

Serum levels of IL-17 in patients with vernal keratoconjunctivitis: a preliminary report

A.M. ZICARI, M. NEBBIOSO¹, A. ZICARI², E. MARI², C. CELANI, F. OCCASI, F. TUBILI, M. DUSE

Department of Pediatrics, ¹Department of Sense Organs, ²Department of Experimental Medicine Umberto I Polyclinic, School of Medicine, Sapienza University of Rome, Rome, Italy

Abstract. – BACKGROUND AND AIM: Vernal Keratoconjunctivitis (VKC) is a chronic and often severe form of bilateral tarsal and/or bulbar conjunctivitis. The purpose of the present study is to measure the Interleukin-17 (IL-17) serum levels in children with VKC evaluating the role of the systemic inflammation in patients affected by VKC.

PATIENTS AND METHODS: Fifteen patients were enrolled with VKC aged between 6 and 10 years of life. Serum were obtained from the peripheral blood samples collected from all the children included in the study to evaluate serum level of IL-17.

RESULTS: Serum levels of IL-17 were significantly higher in patients with VKC than in healthy controls (10.3 ± 9.36 pg/ml vs. 3.3 ± 6.20 pg/ml respectively; $p < 0.04$).

CONCLUSIONS: The presence of a significantly higher level of IL-17 in patients with VKC suggests a possible role of this cytokine in the pathogenesis of VKC.

Further studies on larger samples of patients are warranted to confirm These findings in order to identify new possible therapeutic targets.

Key Words:

Atopy, Vernal keratoconjunctivitis, Ocular inflammation, Interleukin-17 (IL-17).

Introduction

Vernal Keratoconjunctivitis (VKC) is a chronic and often severe form of bilateral tarsal and/or bulbar conjunctivitis. It is more common in children and young adults with an atopic background. VKC usually begins during the first decade of life and disappears during the second decade¹. It was first mentioned in the ophthalmic literature 150 years ago and some Authors have described the various aspects of this disease. Although the allergic nature of this entity has been accepted for a long time, its exact etiology and pathogenesis is still unclear.

Previous studies demonstrated, through the analysis of some immunological data, that the pathogenesis of VKC is much more complex

than a mere type 1 hypersensitivity reaction; so that role played by genetic and environmental factors in its onset has been hypothesized.

A prevalent local helper T-cell type 2 response with the presence of Th2 cytokines in tears and conjunctival biopsy specimens of VKC patients is given by Leonardi et al² and confirms the importance of these factors even if the factors stimulating these varied cells to increase their cytokine production were not identified.

Topical corticosteroids represent an effective treatment for VKC, but their prolonged use is often associated with important complications such as glaucoma, cataracts, and opportunistic infections. Other topical drugs such as antihistamines, inhibitors of mast cell degranulation, and nonsteroidal anti-inflammatory have been used in the treatment of the disease but their effectiveness has been demonstrated only in a few cases³. On the other hand, the administration of topical cyclosporine A (CsA) is very effective in treating moderate and severe VKC, thus, it plays an immunomodulatory effects on VKC conjunctiva leading to a reduction of inflammatory cell particularly T cells, HLA-DR+ cells and plasma cells^{4,5}.

Some studies have recently demonstrated the important role played by a specific cytokine, the Interleukine 17 (IL-17), in many autoimmune inflammatory diseases such as rheumatoid arthritis (RA), Sjogren's Syndrome (SS) and systemic lupus erythematosus (SLE). IL-17 seems to be up-regulated in patients with ocular disease (uveitis, scleritis, dry eye syndrome)⁶⁻⁸.

IL-17, mainly produced by Th-17 cells, is a pro-inflammatory cytokine and it plays a powerful effects on stromal cells, resulting in the production of inflammatory cytokines and the recruitment of leukocytes, especially neutrophils⁹. IL-17 amplifies the inflammation through the induction of tumor necrosis factor (TNF- α), Il-1 and Il-6 in epithelial, endothelial cells and others cells type such as keratinocytes, synoviocytes, fi-

broblasts and macrophages. The purpose of the present study was to measure the IL-17 serum levels in children with VKC in order to investigate the role of systemic inflammation in the pathogenesis of this disease.

Patients and Methods

Fifteen patients (10 males; 66%) with VKC aged between 6 and 10 years of life and 8 healthy children (4 males; 50%) were enrolled. In accordance with the Helsinki Declaration, all parents were informed about the use of their data and informed consent was obtained.

The diagnosis was performed by oculist with a score based on ocular signs (papillae, giant papillae, conjunctival hyperemia, and corneal infiltrates) and on subjective ocular symptoms (itching, photophobia, foreign body sensation, tearing, secretion) according to Bonini et al¹⁰. Each variable was graded as follows: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. In the score two supplemental parameters were included: the duration of symptoms (0 if < 1 years; 1 if > 1 years and 2 if > 2 years) and the worsening of symptoms in spring and summer (0 if not present; 1 if present). Children with a total score ≥ 7 were included in the study.

Each patient performed a skin prick test (SPT) to common airborne and food allergens (Lofarma, Milan, Italy): *Dermatophagoides pteronissynus* (Der P), *Dermatophagoides farina* (Der F), dog/cat dander, *Olea europea*, *Lolium perenne*, *Alternaria tenuis*, *Parietaria officinalis*, lactalbumin, β -lactoglobulin, casein, egg white and yolk, soy, codfish. A wheal of 3 mm after 15-20 min was considered as positive.

Serum were obtained from the peripheral blood samples collected from all the children included in the study to evaluate serum level of IL-17.

The serum levels of IL-17 were measured by the ELISA method according to the Manufacturer's instructions (IBL International GMBH; Hamburg, Germany).

Results

In our sample, 10 children with VKC were atopic (66.6%). Moreover, the most important allergens were house dust mites and grasses (53.3% and 26% respectively).

Concerning ocular symptoms, itching and photophobia were more often severe (grade 3) (33.3% and 26,7% respectively) when compared with other symptoms such as secretion or tearing (20%) and conjunctival hyperemia (20%).

All the children affected by VKC showed an exacerbation of symptoms during spring and summer.

Serum levels of IL-17 were significantly higher in patients with VKC than in healthy controls (10.3 ± 9.36 pg/ml vs 3.3 ± 6.20 pg/ml respectively; $p < 0.04$) (Figure 1).

The IL-17 levels did not show a significant correlation with patient age, sex or atopy.

Discussion

According to our knowledge, this is the first study investigating IL-17 levels in patients affected by VKC. Our findings showed that serum levels of IL-17 were higher in children with VKC than in healthy controls.

Several mechanisms were proposed to better understand the pathogenesis of ocular inflammation in VKC but its etiology remains still unclear.

The findings of inflammatory cells and other inflammatory mediators in the conjunctiva of patients with VKC might not be fully explained by atopy. The prevalence of atopy in our study is 66% and this finding is in line with data reported by other Authors; skin prick test positivity is not considered a typical characteristic of this ocular disease.

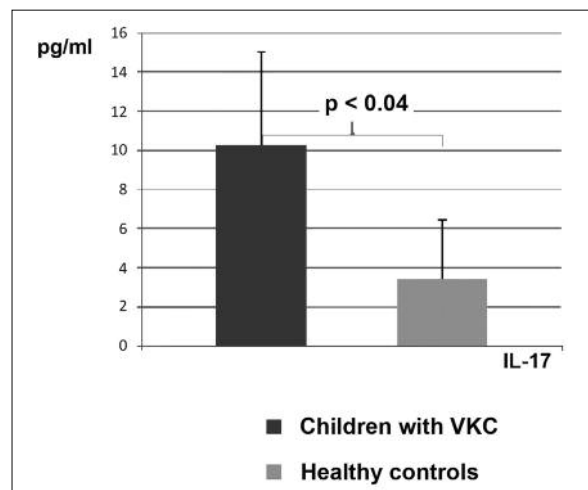


Figure 1. Serum levels of IL-17 in children affected by vernal keratoconjunctivitis (VKC) and in healthy children.

Oh et al⁹ have recently published a study on the association between dry eye syndrome and serum level of IL-17 in patients with systemic immune mediated disease and they found a correlation between serum level of IL-17 and disease severity. This cytokine seems to be involved in the chronic inflammation associated with many autoimmune diseases such as rheumatoid arthritis and SS¹¹.

Conclusions

The presence of a significantly higher level of IL-17 in patients with VKC suggests a possible role of this cytokine in the pathogenesis of VKC.

Further studies on larger samples of patients are warranted to confirm our findings in order to identify new possible therapeutic targets.

Conflict of Interest

None declared.

References

- 1) BONINI S, BONINI S, LAMBIASE A, MARCHI S, PASQUALETTI P, ZUCCARO O, RAMA P, MAGRINI L, JUHAS T, BUCCI MG. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophtalmology* 2000; 107: 1157-1163.
- 2) LEONARDI A, DEFANCHIS G, ZANCANARO F, CRIVELLARI G, DE PAOLI M, PLEBANI M, SECCHI AG. Identification of local Th2 and Th0 lymphocytes in vernal conjunctivitis by cytokine flow cytometry. *Invest Ophthalmol Vis Sci* 1999; 40: 3036-3040.
- 3) AVUNDUK AM, AVUNDUK MC, KAPICIOGLU Z, AKYOL N, TAVLI L. Mechanism and comparison of anti-allergic efficacy of topical lodoxamide and cromolyn sodium treatment in vernal keratoconjunctivitis. *Ophthalmology* 2000; 107: 1333-1337.
- 4) TESSE R, SPADAVECCHIA L, FANELLI P, RIZZO G, PROCOLI U, BRUNETTI L, CARDINALE F, MINIELLO VL, BELLIZZI M, ARMENIO L. Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children. *Pediatr Allergy Immunol* 2012; 21: 330-335.
- 5) EL-ASRAR AMA, TABBARA KF, GEBOKS K, MISSOTTEN L, DESMET V. An immunohistochemical study of topical cyclosporine in vernal keratoconjunctivitis. *Ocul Immunol Inflamm* 1994; 2(Suppl): S17-S39.
- 6) NEBBIOSO M, BELCARO G, KOMAIHA C, CELANI C, PESCOSOLIDO N. Keratoconjunctivitis by confocal microscopy after topical cyclosporine. *Panminerva Med* 2012 nov. 5; [Epub Ahead of print].
- 7) PESCOSOLIDO N, KOMAIHA C, DAPOTO L, LENARDUZZI F, NEBBIOSO M. Corneal haze in course of Fuchs' Endothelial Dystrophy. *Clin Ter* 2012; 163: e169-171.
- 8) AMADI-Obi A, YU CR, LIU X, MAHDI RM, CLARKE GL, NUSSENBLATT RB, GERY I, LEE YS, EGWUAGU CE. TH17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. *Nat Med* 2007; 13: 711-718.
- 9) OH JY, KIM MK, CHOI HJ, KO JH, KANG EJ, LEE HJ, WEE WR, LEE JH. Investigating the relationship between serum interleukin-17 levels and systemic immune-mediated disease in patients with dry eye syndrome. *Korean J Ophthalmol* 2011; 25: 73-76.
- 10) BONINI S, SACCHETTI M, MANTELLI F, LAMBIASE A. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 2007; 7: 436-441.
- 11) KIM J, KANG S, KIM J, KWON G, KOO S. Elevated levels of T helper 17 cells are associated with disease activity in patients with rheumatoid arthritis. *Ann Lab Med* 2013; 33: 52-59.