CONTENTS

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Complement and Properidin Deficiencies in Meningococcal Disease

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Fortunately meningococcal sepsis and meningitis are rare events, and such infections usually are a rare presentation for acquired or congenital immunodeficiency. However, certain congenital or acquired immune deficiencies may be first recognized by the occurrence of bacterial meningitis or sepsis caused by *Neisseria meningitidis,* and this presentation may be the first and only clinical signal of an underlying, previously unrecognized immunodeficiency.

Development of systemic infections with *N. meningitidis* is usually caused by an absence of specific protective antibodies, or rarely susceptibility may be caused by the presence of IgA antibodies that block serum antineisserial bactericidal activity. Meningococcal infection has been associated with distinct immunodeficiencies caused by low levels or dysfunction of the terminal components of complement or properidin proteins.[1–4] Meningitis occurs in ~39% of individuals with late component complement deficiencies and up to 6% of those with properidin deficiencies.[5] Also, although most cases of meningococcemia occur among individuals without previously known complement deficiency, this infection may complicate the course of disease-associated complement deficiency such as systemic lupus erythematosus.[6]

COMPLEMENT DEFICIENCIES

Investigators have documented complement deficiencies in persons who presented with meningococcal sepsis or meningitis for over 50 years; these occur in association with single or combined deficiencies of C5, C6, C7 and C8.[7] Investigators in Japan have found a higher prevalence of meningococcal infection among patients with C9 deficiency.[8] Unusually frequent, long or severe infections, or chronic courses of infections, have been recorded in association with complement deficiencies. This suggests that the terminal attack sequence of complement is critical for the host's defense against pathogenic meningococcal organisms and that these deficiencies occur in association with a concomitant loss of "serum bactericidal activity" against *N. meningitidis*.

The incidence of complement deficiencies among persons with meningococcal infection has been debated. Others have suggested that complement deficiencies may be associated with more severe sequelae. Mayatepek et al[3] found the frequency of complement deficiencies with neurologic sequelae occurred in 26.6% of patients with hearing deficiency and meningococcal group Y or W135 infections compared with none among patients without complement deficiency. Ellison et al[2] noted terminal or other complement dysfunction in 6 of 20 patients (30%) presenting with a first episode of meningococcal meningitis or meningococcemia or meningococcal pericarditis; 3 of these 6 patients (15%) had a congenital terminal pathway protein deficiency (C6 or C8), and 3 (15%) had multiple complement deficiencies associated with underlying systemic lupus erythematosus or multiple myeloma. Leggiadro and Winkelstein[9] prospectively determined a complement deficiency in 18% of pediatric patients from Long Island, NY with a first episode of systemic meningococcal infection. However, Hackett and Flood[10] have argued that the prevalence of congenital complement deficiencies varies widely from <1% to 50%, based largely on the work of Densen,[11] who also noted that the incidence of complement deficiency increases as the incidence of the disease decreases.

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PROPERIDIN DEFICIENCIES

Deficiency or dysfunction in the properidin alternate pathway also may be associated with invasive or severe infections caused by meningococcal organisms. Properidin promotes activation of the alternative pathway of complement by stabilizing C3 convertase. Previous studies have suggested that properidin dysfunction is often X-linked, and serogroup B, C, Y and W-135 have been reported from patients with properidin dysfunction during episodes of meningitis or sepsis caused by *N. meningitidis.*

The first case was identified in a Swedish family with 4 case of meningococcal disease[12,13] and additional cases have occurred in Europe, especially in Spain.[5] However cases have been described in the United States, including a large case of X-linked deficiency in a Hispanic family in New Mexico.[14] This family has lost 5 male members to death from meningitis, and 6 other clinically stable male members had type 1 properidin deficiency. Carrier states were detected in the mother and sister of an index case. Many of the affected male members had normal total classical complement (CH50) and alternate complement (AH50); diagnosis of properidin deficiency was established by absent levels. Three types of properidin deficiency have been recognized: type 1, the most common, with a total absence of properidin antigen; type 2 with low serum properidin antigen (1–10% of normal), but functionally active; and, type 3 detected in one family with normal levels but dysfunctional properidin antigen.[15] Meningococcal antibodies generated by immunization with meningococcal vaccines can be protective for patients with properidin deficiency, so vaccines are essential and conjugate vaccines have the potential to protect children at a much younger age. In addition, up to 18% of family members of properidin-deficient patients develop meningococcal infections, so family screening is also essential.[13]

SUMMARY

Complement or properidin deficiency or dysfunction may be present in up to one-fourth of patients with meningococcal disease and may affect both the primary patient and their family members. Although screening may be more cost-effective in low incidence countries, or in those with particularly severe disease or in those with significant sequelae, even a potentially low incidence would indicate the need to test family members at potential risk. Screening with standard CH50 or AH50 may not be sufficient. A strong family history, especially with infection by unusual serotypes, should prompt screening with analysis of properidin levels or function. In addition, the use of current vaccines could greatly reduce the risk in family members.

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