The varied clinical presentations of meningococcal infection

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The clinical presentation of *Neisseria meningitidis* may include bacteremia, septic shock, or meningitis. The polysaccharide capsule of the organism appears to be the major determinant and is necessary for specific immunity. Colonization of the nasopharynx is required for invasion, and persons with complement component deficiencies are particularly at risk of infection. The organism can be detected by culture of blood or spinal fluid, or by antigen detection in spinal fluid. Prompt therapy with penicillin G is necessary for a good outcome. The occurrence of secondary cases requires that prophylactic therapy be administered to close contacts of index cases. The cases presented herein illustrate a variety of manifestations of meningococcal infection, and all of the patients initially were seen in primary care settings. It is important for physicians to be vigilant for these infections so that appropriate therapy may be instituted rapidly.

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The clinical manifestations of meningococcal infection compose a spectrum[1] that includes benign, self-limiting illness as well as fulminant, fatal infections. Because most cases occur in previously healthy individuals, it is imperative that primary care physicians recognize the manifestations of these infections so that treatment may be begun promptly.

Microbiology

The meningococcus, *Neisseria meningitidis,* is a small gram-negative diplococcus that produces a polysaccharide capsule that is an important structure for both pathogenicity and specific immunity.[2,3] Based on capsular type, there are 13 *serogroups*, but the major human pathogens are groups A, B, C, W135, and Y. Noncapsular cell wall antigens, including the outer membrane protein complex and lipooligosaccharide, are the basis for *serotype* determination, which has epidemiologic and pathogenic importance. Some meningococci also express pili that may be important for attachment to host cells.[2,3]

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Immunity

Bactericidal antibody directed against the capsular polysaccharide protects against infection with homologous strains in normal hosts.[2-5] Nasopharyngeal carriage of *N meningitidis* results in development of both *serogroup* specific and cross-reacting antibodies. Antibodies to cell wall antigens and cross-reacting antibod-

ies (*Escherichia coli* K1) also appear to be important.[2,5]

An intact complement cascade is an important part of immunity against the meningococcus, and patients with recurrent or chronic meningococcemia have been shown to have deficiencies in terminal complement components or in properdin.[2,6] Patients with sporadic ("nonepidemic") meningococcal infections have also been shown to have a high prevalence of complement component deficiencies.[2,6]

Pathogenesis

After attachment to nasopharyngeal mucosa, the meningococcus enters the circulation of a susceptible host and causes the many manifestations of infection, including meningitis. Cutaneous hemorrhages, adrenal and renal hemorrhagic infarction, myocardial abscesses, and pulmonary vascular thrombosis occur in severe meningococcal infection.[1,3,7] Septic shock appears to be mediated by lipooligosaccharide in a manner analogous to that of enteric gram-negative bacillus endotoxin.[2]

Epidemiology

Meningococcal disease remains a significant health problem in both industrialized and underdeveloped countries.[2,4,5,8,9] In the United States, the incidence of meningococcal infection is between 1 and 3 cases per 100,000 population,[4] and meningococcal meningitis accounts for approximately 20% of meningitis cases.[8] Infants and young children are affected most often, and the incidence declines with increasing age.[2,4,5,8,9] A shift in cases to older age groups may presage an epidemic.[9]

Serogroups A and C have caused most epidemics of meningococcal disease both worldwide and in the United States; most endemic cases in the United States are caused by group B, followed by groups C, W135, and Y.[2,4,5] Asymptomatic carriage of meningococci is responsible for their spread, particularly in closed populations, and may lead to secondary cases in household contacts of primary cases. "Household contacts" are persons who frequently eat and sleep in the same house with the index case, so school classmates and hospital personnel generally are not considered at high risk for secondary spread. Secondary spread in day-care centers/nursery schools is increased because of the household setting and frequent contact with secretions.[2,4,9]

Clinical aspects

The clinical features of meningococcal infection are described best as a broad spectrum of manifestations. Meningococcemia may occasionally present as a self-limited upper respiratory tract illness, with subsequent "incidental" report of positive blood cultures.[1] It may also present as "septicemia" with fever, chills, and systemic complaints,[1] and in this setting, most patients will have petechiae or a transient maculopapular rash.[1,3] The most dramatic presentation of meningococcemia is the Waterhouse-Friderichsen syndrome, which is a fulminant, frequently fatal illness characterized by petechiae, ecchymoses, shock, obtundation, and disseminated intravascular coagulation.[1,2] Hemorrhagic adrenal infarction is not necessarily the cause of vascular collapse because the finding is not uniformly present, and when present, is variable in extent.[7]

Patients with meningococcal meningitis have fever, vomiting, and headache, with the majority having confusion.[10,12] Nuchal rigidity may be absent in 20% of cases, especially at the extremes of age.[10,12] Petechiae are present in approximately half of the cases.[10] The history of meningeal symptoms may be brief (less than 24 hours), but the majority of patients will have been ill for 1 to 7 days. Antecedent or concomitant upper respiratory tract symptoms are reported frequently in the latter group of patients.[10] Patients with meningococcal meningitis generally have less severe alterations in mental status than those with pneumococcal meningitis.[10,12]

Other clinical manifestations of meningococcal infection have been reported, including pneumonia, empyema, arthritis, and urethritis.[2]

Management

When meningococcal infection is suspected, blood and spinal fluid cultures should be obtained, because the rate of recovery of organisms in appropriately handled specimens is high.[2] Gram's stain of spinal fluid sediment

also should be performed because accurate information is frequently obtained.[10] Counterimmunoelectrophoresis or latex agglutination tests on spinal fluid may detect the presence of group A, B, C, W135, or Y antigen.[2,11]

Presently, penicillin G is the drug of choice for infections caused by *N meningitidis*, and should be administered promptly. Chloramphenicol and third-generation cephalosporins are also effective, but sulfonamide resistance is widespread.[2,22] In the unstable patient, aggressive supportive measures are mandatory because the disease progresses rapidly. The use of adrenocorticosteroids in the hypotensive patient is controversial and no data from controlled studies support their use.[2,11] Likewise, the use of heparin to treat disseminated intravascular coagulation in this setting has not been shown to be effective.[2] Recent studies of pediatric patients with meningitis suggest that steroids may reduce the incidence of hearing loss after meningitis.[11]

Prognosis

Nationally, the case fatality rate for meningococcal infections is approximately 13% for meningitis and 25% for meningococcemia.[8] Mortality rates are lower for meningococcal meningitis than for pneumococcal meningitis.[10,11] Factors associated with a poor prognosis for meningococcal meningitis include poor mental status on admission (that is, stupor, coma, seizures), bacteremia, hypotension, and delay in diagnosis/treatment.[10,12] The overall complication/sequelae rate is less for meningitis caused by *N meningitidis* than for that caused by the pneumococcus or *Haemophilus influenzae*.[10] After recuperation from meningococcal infection, patients should be screened for complement component deficiency.[6]

Prevention

Meningococcal disease is prevented by administration of vaccine or antibiotics. A tetravalent vaccine (groups A/C/W135/Y) made from capsular polysaccharides is available for persons at high risk for infection, such as those persons in closed populations or those persons with complement deficiencies.[2,6,13,14] Group B polysaccharide does not induce a protective immune response, but other group B cellular product vaccines are being investigated.[2]

Table
Prophylaxis for Meningococcal Disease[13,14]

Drug and dosage
Rifampin every 12 hours for 2 days
- Adults: 600 mg each dose
- Children: 10 mg/kg (maximum 600 mg) each dose
- Infants < 1 month old: 5 mg/kg each dose

Indicated for:
- Household contacts
- Day-care/nursery school contacts
- Other individuals having contact with respiratory tract secretions (eg, via kissing, mouth-to-mouth resuscitation)

Generally not indicated for:
- Casual contacts
- Schoolroom contacts
- Medical personnel (except those having contact with respiratory tract secretions through mouth-to-mouth resuscitation)

Chemoprophylaxis of close contacts of persons with meningococcal disease (*Table*) should be initiated as soon as possible after identification of the primary case.[13,14] The primary patient should also receive rifampin to eliminate pharyngeal carriage of the organism.[13] All contacts of primary cases should be monitored clinically for development of infection.[14]

Report of cases

The following cases illustrate the clinical spectrum of meningococcal disease.

Case 1

A previously healthy 89-year-old woman was admitted to the emergency department with a 4-day history of nausea, vomiting, and dizziness. Past medical history included hypertension and severe arthritis, for which she took a diuretic and indomethacin. She also complained of occipital headache that was exacerbated by head movement, but she denied having fever or chills.

On physical examination, her vital signs were normal and she was afebrile; the findings of the remainder of the examination were unremarkable except for a restricted range of motion in her neck and guaiac-positive stools.

The white blood cell (WBC) count was 12,400/mm^3 without left shift.

The patient was admitted to the hospital for intravenous rehydration and esophagogastroduodenoscopy. The morning after admission, she was hyperventilating and hypothermic, and her mental status had rapidly declined. Findings on emergency computed tomography of the brain were unremarkable. Lumbar puncture revealed turbid cerebrospinal fluid (CSF), which contained 6400/mm^3 of which 90% were polymorphonuclear cells (PMNs). The glucose level was zero mg/dL and the protein level was 360 mg/dL. Gram's stain of unspun CSF showed large numbers of PMNs and gram-negative diplococci. Penicillin G therapy (2 million units intravenously every 2 hours) was started. The latex agglutination test of CSF was positive for *N meningitidis* group C; blood and CSF cultures subsequently grew this organism. The remainder of the patient's hospital course was marked by instability of vital signs, decreasing urinary output, and worsening respiratory status. She died of cardiopulmonary arrest resulting from multisystem organ failure 5 days after admission.

This case is unusual in that meningococcal meningitis is uncommon in this age group.[12] The lack of "meningeal" findings at the time of admission served to obscure the diagnosis but, at the extremes of age, the "typical" findings of bacterial meningitis may not be present.[10,12]

Case 2

A 42-year-old woman was seen in the emergency department with a 1-week history of nonproductive cough, fever, nausea, and diarrhea. These symptoms had resolved after a few days and then recurred on the day before admission. She had no previous medical problems, and she was employed as a junior high school teacher. She was taking erythromycin ethylsuccinate, 400 mg orally every 6 hours, that had been prescribed by her family physician for the cough.

Physical examination revealed her vital signs to be normal except for a temperature of 101.7°F. The findings of the remainder of the examination were unremarkable; there was no evidence of rash. Several hours after admission, the patient was reexamined and found to be in moderate distress, confused, and agitated. Her temperature was 105°F and she had marked nuchal rigidity. Lumbar puncture produced cloudy fluid with a WBC count of 6072/mm^3 with 92% PMNs. The glucose level was 10 mg/dL and the protein level, 50 mg/dL. Gram's stain of unspun CSF revealed large numbers of PMNs and gram-negative diplococci. Penicillin G therapy (2 million units intravenously every 2 hours) was instituted, and the patient recovered without complications or sequelae. Spinal fluid grew *N meningitidis* and blood cultures were negative.

This patient had meningitis after respiratory tract illness, as described by Carpenter and Petersdorf.[10] An important aspect of this case is chemoprophylaxis, given the patient's contact with students. The students were not routinely given chemoprophylaxis, and there were no secondary cases. However, the entire hospital supply of rifampin was exhausted by prescriptions given to the emergency department staff even though none had had contact with the patient's nasopharyngeal secretions. This case illustrates the need for education and reassurance of staff who believe they are at risk for meningitis.

Case 3

A previously healthy 15-year-old boy was seen in the emergency department with a 3-day history of high fever, diarrhea, upper respiratory tract symptoms, and painful rash on the ankles. On physical examination, the patient was found to be lethargic and had a temperature of 103.6°F. He had purpura on his feet, palatal petechiae, and conjunctival hemorrhage. He had no nuchal rigidity. The peripheral WBC count was 4200/mm^3 with 54% PMNs and 14% band forms. The serum creatinine level was 2.2 mg/dL, and the serum glucose level was 77 mg/dL. Urinalysis showed 1+ RBCs/mm^3 and 3+ protein. Lumbar puncture revealed 20 WBCs, 100% monocytes. Latex agglutination studies for bacterial antigens and Gram's stain of CSF sediment were negative. The patient was started on ampicillin and chloramphenicol therapy. Blood cultures subsequently grew *N meningitidis*, and the spinal fluid grew no

organisms. The antibiotic therapy was changed to penicillin G.

The patient was observed to have bilateral swelling of the ankles on the day after admission; 3 mL of turbid fluid was aspirated from the left ankle. Gram-negative diplococci were seen on smear, but the fluid grew no organisms on culture. The patient stabilized clinically and eventually recovered. However, he had a prolonged hospitalization because he needed multiple debridements and skin grafts at the areas of purpura on the feet.

This patient's case illustrates meningococcemia without meningitis, where the absence of poor prognostic signs favored his recovery. Arthritis complicates systemic acute meningococcal infection in 5% of children and 11% of adults.[15] The pathogenesis involves either infection or secondary allergic response. In this patient, infection was documented based on Gram's stain of joint fluid. Culture presumably was negative because antibiotic therapy was ongoing.

Case 4

A previously healthy 68-year-old man was brought to the emergency department by his family, who related that the patient had a 12-hour history of nausea, diarrhea, rigors, and altered mental status. On arrival, the patient's vital signs were pulse, 168 beats/min; respirations, 48 per minute; blood pressure, 110/70 mm Hg; and temperature, 106.6°F. Physical examination revealed the patient to be disoriented and agitated and to have diffuse petechiae and purpura.

The peripheral WBC count was 5000/mm^3 with 68% PMNs and 16% band forms. The platelet count was 117,000/mm^3, prothrombin time was 22 seconds, and the activated partial thromboplastin time was greater than 150 seconds. The fibrinogen level was 10 mg/dL (normal, 200-400 mg/dL) and fibrin split products were greater than 40 μg/mL (normal, < 10 μg/mL). Arterial blood gases revealed coexistent respiratory alkalosis and metabolic acidosis. Lumbar puncture yielded clear fluid with 4 WBCs/mm^3; the glucose level was 69 mg/dL, and the protein level, 51 mg/dL. Latex agglutination tests for bacterial antigens and Gram's stain of CSF sediment were negative. The patient was given penicillin G, 2 million units intravenously; nafcillin, 2 g intravenously; and amikacin, 500 mg intravenously. However, in spite of aggressive supportive measures, the patient died of vascular collapse and cardiopulmonary arrest a couple of hours after coming to the emergency room. Blood cultures subsequently grew *N meningitidis*; spinal fluid grew no organisms. Autopsy was not performed.

This case illustrates fulminant meningococcemia, the Waterhouse-Friderichsen syndrome. The patient had rapidly progressive symptoms, disseminated intravascular dissemination, and vascular collapse. All of these manifestations were refractory to appropriate therapeutic measures.

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