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• PURPOSE: **To identify clinical, demographic, immunologic, and health-related quality-of-life data from a cohort of vernal keratoconjunctivitis (VKC) patients with the onset of the disease after puberty (VKC-like disease).**
• DESIGN: **Retrospective, observational case series.**
• METHODS: **Forty-nine patients with late-onset VKC-like disease from among 600 consecutive VKC patients. History of disease, test results for allergen sensitivity, signs and symptoms, impact of disease on work productivity, health-related quality of life, and treatment satisfaction were assessed. In addition, multiplex bead analysis for Th1/Th2 cytokines were carried out in tear samples from 20 VKC patients (10 adults and 10 children) and from 10 normal subjects.**
• RESULTS: **A family history of allergy was positive in only 28% and positive prick test results were present in 55% of the 49 VKC-like adult patients. Based on typical signs and symptoms, 48% were affected by the limbal form, 33% were affected by the tarsal form, and 19% were affected by the mixed form. Corneal ulcer complicated the disease in only 2 adult patients. Although the disease was not considered a limiting factor for work, productivity was reduced by 26% and social activities were reduced by 31% during active flare-ups. No significant differences were found in tear cytokine pattern production between VKC in children and VKC in adults.**
• CONCLUSIONS: **A late onset VKC-like disease can appear in young adults with signs and symptoms similar to those in pediatric disease, but with less corneal involvement. (Am J Ophthalmol 2013;■:■–■.**

VERNAL KERATOCONJUNCTIVITIS (VKC) IS A CHRONic, bilateral inflammation of the conjunctiva that generally affects children and young adults who have an atopic personal or family history and live in warm climates.[1] Although the allergic nature of this disease is widely accepted, in less than 50% of cases, it is associated with other allergic manifestations and specific immunoglobulin E (IgE) sensitization.[2,3] The predilection for males and the resolution after puberty suggest a role of hormones in the development of VKC; however, the exact mechanisms behind this association are still unknown.

Although it is considered a long-term disease with an average duration of 4 to 8 years, VKC generally subsides before or just after puberty. It can persist or reactivate after puberty; however, a VKC-like disease has been found in young adults without any history of allergic disease in childhood. This new clinical entity is characterized by signs and symptoms similar to the typical VKC. Studies of large cohorts of subjects revealed that VKC is present between 3% to 10% of school-age children in endemic areas such as Cameroon, Turkey, and Israel.[4–8] In Morocco, India, and Senegal, it accounts for 6% of new ophthalmic referrals and up to 90% of new ophthalmic referrals in persons younger than 15 years.[9] A survey of ophthalmologists from 6 European countries has identified a prevalence rate of 3.2 per 10 000 inhabitants in Western Europe.[10] In Italy alone, the incidence of VKC was calculated to be 7 per 100 000 subjects younger than 16 years and 0.06 per 100 000 subjects older than 16 years, with a greater incidence in males only in the pediatric patients.[2] In most of these published retrospective case series, little is known about the exact age of the described young adults in whom the disease developed after puberty. Although the management of VKC in young patients is challenging, adult patients may have a lower compliance to self-administered treatments and higher complication rates.

The aim of the present study was to assess clinical, demographic, immunologic, and health-related quality-of-life data from a cohort of patients with a VKC-like disease that presented after puberty. Additionally, in a subgroup of these patients, multiple cytokines were defined in tears during the inflammatory phase of the disease to identify any potential differences in cytokine patterns between adults and children.

METHODS

• PATIENTS: A 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

Accepted for publication Nov 16, 2012.
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0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2012.11.018

(by the presence of giant papillae more than 1 mm in diameter), limbal (by the presence of limbal infiltrates and Trantas dots), or mixed (by the presence of both limbal and tarsal signs). The database, created using the Access software program (Microsoft Corporation, Redmond, Washington, USA), included 600 consecutive VKC patients referred to the Ocular Allergy Service of the Ophthalmology Department at the University of Padua from 1996 through December 2011. This retrospective observational case series study complied with the tenets of the Declaration of Helsinki and was approved by the Padova University Hospital Review Board. The following information was collected: family and personal medical history, age at onset and resolution of the disease, associated allergic manifestations, results of skin prick test for allergen sensitivity, serum specific IgE to a panel of 24 allergens (FEIA, CAP System; Pharmacia, Uppsala, Sweden), total serum IgE (UNICAP; Pharmacia), serum levels of eosinophil cationic protein (UNICAP), treatment history, and outcome. The patients' written informed consent to obtain blood samples and to analyze clinical and demographic data was confirmed on record.

To define the adult onset of VKC, a fixed cutoff age of 15 years was chosen, with the assumption that at this age, most patients already had attained puberty. Patients with a diagnosis of VKC in childhood and recurrence of signs and symptoms after puberty were excluded (11 of 600). The presence or history of eczema was an exclusion criterion. Clinical findings of a complete ophthalmic examination, performed at least once yearly, were recorded. An overall clinical score for disease severity, considering immediate signs and symptoms as well as permanent changes (i.e., papillae size or corneal scars), was defined as follows: 0 = quiescence or absence of symptoms; 1 = mild seasonal signs and symptoms without corneal involvement, 2 = mild persistent signs and uncomfortable seasonal symptoms without corneal involvement, 3 = severe intermittent signs and uncomfortable persistent symptoms with mild corneal involvement, and 4 = very severe persistent signs and symptoms with diffuse superficial keratopathy or ulcer graded by a standardized clinical grading system.[11,12] Single signs and symptoms also were graded using a predefined 0-to-4 scale.

Tear samples were collected from the outer canthus with a microcapillary tube, and the percentages of eosinophils, neutrophils, and lymphocytes present in 5 microscopic fields were counted on precolored slides (Testsimplets; Waldeck GmbH & Co, Münster, Germany) using a Zeiss microscope (Carl Zeiss Microscopy GmbH, Jena, Germany) at ×312 magnification.

The impact of the disease on work or study productivity, on social life, and on treatment satisfaction was evaluated using a visual analog scale (in which 0 indicated no symptoms and 100 indicated the worst symptoms ever experienced).

A modified version of the Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire[13] was completed by the adult VKC-like patients (Table 1), all of whom were recalled and were examined during their active phase. The original final version of the QUICK questionnaire was designed specifically to be completed easily and quickly by 5- to 12-year-old children with chronic keratoconjunctivitis.[13] For the purpose of the present study in adult patients, items regarding school or play activities were deleted and answers were graded with a 0-to-4 scale scoring system similar to that of signs and symptoms (0 = absence; 4 = very severe/persistent all the time).

• **TEAR CYTOKINES:** Tear samples were collected with a capillary tube from a subgroup of 10 adult active VKC-like patients (5 affected by the tarsal form and 5 by the limbal form), from 10 children affected by active VKC (5 affected by the tarsal for and 5 limbal VKC), and from 10 normal subjects. Samples were diluted 1:1 and were analyzed using multiplex bead analysis, which uses microspheres as a solid support for immunoassays and allows for analyses of all molecules in each sample. Th1-type (interleukin [IL]-2, IL-12, interferon-γ), Th2-type (IL-4, IL-10, and granulocyte-macrophage cell stem factor), and proinflammatory cytokines (IL-1β, IL-6, IL-8, and tumor necrosis factor-α) were measured according to the manufacturer's instructions (Upstate Biotechnology UK, Buckingham, UK). Briefly, samples were incubated with antibody-coated capture beads for 2 hours at 20 C. Washed beads were incubated further with biotin-labeled antihuman cytokine antibodies for 1 hour followed by streptavidin-phycoerythrin for 30 minutes. Samples were analyzed using a Luminex 100 (Luminex, Austin, Texas, USA) with Starstation software (Applied Cytometry Systems, Sheffield, UK). Standard curves of known concentrations of recombinant human cytokines were used to convert fluorescence units to cytokine concentration (picograms per milliliter). Minimum detection levels for each cytokine were as follows: 20 pg/mL (IL-2), 10 pg/mL (IL-1βIL-8, IL-12, tumor necrosis factor-α, 5 pg/mL (IL-4, interferon-γ), 2 pg/mL (IL-10), and 1 pg/mL (IL-6).

• **STATISTICAL ANALYSIS:** Differences between percentages were compared using the chi-square test. Differences between mean values were compared using the Student *t* test. The cytokine data sets were analyzed for normal distribution using the Kolmogorov-Smirnov normality test. Because most of the data sets were not normally distributed, the nonparametric Kruskal-Wallis analysis with the Dunn multiple comparison posttest was used. The minimal level of confidence at which the results were judged significant was $P < .05$. Data are reported as mean ± standard deviation.

RESULTS

OF THE 600 VKC PATIENTS CLASSIFIED IN OUR DATABASE from 1996 through December 2011, 49 demonstrated

TABLE 1. Quality-of-Life Questionnaire Modified for Adult Vernal Keratoconjunctivitis-like Patients from the Original Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire[13]

In the Last Month, Because of Your Conjunctivitis, Did You:
Feel burning in your eyes?
Have trouble staying in air-conditioned rooms?
Have itchy eyes?
Have to use tissues?
Have eye secretion?
Have puffy eyes?
Have red eyes?
Have problems in the light?
Have tearing?
Have eye secretion?
Have closed and sticky eyes in the morning?
Have blurred vision?
Have to use eye drops?
Have difficulties concentrating at work or other activities?
Have difficulties in reading?
Have trouble meeting your friends?
Have trouble practicing sports?
Have trouble going to the pool?

a VKC-like disease after 15 year of age. Of these, 32 (65.3%) were male and 17 (34.7%) female, with a male-to-female ratio of 2:1, which was statistically significant less than the male-to-female ratio found in our pediatric VKC population (Table 2). In the VKC-like patients, the mean age of disease onset was 20 ± 4 years, with no significant difference between males and females or clinical form of the disease. The disease resolved completely in only 9 patients. In this subgroup, the mean length of the disease was 6.4 ± 4.8 years, with 1 case lasting 13 years. All patients were recalled and examined at least once yearly and at the time of this retrospective study.

All VKC-like patients had a clinical history of conjunctivitis with annual recurrences between March and October, with symptoms characterized by itching, burning and discharge, onset after puberty, and no history of VKC, seasonal allergic conjunctivitis, or atopic dermatitis in childhood. The skin of the lid and lid margin was not involved in all of these patients. Based on the overall severity score, during the season, 75% of the patients were considered to have a grade 2 or 3 of the disease. Tear cytologic analysis showed the presence of eosinophils in all VKC-like patients during their active inflammatory phase, with a percentage of eosinophils between 5% and 45% of the inflammatory cells in tears.

A significant association with ovarian cysts unaccompanied by hyperandrogenism was reported in the female population (50%).

• **CLINICAL FORMS:** The tarsal form of the disease in adult patients appeared either as a diffuse thickness of the upper tarsal conjunctiva with a diffuse subepithelial fibrosis without giant papillae or with formation of the typical giant papillae of variable size and shape (Figure 1). The limbal form was characterized by the presence of transient grayish, gelatinous-like or yellow-white nodules at the limbus associated with conjunctival hyperemia more pronounced in the limbal and in the perilimbal area (Figure 2). Family history for allergy, distribution of clinical forms, and incidence of corneal ulcers in adult and children VKC patients is shown in Table 2, as well as associated allergic manifestations and allergy serum biomarkers results. No significant permanent reduction of best-corrected visual acuity or keratoconus was reported in the VKC-like group of patients.

• **ALLERGY DIAGNOSTIC TESTS:** A positive skin prick test was identified for at least 1 allergen in 55% of adult VKC-like patients (27 of 49 patients) and in 43.2% of VKC children. In the adult group, the results of the test identified a sensitization to *Dermatophagoides* in 40.4%, to *Graminaceae* in 39%, to *Parietariae* in 13.7%, and to food allergens in 2.6%, with no significant differences compared with the distribution of specific sensitizations in children. The limbal form in adults was associated more frequently with positive prick test results (65.2%) compared with children (37.1%). This difference was statistically significant ($P = .0093$).

Specific serum IgE tests demonstrated positive results for at least 1 allergen in 57% of the adult patients (28/49 patients) and in 51% of children. In the adult group, the results of specific serum IgE were associated with the results of prick tests in 70% of the cases and identified a positive sensitization to *Graminaceae* in 28% of patients, to *Dermatophagoides* in 36% of patients, to *Alternaria* in 11% of patients, to tree pollens in 10% of patients, to *Parietariae* in 14% of patients, to *Compositae* in 3% of patients, and to food allergens in 3.7% of patients. Levels of total IgE were significantly higher in prick test-positive and specific IgE-positive patients (271 ± 390 KU/L) compared with patients with negative results (59 ± 66 KU/L; $P < .05$). Similar results also were found in VKC children (positive prick test results, 849 ± 1761 KU/L; negative prick test results, 140 ± 193 KU/L; $P < .0001$).

• **QUALITY-OF-LIFE TEST IN ADULT VERNAL KERATOCONJUNCTIVITIS PATIENTS:** The mean duration of symptoms was 6.21 ± 2.5 months/year (range, 3 to 12 months/year), especially between April and September. The most common nonspecific trigger factor was environmental exposure to sun and dust (scores of 3 to 4 in 50% of patients; Figure 3). Only 31% of patients indicated pollen exposure as a severe (score 4) triggering factor.

Among the symptoms, itching was considered the most limiting and disturbing to quality of life (scores of 3 to 4 in 89.5% of patients), followed by foreign body sensation (79%). Burning and photophobia were given high scores

TABLE 2. Epidemiologic and Clinical Data and Biomarkers in Adults and Children Affected by Vernal Keratoconjunctivitis

	Male-to-Female Ratio	Tarsal Form (%)	Limbal Form (%)	Mixed Form (%)	Positive Family History for Allergy (%)	Corneal Ulcer (%)	Asthma (%)	Rhinitis (%)	Skin Diseases (%)	Total Serum IgE (KU/L)	Eosinophil Cationic Protein (μg/L)
Adults	2:1	45	33	19	28.6	4.2	10	22	12	154 ± 281	29 ± 19
Children	4:1	28	57	15	42.8	18.2	12	26	16	469 ± 1214	34 ± 32
P value	.049	NS	NS	NS	.06	.011	NS	NS	NS	.01	NS

IgE = immunoglobulin E; NS = not significant.

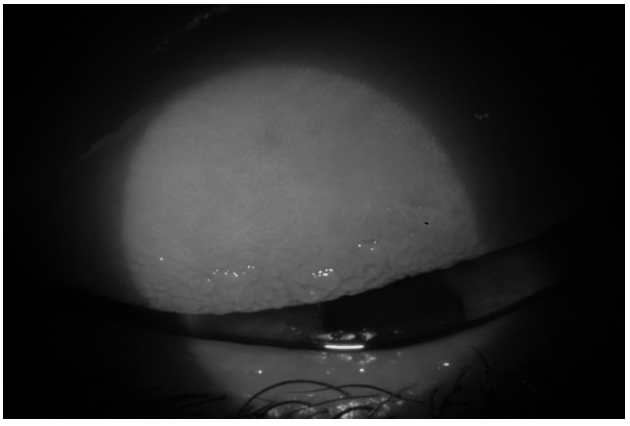

FIGURE 1. Photograph showing tarsal vernal keratoconjunctivitis-like disease in which diffuse thickness of the upper tarsal conjunctiva with subepithelial fibrosis and typical papillary hypertrophy are present in an adult patient.

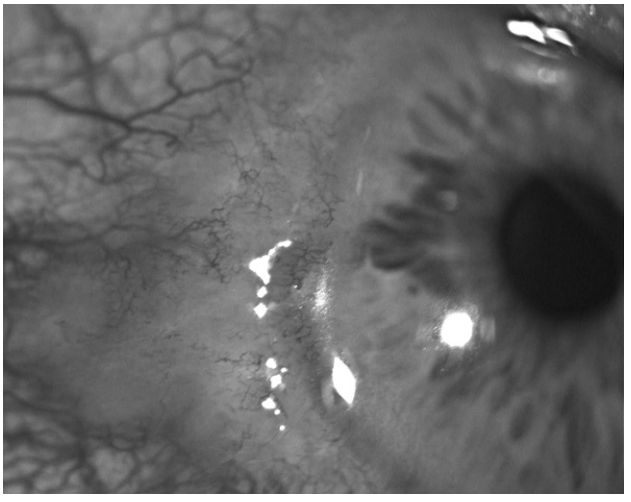

FIGURE 2. Photograph showing limbal vernal keratoconjunctivitis-like disease in which grayish, gelatinous nodules at the limbus associated with perilimbal hyperemia are present in an adult patient.

in 63% and 46.8% of patients, respectively (Figure 4). Among clinical signs reported by patients, discharge (73.7%) and redness (68.4%) were given high scores (≥ 3), whereas tearing and swelling were less relevant.

In 42% of patients, during the active phase of the disease, signs and symptoms were continuous either in the outdoor or indoor environment, with exacerbation of symptoms in the outdoor environment in 36.8% (trouble of practicing sports, trouble going to the pool, trouble meeting your friends) and in the indoor environment in 21% (difficulties in reading and concentrating at work, trouble staying in air-conditioned rooms). The disease was not considered a limiting working factor because the percentage of productivity was reduced only by 26% (100% productivity outside the allergic season). However, there was a wide range of results (range, 20% to 100%) because of different kinds of work activities: patients with more vision-related activities (computer, photography) reported the worst productivity index. Most of the patients did not lose a relevant number of working days, excluding days for ophthalmologic or allergy-related medical visits. Social activities were more compromised during the active phase of the disease, 69% (31% decrease) compared with 100% (unaffected) during normal periods.

The mean satisfaction for VKC treatment was 66% (100 = full satisfaction, 0 = completely unsatisfied), with a wide range reported: between 0% (in a single case) and 100%. Of the 6 patients with 100% satisfaction, 5 were using topical cyclosporine 1% 4 times daily. Patients using topical cyclosporine reported a mean satisfaction of 94.3%.

Economic impact showed a wide variety, ranging from €35 to €1000 of annual expense, with mean values from €246 to €170. Most expenses were related to private visits (not in public health facilities and before diagnosis) or specific immunotherapy. Interestingly, 42% of the patients tried different homeopathic treatments before diagnosis. After diagnosis and follow-up in our ocular allergy service, all patients reported an improvement in satisfaction for treatment and a great reduction in costs mostly because of the transfer to a public service and to the reduced cost of medications.

• **TEAR CYTOKINES:** Considering adults and children VKC patients together, tear levels of IL-4, IL-6, IL-8, and IL-10 were increased significantly compared wit those of

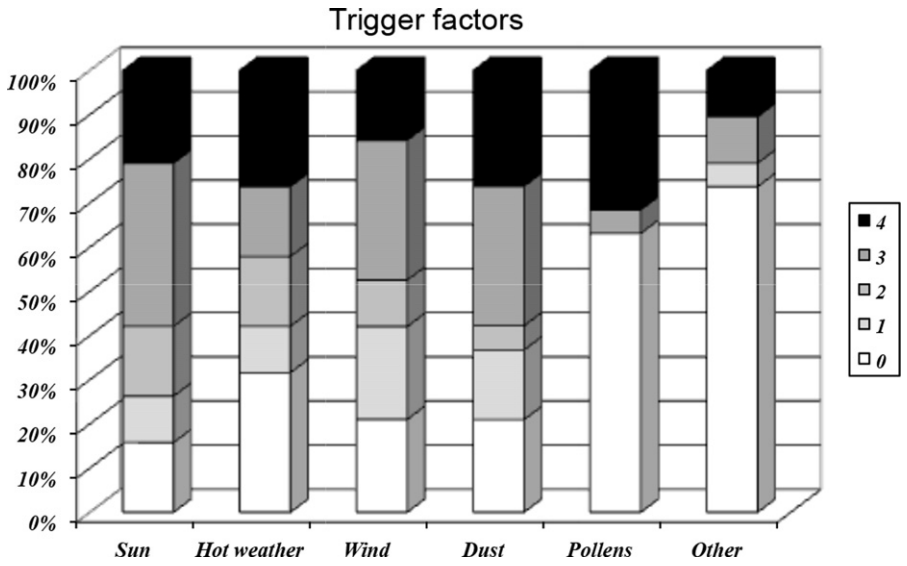

FIGURE 3. Bar graph showing nonspecific trigger factors that were reported to exacerbate adult vernal keratoconjunctivitis-like disease.

normal subjects (data not shown). Cytokine tear levels were similar in pediatric VKC and adult VKC-like patients (Table 3). In both groups, no differences were found between IgE-positive and IgE-negative patients, with either the tarsal or the limbal form of the disease. In VKC-like patients, increased levels of IL-1, IL-2, IL-12, interferon-γ, and granulocyte-macrophage cell stem factor were found in the limbal compared with the tarsal form of the disease ($P < .01$).

DISCUSSION

THE LACK OF STANDARDIZED DIAGNOSTIC CRITERIA AND lack of common language among physicians regarding the grading of VKC make this disease difficult to diagnose and treat. A tentative clinical grading system based on VKC severity recently was proposed to provide a common description of the disease and to avoid selection bias in the recruitment of patients for clinical trials.[11] Based on criteria that define the severity of this disease,[1,12] all the clinical features described in typical VKC children were present in the VKC-like disease here described in adults.

Several epidemiologic studies have been published on VKC from patient information collected from single tertiary centers.[2–4,14,15] VKC was the leading cause of outpatient ophthalmic morbidity among Palestinians of East Jerusalem, accounting for 10% of 74 400 annual outpatient visits to ophthalmic clinics in Israel.[8] In 2 of the largest series of VKC patients, 400 cases in Israel and 530 cases in Pakistan, there was no mention of VKC in adults or starting in adulthood, and in none of the other observational studies was the relevance of VKC in adults considered.[15,16]

In the present study, we highlight that an adult-onset, VKC-like disease can appear as a new entity after puberty or in young adults. VKC patients with recurrences of the disease in adulthood were not included in the adult VKC-like disease group because the onset was still in childhood. This number is unknown because it was not possible to follow up all child patients after remission. Similarly, patients with a history of any kind of conjunctivitis before puberty or those with eczema were excluded from the adult VKC-like group. This information is based only on an accurate history and not on objective data, but may represent a potential source of bias for the results of the present study.

Signs and symptoms are identical to those typical of VKC in children, yet adults have a significantly lower rate of corneal ulcers. This may be the result of less scratching and epitheliotoxin release in adults who endure the intense itching associated with this disease much more than children. None of the VKC-like patients demonstrated a significant limbal stem cell deficiency as a complication of severe and persistent limbal inflammation, as reported recently in children and adult Indian VKC patients.[17] This may be because of the different severity of the disease in India compared with Italy, different genetic background, environmental conditions, and management of the disease from the early stages.

Another difference between adults and children with VKC may be the morphologic appearance of the tarsal plate in adults, in whom a diffuse subepithelial thickening and fibrosis without giant papillae formation was more frequent than in the classic tarsal form of VKC in children. There also seemed to be lower levels of eosinophils in tears of VKC-like adults compared with our previously reported 49 ± 15% eosinophils in tears of children with VKC.[18] However, this preliminary finding will need further confirmation.

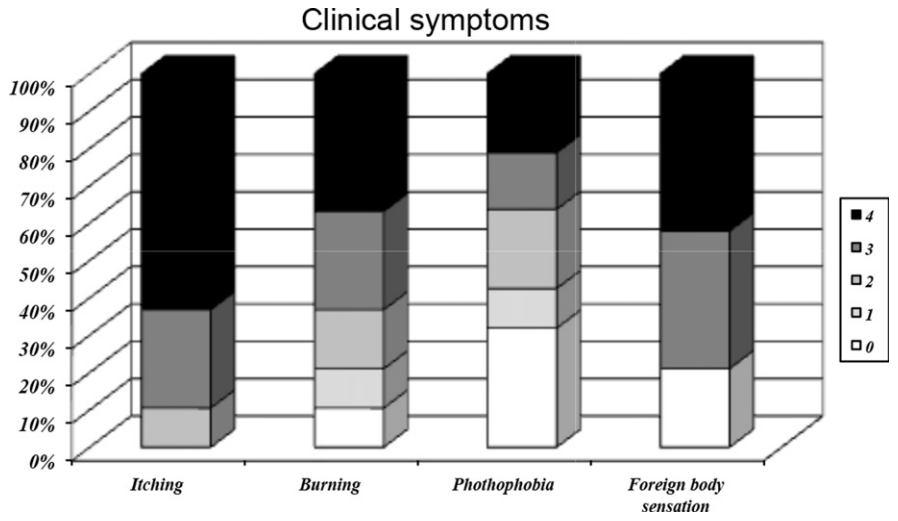

FIGURE 4. Bar graph showing clinical symptoms reported by adult-onset vernal keratoconjunctivitis-like patients. Itching was considered the most limiting and disturbing factor (score of 3 or 4 in 89.5% of patients), followed by foreign body sensation, burning, and photophobia, which were given high scores by 79%, 63%, and 46.8% of patients, respectively.

TABLE 3. Cytokine Levels (pg/mL) in 10 Adults and 10 Children Affected by Vernal Keratoconjunctivitis

	IL-1	IL-2	IL-4	IL-6	IL-8	IL-10	IL-12	TNFα	IFNγ	GM-CSF
Adults	9 ± 7	35 ± 33	6 ± 7	216 ± 215	2740 ± 628	9 ± 7	12 ± 10	13 ± 20	9 ± 12	30 ± 27
Children	15 ± 15	30 ± 43	10 ± 11	611 ± 963	8916 ± 313	26 ± 45	14 ± 19	16 ± 17	8 ± 18	42 ± 45
P value	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

IFN = interferon; IL = interleukin; GM-CSF = granulocyte macrophage cell stem factor; TNF = tumor necrosis factor.

Prolonged and recurrent conjunctival inflammation affects physical activity, psychological and social status, and somatic sensation in young patients.[13] In the present study, we administered a disease-specific quality-of-life questionnaire, modifying the QUICK questionnaire for adults by excluding questions concerning activities typical of children. The QUICK questionnaire was developed to be used specifically in children with severe forms of ocular allergy, and at present, it is the only validated questionnaire specific for the assessment of health-related quality of life in VKC.[13] Our results showed that VKC-like disease in adults has moderate to severe ocular symptoms that undoubtedly interfere with quality of life. In addition to their intense ocular discomfort, adults with VKC-like disease often experience the negative consequences of limiting many preferred activities, such as practicing sports and meeting friends, in an attempt to avoid worsening signs and symptoms and psychological embarrassment. Itching, burning, redness, photophobia, and the need to use eye drops were the most frequent symptoms reported, in direct proportion to the severity of the active allergic inflammation. Patients reported limitations in outdoor activities that cause exposure to allergens as well as to sunlight and other nonspecific irritating stimuli and in going to the pool, because of the notoriously powerful irritating effects of chlorinated air and water. VKC is related to exposure to environmental factors and to specific and nonspecific mucosal hyperreactivity. In adult patients, symptoms most often were under control when treated adequately, but still the number of complete remissions was low. This may be one of the differences between VKC in adults and children, because children will experience hormonal and unknown immunologic changes at puberty, but adults already have experienced such changes. This also may explain the lower ratio of males to females in the adult group.

With regard to cytokine pattern production evaluated in a limited subgroup of patients, as expected, we found significant differences between pathologic and control samples. These data are similar to our previous findings of multiple cytokine tear levels in ocular allergic diseases.[18] We did not find differences in the cytokine distribution between adults and children with VKC. However, we found that the limbal disease in adults has a more Th1-type cytokine profile compared with the tarsal form. A possibly heightened Th17 cellular response in these patients is an object of further investigation.

In this cohort, signs and symptoms of adult onset VKC-like disease were present in both males and females, were associated clearly with the spring and summer season, and were strikingly similar to the classic signs and symptoms typical of VKC in children, albeit with less severe photophobia and corneal involvement. Nevertheless, the observed association of this VKC-like disease with polycystic ovaries unaccompanied by hyperandrogenism in 50% of the females strengthened the proposed role of the endocrine system in VKC. It also was suggestive of the itchy-dry eye-associated syndrome recently described,[19] which is associated with tear film dysfunction, goblet cell hyperplasia, and hormonal imbalance, as well as having characteristics in common with the previously described and poorly understood mucus fishing syndrome.[20] Dysfunction of sex hormones has been linked for some time to the severity, progression, and treatment response of VKC.[21] In addition, the physiologic rise of androgen serum levels at puberty has been associated with improved signs and symptoms of VKC.[22] At present, it is not clear how sex hormones affect the ocular surface response in this disease and how they may affect the clinical course of VKC in males and females before and after puberty. The prevalence of a Th1-type cytokine profile in the limbal form and the good response to topical cyclosporine treatment in adult patients indicate that this adult form of VKC may be a distinct subtype of VKC with mixed immune and endocrine abnormalities that need to be clarified.

In conclusion, our study highlighted clinical, demographic, immunologic, and quality-of-life data in adult patients with a disease very similar to that typically seen in childhood. There is still much to discover about VKC in general and particularly in those few patients in whom a VKC-like disease develops after puberty.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported. S. John Curnow receives grant support from the Birmingham Eye Foundation. Involved in Conception and design of study (A.L.); Analysis and interpretation of data (A.L., I.A.F.); Data collection (A.L., D.L., L.M., M.B., V.D.); Provision of materials, patients, or resources (A.L., S.J.C.); Statistical expertise (I.A.F.); Literature search (A.L., D.L., V.D.); Administative, techincal, or logistic support (D.L.); Writing the article (A.L.); Critical revision of article (J.S.C., S.B., I.A.F.); and Final approval of article (J.S.C., S.B., I.A.F.).

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