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ORIGINAL ARTICLE

Autoimmunity and its association with regulatory T cells and B cell subsets in patients with common variable immunodeficiency

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KEYWORDS
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Abstract
Background: Common variable immunodeficiency (CVID) is one of the most prevalent symptomatic primary immunodeficiencies (PIDs), which manifests a wide clinical variability such as autoimmunity, as well as T cell and B cell abnormalities.
Methods: A total of 72 patients with CVID were enrolled in this study. Patients were evaluated for clinical manifestations and classified according to the presence or absence of autoimmune disease. We measured regulatory T cells (Tregs) and B-cell subsets using flow cytometry, as well as specific antibody response (SAR) to pneumococcal vaccine, autoantibodies and anti-IgA in patients.

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Results: Twenty-nine patients (40.3%) have shown at least one autoimmune manifestation. Autoimmune cytopenias and autoimmune gastrointestinal diseases were the most common. A significant association was detected between autoimmunity and presence of hepatomegaly and splenomegaly. Among CVID patients, 38.5% and 79.3% presented a defect in Tregs and switched memory B-cells, respectively, whereas 69.0% presented CD21^{low} B cell expansion. Among patients with a defect in Treg, switched memory and CD21^{low} B cell, the frequency of autoimmunity was 80.0%, 52.2% and 55.0%, respectively. A negative correlation was observed between the frequency of Tregs and CD21^{low} B cell population. 82.2% of patients had a defective SAR which was associated with the lack of autoantibodies.
Conclusions: Autoimmunity may be the first clinical manifestation of CVID, thus routine screening of immunoglobulins is suggested for patients with autoimmunity. Lack of SAR in CVID is associated with the lack of specific autoantibodies in patients with autoimmunity. It is suggested that physicians use alternative diagnostic procedures.

Introduction

Common variable immunodeficiency (CVID) is the most frequently encountered symptomatic primary immunodeficiency (PID), known by highly heterogeneous clinical presentations and immunological features.[1] The affected patients are characterised by increased susceptibility to recurrent infections, along with low levels of serum immunoglobulin (Ig), as well as reduced specific antibody response to protein and polysaccharide antigens.[2] Patients may also have a wide variety of non-infectious complications, including enteropathy, lymphoproliferative disorders, malignancy, and autoimmune diseases.[3]

The association of CVID and autoimmunity is well recognised in several studies.[4,5] It is proposed that 20–40% of CVID patients have autoimmune complications[6,7] which are poorly understood and in some cases are difficult to manage.[1,8] The most common autoimmune disorder observed in CVID is autoimmune cytopenia including idiopathic thrombocytopenic purpura (ITP) and autoimmune haemolytic anaemia (AIHA), but autoimmune enteropathies and autoimmune rheumatological and dermatological disorders have also been reported.[4,6,7,9,10] Defects in the frequency and function of B- and T-cell subsets, especially regulatory T cells (Tregs), have been described in CVID patients with autoimmunity.[11,12]

The aim of this study was to assess the prevalence of autoimmune manifestations in patients with CVID and to evaluate the probable associations between autoimmunity and other clinical and immunological features in these patients.

Patients and methods

Study design and patients

Among all registered patients in the national registry of PID patients,[13,14] a total of 72 patients with CVID who were diagnosed and treated at the Children's Medical Center affiliated to Tehran University of Medical Sciences agreed to participate in this study. The diagnosis was made according to standard criteria,[15,16] which included a reduction of at least two serum immunoglobulin (Ig) isotypes (IgG, IgA, and IgM) by two SDs from normal mean values for age where no other cause can be identified for the immune defect. We excluded patients under four years of age to rule out a probable diagnosis of transient hypogammaglobulinaemia of infancy. The study was performed in 2015–2016 and approved by the ethics committee of Tehran University of Medical Sciences (ref: 94-01-159-28966 and 94-02-154-29492). Informed consent was obtained from patients or their parents.

Methods

A detailed questionnaire was completed by interview for all patients to record demographic data, clinical and laboratory data, past medical history of documented autoimmunity, recurrent and chronic infections, and other complications. At diagnosis, serum levels of IgG, IgA, IgM, IgE and specific antibody responses against diphtheria and tetanus toxoids and pneumococcal polysaccharide vaccine as well as lymphocyte subsets were measured using standard immunological methods.

We also evaluated a number of parameters and cell types which were involved in the pathogenesis or diagnosis of autoimmunity in our study. The absolute count and percentage of Tregs and B cell subsets (including naive, marginal zone-like, switched memory, transitional and CD21^{low} B cells) were assessed using flow cytometry analysis as previously described by Arandi et al.[17,18] and Yazdani et al.[19] IgG anti-IgA antibody levels were measured by the enzyme-linked immunosorbent assay method as previously described.[20] The diagnosis of autoimmunity was based on clinical and complementary paraclinical findings such as endoscopy, colonoscopy and biopsy results, laboratory tests [complete blood count (CBC), direct coombs test, antinuclear antibody profile (ANA profile), fluorescent

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