

Chronic meningococchemia in a child with a deficiency of the sixth component of complement

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Chronic meningococchemia represents an uncommon manifestation of meningococcal disease. Microbial and host factors which may predispose to this form of meningococcal disease are not understood. Although acute meningococcal disease is frequently found in patients with terminal complement deficiencies, the relationship of chronic meningococchemia to complement deficiencies is unclear. We present a case report and a review of the literature describing chronic meningococchemia in association with deficiencies of the complement system. A total of eight cases were identified, all of whom were male. Six of the eight patients were children and two of the eight had a previous history of meningococcal disease. This case report, in conjunction with the previously reported cases, suggests an association between complement deficiencies and chronic meningococchemia.

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Chronic meningococchemia is a relatively rare infectious disease characterized by prolonged bacteremia due to *N. meningitidis* without localization to the meninges. The classic clinical presentation includes intermittent or sustained fevers; recurring maculopapular, nodular, or petechial eruptions; and migratory arthritis or arthralgias with little systemic toxicity (1, 2).

The complement system, especially the terminal complement components (C5-C9), plays an important role in host defense against systemic meningococcal infections. Individuals deficient in any of the terminal components, or components necessary for their activation, are therefore at increased risk for acute meningococcal sepsis and/or meningitis (3, 4).

The relative rarity of chronic meningococchemia has made it difficult to establish whether or not there is an association between chronic meningococchemia and deficiencies of the terminal complement components. We recently encountered a 3-year-old black male with chronic meningococchemia who was found to have an associated C6 deficiency. The following report describes this patient and reviews the literature on chronic meningococchemia in patients with genetically determined complement deficiencies.

Case report

The patient is a 3-year-old black male who presented with a three-month history of intermittent fever, joint pain and an erythematous maculopapular rash. His physical exam was remarkable for a febrile, non-toxic appearing child with scattered erythematous papules on his arms and legs. A blood culture drawn 10 days earlier was positive for *N. meningitidis* type B. At the time of admission, his WBC was $11,900/\text{mm}^3$ with a normal differential. The CSF was clear, without pleocytosis. A repeat blood culture was also positive for *N. meningitidis* type B. Cultures of urine and CSF were negative. His past medical history was remarkable for an episode of periorbital cellulitis at age 12 months (etiologic agent unidentified). There was no history of consanguinity.

He received 7 days of IV penicillin without any recurrence of fever or rash. His initial immunologic evaluation was notable for total hemolytic complement (CH_{50}) of < 5 units/ml (normal = 20-50 units/ml). No antigenic C6 could be detected in his serum when tested by Ouchterlony double diffusion in agarose gel. Additional analysis revealed that he had less than 1% of the normal amount of functional C6 in his serum (patient = < 1 u/ml;

Table 1. Complement deficiencies in patients with chronic meningococemia

Sex	Age (yr)	Complement deficiency	Comments	Reference
M	3	C6	Serotype B	This report
M	5	C6		8
M	6	C6	Serotype B	7
M	11	Properdin	H/O meningococcal sepsis & meningitis	11
M	12	C5	H/O meningococcal meningitis	6
M	15	C7		8
M	40	C7		10
M	—	C6	Serotype B	9

normal pool = 2700 u/ml) (5). Addition of purified human C6 (Cordis Laboratories) to his serum completely restored hemolytic activity. A CH_{50} performed on the mother was completely normal. Unfortunately, other family members were not available for testing.

Literature review

All cases of chronic meningococemia reported in the literature to date were reviewed for documentation of an associated complement deficiency. Patient characteristics were noted, as well as any history of other meningococcal infections. Eight cases (including this report) of chronic meningococemia and associated complement deficiency were found (Table 1). All of the patients reported to date have been male. Six of the eight patients (75%), including the current case, were children. Only one of the patients was an adult, and in one case, age was not given. One patient had C5 deficiency (6), four patients had C6 deficiency (7, 8, 9, this report), two patients had C7 deficiency (8, 10), and one patient had properdin deficiency (11). Two of the patients, both children, had a previous history of meningococcal meningitis (6, 11). In the remaining patients no additional history of meningococcal disease, recurrent infection, or rheumatologic abnormalities were given.

Discussion

The clinical presentation of chronic meningococemia in children is characterized by the abrupt onset of fever, usually with daily "spikes" and frequently accompanied by chills and headache. An evanescent eruption (nodular, maculopapular, petechial, or purpuric) distributed mainly over the trunk and extremities and excluding the palms and soles usually occurs in synchrony with the fever curve. Arthritis or arthralgias occur in 50% of the cases (1, 2). Most children remain clinically stable and the

mean duration of illness is about 7 weeks, with the range being from 1 to 40 weeks (2). Complications include meningitis, carditis, nephritis, epididymitis, conjunctivitis, iritis and retinitis (2). To date, there have been no host factors that distinguish between individuals who develop chronic meningococemia from those with acute meningococcal disease.

Although all eight patients reviewed here were male, the available statistics on chronic meningococemia do not demonstrate a male predominance (2). Another distinctive feature of the complement deficient patients with chronic meningococemia is the age of presentation. Six of the eight patients reviewed here were children, whereas the mean age of presentation with chronic meningococemia in complement sufficient hosts is 28.7 years (2). Finally, although C6 deficiency was the predominant late-complement component deficiency in the patients reported here (4 of 8), it has been reported no more frequently than C5, C7 or C8 deficiency (3, 4).

The complement system, particularly the terminal complement components, is known to play an important role in host defense against systemic Neisserial infections. Acute meningococcal meningitis and/or sepsis has been reported in 50–60% of patient with deficiencies of C5–C9 (3, 4). These patients also have an increased rate of relapse (6.3%) and recurrence (45%) (3, 4). Conversely, the frequency of inherited complement deficiency states among patients with endemic neisserial disease is about 5–10%, and dramatically increases to approximately 30% among individuals who have had more than one episode of meningococcal infection (4).

The basis for the increased susceptibility of complement-deficient patients to acute meningococcal infections is felt to be the inability of their sera to generate complement-dependent bactericidal activity. However, the mechanism(s) by which complement deficiency might predispose individuals to chronic meningococemia are unknown. In this regard, it is interesting to note that mortality from

meningococcal disease is lower in complement-deficient individuals than it is in normals (3, 4). It has been suggested that their lower mortality rate may be in part due to the fact that they would not be able to generate the inflammatory products of C5–C9 (3, 4). Whether the inability of complement-deficient patients to generate C5–C9 mediated inflammation predisposes them to chronic meningococcemia is unknown.

Because of the rarity of chronic meningococcemia, its association with terminal complement component deficiencies has been difficult to determine. Of the over 500 cases of complement deficiency reported (3, 4), only eight have had a diagnosis of chronic meningococcemia (6–11 and this report). Only one study has examined a series of patients with chronic meningococcemia in an effort to establish the prevalence of complement deficiencies in this group. In that study, one of 15 patients (7%) was found to be properdin deficient (11).

This case report, in conjunction with the seven previous cases, strongly suggests there is an association between complement deficiencies and chronic meningococcemia. Therefore, a history of meningococcal disease of any type, including chronic meningococcemia, warrants screening tests for complement deficiency. Since these individuals are at significant risk for recurrent disease, identifying patients with systemic meningococcal disease who have an underlying complement deficiency is extremely important. Although there is no data on the efficacy of the tetravalent meningococcal vaccine in preventing recurrent meningococcal disease in individuals with late-complement component deficiencies, it seems prudent that once identified, these patients receive the vaccine.

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