Human Immunology 77 (2016) 7–11

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

The prevalence of Selective Immunoglobulin M Deficiency (SIgMD) in Iranian volunteer blood donors

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ARTICLE INFO

Article history:
Received 2 October 2013
Revised 7 May 2014
Accepted 27 September 2015
Available online 30 September 2015

Keywords:
Immunodeficiency
Selective IgM deficiency
Iranian healthy donors
Prevalence

ABSTRACT

Background: Selective Immunoglobulin M Deficiency (SIgMD) is known as a rare primary immunodeficiency characterized by an isolated deficiency of serum IgM. Other immunoglobulin levels and T-cell immunity are usually normal; although IgE may be elevated. SIgMD can be asymptomatic or with various bacterial and viral infections. It can also be associated with autoimmune diseases or malignancies. In the present study, we report for the first time, the prevalence of SIgMD in Iranian healthy adult population.
Materials and Methods: A total of 3436 healthy donors were examined in the study; from August, 2006 to April, 2008. Serum IgM concentration was measured using the nephelometric method. We considered serum IgM less than 30 mg/dl as IgM deficiency.
Results: Among 3436 participants, 65% were male and 34% were female; aging from 17 to 72 years (38.18 ± 10.78). Thirteen individuals were detected as IgM deficient subjects with the male to female ratio of 11/2, the prevalence of 0.37% and the frequency of 1/265. The mean serum IgM level was 24 ± 4.56 (16–29 mg/dl) in these cases. Among 13 IgM-deficient subjects, 7 cases were available for evaluating the clinical manifestations. In addition to atopic dermatitis which was the most common symptom in these patients, others were allergic rhinitis, food allergy, urinary tract infection and skin fungal infection. Two patients had no history of infectious disease or atopic conditions.
Conclusion: In the present study we could determine the prevalence of SIgMD in our adult population (0.37%). The most common comorbid condition was atopy. Neither severe or life-threatening infections, nor autoimmune diseases (based on their history; the antibody screening was not performed as part of this study) or malignancies were found in these patients. Further evaluation is recommended to elucidate the prevalence of SIgMD among patients with recurrent infections.

1. Introduction

IgM is the first immunoglobulin to be produced in humans and is the first antibody formed after new antigen exposure [1,2]. Selective IgM deficiency is an isolated absence or profound deficiency of serum IgM while the other immunoglobulin levels and/or T-cell immunity are usually normal [3,4]; although IgE level may be elevated [1].

It's known as a rare primary immunodeficiency [4]. There is not an exact definition for the level of IgM that is necessary for diagnosis and selective IgM deficiency is characterized as a low level of serum IgM (less than 2SD from the mean or less than 10% of the mean for age). So IgM levels less than 10–15 mg/dl in infants and children and less than 20–30 mg/dl in adults can be used as a diagnostic guideline [3]. Levels of Igs may vary based on gender and race. According to a survey conducted for determining the normal ranges of immunoglobulins in Iranian healthy donors, the mean level of IgM was higher in females compared to males [5]. Also, a slightly higher penetration of SIgMD in males (1.97%) than females (1.42%) has been obtained [6].

SIgMD seems unlikely to be an uncommon disorder, regarding the prevalence of 0.03% in a community-based study [6], 0.26% in

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http://dx.doi.org/10.1016/j.humimm.2015.09.051
0198-8859/

an adult allergy and immunology clinic [1], 0.07% in an allergy and immunology clinic and 1.6% in an unselected community health screening [7]. In addition, there are some reports presenting the prevalence of 1% [8], 3% [9], 3.8% [10] and 6% [11] in various studies.

The definitive etiology of selective IgM deficiency is still unclear. Various mechanisms have been reported, such as increased IgM-specific T-cell suppressor function [12,13], defect in helper T-cell function [14–16], defect in B-cell differentiation into IgM immunoglobulin secreting cells [17–19] and failure of μsmRNA (secreted mRNA) synthesis [20]. Number of B-cells with surface IgM are generally normal in peripheral blood [15,20,21]. No complement or phagocytosis deficit has been reported. Chromosomal anomalies, such as partial deletion of chromosome 18 [22], chromosome 1 deletions [23], and chromosome 22q11.2 deletion [24] have been reported in a limited number of cases.

SIgMD can be asymptomatic or with infections caused by encapsulated or gram negative microorganisms [1,7,25]. Asymptomatic cases are typically found during the investigation of other diseases (autoimmune disease or cancer), in family members of patients with immunodeficiency, or by chance. It has been suggested that with a longer follow up period many asymptomatic cases will transform into symptomatic cases [1]. Various bacterial and viral infections have been shown in symptomatic patients with SIgMD, such as upper and lower respiratory tract infections, diarrhea, skin infections, meningitis, dermatitis and in some patients, life-threatening infections and death [1,26]. SIgMD can also be associated with autoimmune diseases or malignancies [1,7,27]. It has been reported in one research that deficiency in serum IgM may increase propensity to spontaneous autoimmunity by the development of serum IgG anti-DNA antibodies [2]. These observations suggest that autoimmune diseases may be secondary manifestation of SIgMD. Patients with other primary immunodeficiency diseases also have higher incidence and prevalence of autoimmune diseases [11]. Transient SIgMD has been reported with celiac disease [1,26] and Hashimoto thyroiditis [18], as IgM levels returned to normal after treatment.

Due to the previous studies, it seems that atopy is a common manifestation in patients with SIgMD [1,26,27]. Some cases of SIgMD have been found with congenital disorders like Bloom syndrome [20], Wiskott–Aldrich syndrome and Russell–Silver syndrome [1]. In addition, it has been reported that SIgMD may progress to common variable immunodeficiency as well [28].

According to a survey previously conducted in IAARI, the normal range of serum IgM in Iranian adults was determined 39–283 mg/dl [5]. There is no comprehensive study on the prevalence of SIgMD in Iran. In the present study we investigated the prevalence of SIgMD in Iranian blood donor volunteers.

2. Materials and methods

A total of 3436 Iranian healthy adult blood donor volunteers who were referred to the Iranian blood transfusion center in Tehran were examined in the study from August 2006 to April 2008. The baseline interview elicited data on demographics, medical history, injection drug use and sexual behaviors. The selection of healthy individuals was based on a detailed medical history and normal physical examination performed by a general physician. Serological screening was done for blood-transmitted viral infections which were negative in all sera. Then blood samples were collected, their sera were separated and stored at −20 °C until analysis.

Serum IgM concentration was measured by nephelometric method (MininephTM Human IgM Kit, The Binding Site Ltd., Birmingham, UK) based on the formation of insoluble complexes between serum IgM and specific IgM antiserum. By passing light through the formed suspension a portion of scattered light is detected by a photodiode that is directly proportional to IgM concentration in sample. Also, low and high concentrations of IgM in control sera were measured to check the validity and accuracy of assay. Highly lipaemic, contaminated, turbid, or hemolysed samples were excluded due to interference with nephelometric determinations.

Based on other papers and references in this field, SIgMD is defined as IgM level less than 2SDs from the mean or less than 10% of the mean for age [1,3]. In the third reference by Stiehm and Ochs, they said that: 'IgM levels less than 10–15 mg/dl in infants and children and less than 20–30 mg/dl in adults are distinctly abnormal and can be used as diagnostic guidelines' [3]. So according to this reference, we have used IgM less than 30 mg/dl as our cut-off and we have considered adults with IgM level less than 30 mg/dl as IgM-deficient subjects.

IgM deficient samples were retested to confirm the initial results. Thereafter, thirteen SIgM-deficient patients were invited to Immunology, Asthma and Allergy Research Institute (IAARI) in Tehran to further follow-up by performing advanced immunological tests. For completing the evaluation of immune system, the following assessments were done: peripheral blood leukocyte counts and differentiation, measurement of other serum immunoglobulins by nephelometric method (The Binding Site Ltd., Birmingham, UK), Isohemagglutinin Titration using appropriate 5% red blood cell suspensions, assessment of complement levels by nephelometric method (The Binding Site Ltd., Birmingham, UK), complement function by CH50 tube test based on optical density method, flow cytometric analysis of lymphocyte subsets by monoclonal anti-human CD markers (Dako, Glostrup, Denmark) and finally phagocytic function using Nitro Blue Tetrazolium (NBT) test (Roche Diagnostics, Mannheim, Germany). A questionnaire was filled out to elicit the patients' characteristics such as age, gender, medical history, clinical manifestations, complications, treatment and family history. About the history of exposure to immunosuppressive, none of the patients mentioned long time usage of Immunosuppressive includes oral, topical or inhaled steroids; only may have taken topical or inhaled steroids temporarily in the time of disease attack. In our study, the patients have not been tested for autoantibodies and response to vaccines. Only we checked the symptoms and history of autoimmune diseases in our patients. No one had the history of autoimmune diseases or its symptoms so we didn't evaluate the laboratory data for them. SPSS 18 software was used for statistical analysis.

3. Results

Among 3436 studied Iranian healthy adult cases, 2252 voluntary blood donors were male (65%) and 1184 were female (34%). The mean (±SD) age estimated as 38.38 ± 10.23 in males and 37.81 ± 11.74 in females, aged 17–72 years (mean ± SD: 38.18 ± 10.78 years).

Of all 3436 participants, 13 IgM deficient cases (0.37%) were identified including 11 males and 2 females, aged 30–63 years. The range of serum IgM in these cases was 16–29 mg/dl (mean ± SD: 24 ± 4.56). Repeated evaluation of these cases' sera confirmed the low concentration of IgM. Other immunoglobulin levels were normal. Among all 13 invited IgM-deficient individuals only 7 cases accepted our invitation and the remaining persons were not available or did not accept our invitation. In addition to serum immunoglobulin levels, the other immunological screening tests were done for referred 7 patients in IAARI.

The most common manifestation was atopic dermatitis (patients 3–6). Others were allergic rhinitis (patients 3 & 4), food