

Case Report

Meningococcal disease: a case report and discussion of clinical presentation and management

PK Sethi^a, R Thukral^a, NK Sethi^{b,*}, J Torgovnick^c, E Arsura^d, A Wasterlain^b

^aDepartment of Neurology, Sir Ganga Ram Hospital, New Delhi (India)

^bDepartment of Neurology, NYP-Weill Cornell Medical Center, New York (USA)

^cDepartment of Neurology, Saint Vincent's Hospital and Medical Centers, New York (USA)

^dDepartment of Medicine, Saint Vincent's Hospital and Medical Centers, New York (USA)

Abstract. Meningococcal disease caused by the gram negative diplococcus *Neisseria meningitidis* is a relatively common infectious disease in developing countries of Asia and Africa. Infection usually starts with a non-specific prodrome of fever, vomiting, malaise and lethargy followed by signs of septicemia and shock (tachycardia, tachypnea, cyanosis, oliguria, hypotension) and/or meningitis (stiff neck, headache, photophobia and impaired sensorium). Characteristic meningococcal rash may not appear early in the disease course, potentially delaying the diagnosis and institution of appropriate antibiotic therapy in the patient and isolation and chemoprophylaxis in close contacts. We present here a patient who presented with meningococcal shock associated with characteristic skin lesions of meningococemia and discuss the clinical presentation and management. The importance of early identification of the characteristic skin lesions of meningococemia and timely institution of appropriate antibiotic therapy is emphasized.

Key words: Meningitis, meningococcal meningitis, meningococcal septicemia, meningococcal shock syndrome

1. Case report

A 28-year-old immunocompetent male presented to the emergency room with complaint of high grade fever for two days and rash over the extremities for the past one day. The rash was widespread covering all four limbs, purpuric and associated with ecchymoses (Fig 1 and 2). The patient did not complain of headache or photophobia. There was no clinical evidence of

nuchal rigidity and the patient exhibited a clear sensorium. Laboratory investigations revealed a total leukocyte count of 21000/mm³ and a platelet count of 12000/mm³ which decreased to 7000/mm³. Lumbar puncture was deferred, taking the low platelet count and the initial absence of meningeal signs into consideration. Biopsy of skin lesions revealed gram negative diplococci consistent with *N meningitidis*.

The patient was initially treated with vancomycin (1 gram intravenously every 12 hourly) and ceftriaxone (1 gram intravenously every 12 hourly). Once *N meningitidis* had been definitively identified vancomycin was stopped and ceftriaxone was continued. The patient became hemodynamically unstable (systolic blood pressure of 80 mm Hg and heart rate of 140/min) so hydrocortisone 100 mg thrice daily was administered which was subsequently tapered off with complete resolution of septicemia and skin lesions.

*Correspondence: Nitin K. Sethi, MD
Department of Neurology
New York-Presbyterian Hospital
Weill Cornell Medical Center
525 East, 68th Street
New York, NY 10021 (U.S.A.)
E-mail: sethinitinmd@hotmail.com
Tel: 212-746-2346
Fax: 212-746-8845
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Fig. 1. and 2. Widespread purpuric and ecchymotic rash covering all four limbs.

2. Discussion

2. 1. Pathophysiology and risk factors

Meningococcal disease (MD) caused by the gram negative diplococcus *N meningitidis* is associated with high morbidity and mortality. It primarily affects children and young adults in developing countries of Asia and Africa (1,2). Infection is acquired through close contact with airborne droplets of infected nasopharyngeal secretions. MD has two main clinical presentations: meningitis and septicemia which may occur together in about 40% of cases. While meningococcal meningitis has high morbidity and mortality, meningococcal septicemia is far more likely to kill with case fatality rates reaching as high as 50% if the patient is already in shock by the time he or she reaches medical care. Individual susceptibility to MD varies. Household contacts of infected individuals are 300-1000 times more likely to acquire MD than those in the general population. Patients who are immunocompromised (HIV positive patients, alcoholics, elderly, asplenic state, people with complement deficiency) are more vulnerable to fulminant MD (3-5). The complement system provides a particularly important defense against meningococcus. Complement deficiency increases the risk of acquiring MD approximately 10,000-fold; conversely, MD accounts for 75% to 85% of infections in complement deficient patients. MD is most commonly associated with deficiency of the terminal components of the complement pathway (C5-C9). Interestingly, for reasons still unclear, despite the increased risk of acquiring MD, probability of death is 5 to 10 times lower in complement-deficient patients. Genetic polymorphism of molecules such as mannose binding lectin increases susceptibility to

meningococcal disease. For example, plasminogen activator inhibitor-1 (PAI-1) polymorphisms may predict the severity of MD. Four conditions must be satisfied in order for invasive disease to occur: (i) exposure to pathogenic bacteria, (ii) colonization of nasopharyngeal mucosa, (iii) passage of the bacteria through the mucosa, and (iv) infection of the bacteria in the bloodstream (9). Characteristics of the bacterium, the environment of the patient, history of infection, and the strength of the patient's immune system contribute to whether invasive MD will develop.

2. 2. Diagnosis

Meningococcus can be detected by Gram stain of a skin biopsy specimen, blood culture or cerebrospinal fluid culture (6). Prior antibiotic use can make it difficult to recover bacteria from blood, producing a false negative result; by contrast, skin biopsy tests are unaffected by previous antibiotic therapy. Other diagnostic methods that are not impacted by prior antibiotic use are meningococcal antigen detection and polymerase chain reaction (PCR) amplification of meningococcal DNA. While skin biopsy, antigen detection and PCR amplification provide a more reliable diagnosis, blood cultures are most commonly used because they are relatively easy to obtain even in countries with limited resources.

2. 3. Symptoms and signs

MD begins with a nonspecific prodrome of fever, lethargy, drowsiness, nausea and vomiting. In the pediatric age group this prodrome may consist of irritability and poor feeding (7). Hence early on in the disease course it is difficult to distinguish it from other common bacterial and viral febrile illnesses. Rash is the most common reason that patients with MD seek medical help. The purpuric ecchymotic rash is characteristic

though it may not be noticeable until 12-24 hours after disease onset. In its earliest stages the rash may be blanching and maculopapular later developing into a non-blanching red or brown petechial rash. Initially it may present with isolated pin-prick spots and hence may be missed unless a diligent whole skin examination in good lighting is carried out. In dark skinned people it may be visible in paler areas such as soles of feet, palms of hand, conjunctivae, skin of abdomen and palate. The meningococcal rash may spread rapidly; lesions may coalesce to form large ecchymotic lesions which may then get secondarily infected (8). The rash may continue to evolve and become more prominent even though the patient may start showing clinical improvement while being treated with antibiotics. As most patients with meningococcal disease develop a rash it is one of the clearest and most important signs to recognize. The rash may be very scanty or even absent in meningitis. A non-blanching petechial rash in a febrile patient should raise the suspicion for MD as other signs may be subtle even in a patient with advanced disease. If early antibiotic therapy is not instituted, circulatory and vasomotor collapse ensues with signs of hypoperfusion (collapsed peripheral veins cause cold hands and feet), hypotension, tachycardia, tachypnea, arthralgias and oliguria. During the early stages of shock, tachycardia may be the sole sign. By the time hypotension develops, hemodynamic reserve is precariously low. Decreased level of consciousness is a late clinical sign. Concomitant meningitis presents clinically with headache, depressed sensorium, stiff neck and photophobia (neck stiffness and photophobia may be absent in young children). Infants with meningococcal meningitis are irritable with a high pitched cry, mottled skin and bulging fontanelle.

2. 4. Indicators of septic shock

As per the British Infection Society guidelines signs which may warn health care providers of impending shock, respiratory failure or signs of increased intracranial pressure include rapidly progressive rash, poor peripheral perfusion (capillary refill time >4 seconds, oliguria and systolic BP <90), respiratory rate <8 or >30, pulse rate <40 or >140, acidosis (pH <7.3), WBC count <4000/mm³, GCS <12, focal neurological examination, persistent seizures and papilloedema. Poor prognostic indicators for patients with meningococcal septicemia include extreme youth and old age, rapid onset of disease, the absence of meningitis, extensive skin lesions, shock, hypotension, metabolic acidosis, elevated

protein C and/or cytokine serum concentrations, the absence of leukocytosis, and the presence of thrombocytopenia and disseminated intravascular coagulation (DIC).

2. 5. Complications

Coagulopathy is a complication of meningitis and other infectious diseases, and is mostly multi-factorial. The coagulopathy associated with meningococcal septicemia is characterized by marked inflammatory cell activation, disseminated intravascular coagulation, and vascular compromise. In comparison to other forms of septic shock, the coagulopathy and microvascular thromboses that develop in this type of sepsis are severe with thrombosis of the large vessels and infarction of the digits and limbs.

Meningococcal endotoxin produces a severe proinflammatory response and cytokines stimulate the release of tissue factors, leading to the formation of thrombin and fibrin clots. Imbalance between coagulation and fibrinolytic systems leads to microvascular thrombosis, which in turn may lead to hypoperfusion, shock, disseminated intravascular coagulation (DIC) and multi-organ failure. Waterhouse-Friderichsen Syndrome (WFS), is a condition characterized by abrupt onset of fever, purpuric rash, weakness and myalgias leading to hemorrhagic necrosis of the adrenal gland. WFS is most commonly associated with meningococcal septicemia, but may also occur with sepsis caused by other bacterial infections. Children and patients with a prior history of splenectomy are particularly susceptible to WFS.

2. 6. Management

Early aggressive fluid resuscitation and appropriate antibiotic therapy form the cornerstones of management of meningococcal shock syndrome.

2. 7. Fluid resuscitation

Fluid resuscitation should be initiated at the first sign of shock (i.e. at the stage of tachycardia) with the aim of reestablishing physiological parameters (heart rate, blood pressure, urine output and capillary refill time). Ideal resuscitation fluid is normal saline. Controversy exists on the use of colloids (albumin). The aim should be to correct the fluid deficit rapidly. Vasoactive agents such as dopamine and dobutamine are used if there is evidence of myocardial depression despite adequate fluid loading. Epinephrine or norepinephrine is started if the patient has ongoing hypotension or evidence of progressive organ dysfunction despite sufficient fluid and

dopamine or dobutamine, depending on whether the hemodynamic pattern is most consistent with poor myocardial contractility (epinephrine) or distributive shock (norepinephrine). Arginine vasopressin (0.001 units/kg/min), low-dose hydrocortisone (1 mg/kg 8 hourly), and calcium infusions (0.2 ml/kg/day) can be considered in cases of refractory hypotension. A further subgroup of these critically ill patients develop progressive hypotension with or without organ dysfunction associated with dilated, poorly functioning ventricles on echocardiography, increasing serum lactate, or decreasing central venous oxygen saturation and may require extracorporeal membrane oxygenation (ECMO). Patients frequently require venoarterial ECMO using the highest flows (150 to 300 mL/kg/min) achievable to maintain adequate peripheral perfusion. ECMO flow rates need to be adjusted to achieve maximal systemic perfusion at age-appropriate perfusion pressures. The associated maldistribution of tissue perfusion requires increased flows to adequately perfuse tissue and avoid hypoxic ischaemia. Studies have shown that persistent shock has an adverse effect on survival in a time-dependent manner (10). Delayed treatment leads to increased mortality and on the other hand there is 94% rate of survival if shock is reversed within 75 minutes of presentation. Shock and DIC are interrelated, and reinforce each other. As such, anti-shock therapy is an effective treatment for DIC, and usually reverses clotting abnormalities. Treatment with fresh frozen plasma may be warranted if clotting parameters are severely deranged and there is evidence of bleeding. Heparin may be used as an alternative treatment, but has not yet shown a net reduction in mortality from DIC; at present there is no evidence for routine use of activated protein C in severe meningococcal sepsis.

2. 8. Antibiotic therapy

Mortality from MD is reduced by early appropriate antibiotic therapy. In the past, meningococcal infections were usually treated with penicillin, ampicillin, or a combination of penicillin and chloramphenicol. Isolates of *N meningitidis* with increased levels of resistance to penicillin have been reported in the last few years from different countries. Resistance is due in part to development of altered forms of the penicillin-binding protein (PBP 2), and in some isolates to the production of beta lactamase. Minimum inhibitory concentrations (MICs) for penicillin-intermediate isolates (0.12 to 1 µg/ml) are 2 to 20 fold higher than those for the susceptible ones (≤ 0.06 µg/ml). Hence, current recommendations

are to use third generation cephalosporins (Ceftriaxone or Cefotaxime), a class of beta-lactam antibiotics that are particularly potent against gram-negative bacteria and able to penetrate the CNS. Drug doses for septicemia and meningitis vary (1 g intravenously twice daily of Ceftriaxone for septicemia while anti-meningitic dose is 2 g intravenously twice daily). Penicillin is the drug of choice if third generation cephalosporins are unavailable, and chloramphenicol may be used in patients with a history of anaphylaxis to both cephalosporins and penicillin.

2. 9. Role of steroids in meningococcal meningitis

Steroids are sometimes used in conjunction with antibiotics for the treatment of MD, as steroids facilitate the transport of antibiotic molecules across the blood-brain barrier. The European Dexamethasone in Adulthood Bacterial Meningitis Study found dexamethasone to be most beneficial in patients with pneumococcal meningitis with a reduction in the risks of both unfavorable outcome and death. It did not have a beneficial effect on neurologic sequel, including hearing loss. The small number of patients with meningococcal meningitis prevented detection of a beneficial effect though the authors recommended dexamethasone treatment for all patients with acute bacterial meningitis. Hence paucity of data precludes a recommendation that dexamethasone be administered routinely in adults with meningococcal meningitis. The duration and timing of dexamethasone therapy is important. Though data suggests that two-day and four-day regimens are equally effective, the authors recommended 10 mg every six hours for four days initiated before or with the first dose of antibiotics. Importantly, this treatment did not increase the risk of gastrointestinal bleeding.

2. 10. Role of steroids in septic shock

The use of steroids in septic shock has been investigated in the past. While the use of high dose steroids (30 mg/kg of methylprednisolone or equivalent) for a short period has not been proven to improve outcomes, use of low dose steroids (200-300mg of hydrocortisone, 2-5 mg/kg/day in children) as replacement therapy has shown promising results with reduction in the duration of inotropic requirement and 28-day mortality. Meningococcal septic shock presents with an early massive inflammatory response. While absolute adrenal failure due to adrenal hemorrhage is rare, partial adrenal insufficiency is quite common, thus current recommendations are to use hydrocortisone in patients with septic shock requiring catecholamines for blood

pressure support and with laboratory evidence of adrenal insufficiency (12-14).

2. 11. Treatment of hyperglycemia

Hyperglycemia may increase mortality in these critically ill patients with recent studies showing that the intensity and duration of hyperglycemia is associated with outcomes. The use of insulin to treat hyperglycemia improved outcomes in children, but data has been less conclusive in the adult population. At present the use of insulin to treat hyperglycemia and normalize blood glucose levels should be made on a case by case basis until more definitive information is obtained from future studies (11).

3. Prevention

3. 1. Vaccination

Vaccination is the most effective preventative measure against MD. Serogroups B, C, and Y are the major causes of meningococcal disease in the United States, each being responsible for approximately one third of cases. In the United States a tetravalent polysaccharide-protein conjugate vaccine ((MCV4) Menactra™, manufactured by Sanofi Pasteur, Inc, Swiftwater, Pennsylvania) effective against serogroups A, C, W-135 and Y is currently available, and licensed for use among persons aged 11-55 years (15). CDC's Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of young adolescents with MCV4 at the preadolescent health-care visit (at age 11-12 years). Outbreaks of serogroup B meningococci (NMB) have been reported worldwide and it is now the predominant disease causing isolate in industrialized countries. Because group B polysaccharide mimics the neural cell adhesion molecule, a vaccine against group B would risk inducing autoimmunity; moreover, the antibody response to the group B capsular polysaccharide is limited, and thus cannot be used to develop an effective vaccine and it remains unclear whether recent advances in vaccine development shall lead to a universal NMB vaccine in the foreseeable future (16). Few studies are ongoing in some European countries and New Zealand with the serogroup B vaccine. In 1999 the meningococcal group C polysaccharide-protein conjugate vaccine (MenC) was introduced in the United Kingdom into schedules for routine infant immunization. MenC provides significant herd immunity and the introduction of this vaccine led to a significant decrease in group C carriage and disease. Group A disease is responsible for large epidemics in Africa. MenAfriVac is an affordable conjugate vaccine against group A developed

through collaboration between the Meningitis Vaccine Project (WHO) and the Serum Institute of India. Clinical trials are ongoing and shall determine whether the vaccine provides long-lasting protection in infants (17).

3. 2. Chemoprophylaxis

The Centers for Disease Control (CDC) recommends chemoprophylaxis for intimate and household contacts of a patient with MD with rifampicin, ciprofloxacin, ofloxacin, or ceftriaxone (for pregnant women). The purpose of chemoprophylaxis is to eliminate carriage in the contact group; it does not prevent illness in those already infected, so contacts should continue to be alert to the symptoms of MD and seek medical attention at the earliest sign of infection. Sulfonamides should only be used if there is known susceptibility.

4. Conclusion

MD is an important infectious cause of morbidity and mortality in the developing world. The disease has two main clinical presentations: meningitis and septicemia which may occur together in about 40% of cases. MD can spread rapidly and a high index of suspicion is needed to diagnose it in its initial stage as the characteristic purpuric skin lesions may not be apparent until 12-24 hours after disease onset. Early and aggressive fluid resuscitation and timely appropriate antibiotic therapy improves the outcome in meningococcal shock syndrome. Chemoprophylaxis with either rifampicin, ciprofloxacin or for pregnant contacts, ceftriaxone is recommended for intimate and household contacts of a patient with MD.

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