotropia and seven manifest exotropia. One patient with manifest exotropia had Brown syndrome. Three patients with acquired esodeviations had A syndrome.

Table 2 shows the presence of strabismus (all and separate esodeviations) in different groups of spherical equivalent refractive errors. The frequency of strabismus was lowest in the high-grade hyperopia group (5%). Concerning esodeviations, fewer cases were found in the high-grade hyperopia group. Most of the cases with esodeviations were in correlation with myopia and emmetropia and the low-grade hyperopia refractive group.

TABLE 3 Classification of esodeviations in 32 children and young adults with DS.

Type of esodeviations	Subjects, *n*
Infantile	4
Associated with emetropia	4
Acquired	28
Associated with hyperopia	13
Associated with myopia	9
Associated with anisometropia	3
Associated with emetropia	1
No refractive state provided	2
Total	32

Classification of the esodeviations in 32 children and young adults with DS is presented in Table 3.

The patients with acquired esodeviations associated with hyperopia were classified as: nonaccomodative esodeviations ($n=10$), partially accommodative ($n=2$) and one patient had refractive accommodative esodeviations ($n=1$). Only one patient had convergence excess.

Concerning astigmatism and strabismus, 31% of the strabismus patients showed the presence of clinically significant astigmatism. In three strabismic patients, the refractive state was not provided.

Two patients with intermittent exotropia had low-grade myopia and low-grade hyperopia. Seven patients with alternate exotropia had all mostly moderate grade hyperopia. In one patient with alternate exotropia, no refractive status was provided.

The age of the nine subjects with exodeviations is shown in Table 4. The age of 32 subjects with esodeviations is shown in Table 5. The mean age of the exodeviation group was 17.6 ± 8.48 years and the esodeviation group had a mean age of 14.1 ± 7.36. There was no statistical difference in age between the two groups ($P=0.23$).

Concerning the four patients with vertical strabismus (all hypertropia), one had moderate hyperopia, while the other patient had high grade myopia. In one

TABLE 4 Exodeviations and age of children and young adults with DS.

Type of exodeviations	Age of subjects (years)
XT alternans	7.0
XT intermittens	10.3
XT monocularis	11.0
XT alternans	12.0
XT alternans	16.0
XT alternans	21.0
XT intermittens	23.0
XT alternans	25.0
XT alternans	33.0

patient with vertical strabismus, no refractive status was provided.

Refractive errors

Of the 170 individuals, 25 did not co-operate well. The age distribution of 145 subjects, where refractive error was analyzed is given in Fig. 2. The refractive state (spherical equivalent) showed emmetropia 35(24.1 %), more hyperopia 80(55.2%) and myopia 30(20.7%) (Fig. 3). In the present study, 5 of 30 subjects with myopia have snow-flake opacities and one has keratoconus.

Most of the myopic patients were in the range ≥ −6.0 D and aged ≥ 15 years (Fig. 4). The highest value of myopia was −22.0 D.

Hyperopia in this population was mostly within range power +1.00 D to +2.75 D and at the age ≥15 years (Fig. 5). Overall, hyperopia increases with age group.

Astigmatism was present in 105 subjects of 145 (72.4%). The most prevalent form of astigmatism was oblique astigmatism 55/105 (52.4%) (Table 1). Astigmatism as a function of age is presented in Fig. 6 where the prevalence of oblique astigmatism is seen to gradually increase with the age of the subjects.

A total of 25% of the children and young adults with DS were corrected before the study but 36% of subjects needed a correction and did not have one at the time of the study.

Full hyperopic correction has been prescribed to all hyperopic patients with esodeviations exceeding 2.50 D.

Nystagmus

Nystagmus was observed in 18 patients (11%) (16 manifest; 1 manifest-latent; 1 latent). Sixteen children had a horizontal jerk nystagmus, two had a pendulating nystagmus.

Ten of 18 patients with nystagmus, had high-grade myopia and seven had hyperopia. Five of 18 patients with nystagmus, also showed clinically significant astigmatism. Ten of 18 patients with nystagmus also showed strabismus (9 esodeviations, 1 exotropia). Most of the patients with nystagmus and strabismus had high-grade myopia. Refractive errors in the nystagmus group are shown in Fig. 7.

TABLE 5 Esodeviations and age of children and young adults with DS.

Type of esodeviations	Age of subjects (years)
ET infantilis essentialis (monocularis; no surgery was performed)	3.0
ET alternans	4.4
ET alternans	5.0
ET alternans	6.0
ET infantilis essentialis (monocularis; no surgery was performed)	7.2
ET infantilis essentialis (monocularis; no surgery was performed)	7.6
ET monocularis	7.9
ET alternans	8.0
ET alternans	8.0
ET alternans	8.0
ET alternans	9.3
ET monocularis	10.9
ET alternans	11.4
ET alternans	12.0
ET alternans	12.0
ET alternans	12.0
ET alternans	12.9
ET alternans	14.0
ET alternans	14.0
ET monocularis	16.0
ET alternans	17.0
ET alternans	17.0
ET monocularis	17.3
ET infantilis essentialis (monocularis; no surgery was performed)	17.9
ET alternans	18.0
ET monocularis	20.0
ET alternans	20.0
ET alternans	23.0
ET alternans	23.0
ET monocularis	25.0
ET monocularis	30.0
ET alternans	33.0

Visual Acuity

Of the 170 individuals with DS, 87 were unable to complete acuity testing. Visual acuity was evaluated in 83 (49%) children and young adults, using best correction and presented in decimal Snellen.

The frequency of amblyopia in 83 patients, who were able to complete acuity testing in our study, was 16.9%. The degrees of amblyopia in amblyopic subjects are presented in Table 6.

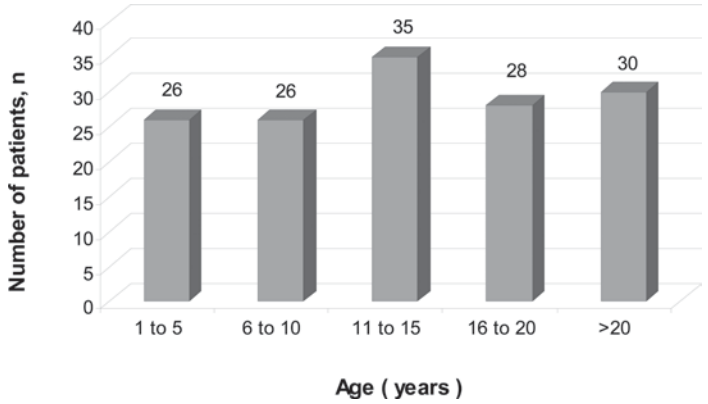

FIGURE 2 Age distribution of 145 subjects with DS for whom refractive errors were analyzed.

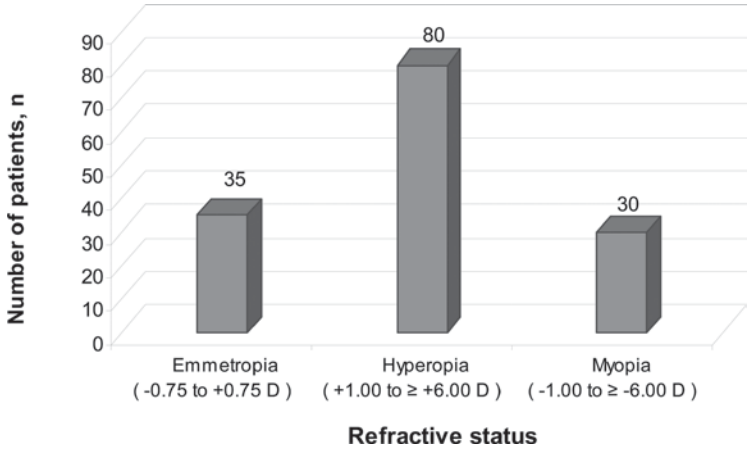

FIGURE 3 Refractive status (spherical equivalent) in 145 subjects with DS.

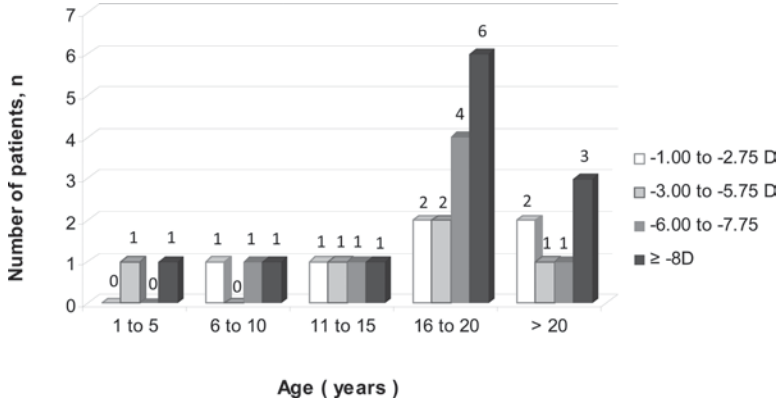

FIGURE 4 Myopia (spherical equivalent).

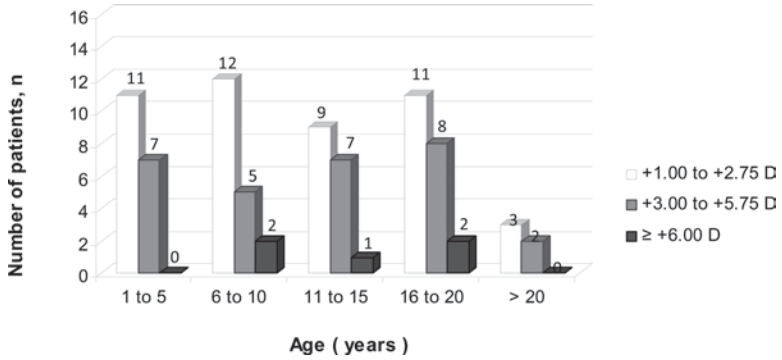

FIGURE 5 Hyperopia (spherical equivalent).

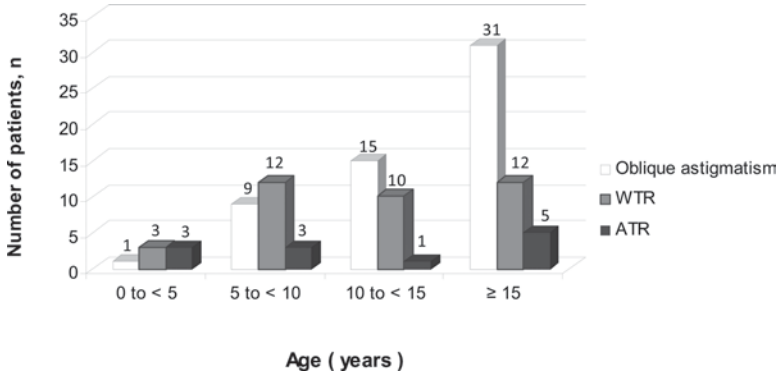

FIGURE 6 Astigmatism as a function of age. WTR, with the rule; ATR, against the rule.

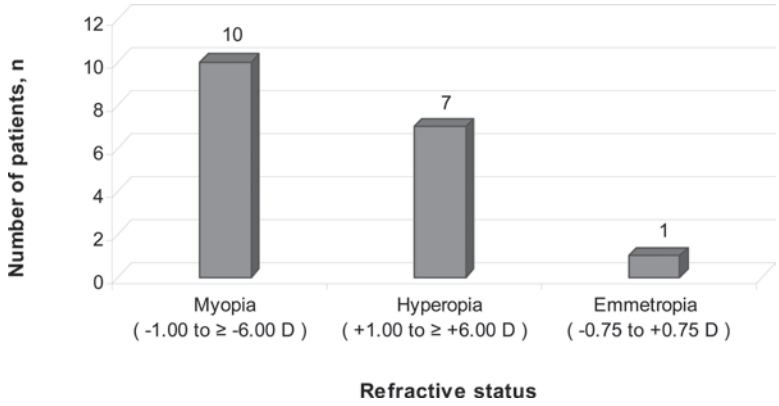

FIGURE 7 Refractive errors in the nystagmus group.

TABLE 6 Degree of amblyopia in 14 amblyopic subjects with DS.

Degree of amblyopia	Subjects, *n*	Subjects, %
Mild (2–4 rows difference)	12	85.7
Moderate (5–7 rows difference)	2	14.3
Profound (> 7 rows difference)	0	0
Total	14	100

DISCUSSION

Although the presence of strabismus in DS may be predictive of a significant refractive error, a refractive error is not necessarily indicative of a strabismus. The association between strabismus and abnormal refractive development is unclear.[14] Strabismus is a common finding in individuals with DS. The prevalence of strabismus in our study was 26.5% which is similar to a study by Tsirias who found a prevalence of 22% [11] but lower than Haugen and Høvding[14] who reported strabismus in all refractive groups among their cohort of children with DS with an overall prevalence of 42%, and Jaeger who found a prevalence of 41.3%.[15]

Most authors have identified esodeviations. The prevalence of esodeviations in our strabismic DS population was 71.1%. Exodeviations were found in nine patients (20%) in this study, but it has been reported to be as low as 6%.[11] Exodeviations in our study were most associated with hyperopia and were seen at ages from 7–25 years (Table 4).

Hyperdeviations have been uncommon[11] and associated with A or V patterns, dissociated vertical deviation, Brown's syndrome, or oculomotor nerve palsy. In this study, we observed four patients (8.9%) with hypertropia without these associations, similar to the prevalence rate of da Cunha and de Morreira.[5]

The high prevalence of strabismus in the present study cannot be attributed to the presence of hyperopia. Our data show no association between refraction and strabismus in children with DS.

As other studies have shown, hyperopia is the most common refractive error in DS.[2,5] The incidence of hyperopia (spherical equivalent) in this study was 55.2 % and myopia (spherical equivalent) 20.7%. Haugen[3] and Cregg[17] showed that failure of emmetropization to occur is a characteristic of many children with DS. Doyle[18] showed that axial length correlated with spherical equivalent. A linear association was found between axial length and spherical equivalent refraction.

However, reports show that although hyperopia is more common in individuals with myopia, the degree of myopia can be extremely high.[4,5] In the present study, 12 of 145 subjects had myopia of –8.00 D or greater.

The incidence of astigmatism in the population with DS in Macedonia and Croatia was 72.4% which is higher

than the results of the Woodhouse group in the UK,[2] and similar to the Norwegian population with DS.[4]

Oblique astigmatism was the most common type of astigmatism (52%) in our study group of children and young adults. Haugen[6] found that "with the rule"(WTR) astigmatism is the most common type in Norway's population of infants. An increased frequency of oblique astigmatism among young people with DS has previously been reported by Doyle.[18]

Upward slanting of the palpebral fissure, thinner cornea and mechanical pressure exerted on the cornea of eye lids and the palpebral fissure probably is an important causative factor of oblique astigmatism.[14]

The frequency of nystagmus (11%) and generally horizontal pattern in our study fits roughly with the reported 5–30% in other studies[5,7,11,13,19] of individuals with DS; and generally with the horizontal and pendular pattern.[13,19] The subjects with nystagmus in the present study usually had refractive errors, which is in line with other studies reporting that the nystagmus was associated with refractive errors.[20,21]

Da Cunha and de Morreira[5] reported amblyopia in 26% of all 139 patients whose visual acuity was testable. Other authors have found a frequency of amblyopia in patients with DS from 8.5–22%.[11,12,15] The present study found 14 cases of amblyopia among the 83 subjects who were testable (16.9%).

The subjects from the cohort did not have follow up and there were no reports to schools. The parents were aware of poor visual acuity of individuals with DS.

In our study 100% of persons with high hyperopia and any myopia were prescribed optical correction. In some individuals with DS, the optical correction was not accepted because of intellectual deficit

Our study showed that in young adults with DS high myopia had a higher prevalence in individuals aged over 20 years. Focal lens cortical changes and cortical liquefaction have been reported in patients with DS over 14 years.[22] There is evidence supporting the hypothesis that trisomy 21 patients have an increase in free radical reactions. These findings suggest impairment in the antioxidant system, which may be a possible mechanism for early cataract formation in DS. Lens changes or keratoconus could account for the increase in myopia in young adults with DS. In the most recent study, evaluation of DS lenses revealed a characteristic pattern of supranuclear opacification accompanied by accelerated supranuclear Aβ accumulation, co-localizing amyloidal pathology, and fiber cell cytoplasmic Aβ aggregates (~5–50 nm) identical to the lens pathology identified in Alzheimer's disease.[23]

Considering the high prevalence of myopia in the age group over 20 years we propose the clinical guidelines for young adults with DS to be modified. Instead of every 5 years,[24] we recommend ophthalmologic and refractive screening every second year after 6 years of age.

Refractive errors, strabismus and nystagmus appear in a higher percentage in the DS population compared with the general population. Association between snowflake lens opacities and keratoconus with high myopia in the older age group should be the object of further study. Screening, evaluation and treatment of ocular and refractive findings in children and young adults with DS is regularly needed.

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