SHORT ARTICLE

Clinical presentation of meningococcal disease in childhood

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Key words

Meningitis • Meningococcal disease • *Neisseria meningitidis*

Summary

Although relatively rare, meningococcal disease represents a global health problem being still the leading infectious cause of death in childhood with an overall mortality around 8%. Meningococcal meningitis is the most commonly recognized presentation, accounting for 80% to 85% of all reported cases of meningococcal disease (in half of these cases sepsis is also present concomitantly). The remaining 15-20% of cases are most commonly bloodstream infections only. Meningococcal serogroups A, B, and C account for most cases of meningococcal disease throughout the world. Recently, serogroups W-135 and X (predominantly in Africa) and group Y (in the United States and European countries) have emerged as important disease-causing isolates. Despite recent advances in medical management, the mortality rate of fulminant meningococcemia ranges from 15% to 30%. However, among survivors, 10-30% could have long term sequelae (i.e. sensoneural hearing loss, seizure, motor problems, hydrocephalus, mental retardation, and cognitive and behavioral problems). Considering the clinical severity of meningococcal disease, prevention represents the first approach for avoiding serious complications and possible deaths. The availability of new vaccines able to cover the emerging serotypes including A and Y as well as the availability on the market of new products that could prevent meningococcal B infection represent a great opportunity for the decrease of the burden of this complicated disease.

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Introduction

Although relatively rare, meningococcal disease represents a global health problem being still the leading infectious cause of death in childhood with an overall mortality around 8% [1]. *Neisseria meningitidis* is pathogenic only in humans and it colonizes the nasopharynx asymptomatically in up to 5-10% of the adult population, although occasionally can cause invasive disease [2]. Meningococcal infection occurs in small clusters throughout the world with seasonal variation and accounts for a variable proportion of epidemic bacterial meningitis. The meningococcal invasive disease is associated only with six serogroups classified on the basis of polysaccharide capsule surrounding the bacterium (A, B, C, W-135, X, and Y) [3]. Serogroups A, B, and C account for most cases of meningococcal disease throughout the world. In particular, serogroups A and C are responsible for large epidemics in Africa and Asia, whereas serogroups B and C cause disease predominantly in industrialized and newly industrialized countries including Europe and the Americas [3]. Recently, groups W-135 and X (predominantly in Africa) and group Y (in the United States and European countries) have emerged as important disease-causing isolates [3, 4].
Meningococcal disease occurs sporadically in industrialized countries with an incidence of 0.35 cases per 100,000 population in the United States and 1.01 per 100,000 in Europe [1, 3].The major disease burden is in developing countries in which the incidence can be higher than 500 per 100,000, especially in the area of sub-Saharan Africa known as the meningitis belt (it stretches from Senegal in the west to Ethiopia in the east) [1, 3]. During the dry season between December to June, dust winds, cold nights and upper respiratory tract infections combine to damage the nasopharyngeal mucosa, increasing the risk of meningococcal disease. At the same time, transmission of *N. meningitidis* may be facilitated by overcrowded housing and by large population displacements at the regional level due to traditional markets. This combination of factors explains the large epidemics which occur during the dry season in the meningitis belt [4, 5].
Since the majority of deaths occur in the first 24 hours, the challenge for the pediatricians is to identify those patients who will progress from nonspecific early presentation to fulminant disease.

Clinical presentations of meningococcal disease

Meningococcal disease usually develops within 1 to 14 days following acquisition of *N. meningitidis* in the nasopharynx [6, 7]. The features that appear earliest (i.e. within the first 4-6 h of the onset of meningococcal disease) are common to many self-limiting viral illnesses seen in primary care [1, 2, 6]. Meningococcal meningitis is the most commonly recognized presentation glo-

bally, accounting for 80% to 85% of all reported cases of meningococcal disease (in half of these cases sepsis is also present concomitantly), although bloodstream infection may be under-recognized. The remaining 15-20% of cases are most commonly bloodstream infections [1, 2].

Initial unspecific symptoms and clinical presentation may differ according to the age of patients. Fever can be the first symptom to be noticed in children younger than 5 years, whereas headache is often the first to be seen in those older than 5 years [1, 2]. The majority of children developed fever at some point and most young children appear irritable. Loss of appetite, nausea, and vomiting are early features for all age groups, with many children also having upper respiratory symptoms (otalgia, sore throat and coryza) [1, 2]. Sore throat can be a frequent complaint in teenagers aged 15 to 19-years [1, 2]. These features, which are not specific to meningococcal disease, lasted for about 4 h in younger children but as long as 8 h in adolescents. Symptoms progress rapidly over a period of a few hours [1, 2].

Acute meningococcaemia presents in a nonspecific manner with fever, lethargy, reduced feeding, headache, nausea and vomiting, cold or discoloured extremities, arthralgia and myalgia [2]. Neck stiffness is typicall absent. The clinical signs of sepsis are fever, tachycardia, and tachypnea. A specific characteristic of a meningococcal sepsis is its rapid progression. The cardinal feature of a meningococcal sepsis is the purpuric rash (Fig. 1), which is a late sign of the disease and consists in the beginning of erythema but later in petechiae and purpura characterized by dermal microvascular thrombosis and perivascular hemorrhage [8].

Thompson et al. have identified three important clinical features that are signs of early acute meningococcaemia in children and adolescents [1]. These features are represented by leg pain, cold hands and feet, and abnormal skin colour and generally occur within the first 12 h of the onset of illness. Cold hands and feet, and abnormal skin colour are features of early sepsis that represent changes in the peripheral circulation. Leg pain is less well recognised, although pain in the limbs, with or without refusal to walk, could be a response to a range of inflammatory mediators released during the early septic process (tumour necrosis factor or other cytokines, or other pro-inflammatory mediators). The presence of these three features also suggests that vital signs (i.e. pulse, respiratory rate, and capillary return) might also be abnormal.

In the rash phase, there is a possible differential diagnosis with other diseases leading to a petechial rash [8]. It is important to observe that approximately 95-99% of children with fever and petechiae will have a cause other than meningococcal infection (i.e. enterovirus or adenovirus infection), and the incidence of meningococcemia in these patients accounts for 2 to 20% of the cases. However, it may not be easy to distinguish between the two without investigations and/or a period of observation [2, 8]. Wells et al. analyzed the likelihood of a meningococcal infection in children with an acute nonblanching rash [9]. From the 233 children studied, 11% had a meningococcal infection: they were ill, had fever of ≥ 38.5°C, and had a delayed capillary refill time. Laboratory investigations were not helpful in distinguishing meningococcal cases. A comparable study was carried out by Nielsen et al. [10]: from 264 infants and children hospitalized with fever and skin hemorrhages, 15% had meningococcal disease. The patients with skin hemorrhages of characteristic appearance universally distributed and a minimum diameter of 2 mm as well as with poor general condition had a likelihood of 97% of having a meningococcal infection [10].

The purpuric rash may progress to *purpura fulminans*, which is a cutaneous manifestation of disseminated intravascular coagulation. It presents as a purpuric rash and symmetric gangrene that often necessitates amputation and is often associated with a shock state characterized by the rapid onset of hypotension, acute adrenal hemorrhage (the Waterhouse-Friderichsen syndrome), and multiorgan failure (Fig. 2) [4, 8] In these cases death can occur within 24 hours [4, 8].

Fig. 1. Purpuric rash in meningococcal sepsis.

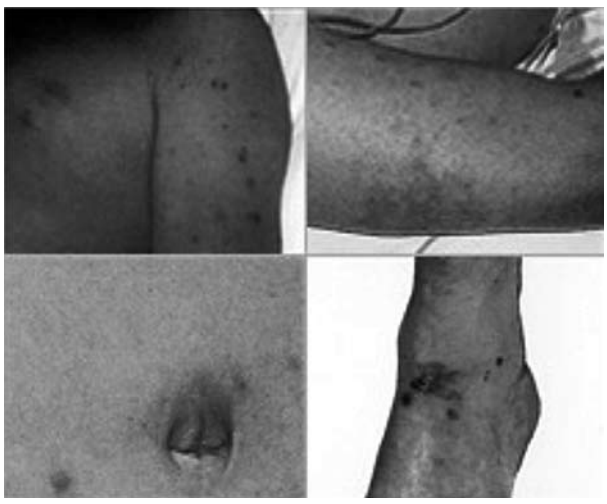
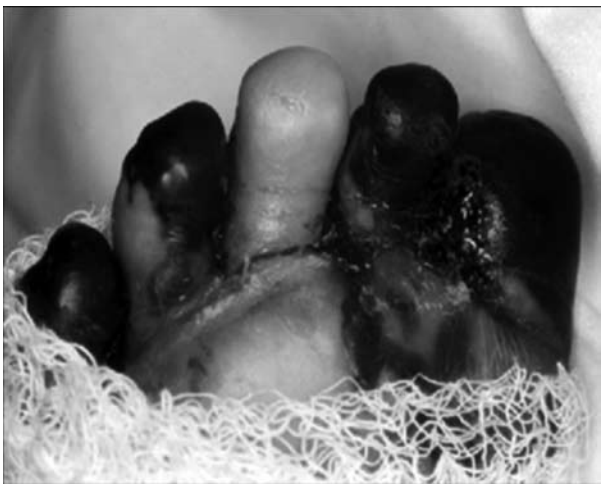


Fig. 2. Gangrene caused by *Neisseria meningitidis*.



Meningeal infection resulting from hematogenous spread and is similar to other forms of acute purulent meningitis, with a sudden onset of headache, fever, and stiffness of the neck (i.e. classical triads observed more often in teenagers), sometimes accompanied by nausea, vomiting, photophobia, an altered mental status and seizures [1, 2, 8]. In infants, meningeal infection may have a slower onset, with nonspecific signs and without stiffness of the neck; a bulging fontanelle is occasionally noted [1, 2, 6].
Pneumonia occurs in 5-15% of patients with invasive meningococcal disease [4]. Meningococcal pneumonia may not always be diagnosed because isolation of the organism from sputum does not distinguish persons who are carriers of the bacteria from those with pneumonia caused by *N. meningitidis* and because physicians may not consider the organism as a possible cause of pneumonia [4].
Much less frequently other syndromes are associated with meningococcal disease, including conjunctivitis, otitis media, epiglottitis, arthritis, rabdomyolisis, urethritis, and pericarditis [4]. Acute peritonitis as initial manifestation of meningococcemia is also described in worldwide literature [11]. In rare cases, patients may present with chronic meningococcemia, a syndrome characterized by prolonged, intermittent fevers, rash, arthralgias, and headaches [4].

Serious outcomes of meningococcal disease

Meningococcal disease is a life-threatening disease, related with serious complication and sequelae. Despite recent advances in medical management, the mortality rate of fulminant meningococcemia ranges from 15% to 30% [1, 2, 4]. However, many children who survive the initial phase of shock develop vascular insufficiency, compartment syndrome, or peripheral gangrene. Among initial survivors, 10-30% present with skin necrosis and limb ischemia needing orthopedic surgical management such as debridement, skin grafting, muscular flap coverage for limb salvage and, sometimes, even limb amputation [4]. Children requiring surgery for *purpura fulminans* are often limited by physical disability due to amputation, scarring, and abnormal bone growth.
The incidence rate of residual abnormalities in post meningitic children is approximately 15% (with a range of 10% to 30%) [12]. The most common sequelae in post-meningitis children are sensoneural hearing loss, seizure, motor problems, hydrocephalus, mental retardation, and cognitive and behavioral problems [12]. Among risk factors associated with sequele due to meningitis, there are duration of illness before admission, presence of convulsion, focal neurologic deficits, depressed level of consciousness, absence of petechiae on admission and low cerebrospinal fluid glucose.

Antibiotic therapy and prophylaxis in meningococcal disease

Early recognition of children with meningococcal infection is mandatory in order to avoid the development of sequelae. Identification of *N. meningitidis* in blood as well as in cerebrospinal fluid (CSF) by culture and/or polymerase chain reaction is mandatory for etiologic diagnosis [1, 2, 4]. In some cases, blood and CSF may result negative because of previous oral antibiotic therapy. However, in meningococcal disease intravenous administration of antibiotics for 7-10 days is recommended [13, 14]. Usually, 3rd generation cephalosporins (e.g. ceftriaxone 100 mg/kg/day i.v. in one daily dose or cefotaxime 100 mg/kg/day i.v. divided in three times per day) represent the recommended treatment of bacterial meningitis and are effective also in meningococcal cases [13, 14]. For this reason, 3rd generation cephalosporins are usually maintained until the end of treatment, although penicillin G represents a narrow spectrum drug that could be used for the treatment of meningococcal cases [13, 14].
In order to avoid outbreaks, taking in account that the status of carrier of N. meningitis in the nasopharynx is rarely reported, prophylaxis of close contacts of the index case (i.e. family and school contacts) is recommended [14]. Close contacts have to be considered persons who remain with the index case for more than 4 hours in the 7 days before. In these cases, rifampicin 10 mg/kg/day in two daily doses orally for two days in those aged < 1 months, rifampicin 20 mg/kg/day in two daily doses orally for two days in those aged 1 months - 18 years (with a maximum dosage of 600 mg twice per day for two days) and ciprofloxacin 500 mg once orally in those aged > 18 years are the recommended approach [14].

Conclusions

Considering the clinical severity of meningococcal disease, prevention represents the first approach for avoiding serious complications and possible deaths. The availability of new vaccines able to cover the emerging serotypes including A and Y [15] as well as the availability on the market of new products that could prevent meningococcal B infection [16] represent a great opportunity for the decrease of the burden of this complicated disease.

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