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Corneal Alterations in Subjects with Down's Syndrome and Celiac Disease

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Abstract

Aim: *To assess the presence of changes in corneal thickness in. the patients with Down's syndrome (DS) and celiac disease (CD)*

Materials and Methods: *Fortyeight subjects with Down's syndrome (23 men and 24 women) were enrolled in the study.22 subjects were suffered from celiac disease too .*

Results: *4 subjects (8.5%) , including 3 with CD, presented keratoconus at stage 1 or 2 according to the Amsler-Krumeich classification.*

The pachymetric examination in subjects with celiac disease showed in 12(54,5%) a corneal thickness at the lower limit of the relevant range for the respective age groups. and in 10 (45,5) a pathological thickness.

In subjects with only DS the corneal thickness was at the lower limit of the relevant range in 18(72%)

Conclusions: *Subjects with DS and celiac disease too present a reduced corneal thickness and a higher frequency of keratoconus.*

Keywords: *Down's syndrome; Celiac disease; Corneal thickness; Keratoconus.*

Introduction

Down's syndrome (DS), consequent in the vast majority of cases on an autosomal trisome 21, is one of the most frequent chromosomal anomalies. It is manifested with a vast range of somatic alterations and is accompanied, very often, by other genetic anomalies. Various studies have shown that patients with DS present immune dysfunctions that predispose them to recurrent infections and to autoimmune illnesses. A frequent finding is celiac disease (CD), a pathological condition characterized by an inappropriate immune response to wheat gluten and the prolamines of barley and rye, whose manifestations overlap those of Down's syndrome making the quality of life poorer. (1,2,3,4).

In patients with DS low stature constitutes a characteristic whose pathogenesis is linked primarily to hypothyroidism, which may also be sub-clinical (5); some authors have detected a growth hormone (GH) deficit and have emphasized correction of the growth rhythm through administration of the insufficient hormone (6).

People with celiac disease also often have impaired growth, and one of the main causes of its multi-factor pathogenesis is a GH deficit and/or receptor resistance to GH.

Among the receptors for this hormone we have to consider the corneal cells (7), and indeed in subjects with hypopituitarism or with GH receptor resistance a reduction of corneal thickness is observed that can involve alterations of the corneal morphology, exposing people to the risk of keratoconus.

We decided to appraise in DS subjects with associated CD the presence of possible alterations of corneal thickness, which could explain the greater frequency of keratoconus in them.

Material and Methods

Forty-eight subjects with Down syndrome (23 men e 24 women) aged 6 to 39 years from a similar ethnic background were enrolled in the study.

All the subjects presented a 21 free trisome in the karyotype study.

22 subjects were suffered from coeliac disease too.

25 subjects, affetti with only DS, contro group.

All subjects with CD were submitted to a complete ophthalmic examination with evaluation of visual acuity, biomicroscopy of the anterior segment, dilatated fundus examination and orthoptic examination with study of ocular motility, degree of convergence and the cover and uncover test both close up and at a distance. Evaluation of refraction was carried out in cyclopegia in all patients through instillation of 3-5 drops of Cyclopentolate 1%.

Visual acuity (VA) was tested with an E chart and best-corrected visual acuity (BCVA) would be measured if the VA was less than 0.5. Cycloplegic refraction was determined by streak retinoscopy 30 min after the last drop to ensure maximal cycloplegic effect.

The refractive error was taken as the spherical equivalent (SE) in diopters (D) and calculated as the power of the sphere plus half the cylindrical power. Eyes with a SE from -0.75 to +1.75 D were classified as emmetropic. Myopia was defined as SE refractive error of at least -0.75 D and hypermetropia as +1.75 D or more.

The corneal thickness was assessed by ultrasonic pachymetry (Pachpen Accutome 24-5100)

The measurements (38) were taken centrally as well as at four paracentral sites 3 mm from the corneal center at the 3, 6, 9, and 12 o'clock positions. The following values were considered normal :

565 + 46 micron between 5 and 9 years (5 -9 years)

555 + 33 micron higher than 9 years (> 9years).

Consent

Written informed consent to participate in this study was obtained from a parent of the patients.

Statistical Analysis

The correlations between weight percentiles and corneal thickness and between theheight percentiles and corneal thickness were examined through linear regression analysis and expressed as a r squared. Data were analyzed by Statistical Software Graph Padprism.

$P<0.05$ was considered statistically significant.

Results

All subjects presented a refraction defect such as myopia and/or astigmatism; hypermetropia was only found in one subject of the group constituted by subjects with DS only (control group).

Keratoconus at stage 1 or 2, according to the Amsler-Krumeich classification, was found in 4 subjects (8.5%), 3 of them DS patients with associated CD (4, 11,21) and 1 in the control group.

Pachymetric examination in 12 subjects (54.5%) of the group with CD (Table 1) showed corneal values at the lower limit of the relevant range for the respective age groups.

10 subjects (45.5%) presented values indicative of pathological corneal thickness.

In the control group (Table 2) only in one subject was the corneal thickness pathological; in the others the values were in the normal range, though in 18 (72%) it was at the lower limit.

Subdividing the subjects into three groups (1-10 years; 11-20 years; > 21 years), the reduction of the corneal thickness in the subjects with CD is more marked in all three groups, with statistical significance: $p = 0.003$ in the group aged 1-10 years and in the group aged 11-20 years and $p = 0.049$ in that of subjects above 20 years.

Table 1. *Patients with Down's Syndrome and Celiac Disease*

No.	Initials	Sex	Age	Refraction defect	CCT
1	P.M.	F	14	Myopic astigmatism compound	518-520 *
2	P.G.	M	24	Myopic astigmatism compound	525-522
3	L.R.	M	34	Myopic astigmatism	530-534
4	G.L.	M	18	Myopic astigmatism - Keratoconus	515-518 *
5	G.A.	M	22	Myopic astigmatism	514-516 *
6	M.A.	M	17	Serious myopia	522-516
7	I.M.S.	F	6	Myopia	510-510 *
8	C.E.M.	F	8	Myopia	514-510 *
9	C.G.	F	13	Myopic astigmatism	520-516
10	C.A.	M	24	Myopic astigmatism	520-520
11	S.M.J.	F	22	Myopia – Keratoconus	514-512 *
12	A.R.	M	20	Myopia	522-520
13	M.C.	F	13	Myopic astigmatism	510-506 *
14	M.M.G.	F	9	Myopic astigmatism compound	512-506 *
15	P.M.	F	14	Myopic astigmatism compound	518-506 *
16	P.G.	M	24	Myopic astigmatism compound	526-528
17	G.A.	F	17	Myopia	530-522
18	G.I.	M	18	Myopic astigmatism	516-518 *
19	AD	M	6	Myopic astigmatism	512-506
20	D.D.F.	M	23	Myopia	528-532
21	G.C.	F	22	Myopia – Keratoconus	510-512 *
22	V.F.	F	39	Myopia	526-520

* Corneal thickness below normal values

Table 2. *Patients with Down's Syndrome only*

No.	Initials	Sex	Age	Refraction defect	CCT
1	C.S.	M	11	Myopic astigmatism	520 - 522
2	C.A.	M	13	Astigmatism	524 - 524
3	C.G.	F	13	Hypermetropia	522 - 524
4	P.P.	M	24	Myopia	526 - 525
5	P.G.	M	13	Myopia	524 - 524
6	P.G.	M	23	Myopic astigmatism	522 - 522
7	P.E.	F	19	Myopia	520 - 520
8	P.C.	F	13	Myopic astigmatism	524 - 524
9	P.V.	F	23	Myopic astigmatism	528 - 526
10	L.P.L.	F.	8	Farsightedness	518 - 518
11	L.C.	F	14	Myopia	522 - 522
12	L.E.	F	14	Myopic astigmatism	522 - 524
13	L.S.	M	24	Myopia	528 - 527
14	G.F.	M	34	Keratoconus	518 - 516
15	G.F.	M	24	Myopia	522 - 524
16	G.R.F.	F	6	Astigmatism	518 - 518
17	G.D.	M	6	Hypermetropic astigmatism	520 - 520
18	C.R.	M	28	Astigmatism myopic	522 - 524
19	S.A.	F	21	Myopia	526 - 526

20	C.R.	F	22	Astigmatism	530 - 528
21	S.D.	M	17	Astigmatism	526 - 526
22	B.R.G.	F	20	Myopia	524 - 528
23	B.R.	F	36	Myopia	530 - 528
24	C.M.	F	30	Myopic astigmatism	524 - 526
25	C.A.	M	24	Myopic astigmatism	528 - 528

Discussion

In the last decade it has been shown that the association between DS and CD is quite frequent and the prevalence of celiac disease in patients with DS is significantly superior to that found in the general population (8). A recent study by K. Marild et al. (1) emphasized that the risk of CD in subjects with DS is 6 times higher than in normal subjects.

Keratoconus too, which affects 1 out of 2000 subjects in the general population, is frequent in subjects with DS with an incidence of up to 15% (9), and a reduction of corneal thickness can be observed in almost all subjects (10). In our patients keratoconus proved to be quite frequent (8.5%), though with lower values than those indicated by Stojber. In the group with CD, nevertheless, the prevalence was higher, going up to 13.6%, very likely because of the presence in these subjects of more severe alterations of corneal thickness.

In subjects with DS numerous studies have also underlined anomalies of cornea shape even in the absence of clinical evidence of keratoconus (9,10.11.12.,13). Vincent et al. (12), moreover, using computerized corneal topography detected the presence of an altered parameter in 39% of the parents of children with DS. This datum would suggest the presence of a genetic anomaly responsible for the reduced corneal thickness. In this connection, most researchers point to complete penetrance of the factors but with varying phenotypic expression. In some patients heterozygous mutations of gene VSX1 are described as the basic genetic defect.

This gene, placed on chromosome 20 (20p 11-21) is involved in synthesis of proteins regulating normal corneal trophism and its mutations are considered responsible for polymorphous corneal dystrophy and keratoconus.

In our patients, independently of the presence or otherwise of CD, we detected corneal thickness values at the lower limit of the normal range or clearly pathological; only in 6 subjects (12.7%) were the values in the normal range.

By contrast, in all subjects also having CD, the corneal thickness clearly proved to be reduced, with a pathological value in 10, and the difference between the two groups, with and without CD, was statistically significant. Indeed, in subjects with DS and CD, the average corneal thickness proved to be lower than in subjects with DS only.

It is consolidated in the literature (14,15) that patients with CD show reduced stature, due, according to some, to a GH deficit (16,17), and according to others to increased resistance of the bone cellular receptors to the hormone. The cornea too, like the bone cells, constitutes a target for GH (7) and subjects with hypophysial reduced stature show a reduction of corneal thickness that can be corrected by administration of the hormone (18) In a previous study on patients with CD we noticed the presence of reduced corneal thickness in the 60% of subjects and we hypothesized that this condition could be connected to an increased resistance of GH receptors or to reduced sensitivity of them; the fact is that the GH values were normal in all subjects except 2, who presented higher than normal values.

Patients with DS also often show impaired stature that can be linked to a GH deficit (6,19) and can be corrected, at least in part, with the hormone replacement therapy. In subjects that also have CD, the response to the therapy is less satisfactory. This could be due to increases in resistance of receptors for the action of the GH and/or of IGF-1 mediated by the inflammatory process at the basis of CD. In this connection, pro-inflammatory cytokines like TNF and IL-6 have been implicated as potential mediators of hormone resistance (20). As further confirmation, in subjects with CD, unlike what is seen in patients with primitive hypopituitarism, in which no alteration of GH receptor sensitivity is found, hormone replacement therapy does not always correct the corneal thickness deficit.

Thus in subjects with DS and celiac disease reduced corneal thickness, with consequent greater frequency of keratoconus, may be linked to reduced sensitivity of receptors for GH and/or IGF-1, a pathogenetic mechanism independent of the genetic anomaly hypothesized by others.

Conclusion

From our study, the first aiming to appraise the presence of alterations of corneal thickness and keratoconus in subjects with DS and CD, it clearly emerges that in these patients the corneal thickness is reduced, with consequent higher frequency of keratoconus. It follows that corneal alteration must be systematically sought in patients with DS and CD, with careful monitoring, especially in the first two decades of life. Only in this way is it possible to identify the corneal thickness deficit and rapidly begin appropriate treatment to prevent the inevitable evolution towards keratoconus, thus helping to improve the quality of life of these patients.

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