

Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study

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ABSTRACT.

Purpose: To evaluate the specific allergic sensitization and epidemiological characteristics of vernal keratoconjunctivitis (VKC).

Methods: This retrospective non-comparative case series included 406 VKC patients. Data included patient and family histories, and results of allergic tests. Annual incidence and prevalence rates were calculated for a cohort of 128 VKC patients from the greater Padua area.

Results: The great majority of VKC patients were male (76%), with a male : female ratio of 3.3 : 1. A skin prick test, specific serum IgE or conjunctival challenge was positive in 43%, 56% and 58% of patients, respectively. In the cohort of patients from the Padua area, the prevalence of the disease was 7.8/100 000, with a higher rate in young males (57/100 000) compared with young females (22/100 000), and lower rates in people over 16 years of age (3.8/100 000 in males, 1/100 000 in females). The incidence of VKC was 1/100 000, with a higher rate in males under 16 years of age (10/100 000) compared with females (4.2/100 000). In people over 16 years of age, the incidence of the disease was 0.06/100 000, with no difference between males and females.

Conclusion: An IgE-mediated sensitization was found in only half of the VKC patients. Vernal keratoconjunctivitis is not a rare event in the paediatric population but is an extremely rare new disease in adults.

Key words: ocular allergy – vernal keratoconjunctivitis – incidence – prevalence – allergy diagnostic tests

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Introduction

Vernal keratoconjunctivitis (VKC) is a relatively rare ocular allergic disease affecting children and young adults

living in warm climates and associated, in approximately half of cases, with other allergic manifestations. The

disease is usually seasonal, lasting from the beginning of spring until autumn. However, perennial cases that are persistent throughout the year are not rare, especially in patients living in subtropical or desert climates. Its predominance during the high pollen season lends credence to the widely accepted hypothesis that VKC is an immunologically mediated, hypersensitive reaction to environmental antigens.

Vernal keratoconjunctivitis appears in two distinct forms primarily involving the tarsal or limbal conjunctiva. The definitive features of these two clinical forms of VKC, giant papillae on the upper tarsal conjunctiva and gelatinous limbal infiltrates, leave no doubt as to the diagnosis of vernal disease.

Although several epidemiological studies have been published on this disease, only a few have dealt with a large series of cases. Epidemiological, clinical and immunological findings reflect information obtained from cohorts of patients referred to single tertiary centres (Neumann et al 1959; Khan et al. 1988; Tuft et al. 1989; Bonini et al. 2000; Pucci et al. 2003). The largest series of patients were published in 1959 (400 patients in Israel) (Neumann et al 1959) and in 1988 (530 cases in Pakistan) (Khan et al. 1988); however, no immunological or

epidemiological data were presented. The largest study in Europe, including an Italian series of 195 patients, reported only demographic and clinical features of VKC (Bonini et al. 2000). All these studies showed that a large proportion of patients have no familial or personal history of atopy and that patients can have negative results on the standard allergic diagnostic tests. In tropical countries, where the limbal form of the disease is prevalent, the association between atopy and VKC is even less frequent (Tuft et al. 1998). These ambiguities are challenging in the effort to provide new answers to the immunopathology of the disease (Maggi et al. 1991; Calder et al. 1999; Leonardi et al. 1999; Montan et al. 2002) and to manage young patients suffering from its grave inflammatory consequences. Although the disease is considered relatively rare, its prevalence and incidence were not calculated in the previous studies, either because the referral centres received patients from different regions and towns or did not have enough patient or population data.

The aim of the present study was to evaluate demographic and immunological data for a cohort of 406 VKC patients. In addition, epidemiological data were calculated using the public population register for the town area because it is a referral centre for general ophthalmologists, paediatricians, and allergists working in the greater Padua area.

Materials and Methods

Diagnosis of VKC was based on the patient's history and the presence of typical clinical signs and symptoms. The disease was classified as tarsal if the patient had giant papillae > 1 mm in diameter, as limbal if the patient had limbal infiltrates, papillae and Trantas dots, and as mixed if the patient had both limbal and tarsal signs.

The database, which was created using Microsoft Access®, included 406 consecutive VKC patients referred to the Allergy Service of the Ophthalmology Department, University of Padua, between 1996 and 2004. The study was approved by the University Review Board. The following information was collected: personal and family medical history, age of onset and resolution of

the disease, associated allergic manifestations, results of skin prick tests, serum specific IgE to a panel of 24 allergens (FEIA, CAP System; Pharmacia, Uppsala, Sweden), including the most common environmental and food allergens in Italy, total serum IgE (UNICAP; Pharmacia), blood eosinophil count, serum levels of eosinophil cationic protein (ECP) (UNICAP; Pharmacia), treatment history and outcome. The conjunctival provocation test (CPT) was performed in patients in a non-active phase of the disease, following the standardized procedures. Briefly, a positive reaction was determined by challenging both eyes with one 20 µl drop of allergen in serial dilutions (10–100–1000 Allergen Unit RAST/ml), increasing the dose every 15 mins until a clinical reaction with a score of 2 plus itching and redness was obtained. A panel of seven allergens was used for this test: *poaceae/graminaceae*, *dermatophagoides*, *alternaria*, *parietariae*, *compositae*, birch and cat dander (ALK-Abello, Lainate, Italy).

The patients gave written informed consent for blood samples to be obtained and clinical and demographic data analysed.

An overall simple clinical score for disease severity considered immediate signs and symptoms as well as permanent changes present (i.e. papillae size or corneal scars) in order to divide patients into four categories: 1 = mild VKC (mild seasonal signs and symptoms); 2 = moderate VKC (persistent signs and uncomfortable seasonal symptoms); 3 = severe VKC (intermittent signs and uncomfortable persistent symptoms), and 4 = very severe VKC (persistent signs and symptoms).

Statistics

Differences between proportions were compared using the chi-squared test. Differences between mean values were

compared using the Student's *t*-test. Results were reported as mean ± standard deviation. Public population register data (ISTAT) on residents in the Padua area from 1996 to 2002 were used. For each of these years, the annual prevalence (number of cases per average population for each year) and incidence (new cases per average population for each year) rates separated by age and gender were calculated.

Results

The great majority of VKC patients (*n* = 311) were male (76%), with a male : female ratio of 3.3 : 1. Sex distribution, clinical forms, age of onset and duration of the disease and family history of allergy are shown in Table 1. The disease was bilateral in 96.7% of the cases; all unilateral cases involved the tarsal form of VKC.

At the time of diagnosis, 83% of patients were under 10 years of age and 4% were over 20 years of age.

Non-ocular allergic manifestations were present in 46% of the VKC cases. The most frequent associated disease was rhinitis (30.1%), followed by eczema (16.3%), asthma (14.6%) and urticaria (4.9%). Three patients were affected by nocturnal apnea.

Based on the clinical scores reported at visits, the overall severity of the clinical course of the disease was considered to be mild in 28.4% of cases, moderate in 38.6% of cases, severe in 25.2% of cases, and very severe in 7.8% of cases. Corneal ulcer complicated the disease in 15.3% of patients, 68.5% of whom were affected by the tarsal form, 20.4% by the mixed form and only 11.1% by the limbal form of VKC. Keratoconus was observed in three patients; however, keratotomy or videokeratography were not routinely performed so this may be an underestimate. Glaucoma, as a

Table 1. Demographic data for 406 VKC patients: data are presented in percentages, or as mean ± standard deviation and range.

	Total VKC (%)	Tarsal form (%)	Limbal form (%)	Mixed form (%)	Age at onset (years)	Duration (years)	Family history of allergy
Males	76.6	37.0	49.0	14.0	7.0 ± 5 (1–33)	6.5 ± 4	51.6%
Females	23.4	15.7	67.4	16.9	7.5 ± 6 (1–35)	7.5 ± 4	42.5%

complication of steroidal treatment, was not reported. Cataract, probably secondary to steroid use, was observed in one patient.

Allergy diagnostic tests

A positive skin prick test (performed in 383 patients) was identified for at least one allergen in 43.7% of patients. The tarsal form was more frequently associated with an allergic sensitization (50.8%) than the limbal form (36.9%) ($p = 0.019$).

Specific serum IgE tests were positive for at least one allergen in 56.7% of the 253 tested patients. Again, the tarsal form was more frequently associated with an allergic sensitization (73.0%) than the limbal form (42.9%) ($p < 0.0001$).

A conjunctival provocation test was performed in 103 patients, who had already been undergone skin tests for the same allergens used for the CPT. The CPT results were positive for at least one allergen in 59% of them. Of the patients who were negative to skin and/or specific serum IgE tests, 42.4% were positive to CPT.

The mean total serum IgE, the mean blood eosinophil count, and the mean level of serum ECP are shown in Table 2. Total IgE (normal range of serum IgE is 0–100 KU/l) was higher in tarsal patients than in limbal patients (617.1 ± 994.9 KU/l versus 327.4 ± 769.1 KU/l, respectively; $p = 0.043$).

Epidemiology

Epidemiological data were calculated for the cohort of patients resident in the greater Padua area ($n = 128$). The mean age at onset of the disease was 6.8 ± 5.3 years, with no significant differences between males (6.7 ± 5.2 years) and females (7.0 ± 5.8 years). The overall severity of the clinical course of the disease, in this cohort of 128 patients, was considered

to be mild in 35.9% of cases, moderate in 40.6% of cases, severe in 18.8% of cases, and very severe in 4.7% of cases. The prevalence curve of the disease from 1996 to 2002 is shown in Fig. 1. Considering this period of time, the mean prevalence of the disease in the Padua population was 7.8 affected patients/100 000 inhabitants. Table 3 shows prevalence rates by age group and gender. The 6–10-year-old group was the most affected (Table 3).

The mean incidence of VKC, independently of gender and age, was 1/100 000 new cases (Table 4). In the population up to 15 years of age, the mean incidence was 7.2/100 000 (10.0/100 000 in males, 4.2/100 000 in females). In the population over 16 years of age, the mean incidence was 0.06/100 000 (0.04/100 000 in males, 0.08/100 000 in females). Interestingly, a peak of 11 new female cases occurred in 1997 compared to five new cases in males (Fig. 2). When patients were divided into smaller age subgroups, the highest incidence of VKC was found in the subgroup of children aged up to 5 years (Table 4).

Discussion

Vernal keratoconjunctivitis is typical of the male paediatric population. However, it may appear in females and, as a new disease, in young adults. In the present large group of VKC patients, the male : female ratio was 3.3 : 1. This tendency is confirmed in the literature, in which the male : female ratio has been reported to be from 4 : 1 to 2 : 1 (Neumann et al 1959; Khan et al. 1988; Tuft et al. 1989; Bonini et al. 2000). Interestingly, females were more often affected by the limbal form, which was also less frequently associated with a specific IgE sensitization. The notable difference between sexes, and the resolution of

the disease with puberty, are features that have persistently suggested that hormonal factors play a part in the development of VKC (Bonini et al. 1995). However, the real basis for these particular features is unknown and calls for further study.

Personal and family histories and the results of allergic tests confirm that an IgE-mediated mechanism is involved in at least 50% of cases. In previous studies, more frequent positive results were demonstrated when specific IgE was measured in tears, reflecting a predominantly local production and an exclusively conjunctival hypersensitivity (Ballow & Mendelson 1980; Sompolinsky et al. 1984; Leonardi et al. 1993). In the present study, a prevalent local IgE response was demonstrated by the higher percentage of positive responses using conjunctival specific allergen provocation. This is supported by pathological findings of IgE-positive cells in the conjunctiva (Montan et al. 1995; Abu El-Asrar et al. 2001). However, the lack of specific IgE sensitivity in the other half of the VKC population confirms that the immunopathogenesis of this disease cannot be explained by IgE-mediated hypersensitivity alone. Non-IgE-mediated mechanisms have been proposed and investigated in several studies, highlighting the crucial role of eosinophils and eosinophil chemotactic and activating factors in the pathogenesis of the disease (Abu El-Asrar et al. 2000, 2003; Leonardi 2002; Leonardi et al. 2003; Ono 2003).

In a recent study from Nigeria, VKC was identified as the most common conjunctival disease in children seen in hospital (Ukponmwan 2003). Interestingly, in this series of 109 patients, only 5% had a positive history of allergy. Similarly, limbal VKC was the sixth most frequent diagnosis seen at an ophthalmology service in Cameroon (McMoli & Assonganyi 1991), where the disease was rarely associated with other allergic manifestations and there was no hereditary tendency. Vernal keratoconjunctivitis was the leading cause of outpatient ophthalmic morbidity among Palestinians in East Jerusalem, accounting for 10% of 74 400 annual outpatient visits to ophthalmic clinics in Israel (O'Shea 2000). In one epidemiological report from Northern Europe, the prevalence of VKC was clearly augmented by the immigration

Table 2. Immunological data in VKC patients: data are presented in percentages or as mean standard deviation and range.

Positive prick test (%)	Positive specific serum IgE (%)	Positive CPT (%)	Serum total IgE (KU/l)	Blood eosinophil count ($\times 10^9/l$)	Serum ECP ($\mu g/l$)
43.7	56.7	58.6	420 ± 814 (0–5840)	1.2 ± 5.5 (0.06–47)	34.2 ± 39 (0.3–257)

CPT = conjunctival provocation test; ECP = eosinophil cationic protein.

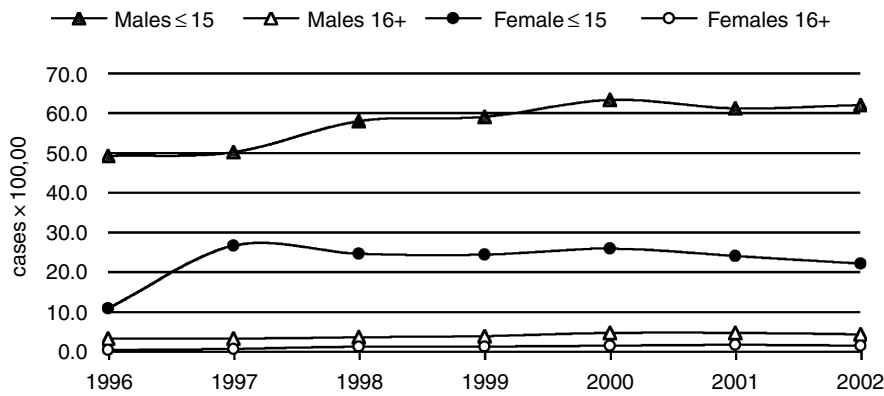


Fig. 1. Prevalence of VKC in Padua area during 1996–2002, in males and females divided into two main age groups, 15 years of age or under, and 16 years of age or over.

of children of African or Asian origin (Montan et al. 1999), suggesting that both genetic and environmental factors are implicated in the incidence of the disease. Until now, however, genetic studies confirming a relationship of VKC with a particular genotype have not been performed.

As few studies on relatively large series of patients exist, no real epidemiological data on prevalence and incidence of the disease have been reported. The prevalence and incidence of the disease were calculated retrospectively using the public register population data for a limited

geographic area. We have assumed that most VKC patients living in the Padua area were seen at our clinic for the following reasons:

- (1) the clinic is a major referral centre for the greater Padua area;
- (2) a network of local ophthalmologists, allergists and paediatricians has been created over the past 15 years to identify potential cases, and
- (3) a significant percentage of VKC cases referred to our centre were not severely affected (75% of the patients had mild or moderate disease), indicating that referral was not limited to severe cases only.

During 1996–2002, the mean prevalence of the disease in the Padua population under 16 years of age was 40/100 000 and had a dissimilar sex distribution. Conversely, as the disease resolves in most cases around puberty, the prevalence of the disease was much lower in the population aged over 16 years, with less difference between male and females.

In the Padua area, approximately seven new cases of VKC per 100 000 inhabitants were reported each year in children up to 15 years of age, with approximately one new case per 1 600 000 people in the population aged over 16 years (0.06/100 000). This confirms that VKC is not a rare event in the paediatric population but is an extremely rare disease in adults. Interestingly, the new cases of VKC were much more frequent in males than in females in the young population, whereas the incidence of the disease in people over 16 years of age was higher in females than in males. This is extremely interesting because a hormonal influence has been proposed as one of the predisposing factors in the development of VKC in male children. However, no real correlations between sex hormones and development of VKC have been shown. Endocrine and/or

Table 3. Prevalence of VKC in Padua area.

Age (Years)	Males			Females			Males + females		
	Inhabitants	Cases	Prevalence	Inhabitants	Cases	Prevalence	Inhabitants	Cases	Prevalence
≤ 5	160 279	70	43.7	151 435	29	19.2	311 714	99	31.8
6–10	134 997	110	81.5	127 914	38	29.7	262 911	148	56.3
11–15	132 349	66	49.9	123 763	24	19.4	256 112	90	35.1
≤ 15	427 625	246	57.5	403 112	91	22.6	830 737	337	40.6
16–20	157 583	37	23.5	151 506	12	7.9	309 089	49	15.9
21 +	2 288 467	57	2.5	2 473 171	15	0.6	4 761 638	72	1.5
16 +	2 446 050	94	3.8	2 624 677	27	1.0	5 070 727	121	2.4
Total	160 279	70	43.7	3 027 789	118	3.9	5 901 464	458	7.8

Table 4. Incidence of VKC in Padua area.

Age (Years)	Males			Females			Males + females		
	Inhabitants	Cases	Incidence	Inhabitants	Cases	Incidence	Inhabitants	Cases	Incidence
≤ 5	160 279	29	18.09	151 435	11	7.26	311 714	40	12.83
6–10	134 997	12	8.89	127 914	4	3.13	262 911	16	6.09
11–15	132 349	2	1.51	123 763	2	1.62	256 112	4	1.56
≤ 15	427 625	43	10.06	403 112	17	4.22	830 737	60	7.22
16–20	157 583	1	0.63	151 506	0	0.00	309 089	1	0.32
21 +	2 288 467	0	0.00	2 473 171	2	0.08	4 761 638	2	0.04
16 +	2 446 050	1	0.04	2 624 677	2	0.08	5 070 727	3	0.06
Total	2 873 675	44	1.53	3 027 789	19	0.63	5 901 464	63	1.07

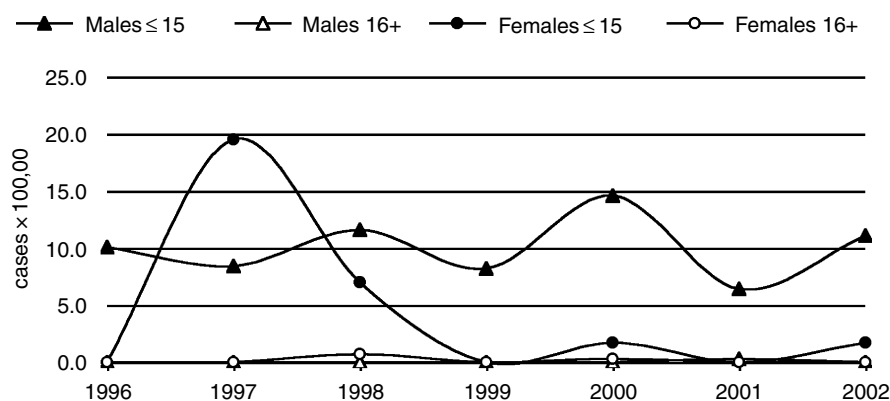


Fig. 2. Incidence of VKC in Padua area during 1996–2002, in males and females divided into two main age groups, 15 years of age or under, and 16 years of age or over.

neuro-endocrine factors may also contribute to the development of immune-mediated diseases (Blalock 1994).

Underestimation of VKC incidence in the Padua region may have occurred due to the underdiagnosis of mild cases not referred to our centre. However, considering that VKC is a relatively rare disease, general ophthalmologists and paediatricians would be very unlikely to treat it without a referral. Furthermore, our centre's distribution of mild and moderate cases was relatively high, indicating that the present estimations may be close to reality.

In conclusion, VKC is not a rare disease in temperate climates. While IgE sensitization is definitely one factor in the development of the disease, other factors seem to play a role as well, as half of the patients, with similar clinical manifestations, gave negative results to allergy tests. A multicentre genetic study is currently ongoing, the results of which may help to elucidate these immunological and epidemiological results.

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