CLINICAL AND TOMOGRAPHIC STABILITY IN YOUNG PATIENTS WITH KERATOCONUS OR SUSPICIOUS TOMOGRAPHIES FOR KERATOCONUS

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Purpose: To evaluate tomographic variables related to ectasia progression in patients < 18 years with keratoconus (KC) or suspicious tomographies for keratoconus (STK) from a private clinic in Medellin, Colombia, to determine the need for crosslinking in a pediatric population.

Design: Mixed prospective-retrospective descriptive study.

Participants: Patients were evaluated from 2012 to 2020. All patients had ~~a~~ tomography by rotating Scheimpflug (Pentacam; Oculus Gmbh, Wetzlar, Germany), with a BAD-D ≥ 1.6 in the included eye(s) on the Belin-Ambrósio display and a minimal repeat image at one year. 43 eyes of 24 patients with a follow up ranging from 1 to 8 years were included.

Methods, Intervention, or Testing: All potential study subjects were reviewed by two independent cornea specialists with extensive knowledge in corneal imaging. Maps were graded as KC, STK or normal. Only patients where there was an agreement were included. Eye rubbing control was the mainstay of therapy with topical antiallergics, anti-inflammatories and an allergist consult if needed. Crosslinking (CXL) was performed only if progression was documented. The definition of progression from 2012 to 2017 required a significant variation in two of four parameters: anterior best fit sphere (BFS), posterior BFS, minimum corneal thickness or an increase in the Kmax (maximum keratometry) values. After June 2017 the Belin ABCD progression parameters were utilized; crossing beyond the solid red line (95% confidence interval for patients with keratoconus) of either the anterior radius of curvature (A), the posterior radius of curvature (B) or the minimum corneal thickness (C) on at least two consecutive occasions was considered progression.

Main Outcome Measures: Percentage of progression as defined above in KC or TSK eyes, number of lines gained or lost of DCVA in all patients, CXL or not, and the variability of the A, B and C values of the ABCD display was calculated in stable, non-progressing TSK eyes.

Results: 4 out of 12 eyes with KC (33,33%) and 1 of the 31 eyes with TSK (3.2%) met the criteria for progression and were and were CXL. No patient in either group lost DCVA with an average follow-up of 4,01 years (±1,78) (range 1,66-6,83) in KC group and of 3,47 years (±1,89) (Range 1,08-8) in TSK group.

Conclusions: Strict control of eye rubbing combined with careful follow-up of children with tomographies suspiciuous of keratoconus or true keratoconus without undue loss of DCVA is successful to indicate CXL treatment and avoid vision loss.

Keywords: Cornea; crosslinking; keratoconus; tomography suspicious of keratoconus; pediatric; eye rubbing , allergy control, Pentacam, Scheimpflug camera, keratoconus progression, children, adolescents.

Abbreviations and Acronyms: *BCVA (best-corrected visual acuity), DCVA (distance corrected best corrected visual acuity), KC (ketoconus), CXL (Crosslinking), TSK (Tomography suspicious of keratoconus), BFS (best fit sphere), Kmax (maximum keratometry), ARC or A (anterior radius of curvature), PRC or B (posterior radius of curvature), Thinnest Pachy or C (minimum corneal thickness), UCVA (Uncorrected visual acuity), QS value (Quality Specification value), CI (Confidence interval), RA (Renato Ambrosio), MB (Michael Belin), IOP (intraocular pressure)*

Introduction

Keratoconus is a progressive, bilateral, asymmetric, non-inflammatory corneal disease (1), that causes visual impairment because due to irregular astigmatism, scarring and deterioration in quality of life in general (2). This disease traditionally manifests in the second decade of life.

Its prevalence is variable around the world, being 54.5 per 100,000 inhabitants in the United States and up to 6,200 per 100,000 inhabitants in Saudi Arabia (3). In children, prevalence has not been widely reported in the literature, the largest study with 2,972 patients under the age of 14 in Lebanon reported an incidence of 0.53% (approximately 1 in 200) (4).

Pediatric cases have been reported to presente in a more severe and to progress more rapidly if it happens (5), with reports of progression of keratoconus in children as high as 88% (6)(7).

The introduction of corneal collagen cross-linking (CXL) has changed the management of keratoconus. It has been reported as a treatment that can block the progression of keratoconus (8) and even allow the regression of ectasia (9).

Most studies describe CXL is a safe and effective treatment for avoiding keratoconus progression in pediatric patients (10) although there have been reports of loss of BCVA up to 30% of cases (11)(12). CXL is not an innocuous procedure with reports of complications such as microbial keratitis, persistent epithelial defects and haze, and worsened BCVA (2)(13)(14). Progression rates ranging from 13% to 24% despite the procedure and need to do a second CXL for further progression have been reported (15)(16).

Several methods have been described in the literature to both evaluate and document progression in keratoconus (17). There is no consistent or clear definition of ectasia progression, furthermore there are considerable differences in opinion on when to perform corneal collagen crosslinking in patients with keratoconus. The most common variables have been increase in the Kmax value, decrease in the thinnest corneal pachymetry, decrease in best corrected visual acuity, or increase in myopia or astigmatism.

Chatzis et al. (6) in 2012 and Barbisan et al (18) in 2019 proposed that awaiting documentation of progression is not mandatory and that CXL should be performed in all children and adolescents as soon as the diagnosis has been made due to the high rate of progression found by them.

Allergic eye diseases (19)(15), eye rubbing, and inflammation are implicated in the pathogenesis and progression of keratoconus (KC). (20)(15) Patients with allergic diseases of the eye and KC tend to present a higher degree of KC (21). Bawazeer in 2000 was the first to report that vigorous eye rubbing was independently associated with keratoconus (22). Continuous eye rubbing has been associated with progression after collagen crosslinking (CXL).

This study aimed to determine if it is possible to control the progression of keratoconus by strictly controlling allergy and eye rubbing, doing a careful tomographic follow up and performing crosslinking only in those patients with documented tomographic progression.

Methods:

This study adhered to the tenets of the Helsinki Declaration and was approved by the University of Antioquia (Colombia) Ethics committee. This was a mixed retrospective-prospective descriptive study of a children (<18 years) cohort evaluated between January 2012 and March 2020 in a private practice in Medellin (Colombia), retrospective phase involved the follow-ups and evaluations carried out between 2012 to 2018 and the prospective phase the follow-ups carried out between January 2019 and March 2020. Demographic, clinical and tomographic variables were evaluated. Patients had complete eye exam including UCVA, refraction, BCVA, slit lamp and dilated fundus exam. Additional evaluations during the first year or in the subsequent years were ordered as needed. The

inclusion criteria were a BAD D value equal or greater than 1.6 in the Belin-Ambrósio display in the baseline exam which had to be of adequate quality both in its anterior and posterior surfaces (QS value) and at least 1 control Petacam exam. Exclusion criteria were the concomitance of significant systemic or ocular (other than refractive defects and allergic conjunctivitis) comorbidities.

Eye-rubbing avoidance was explained in detail (if eye rubbing were to be done at all, patients were instructed to rub with the two index fingers against the lacrimal bones instead of rubbing directly the eye globes). Topical antiallergics (olopatadina 0.2%, Olodina, Ophtha, Colombia initially and then Alercare Plus, olopatadine 0.7%, Abbott, Colombia) was prescribed twice a day on a permanent basis. A consult with an allergist was scheduled if necessary with allergy testing and desensitization if needed. Short courses of topical steroids, tacrolimus or cyclosporine were prescribed when needed. An occasional patient used oral antihistamines. All patients had at least a Pentacam after a year of follow up. From 2012 to June 2017 criteria for progression (two out of four) was decrease greater than 15 µm in the thinnest corneal pachymetry; a decrease of 0.10 mm in the anterior or posterior radius of curvature in the 8.0 mm best fit sphere (BFS); or an increase of 2 D in Kmax. Upon implementation in July 2017 the Belin ABCD progression display was used to detect progression and retrospectively analyzed in the prior patients and prospectively used from then on. Progression was defined as a migration of the A, B or C values above the 95% CI for keratoconus cases (solid red line). The cases analyzed retrospectively with the ABCD met the "red line" criteria for progression/non-progression. To inherent variability of the corneal parameters used to measure progression was tested in the patients that were stable comparing the baseline exam to the first and second follow up exam (Wilcoxon signed-rank test to compare two repeated measurements). Cases deemed progressive were submitted to CXL using riboflavin and UVA 9 mW/cm2 for 7-10 minutes. Both eyes were generally CXL'd due to the discomfort of the procedure and to "avoid" possible progression in the contralateral eye.

After data collection, the results were entered into a database in the Microsoft Excel program (Microsoft Corp., Redmond, WA) with the study variables included. The database was filled and manipulated only by researchers and co-researchers. The analysis of the information was carried out in the statistical package SPSS v21. Qualitative variables were presented as absolute values and percentages. The numerical variables were presented depending on whether or not they distribute normal: the variables that distribute normal were presented according to mean and Standard derivation, the variables that did not distribute normal were presented according to the median and interquartile range.

The percentage difference of variation in absolute numbers between the baseline and the second and last controls (Delta %) was be identified for each of the variables obtained through the Pentacam tomography (ARC, PCR, Thinest Pachymetry, Kmax and BAD-D)

through the Wilcoxon signed-rank test. In all analyzes, a value of $p < 0.05$ was considered significant.

Results

A total of 43 eyes of 24 patients < 18 years with a BAD D > 1.6 in the affected eye were included. All patients had a follow up Pentacam at least one year later. All included Pentacams had to have a normal anterior and posterior quality specification (QS). The tomographies were classified as true keratoconus (KC) or as a topography suspicious of keratoconus (TSK) by agreement of two world-renowned cornea specialists (RA and MB). Only those cases were there was complete agreement were included. In the KC group we had 12 eyes of 8 patients (Table 1). In the TSK group we had 31 eyes of 19 patients. (Table 2). The follow up was 4,01 years (±1,78) (range 1,66-6,83) in KC group and of 3,47 years (±1,89) (Range 1,08-8) in TSK group. Out of those 12 eyes with KC, four eyes (33,33%) (four patients) were deemed progressive. In all these 4 eyes complete eye rubbing control was not possible. Six eyes were CXL in this group, one patient had KC in one eye and TSK in the other, both with progression; two patients were CXL bilaterally eventhough progression was detected only in one eye; and one patient was CXL unilaterally. Out of the 31 eyes with TSK, just one eye progressed (2.6%) and was CXL (the patient mentioned above with contralateral KC)

The clinical characteristics of the patients are described in detail in table 3. Here we detail the date of diagnosis, the initial and final DCVA, the initial Kmax and BAD D, the classification (KC or TSK) and either if they progressed or not and if they were CXL the reason for it.

No eye in either group lost a line of DCVA with a follow up ranging from 1 to 8 years. (Figure 1)

When making the diagnosis of keratoconus it is important to make sure the patient is fixating correctly, and the only way to know this is by doing a second confirmatory exam. If the BAD D was abnormal in the first exam and normalizes by the second with a concomitant shift in the thinnest point location as could be seen in Figure 2 it is probably a fixing problem.

Some patients were already scheduled for keratoplasty such as the one in figure 3 who had a keratoconus with a BAD D 4.8 and 10.62. He was diagnosed at age 6 and was came to our office at age 16 for another opinion after having been scheduled for a keratoplasty somewhere else. We improved the eye rubbing with education, a short course topical corticosteroids and permanent topical antihistamines. His allergies gradually subsided as he grew older and now he is 19 atending college without progression of his cones or any undue loss of DCVA having needed no additional therapy such as CXL or other.

We analyzed the intrinsic variablilty of the Pentacam measurements from one exam to the next in all the TKS patients that remained stable thorought the years and found that the

percent variation of the ARC (expressed in mm) corresponding to the A value of the ABCD Belin progression display varied 0.32 and 0.34% from the baseline Pentacam to the first and the second control respectively (*Wilcoxon, p<0.001*) (Table 4). The PRC (mm) corresponding to the B value of the ABCD varied 1.0 and 1.02% respectively (*Wilcoxon, p<0.001*) (Table 5). The parameter that varied the most making it the less reliable in the follow up was the thinnest pachymetry (C value) which changed 1.34 y 1.57% respectively with a range of -20 to 29 µm and -11 to 32 µm. (Table 6)

We found an interesting data and that we termed the "transient red line transgressors". Five eyes (including the left eye of patient 3, above) had one of the ABC values go beyond the 95% confidence interval for KC (figure 4, black circles) in one exam only to come back in the confirmatory exam,). DCVA in these patients remained stable.

TABLE 1. Baseline characteristics of 12 eyes of 8 pacients with pediatric keratoconus

	Mean (SD)	Range or Percentage
Age (years)	14,62 (±2,6)	(9-17)
Male, n	5	63%
Family history of keratoconus, n	2	25%
Eye rubbing, n	11	92%
Kmax (D)	49,22(±3,56)	(45,00 -57,3)
Thinnest Pachymetry (µm)	503,58(±42,53)	(426-593)
BAD D mean	4,71(±2,07)	(1,75-8,53)
Follow up time (years)	4,01 (±1,78)	(1,66-6,83)

Kmax: maximum anterior keratometry, SD: Standard deviation, BAD D: Belin/Ambrosio enhanced ectasia total derivation value

TABLE 2. Baseline characteristics of 31 eyes of 19 pacients with suspicious tomography for keratoconus

	Mean (SD)	Range or Percentage
Age (years)	13(±3,62)	(5-17)
Male, n	7	37%
Family history of keratoconus, n	8	42%
Eye rubbing, n	18	95%
Kmax (D)	46,4(±2,13)	(43,43 -51,85)
Thinnest Pachymetry (µm)	523 (±35,30)	(454-576)
BAD D mean	2,1(±0,37)	(1,6-3,06)
Follow up time (months)	3,47(±1,89)	(1,08-8)

Kmax: maximum anterior keratometry, SD: Standard deviation, BAD D: Belin/Ambrosio enhanced ectasia total derivation value

TABLE 3. Detailed baseline characteristics of the study eyes, comparition of initial BCVA, Diagnosis made by Michael Belin and Renato Ambrosio reason to CXL explained Michael Belin and Renato Ambrosio

Patient	Eye	Diagnosis Date	Diagnosis	Inicial BCVA (Snellen)	Final BCVA (Snellen)	Inicial Kmax	Inicial BAD D	CROSLINKING	Criteria for CXL
1	OD	dec-12	STK	20/20	20/20	45,5	2,09	NO	
	OS		STK	20/20	20/20	45,9	1,66	NO	
2	OS	may-13	STK	20/20	20/20	49,1	2,22	NO	
3	OD	jun-13	KC	20/25	20/20	49,7	5,87	NO	
	OS		KC	20/50	20/40	57,3	5,46	NO	
4	OD	jun-14	STK	20/20	20/15	47,4	2,42	NO	
	OS	jun-14	KC	20/25	20/20	48,7	2,77	NO	
5	OS	jan-15	STK	20/30	20/25	44,18	1,85	NO	
6	OD	feb-15	STK	20/20	20/15	45,16	2,03	NO	
	OS		STK	20/20	20/20	44,48	1,88	NO	
7	OD	feb-15	STK	20/25	20/25	43	1,79	NO	
	OS		STK	20/25	20/25	43	2,99	NO	
8	OD	mar-15	KC	20/40	20/30	48,4	6,02	YES	Progression contralateral Eye
	OS		KC	20/20	20/20	45	1,75	YES	PRC > CI 95% + Thinest Pachy > CI 95%
9	OD	jul-15	STK	20/20	20/20	45,1	1,81	NO	
	OS	sep-17	STK	20/20	20/20	45,5	1,76	NO	
10	OD	jan-16	STK	20/20	20/20	48	2,72	NO	
	OS		STK	20/20	20/20	48,3	1,85	NO	
11	OD	jun-16	STK	20/25	20/20	47,93	2,2	NO	
	OS		KC	20/30	20/20	48,59	2,76	NO	
12	OD	sep-16	STK	20/25	20/20	44,2	2,5	YES	Thinnest pachy > CI 95%
	OS		KC	20/25	20/20	44,3	2,9	YES	Thinnest pachy > CI 95%
13	OD	nov-16	KC	20/30	20/20	51,2	7,61	YES	Progression contralateral Eye

	OS		KC	20/60	20/20	53,9	8,53	YES	ARC > CI 95% + Thinest Pachy > CI 95%
14	OD	apr-17	STK	20/20	20/20	42,9	1,91	NO	
15	OD	dec-17	STK	20/20	20/20	44,4	1,61	NO	
	OS	sep-17	STK	20/20	20/20	44,7	1,92	NO	
16	OD	sep-17	STK	20/20	20/20	47,2	2,1	NO	
	OS		STK	20/20	20/20	46,7	2,21	NO	
17	OD	sep-17	STK	20/25	20/25	44,6	2,3	NO	
	OS		STK	20/20	20/20	45,2	2,34	NO	
19	OD	jan-18	STK	20/20	20/20	47,8	1,85	NO	
	OS		STK	20/20	20/20	48,4	1,6	NO	
18	OS	feb-18	STK	20/30	20/25	51,82	3,06	NO	
	OD		STK	20/40	20/25	51,16	2,62	NO	
20	OD	may-18	KC	20/20	20/20	47,1	3.96	NO	
	OS		KC	20/20	20/20	45.9	2.8	NO	
21	OD	agu-18	KC	20/20	20/20	50,6	3,45	YES	Thinnest pachy and PRC> CI 95%
22	OD	oct-18	STK	20/20	20/20	48,1	2,1	NO	
	OS		STK	20/20	20/20	44,4	1,78	NO	
23	OS	nov-18	STK	20/20	20/20	46,9	1,95	NO	
24	OD	jan-19	STK	20/20	20/20	47,6	1,87	NO	
	OS		STK	20/20	20/20	47,8	2,36	NO	

BCVA: Best corrected visual acuity; CXL: Crosslinking, kmax: maximun keratometry, 2,BAD D: Belin/Ambrosio enhanced ectasia total derivation value, MB: Michael Belin Concept; RA: Renato Ambrosio concept; KC: Keratoconus; STK: suspicious tomography for keratoconus

NON PROGRESSING EYES for Delta 1 (n=31) for Delta 2 (n=30)

Table 4. Variability of Anterior Radius of Curvature 3 mm				
Measure	**ARC DELTA 1 (mm)**	**ARC DELTA 1 %**	**ARC DELTA 2 (mm)**	**ARC DELTA 2 %**
Mean	0,02	0,32	0,02	0,34
SD	0,02	0,33	0,02	0,30
Median	0,02	0,27	0,02	0,26
IQR: p25	0,01	0,13	0,01	0,14
p75	0,03	0,41	0,03	0,42
min	-0.07	0,00	-0.03	0,00
max	0,13	1,74	0,10	1,31
p Value*	0,001	0,001	0,001	0,001

*Wilcoxon p <0.05 was considered significant. P Value is VALUE p is the result of the comparison of Delta and reference value (0).

Table 5. Variability of Posterior Radius of Curvature 3 mm				
Measure	**PRC DELTA 1 (mm)**	**PRC DELTA 1 %**	**PRC DELTA 2 (mm)**	**PRC DELTA 2 %**
Mean	0,06	1,00	0,06	1,02
SD	0,06	0,96	0,04	0,79
Median	0,04	0,74	0,05	0,80
IQR: p25	0,02	0,33	0,03	0,52
p75	0,09	1,57	0,09	1,56
min	-0.13	0,00	-0.19	0,00
max	0,30	4,89	0,19	3,37
p Value*	0,001	0,001	0,001	0,001

*Wilcoxon p <0.05 was considered significant. P Value is VALUE p is the result of the comparison of Delta and reference value (0).

Table 6. Variability of Thinnest pachymetry				
Measure	**Thinnest Pachy DELTA 1 (um)**	**Thinnest Pachy DELTA 1 (%)**	**Thinnest Pachy DELTA 2 (um)**	**Thinnest Pachy DELTA 2 (%)**
Mean	6,97	1,34	8,23	1,57
SD	5,78	1,10	6,59	1,22
Median	5,00	0,96	6,00	1,16
IQR: p25	3,00	0,61	3,00	0,67
p75	10,00	1,83	12,00	2,34
min	-20	0,00	-11	0,22
max	29,0	5,45	32,0	5,70

p Value*	0,001	0,001	0,001	0,001

*Wilcoxon p <0.05 was considered significant. P Value is VALUE p is the result of the comparison of Delta and reference value (0).

Table 7. Variability of Maximun Keratometry

Measure	K Max DELTA 1 (D)	K Max DELTA 1 (%)	K Max DELTA 2 (D)	K Max DELTA 2 (%)
Mean	0,50	1,01	0,40	0,80
SD	0,99	1,89	0,60	1,14
Median	0,10	0,24	0,14	0,31
IQR: p25	0,05	0,12	0,10	0,21
p75	0,33	0,72	0,40	0,86
min	-1.30	0,00	-1.60	0,00
max	4,38	7,64	2,19	4,39
p Value*	0,001	0,001	0,001	0,001

*Wilcoxon p <0.05 was considered significant. P Value is VALUE p is the result of the comparison of Delta and reference value (0).

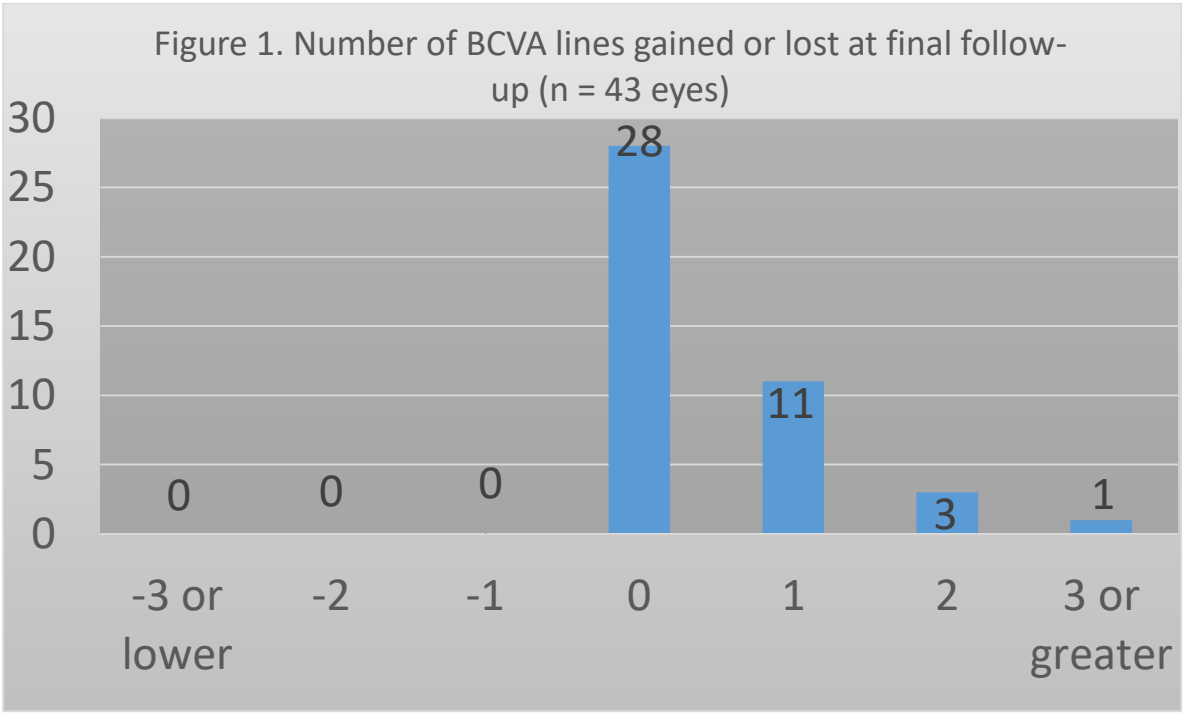

Figure 1. Number of DCVA lines gained or lost

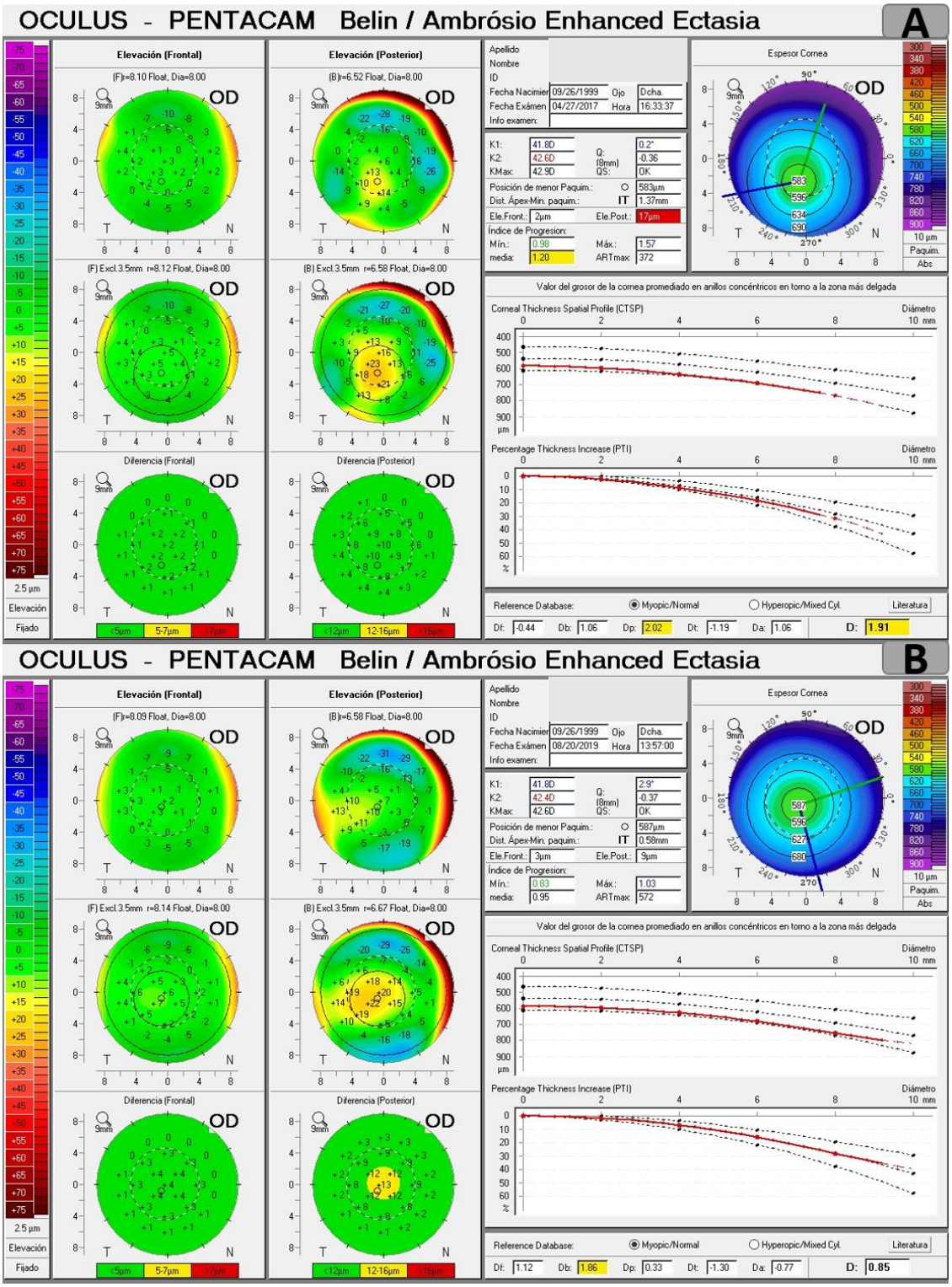

Figure 2. **Initial poor fixation example**. Initial BAD D 1.91 and next (two years later) BAD D was 0.81. **A**. Inicial Belin Ambrósio Display in right Eye **B.** Final Belin Ambrósio Display in right Eye (Note the thinnest point moves more central)

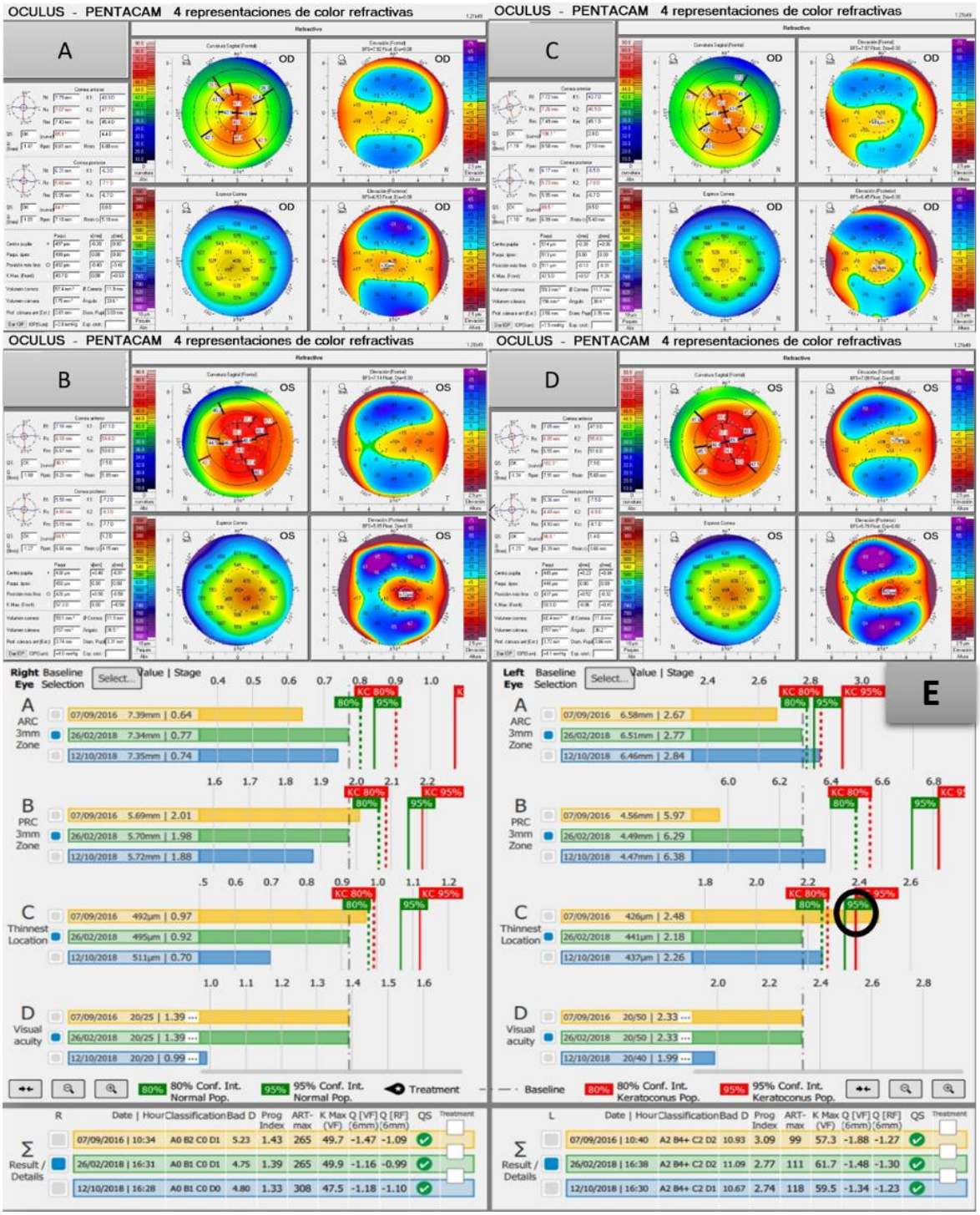

Figure 3. Patient three A. Right Eye inicial 4 refractive Map from 2016. B. Left Eye inicial 4 refractive Map from 2016. C. Right Eye final 4 refractive map from 2018. D. Left Eye 4 refractive map from 2018. E. ABCD progression of both eyes (Note thinnest location on first left eye exam cross the KC 95% (Black circle) and regress on two newest exams)

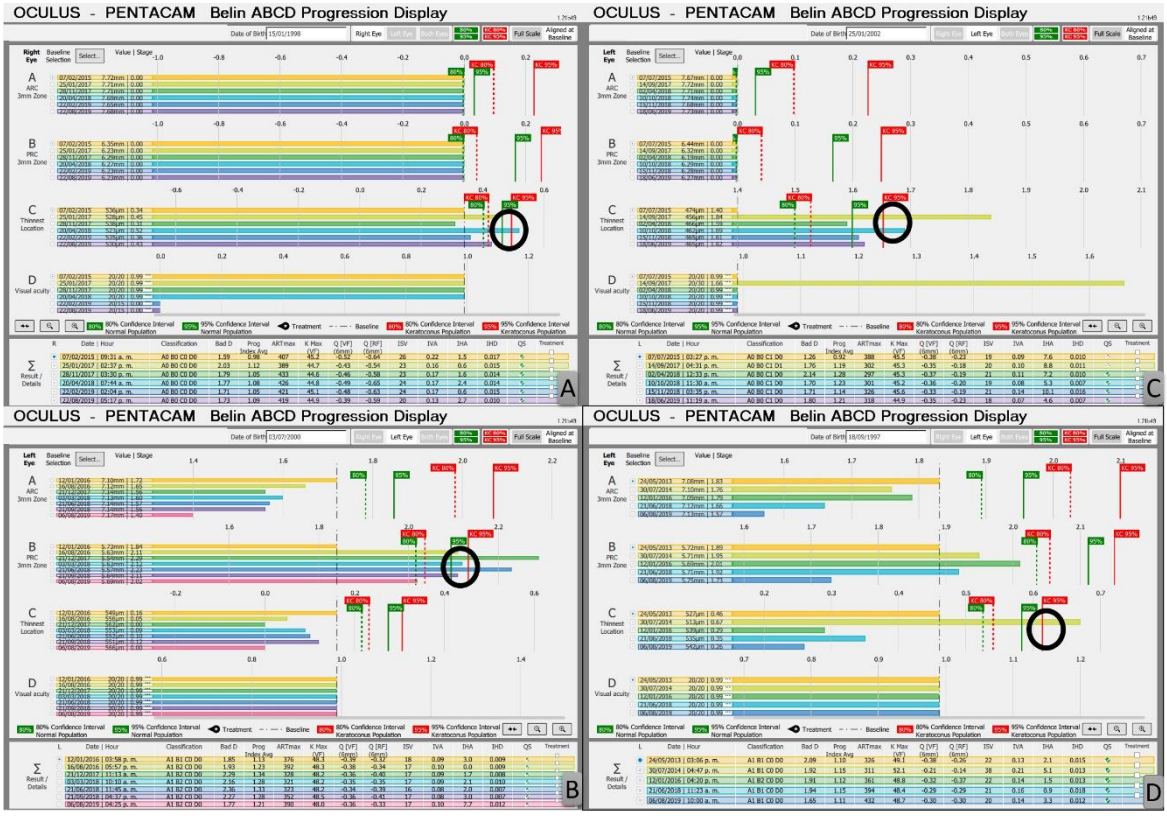

Figure 4. Transient Red Line transgressors for Keratoconus 95% CI (Black circles). A. Patient six ABCD progression display of right eye. **B**. Patient nine ABCD progression display of left eye. **C**. Patient ten ABCD progression display of left eye. **D**. Patient two ABCD progression display of left eye. Note most common transgression are on thinnest location (C value) but patient nine (Figure4-B) cross two times B value (PRC) just to regress on next exams.

Discussion

The most common practice worldwide is to CXL at once all children that present with KC or TSK without even a confirmatory testing of either the diagnosis or the possible progression. This is based mostly in the study by Chatzis and Hafezi (6) where they found a progression rate of 88% using an increase in the Kmax of at least 1.00 D. This same parametrer was used by Vinciguerra et al (23), but they didn't show progression percentage, just an observation of children after CXL . Chatzis et al, postulated that since the progression rate was so high, all children should be CXL at the time of diagnosis. In this study we found that with strict eye rubbing control and careful topographic follow up we can safely observe these patients with KC and TSK over the years where our rate of progression 33,33% and 3.2% respectively. The fact that our results differ from Chatzis et al (6) seem to be related to the severity of the keratoconus since their 59 eyes had a mean Kmax of 55.90 D with a range from 46.30 to 69.80 whereas our 12 KC eyes had a mean kmax of 49.22 D and it ranged from 45.00 to 57.3 D. Our lower number of eyes definitely might have played a role. Another factor that could account for the difference in our results is the intrinsic variability we found in the Kmax measurement in our stable TSK eyes over the year varying 0.50±0.99 D with a range of -1.30 to 4.38 D (similar findings to De Luis Eguileor B et al (24)) which might overdiagnosed some of their eyes as progressors. Another factor was our fastidious eye rubbing control with strict parent and children education about rubbing avoidance; if the urge was to much to do so with the tips of the fingers over the lacrimal bones without touching the globe at all; the permanent use of olopatadine, initially at 0.2% and then at 0.7% when it became available; short courses of topical steroids; long term topical tacrolimus or cyclosporine if needed and a consult with an allergist for allergen avoidance/ desensitization if needed. And finally the use of the ABCD Belin progression display in our cases as a tool to diagnose progression instead of an isolated parameter might have contributed some.

One of the reasons there is a fear of not CXL children at once is that the could rapidly develop hydrops. Wagoner et al (25) found a clear inverse correlation between age and the severity of acute hydrops, they supposed it could be explained on the basis of severity of allergy and rubbing. This study was conducted in Saudi Arabia were patient present with severe keratoconus at a much younger age than in Western populations and have a higher incidence of associated atopic disease, the average age at the time of penetrating keratoplasty in their patient population is 19 years, with nearly one quarter of all cases performed in children 15 years of age or younger. Approximately one fifth of cases have severe vernal keratoconjunctivitis or seasonal allergic conjunctivitis, 30% have a history of hydrops prior to corneal transplantation, and one quarter of the cases have penetrating keratoplasty at 5 years of age or younger. Sometimes it is difficult to separate the variables of intense atopy and forceful eye rubbing in these studies. Childhood is the period of life

where atopy is more intense making forceful eye rubbing more prevalent hence increasing the KC progression rate. We suggest to strictly control eye rubbing by whatever means necessary before attributing progression in children to an unknown and inevitable cause

It is noteworthy that thinnest pachymetry in our non-progressive patients decreased up to 20 µm, (Table 6) beyond the generally accepted values of 10 to 15 µm used in the literature to diagnose progression/CXL. As said before most of the studies of keratoconus progression incorporate Kmax and thinnest pachymetry as the variables to follow and hence a lot of patients might be diagnosed erroneously as progressing.

"Transient red line transgressors" highligh the fact that at least two or three confirmatory exams are needed before deeming that a patient keratoconus is progressing (similar to what is done before submitting a patient to an invasive glaucoma surgery. This again seems to be related to the natural variability of the tomography and not to a real progression of the underlying condition.

Another point that merits consideration when making the diagnosis of keratoconus is possible poor fixation of these young patients (despite normal anterior and posterior quality Specification (QS) value) that could be diagnosed just with a follow up exam where there is a decrease in the BAD D with a shift in the thinnest corneal point as could be seen in our figure 2. This highlights the need to do an additional confirmatory diagnostic test before labeling a patient as KC or TSK.

Ridley in 1959 was the first to describe eye scratching as a risk factor for keratoconus (26). In the present study the percentage of eye rubbing was 96%, concordant with that reported in the literature (44.8% to 100%)(27). More recently, in 2000, Bawazeer et al (22) published their results of a case–control study, which showed in the univariate associations that there was an association between keratoconus and atopy, as well as eye rubbing and family history of keratoconus. However, in the multivariate analysis, they found that only eye rubbing was still a significant predictor of keratoconus. They concluded that atopy may contribute to keratoconus but most probably via eye rubbing associated with the irritation of atopy. Eye rubbing is a common habit (19). Abnormal eye rubbing may be secondary to troublesome symptoms such as dry eyes, itching, or it may be psychogenic with compulsive or unprovoked scratching (28). Atopy and allergy are the dominant risk factors in this chronic habit (29). Also, compulsive behavior, mental stress, as occurred in patient twelve (a first-year medical student), or emotional tension and psychosis are related to abnormal eye rubbing(27). Gentle repetitive scratching and vigorous knuckle scratching are associated with keratoconus progression (27)(30). Gatinel (31)(32) proposed what has been called "keratoconus" is direct consequence of mechanical trauma to the cornea by chronic and incessant eye rubbing, resulting in the progressive deformation and thinning of the corneal wall, the hallmarks of the disease. It is important to increase the awareness of individuals about the risk of eye scratching since most people have it as a habit (33).

It has been documented that the density of keratocytes in human corneas is significantly reduced with light ocular scratching for 10 seconds repeated 30 times over a period of 30 minutes (18). Also, ocular scratching increases the level of metalloproteinase-13, IL-6, and TNF-alpha in the tears of children with keratoconus and without keratoconus, and it is the release of inflammatory mediators that contributes to the development of keratoconus(26). Changes in intraocular pressure (IOP) due to ocular scratching can develop keratoconus, indirect trauma to keratocytes results from significant IOP fluctuations leading to the development of keratoconus (34). The effects of ocular scratching on corneal tomography have been observed, scratching increases the surface irregularity index, after 60 seconds of eye rubbing, it was found to induce 0.5 diopters of astigmatism (35). The youngest patient reported in the literature, diagnosed with bilateral keratoconus (4 years old), it was deemed as secondary to ocular scratching (25). Our youngest patient was 5 years old at diagnosis and we were able to control the eye rubbing and maintain the BCVA for years.

Or et al (36). evaluated the long-term results of corneal collagen CXL for treatment of pediatric keratoconus and the long-term outcomes of the fellow untreated keratoconic eye in 44 patients younger than 18 years old. They found Improvement in DCVA was not statistically significant and average keratometry and corneal thickness reduced significantly in patients in which CXL was performed. For the fellow untreated eyes—during 5 years of follow up, UCVA showed a slight decrease that was not statistically significant. DCVA, average keratometry, and maximum keratometry remained stable. Their conclusion suggests that although CXL is a safe procedure in the pediatric age, there is no urgency in treating pediatric patients with keratoconus without proof of progression.

One downside of the present study is that since we were fastidious in separating our eyes into KC and TKS by two world-renown experts we decrease the numbers in each group. But still we had 43 eyes in total with a very strict tomographic follow up for 1 to 8 years whereas none of the eyes lost a single line of DCVA.

It is notable that not all general ophthalmologists have experience in KC and although it is difficult to make a recommendation, we suggest that if you have a BAD D> 2 confirmed in 2 exams, suppose that the patient has KC and treat it as such, proposing to the family member to observe and wait for progression to intervene or intervene immediately. If you have a confirmed BAD D< 2, treat as TKS with a low degree of progression and observe it.

Conservative management of KC and TKS should include avoiding eye rubbing at all costs, prescribing topical agents such as mast cell stabilizers, antihistamines, or combined agents, (37). During our study, patients were educated on how to avoid scratching or to scratch against the lacrimal bone. Topical antihistamines were used (initially olopatadine 0.2% and later olopatadine 0.7%). Occasionally a short course of steroids was used or a longer regimen with cyclosporine / tacrolimus was necessary, and the allergist was consulted when necessary. An allergist for allergen testing rendering avoidance/desensitization was incorporated in the management when deemed necessary.

Conclusion

Strict control of eye rubbing combined with careful follow-up and selective CXL seems to be a viable alternative in the management of children with KC and TSK. It does not seem to be necessary to perform CXL in all children presenting with TSK since the rate of progression was 2.6% in this series. For children with keratoconus the rate of progression was 33,33% without loss of a single line of DCVA during a follow up of 1 to 8 years opening the door for a discussion with the parents if they want to CXL at once or wait until progression is documented. Due to the observed variability in the Kmax and thinnest pachymetry reading, we advocate using more modern methods of documenting progression such as the ABCD Belin Progression display and obtaining at least one or two confirmatory Pentacams before scheduling the patient to CXL (similar to what is done with visual field or OCT testing before glaucoma surgery). Longer follow-up on a larger group of patients is needed to confirm these findings.

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