Perilimbal conjunctival pigmentation in Chinese patients with vernal keratoconjunctivitis

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CLINICAL STUDY

Abstract

Purpose To document the disease spectrum and evaluate the presence of perilimbal conjunctival pigmentation in Chinese patients with vernal keratoconjunctivitis (VKC).

Method A case-control study was conducted between November 2004 and July 2005. Patients aged 18 or younger with VKC and age-matched children attending our eye clinic for refractive or orthoptic problems were recruited and compared. Detailed slit-lamp examination was performed noting in particular the presence of perilimbal conjunctival pigmentation, the severity of papillary reaction, and corneal complications of VKC.

Results A total of 19 patients and 23 controls were evaluated. The presence of bilateral large tarsal or limbal papillae and epithelial defect were significantly associated with symptoms severity (Fisher's exact test, $P = 0.015$ and $P = 0.035$ respectively). All VKC patients were found to have perilimbal conjunctival pigmentation in at least one eye. There was a significant correlation in the colour and density of pigments between the two eyes (Sperman's $\rho = 0.93$, $P < 0.001$). None of the controls was found to have such perilimbal conjunctival pigmentation (Fisher's exact test, $P < 0.001$).

Conclusion The presence of perilimbal conjunctival pigmentation appears to be a consistent clinical finding in Chinese patients with VKC and may be a useful diagnostic sign for patients with subtle signs or symptoms.

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Introduction

Vernal keratoconjunctivitis (VKC) is a bilateral chronic ocular allergic disorder affecting mainly children and young adults, more commonly in persons of Asian and African origin.¹ Some of the patients have associated atopy or a family history of atopy. The disease may occur on a seasonal or perennial basis. Patients with VKC typically present with ocular itchiness, tearing, photophobia, foreign body sensation, hyperaemia, and mucous discharge. Papillary changes can be seen on the palpebral conjunctiva as well as the limbus. The hallmark feature of VKC is the presence of giant cobblestone-like papillae on the upper tarsal conjunctiva.² In severe cases, associated corneal changes such as superficial punctate keratitis, corneal erosion, epithelial defect, plaque formation and ulcers may also be present.³ In mild or atypical cases of VKC, however, clinical features may overlap with other ocular allergies such as seasonal and perennial allergic conjunctivitis and giant papillary conjunctivitis, leading to misdiagnosis of the disease, although the latter is often associated with contact lens wear or other foreign body response. Recently, a new clinical sign of VKC was reported in Indian patients suffering from this disease and was described as fine, golden brown spotty pigmentations mostly located in the perilimbal bulbar conjunctiva.⁴ A case-control study of Indian patients suffering from VKC showed that the perilimbal pigmentation was a consistent finding in VKC patients and this sign was sensitive and specific.⁵ The aim of this study was to document the presence or absence of perilimbal conjunctival pigmentation in Chinese patients and to examine the relationship between these pigments and the severity and chronicity of the disease.

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Methods

A non-interventional case-control study was carried out in Hong Kong Eye Hospital between November 2004 and July 2005. VKC was diagnosed clinically in patients presenting with symptoms of allergic conjunctivitis together with cobblestone-like papillae on the tarsal conjunctiva or limbus. Consecutive patients aged 18 years or younger attending the cornea and external eye clinic with VKC were recruited into the study after obtaining informed consent from their parents. Age-matched children attending our general ophthalmology clinic for refractive and orthoptic problems were recruited as controls. The study was performed in accordance to the declaration of Helsinki.

A detailed history was obtained from the patients noting in particular the age of onset of the disease, seasonal variation of the symptoms, personal and family history of atopy and other concomitant ocular or systemic diseases. Patients were asked to document the presence of symptoms including hyperaemia, itchiness, tearing, photophobia, and mucous discharge and to grade the severity of the condition on a three-point scale (1—mild, 2—moderate, 3—severe).

The extent and size of papillary changes on the palpebral and bulbar conjunctiva were graded using slit-lamp on a four-point scale based on the grading system by Bonini *et al* (0—no papillary reaction; 1—few papillae <0.2 mm over the tarsal conjunctiva or around the limbus; 2—papillae of 0.3–1 mm over the tarsal conjunctiva or at the limbus; 3—papillae of 1–3 mm all over the tarsal conjunctiva or for 360° around the limbus; 4—papillae >3 mm in the tarsal conjunctiva or a gelatinous appearance at the limbus covering the peripheral cornea).⁶ Corneal complications such as epithelial changes, peripheral vascularisation, plaques, and ulcers were recorded. The presence of the perilimbal conjunctival pigmentation was documented using slit-lamp photography and the colour, location and extent of the pigmentation were recorded.

All data were entered into a statistical software for analysis (SPSS v11.5, SPSS Inc., Chicago, USA). The association between patients' symptoms and clinical signs was analysed using the χ^2 test and Fisher's exact test. Correlation analysis was performed on the characteristics of the perilimbal conjunctival pigmentation between the two eyes using non-parametric Spearman rank-sum test. A *P* value of ≤ 0.05 was considered statistically significant.

Results

Nineteen children with VKC and 23 age-matched controls were recruited in the study. The mean age for

VKC patients and the controls was 11.2 and 10.7 years respectively (two-tailed *t*-test, *P* = 0.59). For the VKC group, 17 (89.5%) were boys and the mean age of disease onset was 7.5 years (range, 4–15 years).

Patients with VKC reported symptoms of itchiness (nine patients, 47.4%), mucous discharge (six patients, 31.6%), hyperaemia (five patients, 26.3%), and tearing (five patients, 26.3%). Fifteen (78.9%) patients graded their overall symptoms as mild, four (21.1%) as moderate and none as severe at the time of the study. The papillae were present in the upper lid only in 28 (73.7%) eyes and 10 (26.3%) eyes had involvement of both the upper and lower lids. In 16 (42.1%) eyes, the papillae were larger than 1 mm. There were limbal papillae in nine (23.7%) eyes, mainly found in the inter-palpebral area. Seven (18.4%) eyes had corneal epitheliopathy, two (5.3%) eyes developed corneal ulcer and three (7.9%) eyes had cornea plaque. None of these symptoms or clinical signs was present in the controls. The presence of bilateral large tarsal (grade 4) or limbal (grade 3) papillae and corneal epithelial defects were significantly associated with symptoms severity (Fisher's exact test, *P* = 0.015 and *P* = 0.035 respectively).

All 19 VKC patients had perilimbal conjunctival pigmentation in at least one eye with bilateral involvement in 16 (84.2%) patients. The pigments appeared as multiple, scattered, discrete, dot-like deposits with colour varying from faint to dark brown and were most frequently found in the interpalpebral conjunctiva (68.6%), followed by inferior bulbar conjunctiva (42.9%), superior bulbar conjunctiva (5.7%) and circumferential (2.9%) (Figure 1). There was a significant correlation in the colour density of pigments between the two eyes (Spearman's ρ = 0.93, *P* < 0.001). The density of the pigments however did not correlate with age, disease severity or the chronicity of disease. Conjunctival pigmentation was not observed in any of the control patients (Fisher's exact test, *P* < 0.001).

Discussion

The pathophysiology of VKC has not been completely clarified to-date but is believed to involve more than one form of immune mechanisms. VKC has been considered as a type I IgE-mediated immune response and this was supported by the personal or family history of atopy, and the laboratory evidence of elevated IgE titres in patients' serum and tears.⁷ However, in a case series of 195 patients with VKC, Bonini *et al*⁶ found a positive response to skin and radioallergosorbent tests in only half of the patients. This suggested that the pathogenesis is probably multifactorial with additional involvement of Th2 lymphocytes, mast cells and eosinophils.⁸ Other neural factors such as substance P and nerve growth

Figure 1 Perilimbal conjunctival pigmentation in a VKC patient.

factors may also play a role.^{9,10} With abundant melanocytes and mast cells around the limbus and complex immune mechanisms involved in VKC, we postulate that the perilimbal conjunctival pigments observed in our patients may be a by-product of these complex interactions and pathways. Growth factors or interleukins may stimulate the melanocytes in producing such pigments around the limbus. These pigments are more commonly found in the interpalpebral and inferior area of the bulbar conjunctiva around the limbus but not in the tarsal conjunctiva. Whether environmental or racial factors have a role in the distribution of the pigments remain to be solved. Immunopathological studies of specimens of these conjunctival pigments from VKC patients may provide additional information.

In our study all 19 VKC patients had perilimbal conjunctival pigmentation in at least one eye with bilateral involvement in 84.2% patients. The pigments appeared as multiple, scattered, discrete, dot-like deposits with colour varying from faint to dark-brown. The differential diagnoses of these pigments in children include severe vitamin A deficiency and chemical injury. However, these diagnoses can be easily distinguished from vernal conjunctivitis. Children with severe vitamin A deficiency may have Bitot spots as well as conjunctival pigments. In cases of chemical injury, there would be a history of trauma and other signs of chemical burn in the lids or the cornea.

Diagnosis of VKC is generally based on the signs and symptoms of the disease. In cases where the diagnosis is difficult, histopathological analysis of conjunctival scraping to demonstrate the presence of infiltrating eosinophils may be helpful.¹¹ However, this is an

invasive procedure and may be difficult to perform in very young uncooperative children. In this study, we have demonstrated that perilimbal conjunctival pigmentation is a consistent clinical sign in patients with VKC in our population. This sign may help to confirm the diagnosis of mild or early VKC cases when palpebral and limbal changes are not very characteristic.

The presence of perilimbal conjunctival pigmentations have been reported in Indian patients with VKC and they were found to occur in all grades of VKC.⁵ These perilimbal conjunctival pigmentations were present even when the disease was in remission.⁵ Our results echoed with the previous publication in the Indian population in that despite a significant correlation in the colour density of pigments between the two eyes, there was no relationship between the density of the pigments with age, severity or the chronicity of disease.

A limitation of our study is the small sample size and cross-sectional design. Further prospective studies with long-term follow-up of a larger population and different racial groups including Caucasians are warranted. It is possible that the presence of this sign may depend on the extent of pigmentation in the eyes as there is no literature on the description of such pigmentation in Caucasian patients.

In conclusion, the presence of perilimbal conjunctival pigmentation appears to be a consistent clinical finding in Chinese patients with VKC. The finding is similar to previous report in Indian patients but has not been reported in Caucasian patients. The presence of perilimbal pigments may be a useful diagnostic sign in VKC patients with early or mild disease when signs and symptoms are subtle.

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