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“Vernal allergic march”

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To the Editor,

Vernal keratoconjunctivitis (VKC) is characterised by itching, photophobia, white mucous discharge, lacrimation, and foreign body sensation, especially during the hot seasons¹. Although this condition typically affects young boys and tends to resolve after puberty², it is currently unknown whether children are susceptible to develop allergic diseases after the recovery. The aim of this study was to investigate the occurrence of other allergic conditions in children recovered from VKC and possible predictive factors. Patients with a previous diagnosis of VKC, performed by an expert pediatric allergologist and confirmed by pediatric ophthalmologist, and followed at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Italy) between January 2016 and June 2018 were eligible. Patients who had not fully recovered from VKC, i.e. with Bonini's grading ≥ 4 , were or on treatment for VKC were excluded. The subjects were prospectively followed-up every 6 months for 2 years. The visits were especially focused on identifying the presence of signs or symptoms consistent with allergic rhinitis⁴, other conjunctivitis (including seasonal allergic conjunctivitis or perennial allergic conjunctivitis)⁴, and asthma⁵. Sensibilization to common inhalants was assessed by prick tests at the beginning and at the end of the follow-up period. A prick test was considered positive if the wheal diameter was ≥ 3 mm. The presence of allergic rhinitis and allergic conjunctivitis was defined according to ARIA's guideline⁴, while the presence of asthma was defined based upon clinical manifestations, spirometry values indicative of an obstructive pattern, and a pathological fractional exhaled nitric oxide (FeNO) (>25 parts per billion)⁵. Finally, the pubertal status was evaluated by the Tanner scale⁶. Information on the severity and family history of VKC was also collected. Results are presented as median and interquartile range [IQR] or absolute frequency and percentages for continuous and or categorical variables, respectively. The multiple logistic regressions for the development of allergic rhinitis and conjunctivitis and the corresponding 95% confidence intervals (CI) were performed including the following independent variables: age at recovery, gender,

familiarity for VKC (no familiarity, first grade or second grade familiarity), end of puberty at recovery, positive prick test against common inhalants at the enrolment. Patients with a previous history of allergic rhinitis or conjunctivitis were not considered in the calculations of the ORs for allergic rhinitis or conjunctivitis, respectively. A p-value <0.05 was considered significant. Missing data were managed by pairwise deletion strategy. R-statistical software 3.5.3 was used for the analyses. The study was approved by the Institutional Ethical Committee (Area 2 Milano, reference 103844). The parents signed an informed consent to participate and the patients gave their oral consent.

All the 59 eligible patients were enrolled and completed the follow-up period. Their median age at the VCK diagnosis was 8.0 [5.5 – 10.7] years and 46 (79%) were males. Median age at recovery was 14.8 [12.9 - 17.2] years. Most patients (N=50, 85%) had no familiarity for VCK, while 8 (14%) had at least one first-degree or one second-degree family member with VKC. The VKC was mild in 51 (86%) and moderate in 8 (14%) cases. A total of 14 (24%) subjects (13 males) had allergic rhinitis, conjunctivitis or asthma at the enrolment: six (10%, five males) were affected by allergic rhinitis, three (5%) males by allergic conjunctivitis, and 13 (22%, 11 males) by allergic asthma. Two (3.4%) males concurrently suffered from allergic rhinitis and asthma, three (5.0%) from allergic rhinitis and conjunctivitis, one (1.7%) male from allergic conjunctivitis and asthma. At the end of the follow-up, 52 (91%) patients presented with allergic rhinitis, conjunctivitis or asthma. Twenty-four (41%) subjects (19 males) had allergic rhinitis, 29 (49%, 23 males) conjunctivitis, and 13 (22%, 12 males) asthma. Ten (17%, 7 males) subjects developed both allergic rhinitis and conjunctivitis, one male allergic rhinitis and asthma, another male allergic conjunctivitis and asthma, and 5 males concurrently developed allergic rhinitis, conjunctivitis and asthma. At the end of the follow-up, we observed a 31% increase in allergic rhinitis cases both among males and females, a 44% increase among males and a 46% one among females for allergic conjunctivitis, and a 3% increase for allergic asthma in males (no difference was observed among females), (Table 1). Thirty-four (58%) patients presented a positive prick test at the enrolment, which increased to 47 (80%) at the end of the follow-up. The frequency of positive prick tests was similar ($p=0.5$) in females and males at baseline ($p=0.5$) and at the end of the follow-up ($p=0.46$). In males, positive prick tests increased by 36% at the end of the follow-up, while no increase was observed in females.

After model selection, prick tests positive for common inhalants at the enrolment were the only predictive factor associated with the development of allergic conjunctivitis (OR 4.8, CI 1.5-15.4) or allergic rhinitis (OR 4.1, CI 1.27 -13.4) at the end of the follow-up.

In this study, we found that approximately 90% of patients develop allergic rhinitis, conjunctivitis, or asthma within 2 years after a full recovery from VKC. An increase by >33% in cases with positive prick tests for common inhalants was also observed. Finally, positive prick tests for common inhalants at the enrolment were the only predictive factor associated with the development of further allergic conditions.

VKC is currently classified as an allergic conjunctivitis. Several studies have shown that about half of the patients affected by VKC concurrently present other allergic conditions and that the ocular symptoms of VKC worsen with exposure to sensitized allergens^{7,8,9}. Since more than 90% of our patients presented some forms of allergy within two years after the recovery, this study further supports the hypothesis of an association between VKC and allergic diseases. The prevalence of allergic rhinitis and conjunctivitis at baseline was in line with that of the general population¹⁰ while it drastically increased at the end of the follow-up. On the other hand, the prevalence of asthma at the enrolment was approximately double that one of the Italian pediatric population¹⁰, and remained stable at the end of the follow-up. Overall, these data point toward a greater susceptibility for allergic conditions in subjects affected by VKC. The risk of allergic conjunctivitis and rhinitis was associated with the presence of a positive prick test at baseline but had no association with age, gender, or pubertal status. All these findings lead us to speculate that VKC might be part of an allergic progression: a sort of "Vernal march". This assumption should be tested in larger studies with longer follow-up periods.

The study has limitations: no patient with a severe VKC was included. Immunoglobulin E were not assessed, and we did not recruit a control group.

In conclusion, this study shows that the recovery from VKC is often followed by the onset of allergic rhinitis and conjunctivitis. The relationship between VKC and other allergic diseases, however, deserves further investigations.

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References

- 1) Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, et al. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmol Scand*. 2006 Jun;84(3):406–410.
- 2) Collum LM. Vernal keratoconjunctivitis. *Acta Ophthalmol Scand Suppl*. 1999;(228):14-16.
- 3) Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 2007;7:436-41
- 4) Bousquet J, Schünemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. 2020 Jan;145(1):70-80.e3
- 5) Boulet LP, Reddel HK, Bateman E, Pedersen S, FitzGerald JM, O'Byrne PM. The Global Initiative for Asthma (GINA): 25 years later. *Eur Respir J*. 2019 Aug 29;54(2):1900598
- 6) Tanner Stages. Emmanuel M, Bokor BR. 2019 May 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–.
- 7) Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Ret Eye Res*. 2002 May;21(3):319–339.
- 8) Bonini S. Allergy and the eye. *Chem Immunol Allergy*. 2014 May;100:105-108.
- 9) Kocabeyoglu S, Bozkurt B, Bilen O, Irkeç M, Orhan M. Serum allergen specific immunoglobulin E levels in patients with allergic conjunctivitis. *Eur J Ophthalmol*. 2008 Sep-Oct;18(5):675-679.
- 10) Sestini P, De Sario M, Bugiani M, Bisanti L, Giannella G, Kaisermann D, et al. [Frequency of asthma and allergies in Italian children and adolescents: results from SIDRIA-2]. *Epidemiol Prev*. 2005 Mar-Apr;29(2 Suppl):24-31.

Table 1. Presence of allergic conditions (allergic rhinitis, conjunctivitis and asthma) and positive prick test for common inhalants allergic disease at the enrolment and at the end of the follow-up in the enrolled subjects. Data are given as absolute and relative frequency.

	At the enrollment		At the end of follow-up		Variation between enrollment and follow-up	
	<i>males</i>	<i>females</i>	<i>males</i>	<i>females</i>	<i>males</i>	<i>females</i>
N	46	13	46	13		
Prick test positive	19 (42%)	9 (69%)	36 (78%)	9 (69%)	+ 36%	0%
Allergic rhinitis	5 (10%)	1 (7%)	19 (41%)	5 (38%)	+ 31%	+ 31%
Allergic asthma	11 (24%)	2 (15%)	12 (26%)	2 (15%)	+ 2%	+ 0%
Allergic conjunctivitis	3 (6%)	0 (0%)	23 (50%)	6 (46%)	+ 44%	+ 46%
Allergic rhinitis + conjunctivitis	1 (2%)	0 (0%)	7 (15%)	3 (23%)	+ 13%	+ 23%
Allergic rhinitis + asthma	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0%	0%