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Mannose-binding Lectin Deficiency in Patients with a History of Recurrent Infections

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ABSTRACT

Mannose-binding lectin (MBL) is a protein of innate immune system that is involved in opsonization and complement activation. MBL deficiency is associated with predisposition to infectious diseases; however subnormal levels are also seen in healthy subjects. The aim of this study was to investigate the prevalence and clinical manifestation of MBL deficiency in patients with increased susceptibility to infection.

We studied the MBL serum concentration of 104 patients with a history of recurrent and/or severe infections referred to Immunology, Asthma and Allergy Research Institute (IAARI) in order to evaluate the primary immunodeficiency (PID). The distribution of MBL deficiency in these patients and 593 healthy subjects of previous study were analyzed.

The frequency of individuals with MBL deficiency was significantly higher in patients with recurrent and/or severe infections (13.5% [14/104]) compared with healthy subjects (4.7% [28/593]; p=0.001; OR 3.1, 95% CI 1.5-6.1). However, in 10.9% (7/64) of patients with recurrent infections without any immunodeficiency background, the MBL deficiency was detected.

On the whole, our findings indicate an association between MBL deficiency and increased susceptibility to infections.

Keywords: Deficiency; Mannose-binding lectin; Recurrent infections

INTRODUCTION

Mannose-binding lectin (MBL) is a collagen-containing C-type lectin (collectin) that plays an important role in innate immunity. A broad range of molecular patterns (e.g. mannose, N-

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acetylglucosamine, and fucose, etc) on the pathogenic surfaces (bacteria, viruses, fungi and parasites) is recognized by MBL leading to opsonization, phagocytosis and complement activation via the lectin pathway, independent of antibody.[1,2,3] Since MBL is one of the most important factors in innate immunity, its deficiency can result in recurrent infections.[4] The first description of an association of MBL deficiency and disease was a case report in 1968 in a small atopic girl with recurrent different bacterial infections in spite of antibiotic and steroid therapy. In vitro assay revealed a defect in the opsonization and phagocytosis of yeast particles that was corrected by infusion of fresh frozen plasma.[5] Subsequent studies showed an opsonic defect in MBL deficient patients.[6] The MBL genetic defect is the consequence of a multiple polymorphism in the MBL gene both in the promoter and coding regions.[6,7] MBL deficiency is defined as an undetectable MBL serum level. Individuals with homozygous variation have plasma concentrations less than 1% of normal levels, heterozygote subjects have about 10% of normal concentration.[8] MBL deficiency is considered as the most common inherited immunodeficiency in human, with a frequency of 5% (homozygote) and 30% (heterozygote).[9] MBL deficiency is associated with susceptibility to recurrent infections often in the form of upper respiratory, abscess, meningococcal disease and sepsis.[8,10] In addition, MBL deficiency is associated with non-infectious diseases including systemic lupus erythematosus, rheumatoid arthritis, cystic fibrosis and common variable immunodeficiency.[11] However, most people with subnormal levels of MBL appear to be clinically healthy.[2] So far, there has not been established any agreement on the clinical relevance or the treatment of MBL deficiency.[12]

Some of the patients referred to Immunology, Asthma and Allergy Research Institute (IAARI) with recurrent infections were remained undefined by routine workup of immunodeficiency screening tests. Measuring MBL level in these patients can be considered as a complementary workup in their diagnosis procedure. Up to now the normal level of MBL and the relation of genetic polymorphism were measured in healthy Iranian subjects in IAARI.[7,13] According to the report on Iranian normal individuals, it would be valuable to investigate the MBL deficiency in patients with recurrent infections.

The purpose of this study was to determine the prevalence and clinical manifestations of MBL deficiency in cases with the history of recurrent and/or severe infections.

MATERIALS AND METHODS

Study Subjects

The study subjects consisted of 104 patients with a history of recurrent and/or severe infections.[10] They were selected from patients referred to IAARI (Tehran University of Medical Sciences, Tehran, Iran) in order to evaluate the PID diseases between 2010 and 2014.

The exclusion criteria were patients who suffered from jaundice, hyperthyroidism and hypothyroidism[14] since these problems according to ELISA kit guide leads to disturbance measurement. This study was approved by ethical committee of IAARI. Informed consent was taken from patients or their parents.

MBL Assay

The serum concentration of MBL was determined by an enzyme-linked immunoassay according to the protocol in the kit (mannose binding lectin ELISA kit, Sanquin, Amsterdam, the Netherlands). The normal range of MBL serum levels in 4 different age groups in Iranian healthy population has been previously published.[13]

Primary Immunodeficiency (PID) Evaluation

The immunodeficiency screening tests including complete blood count with differential, CH50, IgA, IgG, IgM, IgE, NBT, Iso-Hemagglutinin titration were done on blood samples and sera of the patients. In some cases flowcytometry and other complementary tests were done if necessary.[10]

Statistical Analysis

Statistical calculations were performed with SPSS software (version 18). The X^2 test was used to compare frequencies of MBL deficiency in cases with or without primary immunodeficiency. A p value less than 0.05 was considered significant.

RESULTS

Among 104 patients with recurrent infections, there were 63 (60.6%) males and 41 (39.4%) females, median age 5 years old [(Q1, Q3)=(1.82, 9)] with a range of 1 month to 39 years. Consanguinity was seen in 44.1% of cases. The mean concentration of MBL

was 3.077 µg/mL with a range of 0 to 11.306 µg/mL. The percentage of patients with a family history of primary immunodeficiency was 7.8% and the percentage of patients with a family history of autoimmune disease was 2.9%.

The clinical manifestations of diseases in patients were different. The most common main complaints consisted of chronic diarrhea (25.6%), pneumonia (25%), upper respiratory tract infection (24%), otitis media (15.5%) and paranasal sinusitis (12.6%) which are listed in table 1 with other lower frequency symptoms.

According to the patients' history and diagnostic tests, 40 patients (38.5%) considered to have primary immunodeficiency diseases, 7 (17.5%) of them were MBL deficient who their primary immunodeficiency was defined as heterogeneous. The detailed types of PID patients are shown in table 2.

Table 1. The most common main complaints in 104 patients with recurrent infections entered the study

Infectious complaint	Percent	Infectious complaint	Percent
Chronic Diarrhea	25.6	Sepsis	3.9
Pneumonia	25	Skin rash	3.9
Upper respiratory tract infection	24	Brain abscess	2.9
Otitis media	15.5	Warts	2
Sinusitis	12.6	Failure to thrive	2
Recurrent Fever of undetermined origin	8.8	Osteomyelitis	2
Skin absces	7.9	Neutropenia	2
Oral ophtus	7.8	Aseptic arthritis	2
Meningitis	6.9	Lung abscess	1
Hepatosplenomegaly	6.9	Hepatitis	1
Lymphadenopathy	5.9	Liver abscess	1
Eczema	5.9	Septic arthritis	1
Thrombocytopenia	4.9	BCGiosis	1
Hemolytic anemia	4	Onychomycosis	1

Table 2. The number of cases in defined PID patients with/without MBL deficiency

PID type		Number of Cases	MBL	
			Normal	Abnormal
Humoral ID	Common Varriable ImmuneDeficiency IgA Deficiency X-Linked Agammaglobulinemia	17	15	2
Combined ID	Combined Immune Deficiency Severe Combined Immune Deficiency Hyper IgE Syndrome Hyper IgM Syndrome Idiopathic CD4 Deficiency	10	7	3
Phagocytic ID	Severe Congenital Neutropenia Chronic Granulomatous Disease Loop Syndrome	4	7	1
Well defined ID	Wiskott Aldrich Syndrome Chediak Higashi Syndrome	8	3	1
Complement deficiency		1	1	-
Total		**40**	**33**	**7**

Table 3. Age, sex and clinical manifestations of MBL deficient patients with no definite PID diagnosis

Case	Age Y	Sex	Clinical Manifestations
1	3	M	Recurrent non-perforating otitis media
2	39	M	Brain abscess not responding to antibiotic therapy
3	22	M	Chronic infectious pan-sinusitis
4	3.5	F	Recurrent skin abscesses, 3 times hospitalizations (omphalitis- gastroenteritis- abscess drainage)
5	6	M	Recurrent upper respiratory infections, 2 times hospitalizations (both due to pneumonia)
6	1.8	F	Recurrent hospitalizations (3 times due to pneumonia, dysentery, pseudomonas skin ulcers)
7	1	F	Severe sepsis

In 64 patients (61.5%) who had no definite primary immunodeficiency diagnosis, 7 of them (10.9%) had severe MBL deficiency (table 3).

Totally, MBL deficiency was found in 14 cases (13.5%) in which the serum level of MBL was less than 0.05 µg/mL.

The frequency of individuals with MBL deficiency was significantly higher in patients with recurrent and/or severe infections (13.5% [14/104]) compared with the results of our previous study on healthy subjects (4.7% [28/593]; p=0.001; OR 3.1, 95%CI 1.5-6.1). [13] To determine whether MBL deficiency is associated with recurrent and/or severe infections independent of concomitant immunodeficiencies, we next analyzed only patients in whom concomitant immunodeficiencies were excluded. In this subgroup of patients (n=64), the frequency of individuals with MBL deficiency was significantly higher (10.9% [7/64]) than healthy subjects (4.7% [28/593]; p=0.003; OR 3.1, 95%CI 1.4- 7.08). There were no significant differences (p=0.340) in the frequency of MBL deficiency between patients with diagnosed PID (17.5% [7/40]) and patients with history of recurrent and/or severe infections but no PID (10.9% [7/64]).

DISCUSSION

In this study, we observed a significant prevalence of MBL deficiency in patients with a history of recurrent infections, and this association persisted even in the absence of concomitant immunodeficiency.

Regarding to our results, among 64 of our patients who were not diagnosed as PID, 7 of them showed MBL deficiency with recurrent infections. Our findings agree with the previous studies indicating an association between MBL deficiency and increased susceptibility to infections without suffering from other immunodeficiencies.[15-18] However, there are still different unknown effective mechanisms in innate and/or acquired immunities.

Seven out of forty patients in our study with diagnosis of PID diseases showed severe MBL deficiency. This is in accordance with previous study that showed MBL levels are inversely correlated with the frequency of infections in patients with common variable immunodeficiency.[19] Also MBL deficiency may be found in combination with IgG2 deficiency.[1]

In present study, severe MBL deficiency was observed in different PID patients, therefore it can be occurred independent of the types of immunodeficiency disorders. This finding is one of the advantages of this study despite the limited number of patients in each group of PID patients.

The comparison of MBL level was done according to our previous study that the MBL level less than 5th percentile was considered as MBL deficiency.[13] Our results are also compatible with the other studies in which the MBL level less than 0.05 µg/mL considered as severe MBL deficiency and MBL level between 0.05 µg/mL and 1 µg/mL were considered as partial MBL deficiency.[15]

The major limitation of this study is the small number of patients who were referred to IAARI between 2010 and 2014. This affects our interpretation with regard to a direct relationship between MBL deficiency and PIDs. This may also be the reason for different clinical symptoms reported in our study.

Since the coincidence of two genetic diseases is not

impossible, the genetic tests could be helpful to find out the association between PID diseases and MBL deficiency.

Since MBL deficiency may exacerbate the diseases in immunocompromised conditions like chemotherapy[20] or transplantation[21], it is suggested to pay more attention to PID patients who are candidates for stem cell transplantation. Therefore it seems these patients need more care or even MBL substitution therapy.[11,22]

Prospective studies with larger cohorts are required to determine the effect of MBL deficiency in causing recurrent infections.

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