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Vernal keratoconjunctivitis: atopy and autoimmunity

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Abstract. – BACKGROUND: Vernal Keratoconjunctivitis (VKC) is a rare chronic ocular inflammatory disease and it mainly affects boys in the first decade of life. Although it is a self-limiting disease, patients may present many phases characterized by an exacerbation of inflammatory symptoms with a consequent decline of the quality of life.

PURPOSE: define the clinical and immunological profile of patients affected by VKC and investigate their familiar history of autoimmune disorders and their autoimmunity pattern.

PATIENTS AND METHODS: 28 children were enrolled (20 males, 71%) aged between 4 and 14 years of life affected by VKC. Family history of allergic and immunological diseases was collected for each patient. In particular, it was asked whether some components of their families were affected by Hashimoto's thyroiditis, type I diabetes, psoriasis or rheumatoid arthritis and Systemic Lupus Erythematosus (SLE). All VKC children underwent a serological evaluation of antinuclear antibodies (ANA).

RESULTS: A family history of immunological disorders was found in 46% of patients, 28% of Hashimoto's thyroiditis, 14% of type I diabetes, 14% of psoriasis, and 1 of Systemic Lupus Erythematosus. Furthermore, 35% of patients was ANA positive and they corresponded to patients with a higher ocular score and with the most important clinical symptoms.

CONCLUSIONS: the detection of ANA positivity and of a familiar history of autoimmune disorders in a high percentage of children with VKC may help us to better understand the association of this ocular inflammatory disease with systemic autoimmune disorders and atopic condition.

Key Words:
Anti-nuclear antibodies (ANA), Atopy, Autoimmunity, Vernal keratoconjunctivitis.

Introduction

Vernal Keratoconjunctivitis (VKC) is a rare (< 1:10.000) chronic, bilateral disease characterized by an inflammation of the ocular surface occurring mainly in children and young male adults and tending to regress in puberty[1-3].

Although its prevalence is higher especially in dry and hot climates (Mediterranean areas, Central and West Africa and South America), VKC has a wide geographical distribution. It is characterized by conjunctival hyperemia, itching and tearing. Moreover, photophobia is an important feature of VKC and may have different degrees of severity. Symptoms are usually more severe during spring and summer. Although it is a self-limiting disease, patients may present many phases characterized by an exacerbation of inflammatory symptoms with a consequent decline of the quality of life and with a risk of permanent corneal damages. There are three forms of VKC: the tarsal form with giant papillae on the tarsal conjunctiva, the limbar form with Horner-Trantas dots, and the mixed phenotype with intermediate characteristics. The diagnosis is based on the classical symptoms of conjunctivitis (hyperemia, itching and tearing), and on some specific ocular signs such as cobblestone papillae, visible with the eversion of the upper lid, and the presence of Trantas dots, in the limbus. Finally, the corneal involvement is associated with more severe disease[4].

Even though atopy is common among VKC patients, only 50% of patients with VKC has positive Skin Prick Test and/or elevated allergen-specific antibodies[5-6].

The immunopathogenesis of VKC is multifactorial involving a Th2 mediated mechanism with an overexpression of cytokines, growth factors, eosinophil's and eosinophilic proteins. However, the isolated TH2 response might not be considered sufficient to completely understand the pathogenesis of this ocular disease[7-9].

VKC is still considered a diagnosis of exclusion even though a discriminant factor to identify patients might be the lack of response to both systemic and local antihistaminic therapy togeth-

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er with the prolonged use of steroidal eye drops.

The clinical efficacy of cyclosporine (cyclosporine 1% eye drops) highlights a possible correlation between the ocular manifestations and the immune system, as hypotized[10-12]. Therefore, the collection of familiar histories of both atopy and immunological disorders might be important for a comprehensive assessment of patients with VKC[13-14].

Despite VKC resolves spontaneously during the pubertal development, it requires a prompt and appropriate therapy not only to improve the quality of patients life, but even to avoid the risk of corneal degeneration and visual impairment.

The aim of the present study is to better define the clinical and immunological profile of patients affected by VKC and to investigate their family history of immunological disorders and their autoimmunity pattern.

Patients and Methods

The Study was performed in Rome, at the Department of Pediatric Immunology and Allergology of the Umberto I Hospital, "Sapienza University of Rome", and was approved by the local Ethics Committee. In accordance with the Helsinki Declaration, all parents were informed about the use of their data and informed consent was obtained.

We enrolled 28 children (20 males, 71%) aged between 4 and 14 years of life, affected by VKC. The diagnosis was made by an ophthalmologist evaluating all the objective signs of ocular disease with a severity score from 1 to 3 for each typical clinical feature[15-17].

Family history of allergic diseases (dermatitis, rhinoconjunctivitis, and asthma) and immunological diseases was collected for each patient. In particular we asked whether some components of their families were affected by Hashimoto's thyroiditis, type I Diabetes, Psoriasis or Rheumatoid Arthritis and Systemic Lupus Erythematosus (SLE).

All VKC children underwent a clinical examination and a serological evaluation with a complete blood count, total IgE, IgA, IgM, IgG, VES, PCR and anti-nuclear antibodies (ANA).

Moreover, each patient performed Skin Prick Test (SPT) for the commonest inhaled and food allergens (Dust Mites, Alternaria, Parietaria, Grass and Olive pollens, dog and cat epithelium, pine, birch, platanus and cypress, cow's milk proteins, yolk, albumen, fish, wheat and soy). A positive SPT result was defined as the presence of a wheal ≥ 3 mm than the wheal size of control (saline solution).

Statistical Analysis

Descriptive statistics were performed expressing continuous data as means with standard deviations while categorical data were expressed by frequencies and percentages. Comparisons were evaluated using a *t*-test, a chi-square test or a McNemar's test. A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Statistical Package of Social Sciences, Chicago, IL, USA) software version 19.

Results

Among the 28 patients with a diagnosis of VKC, we found a higher prevalence of VKC in males than female (71% vs 29%) in line with data reported in literature. Patients were more often affected by the tarsal form of VKC (71% tarsal vs. 29% mixed) while no child was affected by the limbar form. Moreover, 46% (13) of patients had positive skin prick test for airborne allergens and corresponding high levels of serum IgE. Nineteen patients (67%) had a family history of allergic diseases (mainly rhinitis).

Concerning the immunological disorders, only 1 patient was affected by type I diabetes while 13 patients (46%) reported a family history of autoimmune diseases, 8 (28%) of Hashimoto's thyroiditis, 4 (14%) of type I diabetes, 4 (14%) of psoriasis and 1 of Systemic Lupus Erythematosus (Figure 1A). Furthermore, we found that 10 patients (35%) were ANA positive and they corresponded to children with a higher ocular score and with the most important clinical symptoms. On the other hand, only 2 patients with a family history of immune disorders showed an ANA positive pattern. After topical cyclosporine, only 4 patients (14.3%) were still ANA positive. Moreover, among the 10 children with a positive ANA pattern before treatment, there was an ANA negativisation in a significant percentage of children (6 patients; 60%; $p < 0.03$) (Figure 1B).

Discussion

Although VKC has been always regarded as an IgE-mediated disease, many Authors reported

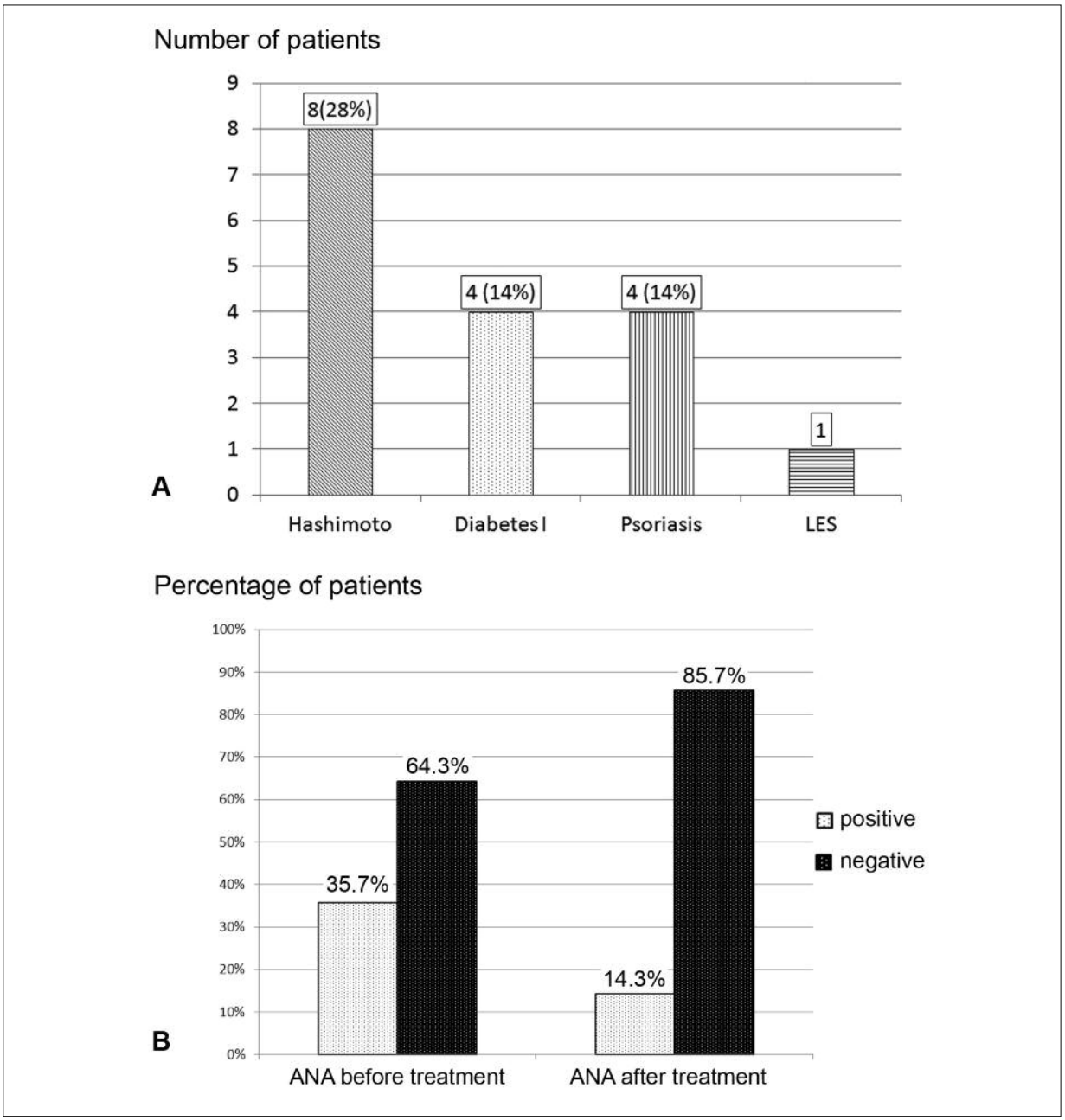

Figure 1. A, Family history of immunological disorders in our sample of children affected by vernal keratoconjunctivitis (VKC). ***B,*** Percentages of children with positive and negative anti-nuclear antibodies. (ANA) pattern before and after treatment.

that only 50% of patients has a positive SPT or high levels of serum IgE. The role of Th2 responses in VKC has been studied for a long time and VKC is actually not regarded just as an ocular disease but as a systemic disease with a T-cell activated response[18-21].

Atopy may not be sufficient to completely understand the pathogenesis of this ocular disease. Notably, two groups of patients with VKC were distinguished for their serum IgE levels: those with normal levels had often a negative history of other types of atopy, and those with elevated levels had often an associated atopic disease[22].

The existence of an immunological deregulation, even in non-atopic patients, might be hypothesized and it might promote the onset and the persistence of the ocular inflammation.

Our findings showed a family history of autoimmune disorders in a large number of patients. Moreover, 35% of patients showed ANA positivity and, many of these, had a high degree of VKC severity. Although ANA positivity is an unspecific parameter[23], its presence in a high proportion of patients might reflect a possible systemic involvement in the pathogenesis of VKC.

VKC was previously regarded as a typical allergic disease. Nowadays, a role of the innate immunity in the ocular allergic inflammation has been proposed and epithelial cells, dendritic cells, natural killer lymphocytes, and mast cells might play a regulatory role in allergy[24].

Recently, many Authors suggested the existence of a cooperation between the allergic (Th2 mediated) and the inflammatory (Th1 mediated) responses[25-27]. This cooperation could explain the lack of efficacy of the antihistaminic therapy which might be sufficient to inhibit the allergic reaction (Th2), but not the inflammatory response (Th1).

Despite the etiology of the VKC is not yet fully known, the detection of ANA positivity in a high percentage of patients in association to the efficacy of topical immunosuppressive therapy may justify the hypothesis of an association with autoimmune disorders. The eye has always been regarded as a "sanctuary" of our organism with its specific pathologies. The topic immunosuppressive therapy may control the ocular inflammatory reactions without influencing the systemic blood parameters, as confirmed by the assessment of negative serum levels of cyclosporine. In our sample, however, the ANA negativisation after topic cyclosporine in a significant percentage of children lead us to hypothesize the possible presence of specific but yet unknown inflammatory signals, leading from the eye to a systemic immunological reaction. Furthermore it should be pointed out that autoantibodies positivity in normal children represents often a transient phenomenon[23].

Further studies on a larger cohort of children are warranted to investigate the role of immune auto-reactivity and of other autoimmune diseases frequently found out in patients affected by VKC.

Conclusions

The present study underlines the importance of recognizing patients with certain anamnestic, clinical and serum characteristics, to set an appropriate therapeutic management and a careful follow up.

Conflict of Interest

None to declare.

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