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Possible Association between Keratoconus and Renal Diseases

Irit Bahar[1]*, Shlomo Vinker[2,3], Eitan Livny[1] and Igor Kaiserman[4]

[1]Department of Ophthalmology, Rabin Medical Center, Petah Tiqva, Israel
[2]Department of Family Medicine, Clalit Health Services, Central District, Rehovot, Israel
[3]Department of Family Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Department of Ophthalmology, Barzilai Medical Center, Ashkelon, Israel

Abstract

Purpose: To compare the prevalence of renal disorders in keratoconus patients with an age-matched, non-keratoconic population.

Methods: This retrospective, observational, comparative case-control study included all members of the Central District of Clalit Health Services in Israel with a diagnosis of keratoconus during the years 2000 to 2007 (study group; n=426) and 1704 healthy age- and sex-matched controls. We calculated the prevalence of chronic renal failure, other kidney diseases, renal malignancy and kidney transplant in both groups. We also evaluated the risk for osteoporosis, diabetes and hypertension in the patients with keratoconus. Data on medication use associated with renal diseases was collected as well.

Results: On average, a significantly higher percentage of chronic renal failure were demonstrated in the study group (1.88%) compared to the controls (0.53%, OR=3.6 95% CI=1.4-9.4). This was also true for other kidney diseases (3.8% vs. 1.7%, OR= 2.1, 1.1-3.9). In the patients with keratoconus, we also noted an increased prevalence of osteoporosis (OR= 2.2, 1.1-4.2), diabetes (OR=1.8, 1.1-3.0) and hypertension (OR=1.4, 0.94-1.9), and a significant higher trend in the use of ACE inhibitors, alpha blockers, beta-blockers, corticosteroids, nonsteroidal anti-inflammatory drugs, immunosuppressant's and biphosphonates.

Conclusions: Renal disorders were significantly more common among keratoconus patients.

Keywords: Keratoconus; Renal disease; Renal failure

Introduction

Keratoconus is a progressive non-inflammatory corneal ectasia of unknown etiology [1] and has a reported incidence of approximately 1 in 2000 cases per year [2]. The onset of this disorder usually appears at puberty and is progressive until the third to fourth decade of life, when it stabilizes [2].

A positive association between keratoconus and many conditions has been suggested, including atopy, eye rubbing, contact lens wear, cardiovascular disease (especially mitral valve prolapse), ocular trauma, collagen vascular disorders, Leber congenital amaurosis and Down's syndrome [2].

Several reports have suggested a correlation between keratoconus and renal disorders [3-8]. In the present study, we studied the association between keratoconus and renal disorders.

Patients and Methods

Study group

The electronic medical records were reviewed of all members of the "central district" of the "Clalit Health Services" Health Maintenance Organization (HMO) in Israel between Jan 1st, 2000 and Dec 31st, 2007 who were diagnosed with keratoconus and had not terminated their membership until Dec 31, 2007 (study group; n=426). The diagnosis of keratoconus was made by a certified ophthalmologist based on clinical examination, refraction and corneal topography.

For every patient with keratoconus in the study group, 4 members of the HMO (n=1704) who were matched for age and sex were randomly selected (controls). The study was approved by the local institutional review board.

Observation procedures

The "Clalit Health Services" HMO maintains a chronic disease registry database which includes information collected from a variety of sources: primary care physician reports, medication-use files, hospitalization records and out-patient clinic records. We used a similar method for registry acquisition and maintenance as described by Renner and Peterburg [9]. Data were collected from the registry regarding the prevalence of renal diseases and associated disorders in our study population.

We also collected data on medication use associated with renal diseases. This was performed by documenting all medications prescribed to HMO members during the study period; all community pharmacies attached to the HMO are computerized and reported to one central repository. The HMO dispenses medications with nominal and almost equal co-payment which ensures that drug selection is not influenced by financial aspects. Since there is co-payment, we assume that most of the medications that were prescribed were indeed used by the patients.

***Corresponding author:** Irit Bahar, MD, Department of Ophthalmology, Rabin medical Center, Petah Tiqwa, Israel, Tel: 972-3-9376101; Fax: 972-3-9219084; Email: iritbahar@yahoo.com

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Parameters studied included age, sex, ethnicity, place of living (rural versus urban), marital status, socioeconomic class and use of medications.

Statistical analysis

Student's t-test was used for continuous variables and χ^2 test with Yates' correction for proportions (SPSS ver.12 [SPSS Inc. Chicago, IL, USA]). For small sample sizes (<20), we used the Fisher exact test. P <0.05 was considered statistically significant.

Results

A total of 426 patients had a diagnosis of keratoconus. Table 1 shows the baseline characteristics of the patients with keratoconus and matched controls. As can be seen, the two groups were similar in age, sex, marital status, socioeconomic class, and living preferences.

The only significant demographic difference was that the percentage of Ashkenazi patients was significantly lower in the study group than in the matched controls ($p < 0.0001$).

Table 2 shows the prevalence of renal disorders in both groups of patients. Chronic renal failure, and other renal diseases as well as osteoporosis were significantly more prevalent in patients with keratoconus. Kidney transplant, diabetes and hypertension were also more prevalent in the study group, but did not reach statistical significance.

More medications for associated renal diseases were prescribed to the patients with keratoconous than controls (Table 3). The number of patients who used antihypertensive medications, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, and biphosphonates was higher in the study group than the controls.

Discussion

According to the medical literature, the association between renal disorders and keratoconus has been reported sporadically since 1967 in a number of case reports and small case series [3-8]. This association was demonstrated in Senior-Loken syndrome [3], Noonan's syndrome [4], Alport's syndrome [5] and Leber's congenital amaurosis [6,10]. To the best of our knowledge, this is the only report on the association of renal disorders and keratoconus that focuses on patient drug use, which we believe to be an important factor in this topic.

The kidneys play a key role in body function, not only by filtering the blood and removing waste products, but also by balancing serum electrolytes, controlling blood pressure, and stimulating the production of red blood cells. In renal dysfunction, metabolic acidosis, hyperkalemia and associated arrhythmias, uremia, anemia, hypertension and even congestive heart failure and osteoporosis may occur, depending on the severity of kidney malfunction. All these conditions can be treated pharmacologically.

In our study, the use of corticosteroids, NSAIDs and immunosuppressant drugs was more prevalent in patients with keratoconus. This could be correlated to the higher prevalence of kidney transplantation and other kidney diseases in this cohort.

Why is keratoconus associated with renal disorders?

Several studies indicated that the molecular deficiency in Alport syndrome is a structural abnormality in type IV collagen. The primary event in the pathogenesis of Alport's glomerulopathy is COL4A5 gene mutation (the gene encoding the alpha-5 chain of type IV collagen), as demonstrated by Barker et al. [11]. This gene has been localized to the region of the X-chromosome containing the Alport gene locus [12,13]. However, the mechanisms by which these mutations result in glomerulosclerosis and renal failure have yet to be established. A mutation at this locus causes widespread basement membrane changes involving the vas spirale (inner ear), Descemet's and Bruch's membranes, lens capsule and the glomeruli basement membrane [14-16].

Paired box genes (PAX) play a critical role in human development and embryogenesis. PAX 2 gene is expressed in the human kidney, ureter, eyes, ears and central nervous system. Papillorenal syndrome is an autosomal dominant syndrome caused by PAX2 gene mutation, involving optic nerve malformation, severe myopia and renal deficiencies [17]. PAX 6 gene was previously described as playing

	Keratoconus patients (n=426) (%)	Matched controls (n=1704)(%)	P value
Age	37.31±13.49	37.34±13.49	0.96
Males	242(56.8%)	962(56.9%)	0.98
Married	231 (54.2%)	940 (55.6%)	0.64
Low socioeconomic class	47 (11.0%)	133 (7.9%)	0.05
Living in rural settlements	79 (18.5%)	265 (15.7%)	0.18
Ashkenazi origin	54 (12.7%)	588 (34.8%)	P < 0.0001

Table 1: Comparison of demographics among keratoconus patients vs. matched controls.

Diagnosis	KC patients (n=426)	Matched controls (n=1704)	Odds Ratio	95% Confidence interval
Chronic Renal Failure	8 (1.88%)	9 (0.53%)	3.6*	1.4-9.4
Kidney transplant	2 (0.47%)	1 (0.06%)	8.0	0.7-88.8
Other kidney Disease	16 (3.76%)	28 (1.64%)	2.34*	1.25-4.36
Osteoporosis	14 (3.29%)	26 (1.53%)	2.2*	1.1-4.2
Hypertension	43 (10%)	131 (7.69%)	1.35	0.9-1.9
Diabetes	22 (5.16%)	50 (2.95%)	1.8	1-3

*-Asterisk signifies a statistically significant odds ratio (p<0.05)

Table 2: The prevalence of renal disorders in keratoconus patients vs. age and gender matched control.

medication	Keratoconus patients (n=426)	Matched controls (n=1691)	Odds Ratio	95% Confidence interval
Ace inhibitors	51(11.97%)	137 (8.04%)	1.6	1.1-2.2
Alpha adrenergic blocking agents	14 (3.29%)	26 (1.53%)	2.2	1.1-4.2
Beta blocking agents	20 (4.69%)	14 (0.82%)	6	3.0-11.9
Biphosphonates	17(3.99%)	32(1.88%)	2.2	1.2-3.9
Nsaids	32 (7.51%)	33 (1.94%)	4.1	2.5-6.7
Corticosteroids	145(34.04%)	146(8.57%)	5.5	4.2-7.2
Leukotriene receptor antagonists	6(1.41%)	4(0.23%)	6	1.7-21.6
Immunosuppressant	5(1.17%)	3(0.18%)	6.7	1.6-28.3

Table 3: Drug associated with renal disease that were significantly used more by keratoconus patients than controls.

a role in the development of aniridia and aniridic keratopathy [18]. Wilm's tumor, a renal abnormality is also associated to these conditions. The well studied WT1 gene is located in proximity to the PAX6 gene and it has been suggested that a deletion involving those neighboring genes may contribute to abnormalities both in the kidneys and eyes.

Moreover, there is vast evidence of a direct linkage between the PAX 6 gene and the corneal gelatinase B (a metalloprotease with an important role of corneal structure regulation) [19]. It is possible that a mutant PAX gene or a neighboring gene (i.e. WT1), may contribute to keratoconus and to concomitant renal disorders in varying degrees.

Another common denominator between keratoconus and renal disorder can be the abnormalities in collagen and connective tissue in both diseases. This aspect should be further investigated.

Ashkenazy patients were found to be less prone to develop keratoconus. This observation was noted in other studies that we performed [20]. We are not aware of any association between Ashkenazy patients and renal disease.

Publications during the last 10 years has with increasing evidence documented that keratoconus is not one disease with a common single cause or genetic mutation, but rather multifactorial. Moreover, the patho-physiological mechanisms in both diseases are still to be understood. Thus, we believe that further studies need to be performed in order to confirm and understand our present observation.

This study is limited by its retrospective nature, and the authors cannot rule out the possibility that unmeasured confounders may explain the observed associations. In some conditions (i.e., kidney transplantation), the number of patients was small in both the keratoconus and the control groups. Our results are based on the incidence of uncommon diseases in a relatively small keratoconus group (426 cases).

In conclusion, the present study shows that renal disorders are significantly more common in patients with keratoconus. This observation warrants further studies to confirm this association.

References

1. Krachmer JH, Feder RS, Belin MW (1984) Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol 28: 293–322.
2. Binder PS, Lindstrom RL, Stulting RD, Donnenfeld E, Wu H, et al. (2005) Keratoconus and corneal ectasia after LASIK. J Refract Surg 21:749-752.
3. Oyama T, Usui T, Hasebe H, Miki A, Matsumoto S, et al. (2004) Two cases of Senior-Loken syndrome. Nippon Ganka Gakkai Zasshi 108: 29-37.
4. Ascaso FJ, Del Buey MA, Huerva V, Latre B, Palomar A, et al. (1993) Noonan's syndrome with keratoconus and optic disc coloboma. Eur J Ophthalmol 3: 101-103.
5. Chugh KS, Sakhuja V, Agarwal A, Jha V, Joshi K, et al. (1993) Hereditary nephritis (Alport's syndrome)--clinical profile and inheritance in 28 kindreds. Nephrol Dial Transplant 8: 690-695.
6. Schroeder R, Mets MB, Maumenee IH (1987) Leber's congenital amaurosis. Retrospective review of 43 cases and a new fundus finding in two cases. Arch Ophthalmol 105: 356-359.
7. Sever JL, South MA, Shaver KA (1985) Delayed manifestations of congenital rubella. Rev Infect Dis 7: S164-S169.
8. Goldstein M, Kanarek IE (1979) Bullous retinal detachment associated with renal failure: case report. Ann Ophthalmol 11: 923-930.
9. Rennert G, Peterburg Y (2001) Prevalence of selected chronic diseases in Israel. Isr Med Assoc J 3: 404-408.
10. François J, Hanssens M (1967) Histopathologic examination of a Leber's congenital tapeto-retinal degeneration associated with keratoconus and nephropathy. Bull Soc Belge Ophtalmol 147: 411-426.
11. Barker DF, Hostiken SL, Zhou J, LT Chow, AR Oliphant, et al. (1990) Identification of mutations in the COL4 A5 collagen gene in Alport syndrome. Science 248: 1224-1227.
12. Tishler PV (1979) Healthy female earners of a gene for the Alport syndrome Importance of genetic counseling. Clin Genet 16: 291-294.
13. Perkoff GT, Nugent GH, Dolowitz DA, Stephens FE, Carnes WH, et al. (1958) A follow-up study of hereditary chronic nephritis. Arch Intern Med 102: 733-746.
14. Brunner H, Schroder C, Bennekom CV, Lambermon E, Tuerlings J, et al. (1988) Localization of the gene for X-linked Alport's syndrome. Kidney Int 34: 507-510.
15. Myers JC, Jones TA, Pohjolainen ER, Kadri AS, Goddard AD, et al. (1990) Molecular cloning of alpha 5(1 V) collagen and assignment of the gene to the region of the X chromosome containing the Alport syndrome locus. Am J Hum Genet 46: 1024-1033.
16. Kashtan CE, Kleppel MM, Butkowski RJ, Michael AF, Fish AJ (1990) Alport syndrome, basement membranes and collagen. Pediatr Nephrol 4: 523-532.
17. Sanyanusin P, Schimmenti LA, McNoe LA, Ward TA, Pierpont ME, et al. (1995) Mutation of the PAX2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral reflux. Nat Genet 9: 358-364.
18. Glaser T, Walton DS, Maas RL (1992) Genomic structure, evolutionary conservation and aniridia mutations in the human PAX6 gene. Nat Genet 2: 232-239.
19. Sivak JM, Mohan R, Rinehart WB, Xu PX, Maas RL, et al. (2000) Pax-6 expression and activity are induced in the reepithelializing cornea and control activity of the transcriptional promoter for matrix metalloproteinase gelatinase B. Dev Biol 222: 41-54.
20. Nemet AY, Vinker S, Bahar I, Kaiserman I (2010) The association of keratoconus with immune disorders. Cornea 29: 1261-1264.