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ORIGINAL ARTICLE

Phenotyping and follow up of forty-seven Iranian patients with common variable immunodeficiency

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Abstract
Background: Common variable immune deficiency (CVID) is a heterogeneous syndrome with a wide variety of signs and symptoms. This study describes the phenotyping and survival of the CVID patients in the allergy and clinical immunology department of Rasol-E-Akram Hospital of Iran University of Medical Sciences in Tehran.
Method: We retrospectively reviewed hospital files of CVID patients in our department until January 2014. All patients were diagnosed with standard diagnostic criteria of CVID, treated and visited monthly, during the follow-up period. We divided the patients into four phenotypes; infection only, cytopenia, polyclonal lymphocytic infiltration and unexplained enteropathy. The immunologic, demographic and clinical findings in different phenotypes were analysed.
Results: The study included 47 CVID patients with mean age at onset of symptoms and diagnosis of 11.2 and 20.2 years, respectively. Phenotyping of our patients was: only infection (62%), cytopenia (26%) and PLI (19%) and 94% of cases had only one phenotype. We did not find a significant relation between the clinical phenotypes and immunologic or demographic data.

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Rate of parental consanguinity in our cases was 47%. Parental consanguinity was related to lower age at onset, lower age at diagnosis and higher baseline IgG levels. Patients with malignancy and autoimmunity had significantly higher age at onset. Our patients were followed-up for 6.9 years and the mortality rate during this time was 6%.
Conclusions: Parental consanguinity and age at onset of CVID symptoms may have important roles in CVID manifestations.

Introduction

Common variable immune deficiency (CVID) is a heterogeneous syndrome characterised by hypogammaglobulinaemia, recurrent infections, immune dysregularity and propensity to malignancies.[1–6] The first case of CVID was reported in 1953 by Janeway C.A.[7] Today it is the most common symptomatic primary immune deficiency and its prevalence is 1 in 25,000 to 50,000 in general populations.[8,9] The most common infectious manifestations of CVID are sinopulmonary and gastrointestinal infections.[8,9] On the other hand more than 25% of CVID patients have autoimmune or auto-inflammatory complications.[3,10,11] The only available treatment for CVID is intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) and appropriate management of its complications.[12,13] The mortality rate for CVID patients has been estimated to be 6% in 11.5 years and 20% in about four decades in western countries.[3,9] The purpose of this study is to classify a group of Iranian CVID patients according to the clinical phenotypes defined by Chapel et al. for European patients,[14] and to determine the relationship between these phenotypes and morbidity, mortality, complications, age at onset of the disease and parental consanguinity.

Methods

The Allergy and Clinical Immunology department of Rasol E Akram Hospital of Iran University of Medical sciences, Tehran, Iran is a referral department for primary immune deficient patients of all ages. We retrospectively reviewed hospital files of the immunology clinic of this department until January 2014 and found 47 CVID patients who were diagnosed according to PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiency) diagnostic criteria.[15,16] Patients are diagnosed as CVID when at least four years old, to exclude transient hypogammaglobulinaemia of infancy. Genetic testing to exclude autosomal recessive and X-linked agammaglobulinaemia and hyper IgM syndromes was done as a part of genetic consultation with the Research Center for Immunodeficiencies in the Children's Medical Center of Tehran University of Medical Sciences; cases with known monogenic defect were excluded from the cohort. These patients are being visited at least monthly and treated with IVIG and antibiotics as needed. According to their Clinical and paraclinical data and based on criteria described by Chapel et al.,[14,17] we divided the patients into four phenotypes including; infection only (with no complication other than infections); cytopenia (thrombocytopenia, autoimmune haemolytic anaemia or neutropenia); polyclonal lymphocytic infiltration (granuloma, persistent unexplained lymphadenopathy or lymphoid interstitial pneumonitis (LIP); and unexplained enteropathy (enteropathy insensitive to gluten withdrawal). Information on overlapping phenotypes was also recorded.

Statistical analysis was carried out using STATA 10 software. Quantitative data were reported as mean and range and descriptive variables as proportion. *T*-test and analysis of variances (ANOVA) were used to compare means and chi-square test was used to compare proportions. *P*-values less than 0.05 were considered as significant.

Results

Characteristics of patients

Our study included 47 CVID patients with a mean age of 27 years (range: 4–63) and mean follow-up time of 6.8 years (range: 0.5–23). The mean age of onset of CVID symptoms was 11.2 years (range: 1–32). Table 1 includes demographic and immunologic data, phenotypes and complications of the patients. Phenotyping of our patients was: only infection (62%), cytopenia (26%) and PLI (19%) with no case in the unexplained enteropathy group. 94% of our cases had only one phenotype. We compared immunologic and demographic data between the patients with the infection only phenotype and other phenotypes all together and found no significant difference, except the rate of splenomegaly which was significantly lower in the infection only phenotype (10% vs. 71% *P* value = 0.00001). In 85% of patients the first sign of immunodeficiency was infections, while autoimmune or auto-inflammatory manifestations were the first sign in the other 15%. Sino pulmonary infections were the most common infection of our CVID patients (98%) (Table 2). Twenty patients (43%) complained from chronic/recurrent diarrhoea; among them, eight cases were diagnosed to have inflammatory bowel disease (IBD), five had recurrent bacterial gastroenteritis, two had cytomegalovirus enterocolitis, one had chronic resistant giardiasis, while in four patients, recurrent diarrhoea without endoscopic and pathologic signs of IBD or enteropathy persists with no identifiable germ that responds partially to antibiotic therapy.

Four patients with a mean age at onset of 17 years had history of chronic wart; among them two had IBD, one had recurrent diarrhoea and none of them had neutropenia. Three patients with a mean age at onset of nine years and no lymphopenia had history of oral thrush; among them one