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Vernal keratoconjunctivitis—A rare but serious comorbidity of allergic rhinitis and eustachian tube dysfunction

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ABSTRACT

Objective: To determine the prevalence of symptoms and signs of allergic rhinitis (AR) in children with vernal keratoconjunctivitis (VKC) and evaluate eustachian tube (ET) function using tympanometry.

Methods: The patients underwent an otolaryngological examination and symptoms of rhinorrhoea, nasal obstruction, nasal itching and sneezing were evaluated for the diagnosis of AR. Tympanometry was performed by a middle ear analyzer (Impedance audiometer AZ 26, Interacoustics A/S, Assens, Denmark). Blood samples were collected for determination of peripheral blood eosinophil count (PBEC) and serum total immunoglobulin E (IgE). Allergen sensitivity was also determined by skin prick test.

Results: The study included 26 males (96.3%) and 1 female (3.7%) with a mean age of 12.1 ± 4.4 years. Eight out of 27 subjects (29.6%) had blood eosinophilia and 11 out of 27 subjects had elevated serum IgE (40.7%). A positive skin prick test was identified for at least one allergen in 40% of patients (10/25 subjects). Symptoms and signs of AR were found in 10 subjects (37%). Median serum IgE level in subjects with AR (262.5 kU/L) was higher than without AR (40.2 kU/L) ($p = 0.08$), whereas there were no differences in PBEC or eosinophilia percentage ($p > 0.05$). Mean middle ear pressures in the right and left ears were -66.4 daPa (range between -268 and 4 daPa) and -57.3 daPa (range between -308 and 0 daPa), respectively. The tympanometry results were abnormal in 5 subjects (18.5%) (3 type C and 2 type B tympanogram). Three out of 10 VKC patients with AR (30%) and 2 out of 17 VKC patients without AR (11.8%) had abnormal tympanograms ($p = 0.33$).

Conclusion: AR is commonly associated with VKC and subjects with AR are almost three times more likely to have ET dysfunction than those without. Therefore, ophthalmologists should refer VKC patients to otolaryngologists to delineate associated AR and ET dysfunction. Conversely, patients with OME and/or AR who have persistent allergic eye symptoms may well benefit from ophthalmologic evaluation for seasonal allergic conjunctivitis and VKC.

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1. Introduction

Vernal keratoconjunctivitis (VKC) is a rare (occurring in less than 1%) chronic and severe allergic inflammatory disease of the eye affecting mainly young boys in their first decade of life [1–3]. Itching, photophobia, burning, and tearing are the major ocular symptoms. VKC shows a seasonal recurrency being worst over the warm spring and summer months and is more prevalent in hot and dry climates such as the Mediterranean basin, the Middle East, central and west Africa, Japan and parts of South America [4,5]. The disease may primarily involve the tarsal or limbal conjunctiva leading to different forms of VKC: limbal, tarsal or mixed (both limbal and tarsal) forms. The presence of giant papillae with a

cobblestone-like appearance in the upper tarsal conjunctiva and/or at the limbus is considered as the hallmark of the disease. VKC generally has a good prognosis; however it may be sight-threatening in the presence of corneal involvement [6].

The most common and the least severe form of ocular allergy is seasonal allergic conjunctivitis (SAC). It is mediated by type I hypersensitivity reaction that results from the exposure of the conjunctiva to an environmental allergen such as ragweed and grass pollen and the binding with specific immunoglobulin E (IgE) on the conjunctival mast cells. Allergic rhinitis (AR) is the most common form of non-infectious rhinitis and 75% of these individuals complain of allergic eye symptoms, such as ocular itching, redness, chemosis and lid edema [7,8]. The coexistence of AR and SAC, both of which are induced after allergen exposure by an IgE-mediated inflammation, has led some investigators to use the term 'allergic rhinoconjunctivitis' (ARC) [8,9]. AR is associated with eustachian tube (ET) dysfunction and middle ear disease

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[10,11]. Tympanometry is an easily accessible and non-invasive procedure that assesses middle ear disease in daily clinical practice. It is an objective test that assesses transmission and pressure system integrity in middle ear and measures auditory canal volume and ET function by introducing air under pressure [11].

VKC is more complicated compared to SAC and has a different pathophysiology than SAC. IgE-mast cell mediated process does not explain completely the severity and the clinical course of VKC and a more complicated inflammatory response mediated by T helper (Th2) lymphocytes, eosinophils, mast cells and a complex network of interleukines and cell mediators seems to play role in pathogenesis [12–16].

Patients with VKC have a family history of atopic diseases in one third to half of the cases and have a medical history of other atopic conditions including asthma, rhinitis, and eczema in one third of the subjects [2,5]. However, the association of VKC with AR diagnosed by an otolaryngologist is not well-established yet. Besides, VKC subjects with AR might also have middle ear disease and ET dysfunction. In this study, our aim was to determine the prevalence of both symptoms and signs of AR and ET dysfunction in children with VKC.

2. Methods

The study included VKC patients referred to the Cornea Unit of the Ophthalmology Department, Selcuk University, between 2007 and 2008. The study was approved by the University Review Board. All patients underwent a comprehensive eye examination. Diagnosis of VKC was based on the presence of typical clinical signs and symptoms. The disease was classified as tarsal if the patient had giant papillae >1 mm in diameter at upper tarsal conjunctiva (Fig. 1), as limbal if the patient had limbal infiltrates, papillae and Trantas dots (Fig. 2), and as mixed if the patient had both limbal and tarsal signs.

The patients then underwent an otolaryngological examination and the diagnosis of AR was made according to the clinical definition including symptoms of rhinorrhoea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or with treatment including second-generation oral or intranasal H1-antihistamines and intranasal glucocorticosteroids [17]. Tympanometry was performed by a middle ear analyzer (Impedance audiometer AZ 26, Interacoustics A/S, Assens, Denmark) and the results were analysed according to the standard criteria [18]. The tympanogram was classified as type A (normal) when the pressure in the middle ear was higher than -100 daPa, as type B when no

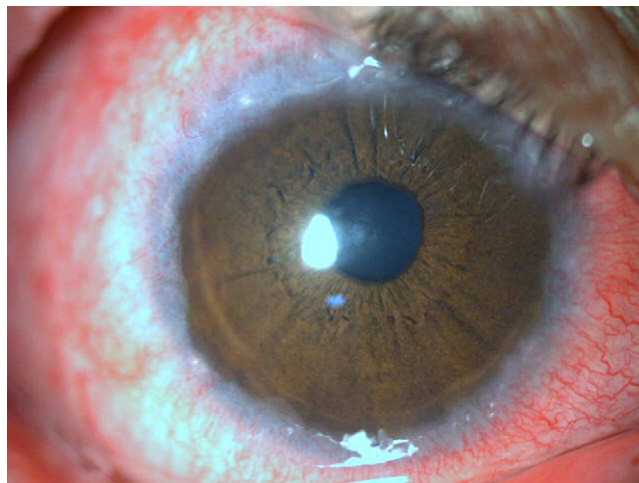


Fig. 2. Limbal papillae.

peak was detectable on the graphic, and as type C when the pressure ranged from -100 to -300 daPa. Tympanograms of type B and C were considered as abnormal.

In Pediatric Allergy and Immunology Unit, a general examination was performed and the personal and family medical history, age of onset and associated allergic diseases were recorded. Blood samples were collected for determination of peripheral blood eosinophil count (PBEC) and serum total IgE. It was considered as eosinophilia when eosinophil number was $\geq 400/\mu\text{l}$. Serum IgE levels were measured with a BN ProSpec[®] system (Dade Behring Inc, Germany) using the nephelometric method. Serum IgE levels were compared with the reference values according to age. The patients underwent epidermal skin tests (prick tests) for house dust mites (D. Farinae, D. Pteronyssinus), tree pollens, weed mix, grasses-cereal, animal hair, moulds and food allergens (egg and cacao). The allergen extracts used for prick test were obtained from Allergopharma Company (Rhenbeck, Palcentia, CA, USA). The antigens were applied to the forearm with Quicktest applicator (Panatrex, CA, USA). The positive, negative controls and allergen extracts were read 15 min after application. A skin prick test reaction was considered to be positive when the wheal diameter was ≥ 3 mm.

3. Results

The study included 26 males (96.3%) and 1 female (3.7%) with a mean age of 12.1 ± 4.4 years. Mean age of disease onset was 7.5 ± 3.1 years (within a range of 3–14 years). Seven subjects had limbal (25.9%), 12 subjects had tarsal (44.4%) and 8 subjects had mixed (29.6%) type VKC. Seventeen subjects (63%) had seasonal exacerbations and 17 subjects (63%) had a family history of allergy.

A positive skin prick test was identified for at least one allergen in 40% of patients (10/25 subjects). Seven subjects had pollen allergy, 2 had food allergy and 1 had yeast allergy. PBEC ranged between 0 and $2000/\mu\text{l}$ with a mean of $396/\mu\text{l}$ and mean serum total IgE level was found to be 179.9 kU/L (17 – 1230 kU/L). Eight out of 27 subjects (29.6%) had blood eosinophilia and 11 out of 27 subjects had elevated serum IgE (40.7%).

Symptoms and signs of AR were found in 10 subjects (37%). Median serum IgE level in subjects with AR (262.5 kU/L) was higher than without AR (40.2 kU/L); however the difference was not statistically significant ($p = 0.08$) (Table 1). There were no differences in PBEC or eosinophilia percentage between VKC subjects with or without AR ($p > 0.05$) (Table 1). Seven out of 10 VKC with AR (70%) and 10 out of 17 VKC subjects without AR

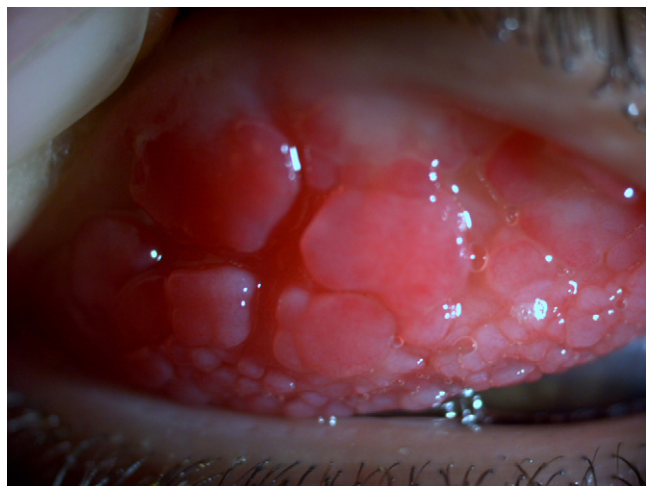


Fig. 1. Cobble stone papillae at the upper tarsus.

Table 1

Comparison of serum IgE, blood eosinophilia percentage, positive prick test results and abnormal tympanometry results between vernal keratoconjunctivitis (VKC) patients with and without allergic rhinitis.

VKC	With allergic rhinitis (n = 10)	Without allergic rhinitis (n = 17)	p-Value
Median IgE level	262.5 (20–1230)	40.2 (17–658)	0.08
Elevated serum IgE	6 (60%)	5 (29.4%)	0.2
Blood eosinophilia	4 (40%)	4 (23.5%)	0.4
Positive prick test	6 (60%)	4/15 (26.7%)	0.12
Abnormal tympanometry	3 (30%)	2 (11.8%)	0.33
Seasonal recurrence	7 (70%)	10 (58.8%)	0.7

(58.8%) had seasonal exacerbations ($p = 0.7$). AR was more common in mixed type VKC (50%), followed by tarsal (33.3%) and limbal (28.6%) type VKC ($p = 0.65$).

Mean middle ear pressures in the right and left ears were -66.4 daPa (-268 and 4 daPa) and -57.3 daPa (-308 and 0 daPa), respectively. Abnormal tympanograms were found in 5 subjects (18.5%) (3 type C and 2 type B) and 22 subjects (81.5%) had normal tympanograms. All of the VKC subjects with abnormal tympanograms had seasonal exacerbations. Three out of 10 VKC patients with AR (30%) and 2 out of 17 VKC patients without AR (11.8%) had abnormal tympanograms, but the difference was not statistically significant ($p = 0.33$) (Table 1).

4. Discussion

The incidence and prevalence of allergic conditions have increased dramatically during the past 40 years worldwide and approximately 15–20% of the world population seems to be affected by some form of allergic disease [19–21]. Allergic eye disease is a common ocular problem. The spectrum of ocular allergy is quite variable from the acute, self-limited, mild form of SAC to chronic, severe, sight-threatening VKC and atopic keratoconjunctivitis (AKC) [22]. SAC which is the most common form of ocular allergy is almost always associated with hay fever and therefore these subjects generally present both to otolaryngologists and ophthalmologists [8,9]. VKC is a more chronic and severe allergic eye disease compared to SAC and in the presence of corneal involvement may be sight-threatening. In addition to a type I hypersensitivity reaction characterised by the early and late-phase allergic responses, a type IV hypersensitivity reaction plays a pivotal role in VKC. In this study, positive skin prick test was identified for at least one allergen in 40% of patients. Approximately 30% of the subjects had blood eosinophilia and 40.7% had elevated serum IgE. These findings also support that a classical type I hypersensitivity reaction does not explain completely the pathophysiology of VKC in at least 60% of the subjects. Symptoms and signs of AR were found in 37% of the VKC subjects. AR was more common in mixed type VKC, followed by tarsal and limbal type VKC. Elevated serum total IgE levels, blood eosinophilia and prick test positivity were higher in VKC subjects with co-associated AR compared to VKC subjects without; however the differences were not statistically significant. Bonini et al. [2] showed that patients with VKC had a family history of atopic diseases in half of the cases and had a medical history of other atopic conditions including asthma (26.7%), rhinitis (20%), and eczema (9.7%). In another study by Leonardi [5], a family history for allergic diseases was found in only 35.5% of VKC cases, and a positivity for other associated allergic manifestations such as asthma, eczema and/or rhinitis was found in 37.1%.

Allergy of the upper respiratory tract is thought to be one the main factors in the etiology of ET dysfunction leading to otitis media with effusion (OME). AR may cause ET dysfunction by 3 potential mechanisms: [23] (1) dysfunction may represent a retrograde spread of edema and congestion of nasal mucosa by allergic inflammation; (2) impaired mucociliary activity may cause secretions to cover the ostium and lead to intraluminal inflamma-

tion; and (3) obstructed lumen of the ET could be the result of hypersecretion by seromucous glands. Antigens in the nasal mucosa induce release of inflammation mediators which also favors obstruction of the ET. Nasal challenge tests with an allergen have shown that ET dysfunction may occur right after exposure, within few hours, or during late-phase [24–26].

The incidence of allergy related to OME and ET dysfunction was reported to range from 5% to 80% [23]. In the study by Osur et al. [27], ET dysfunction was found in 60% of the ragweed sensitive children during natural pollen exposure and was correlated with ragweed skin test wheal size and daily patient symptom-medication scores during pollen exposure. Lazo-Saenz et al. [11] found ET dysfunction, as demonstrated by a tympanogram of C or B type, in 15.5% of subjects with AR, while none of the subjects in the control group had abnormal tympanogram. In an other study by Nguyen et al. [28] 11 of the 45 patients with OME (24%) were found to be atopic and the middle ear effusions of atopic patients had significantly higher levels of eosinophils, T lymphocytes, and interleukin-4 mRNA + cells ($p < 0.01$) compared with nonatopic patients. Hurst [29] has shown that among 89 patients with OME, all have been found to be atopic. He showed that 91% of the patients responded well to immunotherapy versus 0% of the controls, providing further evidence that OME, like AR and VKC, is also an allergic disease. Rózańska-Kudelska et al. [30] have done a study on 60 patients with AR (30 with seasonal and 30 with perennial rhinitis), and found type B tympanograms in 20% of the patients with perennial rhinitis and in 3.33% of the patients with seasonal rhinitis, whereas type C tympanograms in 20% of the patients with perennial and in 6.67% with seasonal rhinitis. OME and retraction pockets were reported to be more common in perennial AR group. However, Leo et al. [31] could not find a difference in the prevalence of abnormal tympanogram results between nonatopic and atopic subjects. Also, in the study of Yeo et al. [32], the prevalence of AR was found as 28.4% in children with OME and 24.1% in controls, which was quite similar. Abnormalities in ET function were the same in patients with AR (6.3%) and controls (3.8%) [32].

Although previous studies evaluated the association of AR in VKC subjects, none of them has yet looked at the incidence of ET dysfunction in these subjects, which makes our study unique and important in this respect. In our study, abnormal tympanograms were found in 18.5% of all VKC subjects and 30% of the VKC patients who had associated AR, which is almost three times more likely than those without. Interestingly, all VKC subjects ($n = 5$) with abnormal tympanograms had seasonal exacerbations. One of the limitations of this study was the small sample size of our study group. The other one was that we had no control group and could not compare the results with the healthy children. Therefore, more studies with larger numbers of VKC patients and healthy subjects are needed to confirm our findings.

Although SAC and PAC are very well known to be associated with AR, VKC, an example of a more complex allergic conjunctivitis, is not yet well known among the otolaryngologists. Furthermore, the association of VKC and ET dysfunction is unrecognized by either otolaryngologists or ophthalmologists. The present study is the first in which VKC subjects were evaluated

by an otolaryngologist for the association of VKC with AR and related ET dysfunction and showed a high prevalence of AR in these subjects. Therefore, ophthalmologists should refer VKC patients to otolaryngologists to delineate associated AR and ET dysfunction. Conversely, patients with OME and/or AR who have persistent “itchy eyes” may well benefit from ophthalmologic evaluation for SAC and VKC.

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