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Article *in* American Journal of Ophthalmology · April 1986

DOI: 10.1016/0002-9394(86)90817-2 · Source: PubMed

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AMERICAN JOURNAL OF OPHTHALMOLOGY®
VOLUME 101 NUMBER 3 MARCH, 1986

A 48-Year Clinical and Epidemiologic Study of Keratoconus

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From 1935 through 1982, keratoconus was newly diagnosed in a total of 64 residents (35 males and 29 females) of Olmsted County, Minnesota. There were no significant trends in incidence rates over time; the overall average annual rate was 2.0 per 100,000 population. The age-specific incidence rates were greatest in the younger groups. The incidence rates did not differ significantly by sex. On Dec. 31, 1982, the overall prevalence rate was 54.5 per 100,000 population. At the time of diagnosis, keratoconus was unilateral in 26 patients (41%) and bilateral in 38 patients (59%). Follow-up of the patients showed that survival did not differ significantly from that of the general population. The cumulative probability of survivorship without corneal transplantation for more than 20 years after diagnosis was greater than 80%.

KERATOCONUS is a noninflammatory disorder characterized by central thinning and protrusion of the cornea; its cause is unknown. It frequently leads to a gradual decrease in visual function. This occasionally becomes severe enough to require corneal transplantation. Although there have been many reports concerning the clinical and demographic characteristics of patients with keratoconus,[1-4] other epidemiologic features of this disease have received relatively little attention.

Reports of keratoconus occurring in association with Ehlers-Danlos syndrome, osteogenesis imperfecta, mitral valve prolapse, and other connective tissue diseases have led to speculation that it may represent a single manifestation of a systemic disorder.[1,5] Information concerning survival after diagnosis of keratoconus would be of value in examining this issue. If survival were found to differ from that of the general population, it might lend support to the view that keratoconus does reflect a systemic disorder.

The primary purposes of this study were to determine the incidence and prevalence rates of keratoconus in a defined population, to examine the progression of disease as indicated by need for corneal transplantation, and to evaluate the survival experience of patients with keratoconus.

Subjects and Methods

The subjects of this study included all patients in the population of Olmsted County, Minnesota, in whom keratoconus had been newly diagnosed during the period 1935 through 1982. These patients were identified through the medical information systems at the Mayo Clinic.[6,7] Diagnoses resulting from examinations performed by ophthalmologists at the Mayo Clinic and at the other medical facilities that serve residents of Olmsted County are coded for entry into this computer-based sys-

Accepted for publication Jan. 21, 1986.
From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation. This study was supported in part by grants EY02037 and AM30582 from the National Institutes of Health and by a grant from Research to Prevent Blindness, New York, New York. This study was presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 8, 1985.
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tem. Because it seemed possible that some patients with mild keratoconus might be discovered and followed up by optometrists without ever being seen by an ophthalmologist, we mailed a questionnaire to every optometrist currently practicing in the Olmsted County area. None of the optometrists indicated that patients with keratoconus had been referred to ophthalmologists outside of the local area and no additional cases were identified through this survey.

Each patient's medical records were reviewed to determine whether the diagnostic and other criteria for inclusion in this study were met. The diagnosis was based on the examiner's description of characteristic irregular light reflexes observed during ophthalmoscopy or retinoscopy or irregular mires detected at keratometry. Although the presence of corneal thinning, protrusion, striae, scarring, or pigment deposition (Fleischer ring) was noted, none of these findings was required for the diagnosis to be made. Other information collected from the medical records included age, sex, family history of keratoconus, use of contact lenses, history of eye-rubbing, presence of other medical disorders, visual acuity, refractive error, keratometric readings, and whether corneal transplantation had been performed.

To evaluate survival and need for corneal transplantation and to confirm information collected from the medical records, we conducted a follow-up study. We were successful in tracing all of the patients either until death or through Feb. 1, 1985. Eight patients had died during the follow-up period. The others all responded to a questionnaire regarding use of contact lenses, history of eye-rubbing, family history of keratoconus, presence of atopic diseases, subsequent diagnosis of keratoconus in the contralateral eye (if it was unilateral at the time of initial diagnosis), and whether corneal transplantation had been performed.

The denominators used in the calculation of incidence and prevalence rates were derived from federal census data. Overall rates were adjusted by age and sex to the 1970 white population of the United States. We used Kaplan-Meier survival analysis methods[8] to evaluate both survivorship without corneal transplantation and survival after the initial diagnosis of keratoconus. The χ^2 method and Fisher's Exact test were applied to test for significant differences between subgroups of patients with regard to various characteristics.

Results

Keratoconus was diagnosed in a total of 64 residents (35 males and 29 females) of Olmsted County, Minnesota, in the period 1935 through 1982 (Table 1). The ages at diagnosis ranged from 12 to 77 years (median, 25 years). Only four patients were 40 years of age or older at the time of diagnosis. We do not know whether these patients had had mild keratoconus for many years before the diagnosis was made, although it seems likely that they did. A greater number of patients had been diagnosed in recent years (Fig. 1). This was primarily the result of steady population increases in Olmsted County during the period studied. The incidence rates showed no statistically significant trend over time.

The mean annual incidence rate was greater among males than among females (Table 1); this difference was not statistically significant. The age-specific incidence rates peaked in the younger groups, with the peak occurring at a slightly younger age for males than for females. The overall mean annual incidence rate adjusted by age and sex to the white population of the United States was 2.0 per 100,000 population.

To determine the point prevalence rates of keratoconus, we used the medical information resources at Mayo Clinic to identify all patients with keratoconus who were residing in Olmsted County on Dec. 31, 1982. For this evaluation, patients were included regardless of whether they had lived in the county at the time of diagnosis. A total of 53 patients (32 males and 21 females) met the criteria for inclusion. The age-adjusted prevalence rate among males (69.5 per 100,000 population) was significantly ($P<.05$) greater than the rate among females (39.2/100,000). The overall age- and sex-adjusted prevalence rate was 54.5 per 100,000 population.

In the 64 patients included in the incidence study, keratoconus was bilateral at the time of initial diagnosis in 38 (59%) and unilateral in 26 (41%). Characteristic irregular light reflexes on ophthalmoscopy or retinoscopy or irregular mires on keratometry were present in all 102 eyes with keratoconus. Visual acuity with correction was equal to or better than 20/20 in 42 eyes; it was worse than 20/40 in only 13 eyes. Corneal findings included protrusion (38 eyes), thinning (17 eyes), striae (six eyes), and pigment deposition or Fleischer ring (two eyes).

TABLE 1
MEAN ANNUAL AGE- AND SEX-SPECIFIC INCIDENCE RATES* OF KERATOCONUS, OLMSTED COUNTY, MINNESOTA, 1935–1982

AGE (YRS)	MALES		FEMALES		TOTAL	
	NO.	RATE	NO.	RATE	NO.	RATE
0–14	5	1.1	0	0.0	5	0.6
15–24	15	7.0	9	3.0	24	4.7
25–34	10	4.3	15	5.9	25	5.1
35–44	4	2.2	4	2.1	8	2.2
45–64	1	0.4	0	0.0	1	0.2
≥65	0	0.0	1	0.7	1	0.4
Total†	35	2.4	29	1.6	64	2.0

*Number per 100,000 population.

†The sex-specific rates were adjusted by age and the overall rate was adjusted by age and sex to the 1970 white population of the United States.

Asthma, eczema, or hay fever occurred in 23 patients (36%) and three patients (5%) had mitral valve prolapse (Table 2). None of the patients in this study had Down's syndrome, Ehlers-Danlos syndrome, Marfan's syndrome, or osteogenesis imperfecta. Of the 26 patients who had unilateral keratoconus at the time of diagnosis, nine (35%) reported that they had rubbed their eyes excessively before keratoconus had first been detected. Although this percentage was greater than that (18%) among those who had bilateral keratoconus, the difference was not statistically significant. Only five patients (8%) reported having worn hard contact lenses before diagnosis of keratoconus. However, hard contact lenses were not widely used during much of the period covered by this study. Four patients (6%) had family histories of keratoconus.

Follow-up ranged from 2.4 to 48 years (mean, 19.2 years) after the initial diagnosis of keratoconus. Eight deaths occurred during the follow-up period. The cause of death varied, with the most common cause (two patients) being cardiovascular or cerebrovascular disease. A Kaplan-Meier survival analysis showed no suggestion that the observed survival of these patients differed from that expected in the general population.

Of the 26 patients with unilateral keratoconus, six reported that the disease had later been diagnosed in the contralateral eye. Decreased visual function because of keratoconus led to corneal transplantation in nine patients, bilaterally in three. The interval from diagnosis to first transplantation ranged from just less than two to 46 years. By Kaplan-Meier survival analysis, the cumulative probability of survi-

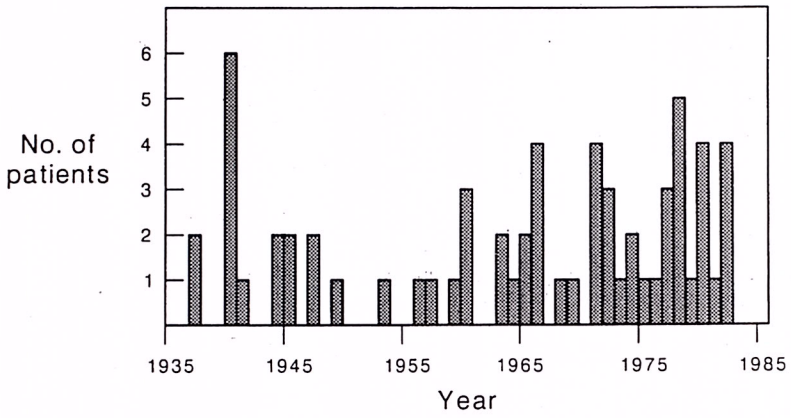

Fig. 1 (Kennedy, Bourne, and Dyer). Distribution of patients by year of initial diagnosis of keratoconus in Olmsted County, Minnesota, 1935–1982.

TABLE 2
CLINICAL FEATURES OF PATIENTS WITH KERATOCONUS

	KERATOCONUS*			
	UNILATERAL (NO. = 26)		BILATERAL (NO. = 38)	
FEATURE	NO.	%	NO.	%
Asthma, eczema, or hay fever	10	38	13	34
Mitral valve prolapse	2	8	1	3
Prior excessive rubbing of eye	9	35	7	18
Prior use of hard contact lenses	0	0	5	13
Family history of keratoconus	1	4	3	8

*Keratoconus was categorized as unilateral or bilateral according to the findings at the time of initial diagnosis.

vorship without corneal transplantation for more than 20 years after diagnosis was greater than 80% (Fig. 2). Transplantations were not performed at the Mayo Clinic before the early 1950s, but the results of an analysis that excluded data from before that time were similar. The number of patients who were followed up for more than 40 years was small, but three patients did have corneal transplantation after that time.

To evaluate whether any factors present at the time of diagnosis might predict future need for corneal transplantation, the nine patients who had transplants were compared to the 55 patients who did not. Males made up 33% of the transplant group (three of nine) and 58% of the nontransplant group (32 of 55); this difference was not statistically significant. The median age at diagnosis was 25 years in both groups. Of the nine patients who underwent corneal transplantation, only two (22%) had unilateral keratoconus at the time of diagnosis; in one of these it later developed in the contralateral eye. In the nontransplant group, 24 of 55 patients (44%) initially had unilateral disease; the difference was not statistically significant.

Of the 102 eyes with keratoconus at initial diagnosis, we compared the 12 eyes that underwent corneal transplantation with the 86 eyes of the 55 patients who had no transplantation with regard to visual acuity, refractive error, and other clinical findings. Visual acuity of 20/20 or better at diagnosis was present in two eyes (17%) in the transplant group and in 40 eyes (47%) in the nontransplant group. The proportions of eyes with visual acuities worse than 20/40 were similar (two of 12 or 17% and ten of 86 or 12%). Corneal thinning or protrusion was detected at the time of diagnosis in seven eyes in the transplant group (58%) and in 36 eyes in the nontransplant group (42%); this difference was not statistically significant. A plot of the refractive errors and keratometric readings at diagnosis showed no apparent relationship between sphere or cylinder power and subsequent corneal transplantation (Figs. 3 and 4).

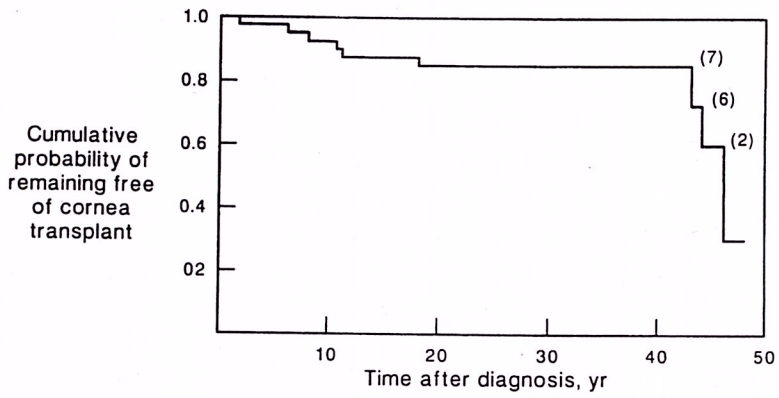

Fig. 2 (Kennedy, Bourne, and Dyer). Survivorship without corneal transplantation after diagnosis of keratoconus in Olmsted County, Minnesota, 1935–1982. The numbers in parentheses indicate the numbers of patients remaining at risk.

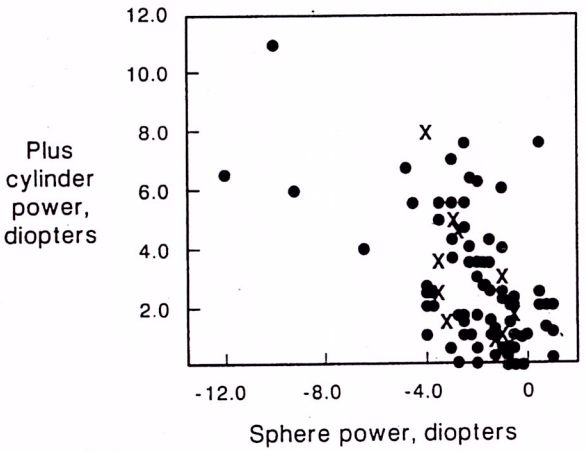

Fig. 3 (Kennedy, Bourne, and Dyer). Refractive error at diagnosis of keratoconus, Olmsted County, Minnesota, 1935–1982. X, Eyes that eventually had corneal transplants. The refractive errors were available for 90 of 98 eyes.

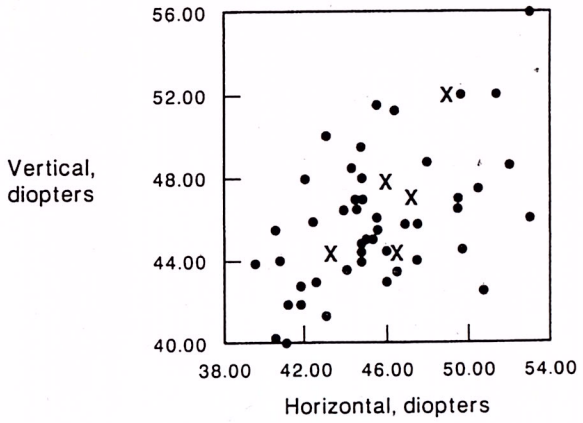

Fig. 4 (Kennedy, Bourne, and Dyer). Keratometric findings at diagnosis of keratoconus, Olmsted County, Minnesota, 1935–1982. X, Eyes that eventually had corneal transplants. The keratometric findings were available for 53 of 98 eyes.

Discussion

Several factors make it difficult to evaluate the incidence and prevalence of keratoconus. The onset of disease is gradual and in some patients it may never progress to anything more than subtle irregular astigmatism. Because patients may not seek medical care for a long time after the onset and some may never visit an ophthalmologist, studies based on medical records, such as this one, tend to underestimate the frequency of disease. However, there is no practical alternative for approaching this problem.

A population survey that involved examination for keratoconus would provide the information required to compute prevalence rates. Because keratoconus is a relatively uncommon disorder, however, such a survey would require sufficient financial and other resources to allow for examination of several thousand subjects. In addition, incidence rates could not be calculated directly from the information provided by a single survey. Prevalence estimates could be derived from data on the proportion of patients with keratoconus among all of those seen at some medical facility. Unfortunately, these estimates would be subject to so many possible biases that drawing any firm conclusions with regard to the general population would probably be precluded. Although limited by the probable loss of at least some patients with mild disease, the incidence and prevalence rates from this study at least provided an estimate of the frequency of clinically significant keratoconus.

The overall age- and sex-adjusted prevalence rate of keratoconus in Olmsted County, 54.5 per 100,000 population, was consistent with the estimates reported by others.[1] After adjustment by age and sex, the overall average annual incidence rate was 2.0 per 100,000 population, with the rate for males being somewhat greater than that for females. We are not aware of any other published incidence rates. Most reports based on series of cases have shown a preponderance of females, although a few investigators have found more males.[1,3,4] There were no statistically significant trends in incidence rates over time. Because of the improvements in diagnostic equipment, in access to medical care, and in physicians' awareness of keratoconus during the past 50 years, it would not have been surprising had a significant increase in incidence rates been found. The lack of such a finding may suggest that the number of residents of Olmsted County with only minimal visual impairment from undiagnosed keratoconus is small.

The proportion of patients in this study with unilateral keratoconus at the time of last follow-up was greater than that usually found.[1] Our value may have been an overestimate because it was derived from the patients' responses to the question of whether the disease

had been diagnosed in the contralateral eye. Overrepresentation of patients with bilateral keratoconus in reports from academic centers could also have explained some of the difference. Such patients would be subject to greater visual impairment and therefore might be more likely than those with unilateral disease to seek medical care and to be referred to academic centers.

The percentage of patients with asthma, eczema, or hay fever (23 of 64 or 36%) was similar to values reported by others.[1,3,4,9,10] In a study that included assessment by echocardiography, Beardsley and Foulks[5] found that the frequency of mitral valve prolapse among patients with keratoconus (38%) was significantly greater ($P<.05$) than that among controls (13%). Mitral valve prolapse had been clinically diagnosed in only three patients (5%) in our study.

Several investigators have suggested that eye-rubbing[1,4,10,11] and the use of hard contact lenses[1,12-14] may be risk factors for the development of keratoconus. Sixteen of our patients (25%) indicated that they had rubbed their eyes excessively before keratoconus had been diagnosed. Interestingly, excessive eye-rubbing was only slightly more common among those with atopic diseases. Others have reported eye-rubbing to be more frequent, with estimates ranging to more than 60% of patients with keratoconus.[1,4,10,11] Because it is almost impossible to quantitate accurately the extent of eye-rubbing and whether it began before or after the onset of keratoconus and to ensure comparability of subjects selected as controls, the question of whether eye-rubbing is a significant risk factor for the development of keratoconus may never be answered satisfactorily.

With regard to wearing hard contact lenses, it may be difficult to determine whether the onset of keratoconus preceded or followed the use of the lenses. Sommer[15] noted that irregular astigmatism occurring as an early change before keratoconus has been diagnosed may lead to the use of hard contact lenses. Consequently, any group of patients with keratoconus might well show a spuriously increased frequency of prior hard contact lens wear relative to that observed among a control group.

Ederer and Ferris[16] discussed this issue further and provided an outline of how it could be approached through a case-control comparison, a cohort study, or a randomized clinical trial. Because of the possible bias suggested by Sommer,[15] they concluded that a case-control study would be inappropriate but that a cohort study or a randomized clinical trial might be feasible if the sample size requirements did not prove excessive. Sommer[15] and Ederer and Ferris[16] agreed that a previous study by Gasset, Houde, and Garcia-Bengochea[14] was sufficiently flawed to preclude drawing any conclusions regarding the role of hard contact lenses in the development of keratoconus. We are not aware of any further attempts to study this issue through any of the three methods discussed by Ederer and Ferris.[16] In 1984, Krachmer, Feder, and Belin[1] indicated that a large prospective randomized study is needed to evaluate whether hard contact lens wear increases the risk of developing keratoconus.

For several reasons, it seems to us that the case-control method offers the most feasible means of approaching this issue. At least three major difficulties would hinder the initiation of a randomized clinical trial. First, because the incidence rates of keratoconus are relatively low even among those in the younger age groups, several thousand subjects would have to be followed up for several years even to detect a three-fold or greater difference in the risk of developing keratoconus. Second, most patients have some definite preference for spectacles or for one of the various types of contact lenses on the basis of the relative advantages and disadvantages of each. Therefore, it would probably be difficult to find subjects who would agree to have their type of optical appliance chosen at random and who would then remain faithful to that choice for the duration of the study. The third problem relates to an ethical issue. Before the initiation of most clinical trials, there must be some evidence to suggest that the intervention under study may be of some benefit, usually in either prevention or treatment of some disease. For a clinical trial of hard contact lens wear and keratoconus, however, the question would be whether the intervention (hard contact lens wear) leads to a harmful effect—the development of keratoconus.

The problem of patient recruitment and the ethical problem could be avoided with either the case-control or the cohort study design. Unlike a randomized clinical trial, however, these designs would be subject to the type of bias suggested by Sommer[15]—use of the suspected risk factor (hard contact lenses) for treatment of early symptoms of the disease (keratoconus) before the diagnosis had been

made. Because a case-control study could be conducted with only a small fraction of the number of patients required for a cohort study, the question of bias could be dealt with more effectively with this design.

To minimize the possibility of bias in a case-control study, it would be necessary to strive for close comparability between the control group and the patients with keratoconus in regard to both spherical refractive error and astigmatism. Once an appropriate control group had been selected, a comparison could be made of the proportion of subjects in each group who had worn hard contact lenses previously. If the bias suggested by Sommer[15] were actually present, it would make any association between hard contact lens wear and keratoconus appear to be greater than it actually was. Therefore, if no significant association were found, the results would provide strong evidence that the use of hard contact lenses does not lead to an increased risk of developing keratoconus. On the other hand, if a significant association were found, further analyses would be required to investigate whether it was the result of bias. Examination of several factors—including the strength and consistency of the association, the reasons given by the patients and controls for having worn hard contact lenses, and the individual durations of hard contact lens use—would all provide further insights regarding this issue.

Several interesting findings emerged from the exceptionally long and complete follow-up of the patients in this study. There was no suggestion of a difference in survival relative to that of the general population. Therefore, if keratoconus does represent a single manifestation of a systemic disease, the underlying disorder does not appear to have any adverse influence on survival. With regard to corneal transplantation, the data showed that more than 20 years after the time of diagnosis the cumulative probability of surviving and not having this procedure was still greater than 80%. This information should be of value in counseling patients regarding the prognosis of keratoconus. The number of patients in this study was too small to allow detailed analysis of factors that might increase the risk of future corneal transplantation and of any that might be confounders. However, age, refractive error, and keratometric findings at the time of diagnosis did not appear to be of value in predicting whether a transplant might eventually be needed.

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