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ORIGINAL ARTICLE

# Lymphocyte subsets, immunoglobulin levels, complement activity CH50, and phagocytic peroxide production in 19 Iranian patients with first episode of bacterial meningitis

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## KEYWORDS

Bacterial meningitis;  
Immunodeficiency;  
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**Background:** Despite the availability of potent antimicrobial drugs, bacterial meningitis remains a serious infection with significant morbidity and mortality. In many studies, pyogenic meningitis is reported in patients with immunoglobulin (Ig) and complement deficiencies. In the present study, a broad range of immunological tests were performed to determine the relative importance of primary immunodeficiency as a predisposing cause of first episode of pyogenic meningitis without any evidence of other major infections in past medical history.

**Methods:** We studied 19 patients with bacterial meningitis confirmed by smear, culture, and cerebrospinal fluid parameters. Immunological tests were performed within 1 to 21 days of diagnosis. Twenty healthy adults served as controls. Serum Ig levels (IgA, IgG, IgM, IgE) and total hemolytic complement (CH50) as screening tests were done. Lymphocytes, neutrophils, and T-cells were enumerated. Nitroblue tetrazolium test was used for the assessment of neutrophil function.

**Results:** Thirteen patients were male and six were female. The mean age of the patients was  $27.8 \pm 19$  years (range 5–73 years). One patient had subnormal IgA levels; five patients had subnormal IgE levels; one patient had lymphopenia and low CD4, CD3, and CD19; and one patient had subnormal IgM and IgE levels with lymphopenia and low CD4, CD3, CD8, and CD19 counts. All patients had normal complement components (C3 and C4), CH50, and nitroblue tetrazolium test.

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**Conclusion:** The most common immunodeficiency in our study was Ig deficiency. Our results support the recommendation that immunological evaluation, especially Ig assay, should be used in patients with bacterial meningitis even in the first episode.

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## Introduction

Bacterial meningitis remains a very important disease worldwide. Despite the use of powerful and effective antibiotics in patients with bacterial meningitis, high mortality (up to 34%) and morbidity (up to 50%) rates are still reported.

It has been shown that cellular damage results from interplay of both pathogen and host-driven toxicity.<sup>1</sup> Both cellular and humoral responses occur in patients with meningitis. However, the exact role of host immune response is not clear. According to different studies, they may play different or contralateral roles. They may have protective roles like decreasing the titer of pathogens in the cerebrospinal fluid (CSF) and reducing the inflammatory reaction of the CSF<sup>1,2</sup> or destructive roles increasing brain edema and intracranial pressure.<sup>3</sup>

Underlying conditions include sinusitis, otitis media, epiglottitis, pneumonia, diabetes, alcoholism, splenectomy or asplenic states, head trauma with CSF leak, and immunodeficiency states, such as hypogammaglobulinemia.<sup>4,5</sup>

Immunodeficiency syndromes are characterized by unusual susceptibility to infection.<sup>6–10</sup> Bacterial meningitis is a rare presentation for acquired or congenital immunodeficiency; thus, most patients who present with bacterial meningitis do not have an identifiable deficiency of immune function.<sup>5</sup> Rarely, however, certain congenital or acquired immunodeficiencies may be first recognized by the occurrence of bacterial meningitis.

In some studies, pyogenic meningitis has been reported in patients with immunoglobulin (Ig)<sup>5,11</sup> and complement deficiencies.<sup>5,12–15</sup> Humoral immunodeficiency may play a role in predisposing patients to acute bacterial meningitis with unusual organisms, such as *Haemophilus influenzae* type F.<sup>16</sup> Meningococcal meningitis occurs in approximately 39% of persons with late complement component deficiencies and 6% of those with properdin deficiencies.<sup>4</sup>

In the present study, patients with first episode of bacterial meningitis were studied in respect to a broad range of immunological tests to determine the relative importance of primary immunodeficiency as a predisposing cause of pyogenic meningitis.

## Materials and methods

We studied 19 patients with first episode of bacterial meningitis who were admitted in different hospitals in Tehran, Iran, between 1994 and 1996. None of them had an evidence of major or recurrent infections in other organs in the past medical history. Twenty healthy adults served as controls. Diagnosis of bacterial meningitis was confirmed by positive smear, culture, or CSF parameters.<sup>4,6</sup> Patients with

known primary or secondary immunodeficiency states, those with underlying diseases (diabetes, chronic renal failure, and chronic liver disease), and those consuming corticosteroids (15 mg/day for more than 2 weeks) were excluded from the study.

Serum Ig levels (IgA, IgG, IgM, IgE), antistreptolysin O titer, isohemagglutinin test, and total hemolytic complement (CH50) were measured. Lymphocytes, neutrophils, and T cells were enumerated.

Nephelometry was used for quantization of serum Igs, IgG-subclasses, and C3 and C4 complements. The percentage of CD4+, CD8+, CD19+, and CD3+ were measured by flow cytometry (FACStar, Becton Dickinson, San Jose, CA, USA). Nitroblue tetrazolium assay was performed by slide test. Serum IgE levels were measured by quantitative enzyme-linked immunosorbent assay. The presence of Howell-Jolly bodies in the peripheral blood smear was used to assess spleen function.

Delayed-type hypersensitivity was evaluated by intradermal injection of 0.1 mL of purified protein derivative (PPD) and diphtheria-tetanus toxoids on the forearm and checked for induration 48–72 hours after injection and noted in millimeters at the greatest diameter.

## Statistical analysis

SPSS computer software version 11.5 (SPSS Inc., Chicago, IL, USA) was used for data analysis. We compared the laboratory results of our patients with age-matched normal values.<sup>7,17,18</sup> The *t* test was used for comparison of means of CD4+, CD8+, CD19+, and CD3+ counts. A *p* value less than 0.05 were considered significant.

## Ethical considerations

Oral informed consent was obtained from the patients before inclusion in the study. The study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences.

## Results

Thirteen patients were male and six were female. The mean age of the patients was  $27.8 \pm 19$  years (range 5–73 years). Immunological tests were performed within 1–21 days of diagnosis. Twenty healthy adults served as controls.

Table 1 shows the characteristics of patients with abnormal laboratory findings. In this study, six patients (31.6%) had Ig deficiency. Patient 17 had subnormal IgA levels of 40 mg/dL [age-matched normal range (AMNR) 70–312 mg/dL]. He was a 40-year-old man with bacterial meningitis because of

**Table 1** Characteristics of patients with abnormal laboratory findings and probable immunodeficiency

Patient number	Age (yr)/sex	History of meningitis	Pathogen	Abnormal laboratory findings	Probable immunodeficiency	Prognosis
4	75/M	No	NG	IgE = 0.6 IU/mL <sup>a</sup>	IgE deficiency	D
5	11/M	No	<i>N meningitidis</i>	See the footnote <sup>b</sup>	T-cell deficiency	A
6	5/F	No	<i>H influenza</i>	IgE = 0 IU/mL <sup>c</sup>	IgE deficiency	A
7	17/M	No	<i>S pneumoniae</i>	IgE = 0.9 IU/mL <sup>a</sup>	IgE deficiency	A
9	28/F	No	NG	See the footnote <sup>d</sup>	CVID	D
17	40/M	No	<i>S pneumoniae</i>	IgA = 40 mg/dL	IgA deficiency	A
18	20/M	No	<i>N meningitidis</i>	IgE = 0.1 IU/mL <sup>a</sup>	IgE deficiency	A

<sup>a</sup> AMNR = 1.5–114 IU/mL.

<sup>b</sup> Abnormal laboratory data in this patient included: lymphopenia (1,000 cells/mL) and decreased CD4 (315), CD3 (732), and CD19 (133) counts.

<sup>c</sup> AMNR = 1.1–68.9 IU/mL.

<sup>d</sup> Abnormal laboratory data in this patient included: low level of IgM, IgG, and IgE (35 mg/dL, 642 mg/dL, and 0.6 IU/mL, respectively); lymphopenia (385 cells/mL); and decreased CD4, CD3, CD8, and CD19 counts (123, 195, 65, and 34, respectively).

A = alive; AMNR = age-matched normal range; CVID = common variable immunodeficiency; D = deceased; *H influenza* = *Hemophilus influenza*; Ig = immunoglobulin; *N meningitidis* = *Neisseria meningitidis*; NG = no growth; *S pneumoniae* = *Streptococcus pneumoniae*.

*Streptococcus pneumoniae*. He was alive but did not come for follow up.

Five patients (Patients 4, 6, 7, 9, and 18) had subnormal IgE levels (Table 1). Patient 9 was a 28-year-old female. IgM, IgG, and IgE levels were 35 mg/dL (AMNR = 56–352), 642 mg/dL (AMNR = 1,158 ± 305), and 0.6 IU/mL (AMNR = 1.53–114), respectively. Other laboratory findings were lymphopenia and decreased CD4, CD3, CD8, and CD19 counts (Table 1). This patient expired because of pulmonary embolism in the end of the course of treatment.

In our study, three patients (Patients 5, 11, and 9) had decreased lymphocyte subpopulation counts. Data pertaining to Patients 5 and 9 are shown in Table 1. Patient 11 had low CD3+ (565) counts. A follow-up study performed for Patient 11 showed that after 3 months, their tests were just within normal range for age.

Mean CD4+, CD8+, CD19+, and CD3+ counts were lower in the meningitis group in comparison with the control group, but there were no significant differences between the two groups ( $p > 0.05$ ).

Mean PPD induration diameter in the case and control groups was  $2.9 \pm 2.5$  mm and  $1.5 \pm 1.4$  mm, respectively, with a statistically significant difference between the two groups ( $p = 0.004$ ). Also, mean diphtheria tetanus diameters in the case and control groups were  $2.8 \pm 2.1$  mm and  $1.1 \pm 1.9$  mm, respectively, with a statistically significant difference between the two groups ( $p = 0.04$ ).

Serum antistreptolysin O titer was in the normal range in all patients. All patients had normal complement components (C3 and C4), CH50, and nitroblue tetrazolium test. Howell-Jolly bodies were not found in the peripheral blood smear of any patients.

## Discussion

Although patients with bacterial meningitis lack adequate protective antibodies against invading pathogens, most do not have an underlying immunodeficiency. Certain comorbid conditions increase the risk of bacterial sepsis and meningitis. Certain congenital complement deficiencies,

antibody production defects, or asplenia may be identified for the first time during assessment of bacterial meningitis, particularly when it occurs in infants and young children.<sup>4,5,7</sup>

The most common immunodeficiency in our study was Ig deficiency (31.6%). In a similar study conducted in 1981 in Australia by Lorraine et al.,<sup>11</sup> a broad range of immunological tests were performed on nine children with pyogenic meningitis, two of whom had combined IgG and IgA deficiency and one had a combination of IgG deficiency and impaired neutrophil chemotaxis.

Children with IgA deficiency mainly suffer from recurrent infections, whereas adult patients mostly suffer from autoimmune diseases.<sup>5,7,19</sup> Isolated IgA deficiency may be associated with IgG-subclass deficiencies, such as IgG2 or IgG4 deficiencies.<sup>19,20</sup> Patient 17 who had IgA deficiency had no history of autoimmune diseases but we did not measure IgG subclasses in this patient.

Patient 9 could be a probable case of common variable immunodeficiency (CVID). This type of primary immunodeficiency may occur at any age from infancy to adulthood, with two peaks at age of first diagnosis, one between the ages 6–10 years, and another between 26–30 years. Some studies report that adults comprise more than two-thirds of these patients.<sup>21–23</sup> The criteria for diagnosis patients with CVID contain two or more times of Ig levels; recurrent infections; and decreased antigens, mitogens, or polysaccharide responses. However, this patient did not fulfill the criteria of CVID because she died before her Ig levels were rechecked. Also, she did not have any history of repeated sinopulmonary infections.

In the present study, four patients had selective IgE deficiency. Selective IgE deficiency is a condition in which there is severe deficiency (<5 IU/mL) or absence of serum IgE levels without other immunologic abnormalities. It is usually asymptomatic but may be associated with recurrent respiratory infections, chronic fatigue, and musculoskeletal complaints.<sup>7</sup> In contrast, the study by Lorraine et al.<sup>11</sup> showed that IgE levels were slightly raised in five patients; no allergic or parasitic basis was detected except in one patient.

Antibody deficiency with normal Ig levels is a rare antibody deficiency syndrome characterized by severe susceptibility to infection; normal or elevated Ig levels; severe deficiency of antibody response to multiple antigens, including protein antigens; and normal cellular immunity. The hallmark of this immunodeficiency is the inability to form adequate antibody response to specific antigens despite the presence of normal or increased levels of all Igs.<sup>7</sup> This type of immunodeficiency was not detected in our patients.

Although primary complement deficiencies are associated with increased susceptibility to pyogenic meningitis, they are much rarer than Ig deficiencies.<sup>11–15,24,25</sup> In the study by Lorraine et al.,<sup>11</sup> only one patient had low complement levels, which was secondary to a mild disseminated intravascular coagulation. They believed that complement levels may increase or decrease in meningitis depending on the phase of disease and the balance between complement production and consumption. In our study, all of the patients had normal complement levels.

The abnormal T-lymphocyte subpopulations detected in three patients in our study may be secondary to the disease process (Patients 11 and probably 5) or because of a true primary immunodeficiency (Patient 9). The T- and B-lymphocyte subpopulations in the patients were within normal range in the study by Lorraine et al.<sup>11</sup> Hassieb et al.<sup>26</sup> also did not detect a significant difference in T-lymphocytes in patients with bacterial meningitis as compared with normal controls.

To confirm the diagnosis of Ig deficiency, Ig levels must be checked two or more times. Bacterial infection may have a probable transient effect on cell-mediated and humoral immunity. Thus, patients with abnormal laboratory findings must be rechecked a few months after recovery; however, we failed to do this in our patients.

In conclusion, the most common immunodeficiency in our study was Ig deficiency. We recommend immunological evaluation, especially Ig assay, to be performed for patients with bacterial meningitis, even in the first episode.

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