

Diarrhea as the Main Initial Manifestation of Meningococemia: 2 Case Reports

Hernández PM¹ and Gómez TV*

¹MD at Pediatric Infectious Diseases, National Institute of Pediatrics, Mexico

*Corresponding authors: Gómez TV, Insurgentes Sur 3700-C col. insurgent Cuicuilco Deleg. Coyoacan CP 04530, México, Email: valeria_172884@yahoo.com

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Abstract

Invasive meningococcal infections show a broad clinical picture in sepsis and meningitis. The clinical reports of the disease do not include diarrhea as an initial clinical presentation, since it is only seldom reported. Here is a description of two cases of meningococcal infection with diarrhea as the main initial clinical manifestation and posterior emergence of the classical signs and symptoms.

Keywords: Meningococcal meningitis; Diarrhea; Meningococemia

Introduction

Meningococcal disease may present as meningitis, sepsis, urethritis, conjunctivitis, pericarditis, epiglottitis, pneumonia and arthritis [1]. Clinically, meningitis, sepsis, or a combination of both, is the most common presentations. The spectrum of the disease includes an episode of fever with nonspecific symptoms rapidly evolving to a septic shock. Early diagnosis of this disease and immediate treatment is crucial for final prognosis [2].

Case Reports

Case 1

Three-year-old female previously healthy. History of imprisoned father in Mexico City, who was released 8 days before the onset of disease in our patient. She started with 6 semiliquid-yellowish-stools with mucus without blood, otalgia and fever of 38°C. Twenty-four hours later, diarrhea and otalgia disappeared. Six episodes of gastric vomiting were added. Trimethoprim-sulfamethoxazole was administered. Drowsiness, fatigue and weakness were added, and she went to the hospital 2 days later.

The patient was found on admission with somnolence alternating periods of irritability, neck stiffness but negative Kernig and Brudzinski, pupils with normal reflexes and isochoric, normal pulses and capillary refill, skin without petechiae, Glasgow 10 (motor 4, verbal 2, ocular 4). Her complete blood count reported hemoglobin 11.8 q/dL, hematocrit 35.1%, leukocytes 8,100/uL, neutrophils 68%, lymphocytes 22%, monocytes 10% and platelets 73,000/uL. Her cerebrospinal fluid (CSF) was slightly shady with microproteins 186 mg/dL, glucose 8 mg/dL (serum glucose 138 mg/dL), countless cells, polymorphonuclear 62% and mononuclear 38%. The smear showed Gram negative diplococci and coagglutination was positive for group C

Neisseria meningitidis. Ceftriaxone treatment was started. Ciprofloxacin prophylaxis was given to close contacts.

The patient had a favorable evolution with recovery of Glasgow to 15 points on the 5th day of hospitalization. She completed 10 days of antibiotic treatment and was discharged, as well as evaluated by the rehabilitation team, who found out moderate neuromusculoskeletal impairment.

Case 2

Eight-year-old female resident of Mexico City started at 5:00 AM with nausea. At 10:00 AM, frequent gastric vomiting with unquantified fever was added. Oral rehydration therapy was given but vomiting persisted. Later at 8:00 PM, she started with watery-stinking-stools, without mucus or blood and attended to the hospital at 00:00 AM on the next day. On physical exam, she was found with Glasgow 15, oriented with preserved mental functions, stringy saliva, decreased peripheral pulses and capillary refill in 3 seconds. Arterial blood gas showed pH 7.30, pCO₂ 33.5 mmHg, HCO₃ 16 mmol/L, and lactate 5.1 mmol/L. Hypovolemic shock was suspected and received crystalloid and colloid boluses, with hemodynamic improvement. That same day at 8:00 AM, Glasgow decreased to 8 points. She was transferred to the pediatric intensive care unit. Endotracheal intubation was performed and 20 minutes later presented generalized tonic-clonic seizures. Only mild hyponatremia of 131 mEq/L was found. Complete blood count reported hemoglobin 12 q/dL, hematocrit 38%, leukocytes 19,200/uL, neutrophils 82%, lymphocytes 10%, monocytes 8% and platelets 236,000/uL. Clotting times were prolonged. On the new exam she had petechial lesions in the anterior area of the left leg. The cerebral computed tomography was reported as normal. She continued with shock, so norepinephrine and ceftriaxone were initiated. A lumbar puncture was done, and the CSF cytochemical reported glucose 4 mg/dL, microproteins 270 mg/dL, countless cells, mononuclear 14% and polymorphonuclear 86%. The smear showed Gram negative diplococci, and coagglutination was positive for group C *Neisseria meningitidis* (Table 1).

The next day, she continued with septic shock and fever of 38°C. She also started with hyperglycemia that required insulin infusion. Amines were stopped 2 days later. She completed treatment with ceftriaxone for 10 days. A catheter-related bacteremia by *Enterococcus durans* sensitive to ampicilin and amikacin was documented and treated. She was discharged afebrile and neurologically without sequelae (Figure 1).

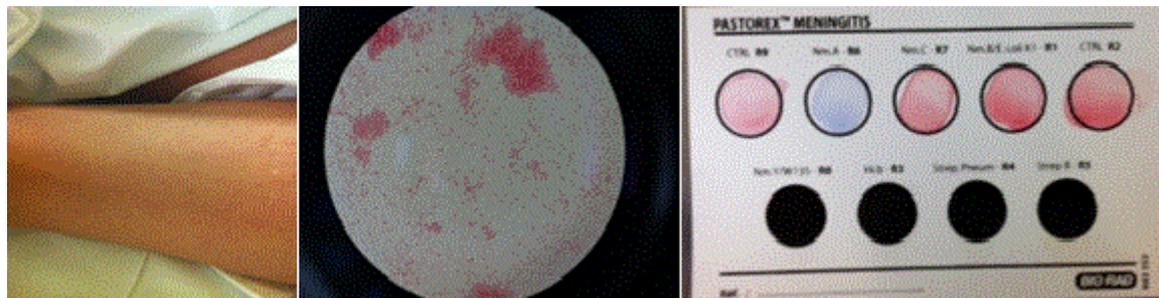


Figure 1: To the left, second case with few petechial lesions in the anterior side of her left leg. To the middle side, smear with Gram negative diplococci suggestive of *Neisseria* spp, found in both cases. To the right, positive coagglutination for group C *Neisseria meningitidis*, also present in both cases.

Signs and Symptoms in Both Patients

Sign/Symptom	Frequency	Case 1	Case 2
Diarrhea	99%	X	X
Fever	95%	X	X
Purpuric/petequial rash	62%		X
Neck stiffness	41%	X	
Hypotension	41%		X

Table 1: Signs and symptoms in both patients

Discussion

Neisseria meningitidis is a Gram negative aerobic diplococcus surrounded by a polysaccharide capsule, which is the main virulence factor. There are 13 serogroups defined by their capsular specificity of which 6 are clinically important: A, B, C, Y, X and W. Its prevalence varies temporally and geographically [3,4].

Meningococcal disease is characterized by the release of endotoxins that trigger an intense cytokine response in the host that can lead to shock, multiple organ failure and death within hours. Meningococcal meningitis occurs when the bacteria reaches the subarachnoid and ventricular spaces during bacteremia [1].

The highest incidence by age of invasive meningococcal disease is consistently observed in infants and children under 5 years, but high incidence rates are also observed in adolescents. The average age is 30 months (study from Arkansas) [5]. In a Croatian study, age incidence in patients under 1 year was 45%, in the group from 1 to 2 years was 22% and in the one from 3 to 6 years was 14% with a minimum rate in older patients [4]. In a Brazilian study, 71% of the cases of meningococcal disease occurred in children under 14 years and the rest between 14 and 60 years. Both in the American and in the Croatian report, greater involvement is reported in males (up to 62% of affected males versus 38% of affected females). In a series of Brazilian cases, females predominated in 51% [4-6].

The incidence of meningococcal disease in Latin America is highly variable. The true burden of disease may be underestimated [7]. In Mexico, *Neisseria meningitidis* is not endemic. However, from 2000 to 2009, 462 cases of meningococcal meningitis were reported.

Furthermore, 56% more cases than those recorded in the previous decade. The cases were distributed in all age groups. The group with the highest number of cases was the one with children under 1 year (22%), followed by the group of children aged 1 to 4 years (18%). In 2010, the Department of Epidemiology reported in Mexico City 42 cases (57% male and 43% female), and a rate of 0.04/100,000 (0.26 in less than 1 year, 0.12 in 1 to 4 years, 0.05 in 5 to 9 years, and 0.01 in 10 to 14 years) [8]. The actual incidence of disease in Mexico is reported as 0.06/100,000 inhabitants [7]. In this report both cases were female.

The prevalence of asymptomatic carriers of *Neisseria meningitidis* in the population of unvaccinated children and adolescents in Mexico ranges from 2.97 to 10.41%. It has been demonstrated the presence of nasopharyngeal carriers among prisoners, and an epidemiological link between cases of community-acquired disease in the last outbreak in Mexico City in 2010 and the strains isolated in inmates in the same period with the information generated by genetic analysis in both cases and the presence of ST11/ET-37CC, which is a hypervirulent meningococcal genetic line [7].

The serogroup C is prevalent in Mexico and Brazil, the serogroup B and recently the serogroup W in the Southern Cone. However, there have been cases with the 4 serogroups [9].

In meningococcal infection the most common signs and symptoms include fever (95%), purpuric/petechial rash (62%), neck stiffness (41%) and hypotension (41%). A 26% of the infected population requires inotropic support and mechanical ventilation [5]. It is not described in the literature a percentage of diarrheas as the initial presentation of meningococcal infection and reports are scarce.

Because one of the most important characteristics of *Neisseria meningitidis* is its ability to invade the meninges, patients with a lower bacterial growth and less blood cytokines have meningitis after 18 to 36 hours. In these patients, blood cultures are usually negative on admission. Due to the limited growth of bacteria in blood and meningococcal planting in the subarachnoid space, patients with meningitis have compartmentalized high concentrations of endotoxins and cytokines in the CSF [2].

Early diagnosis of meningococemia is difficult and requires clinical suspicion. The classical picture of meningococcal disease includes sudden-onset myalgias, chills and fever. After 4 to 6 hours, a transient clinical improvement may be hiding the real decline; also signs and symptoms may be absent or confusing. Initial cutaneous manifestations may resemble a viral rash. Neck is flexible and CSF is

inconclusive. Anecdotal reports of patients with meningococemia that are sent back home after medical exam denote the diagnostic difficulty at the beginning. Perhaps the best guide during the first hours is the concern of parents, since a 60% seek care for 2 or more times prior to hospital admission. Six to 12 hours later is easier to recognize meningococemia, when classical hemorrhagic lesions are seen [2]. Subsequently comes shock, disseminated intravascular coagulation, multiple organ failure and finally death [6].

The early stages of meningococcal meningitis resemble those of meningococemia, because the sudden entrance of *Neisseria meningitidis* in blood determines the initial symptoms. However, the course is typically more insidious. The hemorrhagic lesions are apparent 12 to 18 hours after the initial symptoms and 20% of patients never present these lesions. The diagnosis is obvious when all clinical data are evident (headache, nausea, vomiting, seizures and neurological deterioration) and with positivity in Gram stain, culture and coagglutination subsequently reported in CSF. When gastrointestinal symptoms are present but skin lesions or neurological symptoms absent, the diagnosis can be missed [2,6].

On the other hand, patients with meningococcal infection may present with signs and symptoms of unspecific infection [10,11]. There has been very rarely described in the literature a syndrome similar to gastroenteritis with diarrhea, vomiting and abdominal pain, [10] reason for this two-cases-presentation, as both of them had diarrhea and vomiting prior to the presentation of other typical signs and symptoms.

Meningococcal most serious infection may present as follows: sepsis with or without shock (20-39%), sepsis and meningitis (57.6-62%), and meningococcal meningitis or meningoencephalitis (3.4-18%). Here, the former case evolved with meningitis and the latter with sepsis and meningitis. This classification correlates well with duration of disease prior to hospitalization (5 days in the case of meningitis versus 20 hours in the case of sepsis and meningitis) [2-4,6]. The average time reported in the literature since the onset of illness until hospitalization is from 19 to 34 hours [11].

During the evolution of meningococcal meningitis, occasionally pneumonia, pericarditis, endophthalmitis, arthritis, sinusitis, otitis or osteomyelitis may be also found, which are referred as extrameningeal or systemic manifestations of meningococcal disease. Most systemic manifestations develop during the first 3 days of illness, suggesting a direct pathogenic mechanism induced by *Neisseria meningitidis* per se. If systemic manifestations develop after 7 days, it is more likely that an autoimmune mechanism be associated. These early or late manifestations complicate the evolution of the patient and prolong the need for treatment of meningococcal disease but do not influence on the final prognosis [12].

Cultures are usually reported positive after 12 to 24 hours, although it is difficult the recovery if prior use of antibiotics. Its detection is not affected thereby if antigen detection by PCR in blood or CSF is used [2].

Neisseria meningitidis is sensitive to penicillin and ampicillin, however, since the early 80's there have been detected penicillin-resistant strains. In Mexico, the frequency of resistance is unknown, but there are reports that refer to group C with a resistance as high as 77.7% to penicillin. Third generation cephalosporins are currently used for treatment because there has not been reported resistance [2]

Meningococemia mortality ranges from 20 to 80% according to different series and half of deaths occur in the first 24 hours after onset of symptoms. Skin and limbs necrosis requires amputation or plastic surgery in 10 to 20%. In meningococcal meningitis, mortality ranges from 1 to 5%, and is due almost exclusively to brain stem herniation secondary to intracranial hypertension. Eight to 20% of patients with meningococcal meningitis develop neurological sequelae ranging from sensorineural hearing loss, psychomotor/mental retardation, spasticity and/or seizures, to attention deficit [2].

The main causes of death are multiple organ failure (59%), cerebral edema (29%) and myocarditis (12%). There has been found a high clinicopathological correlation between septic shock and diffuse adrenal hemorrhage (77%), and between respiratory failure and lung injuries (77%), while the correlation is low between heart failure and cardiac lesions (27%), and between diarrhea and enteritis (25%). Myocarditis and microthrombi especially in skin, lungs, and kidneys, dominate in meningococemia and in meningococemia with meningitis, whereas diffuse adrenal hemorrhage and enteritis predominate only in meningococemia. The histopathological findings of enteritis and enterocolitis, especially associated with gastrointestinal bleeding, explain the presence of atypical meningococcal disease manifestations such as diarrhea and abdominal pain [3].

It is mentioned that early diarrhea is one of the signs that worse the prognosis, along with others such as decreased consciousness and cyanosis [3,11]. Other indicators of poor prognosis are extremes of life; a short period between the start of illness and hospitalization; the absence of meningitis; progressive or disseminated skin lesions and shock (capillary refill delayed, hypothermia, hypotension or metabolic acidosis); serum CRP normal or slightly elevated, absence of leukocytosis and the presence of thrombocytopenia; disseminated intravascular coagulation and hypofibrinogenemia; and high concentrations of serum cytokines [2].

Prevention with conjugate vaccines generates better antibody titers and some have better opsonization. The minimum age to give a meningococcal conjugated vaccine is 6 weeks old. A vaccine conjugated to a diphtheric toxoid protein (Menactra -Sanofi Pasteur- is approved for ages from 9 months to 55 years). There are other conjugated and polysaccharide vaccines of 1 and 4 serotypes. The recommended scheme is with the conjugated vaccine at 11 to 12 years old with a booster at 16 years old. Children aged 9 to 23 months with complement deficiency, traveling or living in endemic countries, or at high risk during an outbreak, should receive a series of 2 doses of Menactra with an interval of 3 months. Recently, the combined vaccine Hib-MenCY-TT (MenHibrix, GlaxoSmithKline) was approved by the American Academy of Pediatrics. However, everything depends on the epidemiology and the most affected age group in each country [13].

Conclusion

Neisseria meningitidis infection in the first 4 to 8 hours typically occurs with fever, irritability, nausea or vomiting, somnolence, decreased appetite, sore throat, runny nose and malaise, followed in 12 to 15 hours of hemorrhagic rash, neck pain, meningitis and photophobia, and after 15 to 24 hours confusion or delirium, seizures, unconsciousness and death. The average hospital admission ranges from 19 to 34 hours [14].

The literature shows only few reports of diarrhea as the main initial manifestation of meningococemia, this is the reason of the presentation of both cases. It draws attention to how this common sign

may be the first manifestation of a serious and often fatal condition, so it should not be ignored [10].

Early recognition of sepsis with or without meningococcal meningitis by parents, primary care physicians and physicians in training at the hospital remains difficult, but is extremely important.

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