

Deficiency of the Eighth Component of Complement Associated With Recurrent Meningococcal Meningitis – Case Report and Literature Review

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The authors report a case of deficiency of the eighth component of complement in a young adult with a history of three episodes of meningitis; one of them proved to be meningococcal. The literature was reviewed and meningitis due to *Neisseria meningitidis* strains causing disease in complement-deficient and complement-sufficient patients was demonstrated. Meningococcal disease may be the first manifestation of complement deficiency; screening for complement function must be considered for those with invasive meningococcal disease, with posterior evaluation of the components of the terminal pathway of complement.

Key-Words: Meningococcal disease, *Neisseria meningitidis*, complement deficiency.

The complement system consists of at least thirty proteins responsible for innate defenses against microorganisms; it is also involved in humoral immunity. To function properly, the integrity of all its proteins is necessary; deficiency of components can predispose to autoimmunity, especially systemic lupus erythematosus, and such deficiencies can leave the individual vulnerable to bacterial infections. An association of meningococcal infection with complement deficiency has been reported [1]. We report a case of recurrent meningococcal infections in a patient with deficiency of the eighth component of complement (C8). We also searched MEDLINE and LILACS (1990-2003) for studies linking complement deficiency and meningococcal disease.

Received on 17 April 2004; revised 07 July 2004.

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The Brazilian Journal of Infectious Diseases 2004;8(4):328-330
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Case Report

A 21-year-old man was admitted to the emergency room due to fever, headache, vomiting, somnolence, irritability, thrills and myalgia that had begun 24 hours previously. There was no evidence of previous infection in the upper airways. He had a history of three other episodes of meningitis, one of them proved to be meningococcal. One of his brothers had also had meningococcal meningitis six months before. At physical examination, the patient was somnolent, disoriented and hypotensive, with petechiae in the legs and upper limbs, and he had conjunctival suffusion. A coalescent bleb with erythematous borders was observed in the lower lip. The patient had nuchal rigidity, and no papilledema was observed.

The chest radiograph showed alveolar consolidation in the left lower lobe, and a computed tomography scan of the skull was normal. Cerebrospinal fluid (CSF) was turbid, with 5300 cells/mm³ (97% neutrophils and 3% monocytes), 21 red blood cells/mm³, 74 mg/dL glucose (100 mg/dL serum glucose), and 45 mg/dL protein. Microbiological exams of the CSF were negative, including cultures for mycobacteria and fungi. The anti-HIV serology was negative.

The patient was treated with ceftriaxone, with good response. *Neisseria meningitidis* grew in blood culture; studies performed by the State Health Council (Secretaria de Saúde do Estado do Rio Grande do Sul) indicated the W-135 serotype.

Additional tests ruled out CSF fistulae. The serum immunoglobulin levels were normal. Reduced levels of total complement (CH100) were found, with normal values of C3 and C4. Evaluation of the terminal pathway of complement (C5 to C9) showed deficiency of the eighth component (C8) (Table 1). The patient was immunized against pneumococcus, meningococcus and *Haemophilus influenzae*. He had no further episodes of meningitis during the following 18 months.

deficiency; this is the microorganism responsible for 75% to 85% of the infections identified in these patients [1]. Although infection by meningococcus has been associated with deficiency of any of the plasmatic proteins of complement, it more commonly involves deficiency of the terminal components of the complement pathway (C5 to C9); 39% of these patients presented at least one episode [3,4].

Meningococcal disease in patients with complement deficiency usually shows singular characteristics that suggest a need for further investigation [1]. While the average age at the onset of the first meningococcal infection is three years in the general population, and 56% occur before five years, the average age for complement deficiency

Table 1. Serum levels of complement components in a patient with recurrent meningococcal meningitis

Complement fraction	Observed values	Reference values
CH100	0.64 U/mL	63-145 U/mL
C3	118 mg/dL	75-140 mg/dL
C4	20 mg/dL	10-34 mg/dL
C5	220 mg/dL	130-230 mg/dL
C6	926 mg/dL	800-2400 mg/dL
C7	825 mg/dL	400-1400 mg/dL
C8	60 mg/dL	600-1600 mg/dL
C9	1057 mg/dL	600-2000 mg/dL

Discussion

The common goal of the activation of the different pathways of complement (classic, alternative or from lectin) is the deposit of C3b on the target recognized as foreign, and later activation of the membrane attack complex (terminal components of complement, C5 to C9), increasing the immune response, and resulting in opsonization of the target particle [2].

The importance of the complement system in the defense against meningococcus is illustrated by the higher risk (about 10,000 times higher) of meningococcal disease in patients with complement

patients is 17 years, and only 10% of the cases occur before five years of age. Previous infection with meningococcus in this group of immunodeficient patients does not reduce the risk of new episodes; relapses occur in 7.6% of those with deficiency of C5–C9, and recurrent disease (new infection more than one month after a previous episode) occurs in 45%. These frequencies are 10 and 150 times higher than those found in the general population, respectively. This could be explained in part by the fact that antibodies against subcapsular antigens, although bactericidal and protective, are poor opsonins; they offer little protection in patients with

complement deficiency, as these patients do not have the proteins needed for the expression of bactericidal activity [5].

Another peculiar aspect is that, despite the high risk for meningococcal disease, there is a 5 to 10-fold decrease in the probability of death due to this disease in patients with complement deficiency, when compared to the general population [1]. Therefore, the same condition that predisposes to infection seems to protect against the lethal consequences of the disease, suggesting that an exacerbated response from the host is the main factor associated with the clinical manifestations and the outcome of the disease [6]. This hypothesis is supported by Brandtzaeg et al., who have found an association between the extent of complement activation and mortality due to meningococcal disease [7]. Other manifestations of complement deficiency that may be relevant include less severe disease, higher capacity to tolerate the endotoxins [7] and less damage to host cells. The theory that low numbers of microorganisms are sufficient to provoke systemic meningococcal disease seems attractive, although it has not been proven [8].

Unusual meningococcal serogroups (particularly Y, W-135 and X) usually infect patients with complement deficiencies [1,3], and the frequency of these among patients with meningococcal disease caused by these serogroups is also increased [9]. In a study of 7732 patients with meningococcal disease [10], the prevalence of complement deficiency was 3%. When patients with unusual serotypes were examined, the prevalence of any complement deficiency was 33%, and the prevalence of C8 deficiency was 23%. Pulmonary involvement is common in infections with W-135 serotype [11], as we found in our patient.

Conclusion

Evaluation for immunodeficiency is not indicated for most patients with bacterial meningitis, particularly those who had been healthy, with no recurrent infection and without risk factors for infection by the human immunodeficiency virus. Meningococcal disease may

be the first manifestation of complement deficiency; screening for complement function (CH100) must be considered for those with invasive meningococcal disease, with further evaluation of the components of the terminal pathway of complement (C5 to C9).

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