TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2013) 43: 810-814
© TÜBİTAK
doi:10.3906/sag-1209-69

Evaluation of early corneal topographic changes in children with Down syndrome

Murat ASLANKURT*, Lokman ASLAN, Adnan AKSOY, Muhammed Mustafa KURT, Murat ÖZDEMİR
Department of Ophthalmology, Faculty of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey

Received: 19.09.2012 • **Accepted:** 17.12.2012 • **Published Online:** 26.08.2013 • **Printed:** 20.09.2013

Aim: To evaluate early corneal changes using a Scheimpflug imaging (SI) system (Pentacam) in a pediatric population with Down syndrome.

Materials and methods: This study was carried out in a prospective and nonrandomized fashion. Twenty-seven children with Down syndrome and 30 healthy subjects were enrolled in the study. Corneal measurements were done using a Scheimpflug topography system. Central corneal thickness (CCT), minimum corneal thickness (CTmin), central corneal power (CP), difference of central corneal power (DCP) between 2 eyes, inferior superior steepening (I-S), and keratoconus indices were tested with a SI device.

Results: Mean CCT and CTmin values were significantly lower in the patient group than in the control group ($P < 0.01$). Mean CP and DCP values were higher in the patients than in the control group ($P < 0.001$). Although mean I-S values were not statistically different, 11 eyes in the Down syndrome group and 3 eyes in the control group had 1.20 or higher I-S. Eleven eyes (21.1%) in the patient group and 1 eye (1.7%) in the control group had subclinical keratoconus ($P < 0.01$), and 20 eyes (38.4%) in the case group and 2 eyes (3.3%) in the control group had at least 1 abnormal parameter ($P < 0.01$).

Conclusion: Corneal abnormalities and subclinical keratoconus are more common in children with Down syndrome.

Key words: Down syndrome, keratoconus, Scheimpflug imaging, Pentacam, corneal parameters

1. Introduction

Keratoconus affects the young population and is progressive, noninflammatory corneal ectasia (1). The etiology of the disease is unclear, but it has been associated with eye rubbing, atopy, contact lens wearing, and genetic conditions such as Down, Ehlers–Danlos, and Marfan syndromes. The most common chromosomal abnormality occurring in association with keratoconus is Down syndrome (DS) due to trisomy 21 (2–4). The increased frequency of keratoconus in individuals with DS has been reported by many authors. Habitual eye rubbing, which is also frequently observed in patients with DS, has been postulated as a crucial factor either for the development of keratoconus or the progression of the disease. Although keratoconus frequency in the normal population is 1/2000, the incidence in DS has been reported at up to 15% (5,6,7). These incidences include all age groups with DS and do not include topographic measurement. Although topography-based investigations revealed keratoconus in patients with DS to be more common in adults and at pediatric ages (8–10), there are not enough studies done using the Scheimpflug imaging (SI) system.

SI is useful for identifying early, subclinical cases of keratoconus. In addition to curvature, power, and thickness data, the Pentacam uses the acquired data to compute a number of indices. The software highlights abnormal values and uses them to diagnosis and classify the stage of keratoconus (11,12). These imaging systems make noncontact and fast measurements and provide effective results, especially for the pediatric population with DS.

In this study, children with DS who had no clinical evidence of corneal ectasia upon clinical examination were measured with SI and compared with a control group of a similar age. We aimed to reveal early corneal changes of a pediatric population with DS.

2. Materials and methods

The study was approved by the university's School of Medicine Ethics Committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Informed consent was obtained from the parents of the children.

This study group was made up 27 children: 15 males and 12 females who were Caucasian and had DS. They had

* Correspondence: maslankurt80@hotmail.com

no features of keratoconus evident on clinical examination, and they were referred to the ophthalmology clinic from schools for debilitated children and rehabilitation centers for eye examination as part of a multidisciplinary approach. The control group was made of 15 male and 15 female age-matched, healthy children. Each subject in the study underwent a complete ocular examination including cycloplegic refraction, external eye examination, screening tests for strabismus, slit-lamp biomicroscopy (corneal thinning, hydrops, scar, and Vogt's striae), and fundoscopy. Retinoscopy was performed, and scissoring or oil-drop reflex was addressed.

Children with clinically detectable corneal pathology such as opacity, scar, degeneration, and evident keratoconus were excluded from the study. Evident keratoconus was accepted if the patient had: 1) corneal irregularity determined by distorted keratometric mires, distortion of retinoscopic/ophthalmoscopic retinal red reflex, or both; and 2) at least one of the following findings in slit-lamp examination: Vogt's striae, Fleisher ring, or corneal scar consistent with keratoconus. Subclinical keratoconus was defined as normal corneal appearance in slit-lamp examination, retinoscopy, and ophthalmoscopy, in addition to inferior superior asymmetry and/or an asymmetric bow-tie pattern in the topographic map (11).

2.1. Corneal measurements

Corneal topographic maps were obtained by using a SI system (Pentacam HR, Oculus Inc., Wetzlar, Germany) in mesopic condition by same person specially trained in the use of Pentacam. The seated subject is asked to keep his or her eyes open and look at the fixation light. When the patient's eye reaches the correct alignment, the instrument starts the measurement automatically. The Scheimpflug camera captures 25 images by rotating around the optical axis of the eye in approximately 2 s. Measurements were repeated until acceptable quality imaging was obtained. After the measurements, quantitative topography values evaluated: central corneal thickness (CCT), minimum corneal thickness (CTmin), central corneal power (CP), difference in central corneal power (DCP) between both eyes of each subject, relative steepness of the inferior cornea versus the superior cornea (I-S), and keratoconus indices obtained with the SI device were noted. Index of surface variance (ISV), index of surface asymmetry (IVA), keratoconus index (KI), center keratoconus index (CKI), index of height asymmetry (IHA), and index of height decentration (IHD) are the indices calculated by the Pentacam software.

The I-S value was calculated with the inferior and superior averages at the paracentral zone on a corneal dioptric power map. Average inferior and superior readings at the paracentral zone, which is the most affected area in keratoconus (1), every 30° at 3 mm from the center of the cornea were evaluated. The average reading from the superior half of the cornea was subtracted from that of the inferior half. A positive I-S value represents a relatively steep inferior cornea, whereas a negative value represents a relatively steep superior cornea. More than 1.2 was accepted as abnormal.

Eyes showing abnormal parameter(s) were counted. Average keratometry of ≥47.2, I-S ≥1.2, thinnest pachymetry ≤463 μm, and keratoconus indices derived from the Pentacam device were used as parameters and thresholds for abnormality (13,14).

The data were presented as mean ± standard deviation for continuous variables and as frequencies (in percentages) for the categorical variables. The differences between groups were compared with the independent Student t-test for normally distributed data and the Mann–Whitney U test for not normally distributed data for continuous variables. The chi-square test was used for the categorical variables. Receiver operating characteristic (ROC) curves were used to determine the predictive accuracy of the test parameters. A probability of $P < 0.05$ was considered statistically significant. The statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Fifty-two eyes of 27 DS and 60 eyes of 30 control subjects were evaluated. Age distribution of the groups was similar (8.9 ± 2.4 years, range: 5–13 and 8.8 ± 2.2 years, range 5–12 years, respectively) ($P > 0.05$). Thirty children with DS were prospectively identified as candidates for keratometric measurement. We achieved acceptable readings in 27 of them (25 bilateral). Bilateral measurements could be made in all children in the control group. No subjects were excluded based on the clinical evaluation in either group. Mean CCT values in the right eyes of the study group and controls were 494 ± 47 and 552 ± 34 μm and CTmin values were 487 ± 49 and 552 ± 33 μm, respectively ($P < 0.01$, $P < 0.01$).

Simulated keratometric readings and central power in the right eyes of children with DS were significantly higher than in controls: k1 at 46 ± 1.3 versus 41.5 ± 1.3 and k2 at 45 ± 1.9 versus 43 ± 1.3 ($P < 0.001$, $P < 0.001$). Central corneal power was 45.3 ± 1.5 and 42.8 ± 1.6, respectively ($P < 0.001$).

DCP was 0.94 ± 0.76 in the 26 bilateral measurements that could be done with DS patients and was 0.59 ± 0.55 in the control group. The difference between the 2 groups was statistically significant ($P < 0.001$, t-test).

Although I-S values were not different (0.4 ± 1.6 and 0.6 ± 0.6, $P = 0.449$, t-test) between children with DS and the control group, 11 eyes in the DS and 3 eyes in the control group had I-S values of 1.20 or higher. Other keratoconus indices obtained from the Pentacam device software were all higher in the DS than in the control group (Table 1).

Table 1. Keratoconus indices of DS and control group.

	Down syndrome	Control	P-value
I-S	0.41 ± 1.6	0.62 ± 0.7	P = 0.449*
ISV	35.11 ± 0.17	24.38 ± 9.21	P < 0.01*
IVA	0.31 ± 0.17	0.17 ± 0.07	P < 0.01**
KI	1.05 ± 0.04	0.92 ± 0.28	P < 0.01**
CKI	1.00 ± 0.01	0.98 ± 0.14	P = 0.3*
IHA	9.55 ± 8.17	4.9 ± 4.65	P < 0.01**
IHD	0.024 ± 0.025	0.011 ± 0.006	P < 0.01**

*: t-test, **: Mann–Whitney U test.
I-S: Inferior superior steepening, ISV: index of surface variance, IVA: index of vertical asymmetry, KI: keratoconus index, CKI: central keratoconus index, IHA: index of highest asymmetry, IHD: index of highest decentration.

Keratoconus probability evaluation with the SI device software revealed early subclinical keratoconus in 11 eyes (21.1%) in the DS and 1 eye (1.7%) in the control group. Twenty eyes (38.4%) in the DS and 2 eyes (3.3%) in the control group had at least 1 abnormal parameter according to SI without any clinical signs. The topography of an eye that was reported to have grade 2–3 keratoconus with an I-S rate of 7.77 is shown in the Figure.

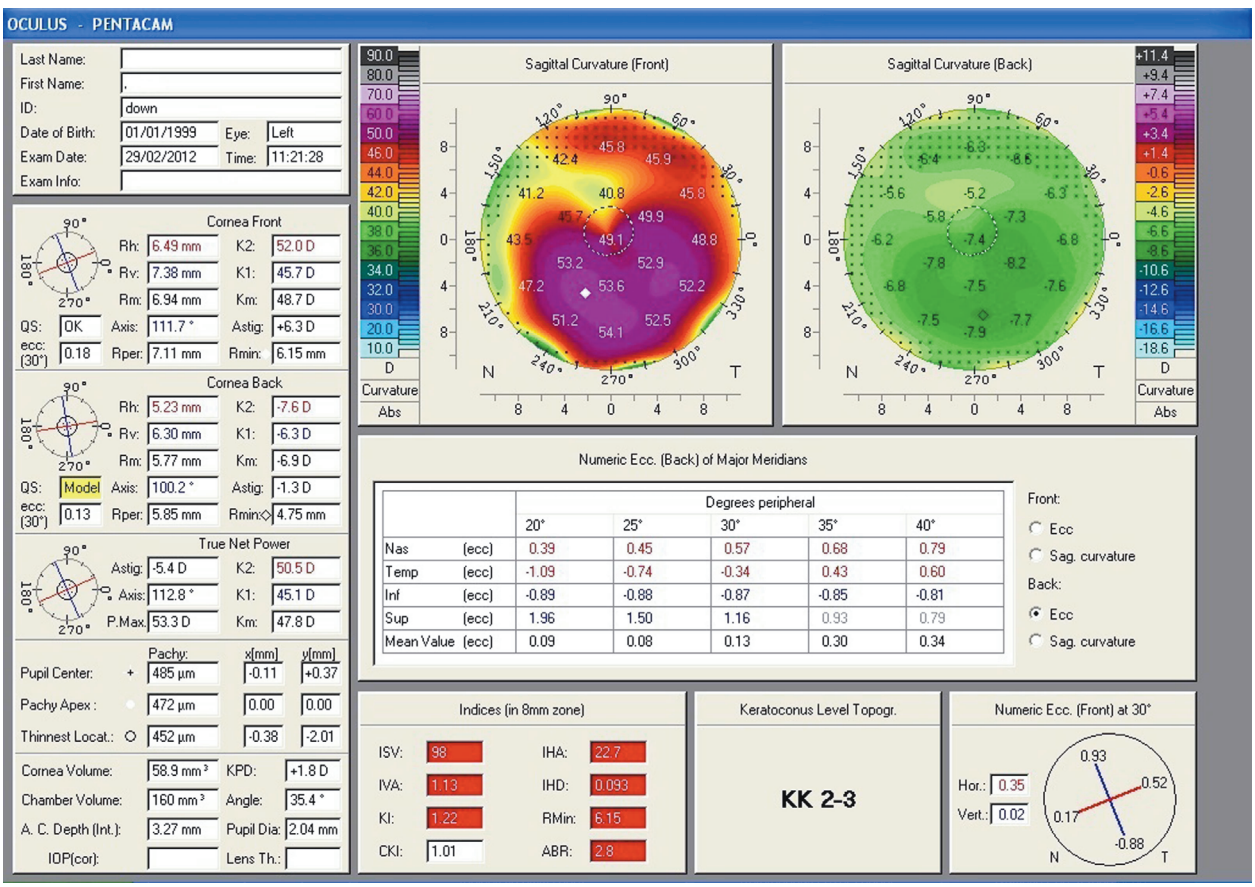

Figure. The topography image of an eye reported as grade 2–3 with I-S value of 7.77.

In the present study, in discriminating eyes with subclinical keratoconus from normal eyes, ISV, IVA, IHD, and CP had the highest area under the curve (AUC) values in ROC analysis (Table 2). However, I-S and DCP values had smaller AUC values than the others and were statistically not significant.

4. Discussion

The literature demonstrates that children with DS are at risk of several ocular disorders. In addition, increased frequencies of refractive and corneal changes in DS were reported in previous studies (1). Diagnosis of early subclinical keratoconus can be difficult. Comprehensive clinical examination may not exclude the diagnosis of early disease (15). Computerized corneal topography had been used to study and detect early diagnosis of keratoconus (1,15,16). The curvature indices, as with any curvature measurement, are reference axis-specific. While there is no measurement that is completely free of orientation effect, there are some that are less susceptible. In general, the minimal corneal thickness (but not location) is relatively insensitive to fixation, as are the overall elevation appearance maps (17). Therefore, we added thickness data to curvature indices. It has been shown that some indices derived from Pentacam measurements, such as posterior elevation data and corneal thickness distribution indices, were the best in discriminating subclinical keratoconus eyes from normal eyes (11).

Table 2. Predictive accuracy of the test parameters with ROC analysis for the subclinical keratoconus versus normal eyes.

Parameter	AUC	SE	P-value
CTmin	0.185	0.09	0.017*
CP	0.818	0.08	0.016*
DCP	0.339	0.133	0.226
I-S	0.604	0.175	0.429
ISV	0.887	0.06	0.003*
IVA	0.860	0.09	0.006*
KI	0.753	0.08	0.05
CKI	0.405	0.134	0.470
IHA	0.482	0.151	0.892
IHD	0.845	0.95	0.009*

AUC: Area under the curve, SE: standard error. *: Statistically significant parameter.
CTmin: Minimum corneal thickness, CP: central corneal power, DCP: difference in central corneal power. See Table 1 for other abbreviations.

Some researchers reported central keratometric measurements in children (18,19). The mean keratometric reading in each age group was seen to decline systematically from birth to about 54 months of age. The mean in the newborn to 6-month-old group was 47.59 D. In the 12. to 18-month-old group, it had decreased to 45.56 D. The cornea appears to stabilize at about 4.5 years, with an average reading of 42.69 D (18) and 43.69 D (19). In our control group consisting of subjects 5–12 years old, the mean CP value (42.8) was close to those previous findings.

Our results using a SI device revealed that corneas of asymptomatic children with DS were steeper (46.0) than in normal control subjects. This is in agreement with findings of some other studies (46.39, 45.6, and 46.6) (20–22).

DCP is a significant early marker of keratoconus (1,17). Although the predictive value was small in our series in the ROC analysis, the mean DCP was significantly higher in the DS group than in the control.

The I-S rate is a good indicator of keratoconus. Steepness in the lower half of the cornea and values higher than 1.2 have been reported in favor of keratoconus (13,14). In these series, the differences between average I-S values of DS patients and controls did not reach statistical significance. However, the number of eyes with an I-S value of 1.20 or higher was significantly greater in the DS group. This result may be due to the relatively small size of the group, or to a potential mistake in our method of determining the I-S values. Abnormal CP and DCP while I-S was normal may also be suggestive of early, nipple-type cones.

According to indices for keratoconus by the Pentacam software (ISV, IVA, KI, CKI, IHA, and IHD), the possibility of keratoconus is graded from 'keratoconus possible' to grade 4. In our series, keratoconus was found in 11 eyes, with the majority being of the grade 'keratoconus possible' and grade 1.

Up to a 15% incidence of keratoconus has been reported in the literature on DS, but this was based on clinical examination data. The frequency of patients who had at least 1 abnormal parameter has been reported at 39%. Precise keratoconus frequency has not been reported in topography-based studies. In our study, 38.4% of the eyes had at least 1 abnormal parameter and 21.1% were diagnosed with subclinical keratoconus.

Although some authors have attributed the high prevalence of keratoconus in patients with DS to chronic eye rubbing (4,6), others have not (22). Some researchers have concluded that there are genetic aspects of the disease. Rabinowitz et al. identified a gene locus on chromosome 21q, which encodes a collagen and defines the relationship between the DS and the keratoconus (23). However, gene loci on chromosomes 20, 16, and 15 related to keratoconus were also identified (24–26). Keratoconus seems

multifactorial and includes genetic and environmental aspects. In the development of keratoconus, patients with DS are exposed to both environmental and genetic effects. Our results suggest that patients with DS have increased keratoconus and corneal shape abnormalities even in the absence of clinical evidence of keratoconus. The increased frequency of keratoconus in DS might be associated with increased corneal steepness, the effect of the 21st chromosome encoding a gene related to keratoconus, or increased eye rubbing factors, alone or together.

In conclusion, keratoconus is more frequent in computerized topographic examination than in clinical examination and corneal abnormalities are more common in cases of DS. Adding computerized corneal topography to routine eye examinations may allow detection of early corneal changes and facilitate therapy to stop the progression of keratoconus. Indices derived from the Pentacam device may also facilitate subclinical keratoconus diagnosis.

References

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42: 297–319.
2. Edwards M, McGhee CN, Dean S. The genetics of keratoconus. Clin Experiment Ophthalmol 2001; 29: 345–51.
3. Da Cunha RP, Moreira JB. Ocular findings in Down's syndrome. Am J Ophthalmol 1996; 122: 236–44.
4. Harrison RJ, Klauda PT, Easty DL, Manku M, Charles J, Stewart CM. Association between keratoconus and atopy. Br J Ophthalmol 1989; 73: 816–22.
5. Karlica D, Skelin S, Culic V, Galetović D, Znaor L, Karlica H et al. The ophthalmic anomalies in children with Down syndrome in Split-Dalmatian County. Coll Antropol 2011; 35: 1115–8.
6. Shapiro MB, France TD. The ocular features of Down's syndrome. Am J Ophthalmol 1985; 99: 659–63.
7. Creavin AL, Brown RD. Ophthalmic abnormalities in children with Down syndrome. J Pediatr Ophthalmol Strabismus 2009; 46: 76–82.
8. Karadag R, Yagci R, Erdurmus M, Keskin UC, Aydin B, Durmus M. Ocular findings in individuals with intellectual disability. Can J Ophthalmol 2007; 42: 703–6.
9. Doyle SJ, Bullock J, Gray C, Spencer A, Cunningham C. Emmetropisation, axial length, and corneal topography in teenagers with Down's syndrome. Br J Ophthalmol 1998; 82: 793–6.
10. Vincent AL, Weiser BA, Cupryn M, Stein RM, Abdolell M, Levin AV. Computerized corneal topography in a pediatric population with Down syndrome. Clin Experimental Ophtalmol 2005; 33: 47–52.
11. Uçakhan ÖÖ, Cetinkor V, Özkan M, Kanpolat A. Evaluation of Scheimpflug imaging parameters in subclinical keratoconus, keratoconus, and normal eyes. J Cataract Refract Surg 2011; 37: 1116–24.
12. Miháltz K, Kovács I, Takács A, Nagy ZZ. Evaluation of keratometric, pachymetric, and elevation parameters of keratoconic corneas with pentacam. Cornea 2009; 28: 976–80.
13. Steele TM, Fabinyi DC, Couper TA, Loughnan MS. Prevalence of Orbscan II corneal abnormalities in relatives of patients with keratoconus. Clin Experiment Ophthalmol 2008; 36: 824–30.
14. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37: 1282–90.
15. Maguire LJ, Bourne WM. Corneal topography of early keratoconus. Am J Ophthalmol 1989; 108: 107–12.
16. Rabinowitz YS, Garbus J, McDonnell PJ. Computer-assisted corneal topography in family members of patients with keratoconus. Arch Ophthalmol 1990; 108: 365–71.
17. Zengin MÖ, Özbek Z, Arıkan G, Saatçi AO. Does central corneal thickness correlate with haemoglobin A_{1C} level and disease severity in diabetes type 2? Turk J Med Sci 2010; 40: 675–80.
18. Ehlers N, Sorensen T, Bramsen T, Poulsen EH. Central corneal thickness in newborns and children. Acta Ophthalmol (Copenh) 1976; 54: 285–90.
19. Asbell PA, Chiang B, Somers ME, Morgan KS. Keratometry in children. CLAO J 1990; 16: 99–102.
20. Haugen OH, Høvding G, Eide GE. Biometric measurements of the eyes in teenagers and young adults with Down syndrome. Acta Ophthalmol Scand 2001; 79: 616–25.
21. Little JA, Woodhouse JM, Saunders KJ. Corneal power and astigmatism in Down syndrome. Optom Vis Sci 2009; 86: 748–54.
22. Vincent AL, Weiser BA, Cupryn M, Stein RM, Abdolell M, Levin AV. Computerized corneal topography in a paediatric population with Down syndrome. Clin Experiment Ophthalmol 2005; 33: 47–52.
23. Rabinowitz YS, Maumenee IH, Lundergan MK, Puffenberger E, Zhu D, Antonarakis S et al. Molecular genetic analysis in autosomal dominant keratoconus. Cornea 1992; 11: 302–8.
24. Aldave AJ, Yellore VS, Salem AK, Yoo GL, Rayner SA, Yang H et al. No VSX1 gene mutations associated with keratoconus. Invest Ophthalmol Vis Sci 2006; 47: 2820–2.
25. Tyynismaa H, Sistonen P, Tuupanen S, Tervo T, Dammert A, Latvala T et al. A locus for autosomal dominant keratoconus: linkage to 16q22.3-q23.1 in Finnish families. Invest Ophthalmol Vis Sci 2002; 43: 3160–4.
26. Hughes AE, Dash DP, Jackson AJ, Frazer DG, Silvestri G. Familial keratoconus with cataract: linkage to the long arm of chromosome 15 and exclusion of candidate genes. Invest Ophthalmol Vis Sci 2003; 44: 5063–6.