Long Eyelashes in a Case Series of 93 Children With Vernal Keratoconjunctivitis

Neri Pucci, MD*; Elio Novembre, MD*; Enrico Lombardi, MD*; Cristina Massai, MD*; Roberto Bernardini, MD*; Roberto Caputo, MD‡; Luciana Campa, MD‡; Cinzia de Libero, MD‡; and Alberto Vierucci, MD*

ABSTRACT. *Objective.* **Vernal keratoconjunctivitis (VKC) is a chronic conjunctivitis that affects children mainly in temperate areas, with exacerbations in spring and summer. Eyelashes provide natural protection for the eyes from sunshine, wind, and foreign bodies. These factors induce a worsening of signs and symptoms in VKC, whereas mechanical protection of the eyes produces relief. The aim of this study was to evaluate eyelash length in a large series of VKC patients and in age- and gender-matched healthy subjects.**

Methods. **Upper eyelash length was measured in 93 VKC patients (mean age: 8.7 years; range: 4–18 years) with a digital caliper. History, clinical form, type of presentation, degree of severity, and drug therapy were evaluated. Skin tests and serum-specific immunoglobulin E for common allergens, serum-total immunoglobulin E, peripheral blood eosinophil counts, and serum eosinophil cationic protein were determined. Two age- and gender-matched control subjects for each VKC patient underwent the same eyelash measurement.**

Results. **The upper eyelashes were significantly longer in VKC patients than in control subjects (mean ± SD: 8.9 ± 1.17 mm vs 7.9 ± 1.07 mm). In healthy subjects, a negative correlation was found between eyelash length and age. With multivariate analysis, unlike control subjects, the eyelash length in VKC patients did not correlate with age, was positively correlated with the degree of severity of VKC, and was negatively correlated with the use of topical cyclosporine.**

Conclusions. **Patients with VKC had longer eyelashes than healthy matched subjects. The ocular inflammation, by unknown chemical mediators, was likely responsible for the excessive eyelash growth. The finding may represent a defensive mechanism against physical agents that might have a crucial role in the etiopathogenesis of this disease.** *Pediatrics* **2005;115:e86–e91. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1555;** ***children, eyelashes, vernal keratoconjunctivitis.***

ABBREVIATIONS. VKC, vernal keratoconjunctivitis; bFGF, basic fibroblast growth factor; s-P, substance P; IgE, immunoglobulin E; s-ECP, serum eosinophil cationic protein; PBEC, peripheral blood eosinophil count.

From the *Allergy and Clinical Immunology Unit and ‡Clinical Ophthalmology Unit, Department of Pediatrics, Anna Meyer Children's Hospital, University of Florence, Florence, Italy.

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Reprint requests to (N.P.) Allergy and Clinical Immunology Unit, Department of Pediatrics, Anna Meyer Children's Hospital, Via Luca Giordano 13, 50132 Florence, Italy. E-mail: n.pucci@meyer.it

Vernal keratoconjunctivitis (VKC) is a chronic and potentially severe[1] bilateral allergic conjunctivitis. In the Mediterranean area and other temperate regions, the intensity of the disease increases in spring and summer and decreases in fall and winter.[2–4] VKC usually starts in the first decade of life and disappears in the second decade.[2,4]

Limbal, tarsal, and mixed forms are described depending on the main site of ocular inflammation. Itching, photophobia, tearing, foreign body sensation, and burn sensation are ocular subjective symptoms. The conjunctival signs include hyperemia, presence of papillae, and giant papillae in the upper tarsal region; in bulbar VKC, limbal papillar hypertrophy is present; corneal ulcers are possible complications. Recent studies have shown a prevalent local Th2 response in VKC,[5,6] with increased numbers of mast cells and eosinophils in the conjunctiva.[4,7] Eotaxin-1 and eotaxin-2, two eosinophil chemotactic and activating chemokines, seem to be implicated in the pathogenesis.[8] Increased levels of activated blood eosinophils and serum eosinophil cationic protein have been detected, indicating a systemic involvement.[9,10] A role for basic fibroblast growth factor (b-FGF) and transforming growth factor β has been suggested,[11] as well as for nerve growth factor and neuropeptide substance P (s-P).[12,13]

Despite a high prevalence of immunoglobulin E (IgE)-sensitized patients (~50%), the causes of the disease remain obscure. We recently reported a significantly lower prevalence of IgE sensitization in limbal than in tarsal and mixed VKC patients in a case series of 110 Italian children.[14] Some environmental variables such as sunshine, wind, and other climatic factors seem to have an important role in the clinical manifestations.[15] A significant improvement in the ocular signs by protecting eyes with caps and dark glasses has been reported.[16] Because the main function of the eyelashes is to protect the eyes[17] and, to our knowledge, no study has so far investigated the eyelash length in VKC patients, we evaluated the eyelash length in a large series of VKC children and in age- and gender-matched control subjects.

METHODS

Subjects and Clinical and Immunologic Parameters

Ninety-three consecutive patients with VKC were recruited into the study. Each patient was evaluated to distinguish among limbal, tarsal, and mixed form and between seasonal and perennial symptoms. Ocular signs were evaluated as recently report-

ed.[14] Briefly, a total objective score was assigned as the sum of hyperemia, papillae, giant tarsal papillae, and limbal involvement scores: each item was graded from 0 to 3. The total score reported was calculated as the mean of at least 2 score measurements in the last 3 months. All patients underwent skin-prick test, and serum determination of specific IgE for common inhalant and food allergens (UniCAP Specific IgE; Pharmacia, Uppsala, Sweden); patients were considered to be IgE sensitized when at least 1 positive skin-prick test response or serum-specific IgE determination (>0.35 kU/L) was present.[18] Serum total IgE, serum eosinophil cationic protein (s-ECP; UniCAP Total IgE and ECP; Pharmacia), and peripheral blood eosinophil counts (PBECs) were measured. Parents were asked how long their children had had VKC. A possible prolonged administration of systemic or topical drugs such as antihistamines, corticosteroids, cyclosporine, and nonsteroidal anti-inflammatory drugs was also investigated. Two age-matched (±3 months), and gender-matched control subjects were recruited for each VKC patient to measure the eyelash length. A total of 186 control subjects were recruited; they had never had any ocular allergic disease.

Measurement of the Length of the Eyelashes

Eyelash length was measured with a commercial available digital caliper (Mitutoyo Corp, Kawasaki, Japan; Series 500, code no. 500-311; battery SR44 1 pc; resolution: 0.01 mm [0.0005″]; repeatability: 0.01 mm [0.0005″]; response speed: up to ~1600 mm (60″)/second).

The inside measuring faces of the caliper were drawn near the central third of the upper eyelid, then the slider was moved along the main blade of the caliper. The distance between each inside measuring face was matched with the eyelash length, without evaluating the curving; the result of the measurement appeared in the display. The length of the lower eyelashes was also measured in 32 VKC patients and 64 matched control subjects.

Each measurement was performed in both eyes of VKC patients or control subjects by 2 different investigators in an open manner; each investigator was not aware of the results of the other. The final result is expressed as the mean value of the overall 4 measurements for each patient or control subject. A single eyelash was randomly removed with tweezers in 10 VKC patients and 18 control children; a measurement of these eyelashes was performed before and after the removal from the eyelid, excluding the bulb. Informed consent to participate in the study was obtained for all participants.

Statistical Analysis

All data were elaborated using a commercially available statistical computer software package (SPSS, Chicago, IL). A *t* test was used for the comparison of means. Linear regression was used to study the correlation between the eyelash length and the single variables. The validity of the regression models was checked by verifying the assumptions of linear regression. A multivariate analysis using multiple regression was performed to examine the independent effects on eyelash length of age, gender, clinical form, time from the start of symptoms, degree of severity, presence of seasonal or perennial form, IgE sensitization, and use of topical cyclosporine. $P < .05$ was considered statistically significant.

RESULTS

Clinical and allergologic features of VKC patients and control subjects are reported in Tables 1 and 2. All patients and control subjects were white Italian

TABLE 1. Characteristics of the Study Population

	VKC Patients	Controls	*P*
No. of subjects	93	186	—
Age, y			
Mean (SD)	8.74 (2.74)	8.75 (2.71)	—
Range	4.0–18.0	3.9–18.0	—
Boys	67 (72%)	134 (72%)	—
Male/female	2.55/1	2.55/1	—
Upper cyclash length, mean mm (SD)	8.90 ± 1.17	7.92 ± 1.07	<.0001

TABLE 2. Other Characteristics of Patients With VKC

Forms (%)			Presentation (%)		Mean Score (± SD)	Time From Start (Years)	Cyclosporine Treatment	IgE Sensitized		Serum Total IgE (kU/L)	s-ECP (μg/dL)	PBECs (cells/mm³)
Tarsal	Bulbar	Mixed	Seasonal	Perennial				Yes	No			
51 (54.8%)	3 (3.22%)	39 (41.9%)	72 (77.5%)	21 (22.5%)	7.7 (±3.24)	3.8 (±1.96)	59 (63.4%)	50 (53.8%)	43 (46.2%)	325.6 (±716.94)	81.0 (±62.9)	438.5 (±266.3)

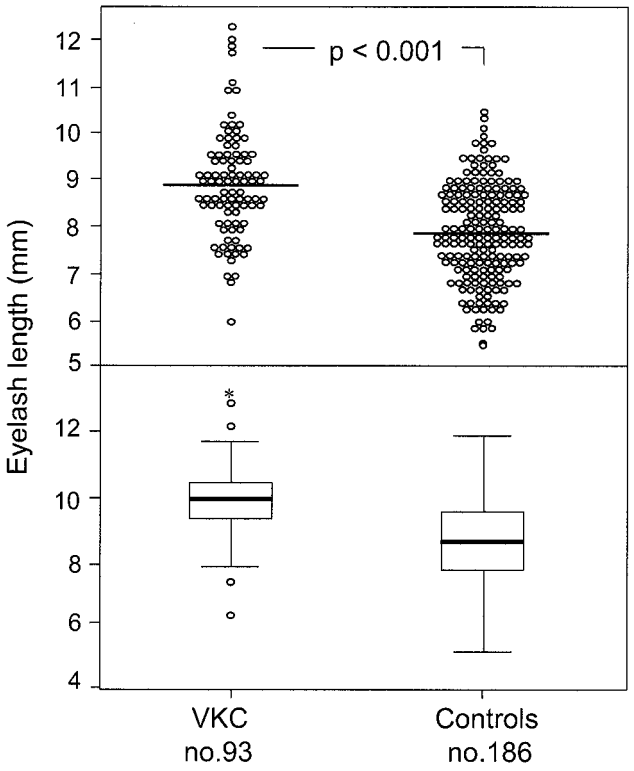

Fig 1. Eyelash length in VKC patients and control subjects. Data distribution and box-and-whiskers plot.

children. Most of them were from Tuscany (n = 56, 60% of VKC patients; n = 133, 72% of control subjects); the others came from the north, the south, or other regions of central Italy, without significant differences between patients and control subjects.

The upper eyelashes were significantly longer in VKC patients than in control subjects ($P < .0001$; Figs 1 and 2). There were no significant differences between the mean eyelash length measured by the 2 observers. The mean ± SD of the differences between the measurement of the 2 observers was 0.025 ± 0.35 mm. We could not observe any obvious difference in the curving of the eyelashes between VKC patients and control subjects.

A positive inverse correlation was found between age and eyelash length in VKC patients and control subjects as a whole (P = .020) and in the control group (P = .010; Fig 3); when considered separately, however, this correlation was not maintained in VKC patients (P = .44). The eyelash length was found to correlate positively with the score of ocular signs (P = .021) and negatively with the time from the start of symptoms (P = .045).

At the evaluation, 59 (63.4%) of 93 patients were being treated with 1% or 2% cyclosporine eyedrops for 1 month to 1 year or more (Table 2). The eyelashes in these children were shorter than in never-treated patients (P = .04; Table 3). No other topical or systemic drug has been used continuously for >2 weeks.

Table 3 shows other results of eyelash measurement in subgroups of VKC patients. No significant difference in eyelash length was found among the 3 clinical forms of VKC by analysis of variance (P = .69). In the control group, the mean eyelash length (±SD) was 7.99 ± 1.05 mm in boys and 7.76 ± 1.03 mm in girls (P = .18). No significant correlation was found among eyelash length and serum total IgE (P = .21), s-ECP (P = .87), and PBECs (P = .83).

A multivariate analysis was performed to evaluate the independent effect of several variables on the eyelash length (Table 4). After adjusting for the other covariates, only objective score and topical cyclo-

Fig 2. Long eyelashes in a patient with VKC.

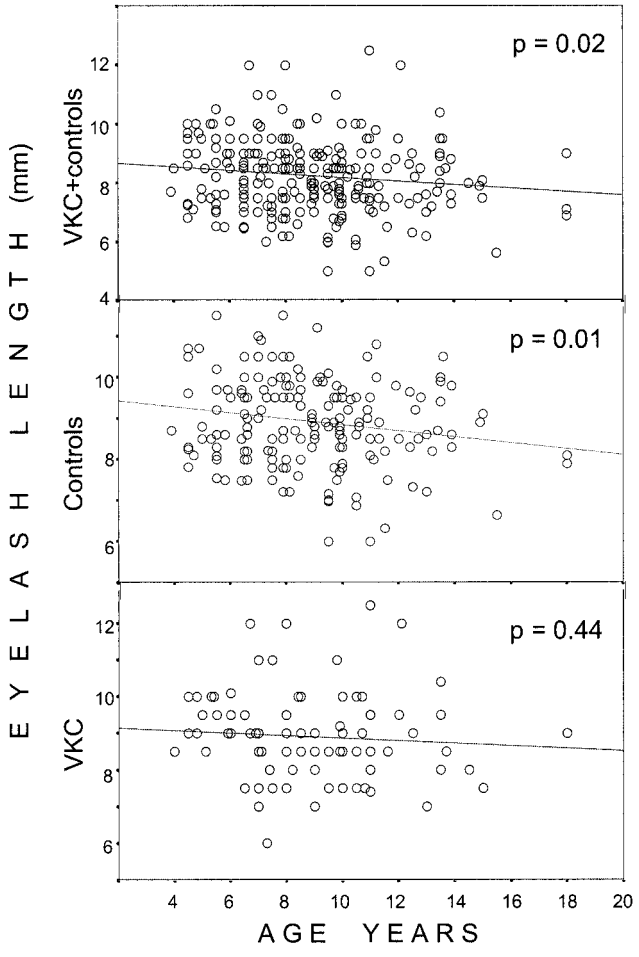

Fig 3. Relationship between eyelash length and age in VKC patients and control subjects.

TABLE 3. Means (±SD) of Eyelash Length in Subgroups of VKC Patients

Eyelash Length		*P*
Boys	Girls	
9.00 ± 1.17	8.67 ± 1.17	.22
Tarsal	Bulbar	
8.99 ± 1.13	8.50 ± 0.00	.46
Tarsal	Mixed	
8.99 ± 1.13	8.83 ± 1.27	.54
Bulbar	Mixed	
8.50 ± 0.00	8.83 ± 1.27	.10
Seasonal	Perennial	
8.83 ± 1.08	9.16 ± 1.44	.25
IgE sensitized	Non–IgE sensitized	
8.78 ± 1.14	9.06 ± 1.20	.35
Cyc-Treat	Non-Cyc-Treat	
8.72 ± 1.16	9.23 ± 1.16	.04

Cyc-treat indicates patients who were treated with cyclosporine eyedrops.

TABLE 4. Multivariate Analysis: Independent Effect of Some Variables on Eyelash Length ($r^2 = 0.20$)

Variables	Regression Coefficient	β	*P*
Age, y	.06	.14	.29
Gender	−.22	−.09	.39
Clinical form (T/B/M)	−.17	−.14	.19
Seasonal/perennial	.14	.05	.64
Time from start	−.14	−.23	.08
Objective score	.10	.29	.009
IgE sensitized	.46	.20	.06
Cyclosporine treatment	−.56	−.23	.02
(Constant)	8.80		

T indicates tarsal; B, bulbar; M, mixed.

sporine use remained significantly correlated with eyelash length in VKC patients.

A good correlation resulted in the measure of eyelashes before (8.31 ± 1.23 mm) and after removal with tweezers (8.50 ± 1.19 mm) in 10 VKC patients and 18 control subjects ($P < .001$). The mean (±SD) of the lower eyelid eyelash length was 5.72 ± 0.61 mm in 32 VKC patients and 6.02 ± 1.15 mm in 64 matched control subjects ($P = .10$).

DISCUSSION

We found that the upper eyelashes in VKC patients were significantly longer than in age- and gender-matched control subjects. This is the first report showing a lengthening of eyelashes directly associated with an ocular disease and in a wide series of patients.

Each human eyelash lives an average of 5 to 6 months. The growth phase of the hair follicle and terminal hair (anagen) lasts 2 to 3 months. At the end of the eyelash growth, a brief transition stage of 2 to 3 weeks follows (catagen), with shortening of the hair follicle. Finally, the follicle enters a resting phase (telogen) of 2 to 3 months, leading to the detachment of the eyelash.[17,19] Approximately 60% to 80% of the eyelashes are in the anagen phase.

Several growth factors are involved with hair follicle growth and cycling. Androgens are the principal hormones that control sexual hair growth by receptors localized in the dermal papilla,[20] but eyelashes seem not to be sensitive.[21] Retinoic acid derivatives affect the hair growth cycle in mice by increasing the length of the anagen phase, and insulin-like growth factor-I slows the hair cycle entry in the catagen phase; growth hormone, insulin, glycocorticoids, and prolactin are also implicated, but there is no evidence to support an involvement of these hormones in eyelash growth.[19]

Excessive growth of eyelashes (trichomegaly) has been reported in some congenital and acquired conditions. Familial trichomegaly was described recently.[22] Rare cases of congenital trichomegaly with pigmentary degeneration of the retina and growth retardation were described (Oliver-McFarlane syndrome).[23] Acquired lengthening of the eyelashes is 1 of the cutaneous manifestation of HIV infection. It has been reported in adults and pediatric patients.[24–26] Possible mechanisms have been suggested: a direct action of some viral proteins to epidermal keratinocytes and pilosebaceous structures,[24] high serum levels of interferon,[25] and, in some cases, zidovudine therapy.[27] An unexplained lengthening of eyelashes has been reported in a 20-year-old woman with dermatomyositis[28] and in a 14-year-old girl with systemic lupus erythematosus.[29]

Topical latanoprost, an analog of prostaglandin $F_{2\alpha}$ used to reduce the ocular pressure, has been showed to increased number, length, thickness, curvature, and pigmentation of eyelashes in a series of patients.[30,31] The ability of prostaglandin $F_{2\alpha}$ and analogues to act as a growth factor or mitogen may explain the altered growth pattern of eyelashes in these patients.[32]

Trichomegaly developed after treatment with interferon-α in patients with chronic hepatitis,[33] B-cell lymphoma,[34] chronic granulocytic leukemia,[35] and cutaneous melanoma.[36]

Four patients showed eyelash hypertrichosis after 3 to 4 months of treatment with systemic cyclosporine.[37] They had received renal allograft (2 patients) or liver allograft (1 patient) or experienced severe thrombocytopenia (1 patient). Cyclosporine may induce resting follicles to enter an active growth phase.[38] However, trichomegaly was not observed in a group of 51 renal transplant recipients who were treated with systemic cyclosporine.[39]

Eyelash lengthening was described recently in a patient who had colon cancer and was treated with cetuximab, a chimeric antibody against the epidermal growth factor receptor.[40] Epidermal growth factor receptors are located in hair follicles, and their inhibition may result in increased terminal differentiation, causing trichomegaly.

Trichomegaly was described recently in 6% of 240 patients with congenital heart disease.[41] Other causes of elongation of eyelashes have been reported[42]: porphyria; malnutrition; anorexia nervosa; hypothyroidism; pregnancy; and medications such as diazoxide, streptomycin, minoxidil, phenytoin, psoralen, and penicillamine. Lengthening of eyelashes in VKC patients has never been described

Using a digital caliper, we could assess the measurement in a wide series of patients and control subjects; we demonstrated that the measurement was reliable as resulted from the measurement be-

fore and after the removal of the eyelash in a sample of 28 subjects. The upper eyelash length in the control group was negatively correlated to the age of the subjects ($P = .01$; Fig 2); to our knowledge, this is the first report indicating such a significant correlation. These data were not observed in VKC patients ($P = .44$), suggesting that the ocular disease might impair the eyelash growth. Furthermore, the ocular signs score (mean of 2 or 3 determinations in the past 3 months) was positively correlated with the eyelash length, indicating a direct involvement of ocular inflammation.

At evaluation, 63% of patients were being treated with 1% or 2% cyclosporine eyedrops; a possible role of this drug in the lengthening of the eyelashes has occasionally been reported in patients who are treated with systemic cyclosporine.[40] Surprising, we found that the overall eyelash length in patients who were treated with topical cyclosporine was lower than in the nontreated patients. We speculated that the improvement in the ocular findings obtained with cyclosporine (data not shown) could induce the phase of catagen or slow the phase of anagen in VKC patients by unknown mechanisms. Among the chemical mediators that contribute to the pathogenesis of ocular inflammation in VKC, b-FGF and s-P have been shown to induce positive effects on hair growth in animal models and humans. The expression of b-FGF, as well as other growth factors, by immunostaining increased significantly in VKC epithelial cells, mast cells, and blood vessel endothelial cells when compared with control samples.[11] Recently, an induced controlled release of b-FGF affected positively the hair follicle growth of mice in different hair cycle stages.[43]

Elevated levels of s-P have been demonstrated in plasma,[12] tears, and conjunctival epithelial cells[13] of VKC patients. s-P is a neuropeptide that can act as a neurotransmitter as well as a chemical mediator; it may induce mast cell and eosinophil activation and T-cell proliferation.[12] In recent studies, s-P was demonstrated to accelerate significantly the anagen progression in murine skin organ culture[44] and to prolong human hair growth in vitro.[45] Therefore, growth factors and neuropeptides such as b-FGF and s-P could be responsible for the eyelash elongation in VKC patients.

The eyelashes seemed longer in the first years of the ocular disease ($P = .045$). However, with multivariate analysis, this finding was not confirmed, whereas the effect of the severity score and topical cyclosporine was maintained. We could not find any significant differences among tarsal, limbal, and mixed VKC forms between genders and between seasonal and perennial presentation. Similarly, IgE sensitization, serum total IgE or s-ECP levels, and PBECs did not show any correlation with the values of eyelash length.

Parents and siblings of affected individuals and control subjects were not tested. Therefore, the possibility that eyelash length has familial tendency was not evaluated. Furthermore, we performed fewer measurements in subjects who were older than 12 years, which might skew the direction of the trend line.

CONCLUSIONS

The data from this study show that VKC patients have eyelashes that are longer than age- and gender-matched control subjects. Different from control children, the eyelash length in VKC patients is independent of age, positively correlated with the degree of severity of VKC, and negatively correlated with the improvement induced by effective drugs such as topical cyclosporine. Chemical mediators of conjunctival inflammation such as growth factors and neuropeptides might be responsible for the excessive eyelash growth. Because the primary function of eyelashes is to protect the eyes from sunshine, wind, and other climatic injuries, these physical agents might have a crucial role in the etiopathogenesis of this ocular disease.

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