Review

Meningococcal disease in childhood: epidemiology, clinical features and prevention

S. BOSIS, A. MAYER, S. ESPOSITO
Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Key words

Children • Invasive meningococcal disease • Meningococcal disease • Pediatric age • *Neisseria meningitidis*

Summary

Invasive meningococcal disease (IMD) represents a public health problem and a leading cause of morbidity and mortality worldwide. IMD can occur as an endemic disease with sporadic cases or epidemics with outbreaks. Neisseria meningitis strains are divided into 13 serogroups, but only five (A, B, C, W-135, and Y) are responsible for most IMD across the world. All age groups are at risk for IMD, but infants and adolescents are particularly vulnerable. The most common clinical manifestations of IMD are meningitis and septicemia, although in some cases both clinical pictures are present. The clinical pattern can differ according to age; in young children, the clinical manifestations may be more insidious and the diagnosis may be more difficult compared to older children or adolescents. Death occurs in 6-10% of cases and sequelae in 4.3-11.2% of cases. Early recognition of children with meningococcal infection is important in order to initiate systemic antibiotic therapy, although vaccination remains the best strategy to control meningococcal disease. Recently, different meningococcal vaccines have been introduced worldwide, resulting in a reduction in the overall burden of the disease. The goal of the next few years should be to increase vaccination coverage against meningococcal diseases, continue to monitor IMD and develop a unique vaccine able to cover all of the main meningococcal strains.

Introduction

Neisseria meningitidis is an anaerobic Gram-negative diplococcus that is responsible for invasive meningococcal disease (IMD), which represents a public health problem and a leading cause of morbidity and mortality worldwide [1, 2]. Globally, the incidence of IMD is 500,000 cases every year, although the incidence varies from <1 per 100,000 per year in North America and Europe to 10-1,000 per 100,000 per year in the "meningitis belt" of sub-Saharan Africa [3, 4]. Death occurs in 6-10% of cases and sequelae in 4.3-11.2% of cases [5].
Meningococcal carriage, which represents the first step of disease transmission, varies with age and setting. It is known that *N. meningitidis* colonizes the nasopharynx in up to 5-10% of adults who are asymptomatic. A recent study demonstrated that the carriage prevalence increases throughout childhood from 4.5% in infants to a peak of 23.7% in 19 year old subjects, then decreases to 7.8% in 50 year old adults [6]. This overview summarizes new data on meningococcal disease in children and the possibilities of its prevention.

Epidemiology

N. meningitidis strains are divided into 13 serogroups on the basis of the immunochemistry of their capsular polysaccharides; however, only five serogroups (A, B, C, W-135, Y, and X) are responsible for most IMD cases around the world [4]. IMD can occur as an endemic disease with sporadic cases or epidemics with outbreaks. All age groups are at risk for IMD, but infants and adolescents are particularly vulnerable due to the disappearance of maternal antibodies early in life and the high rate of nasopharyngeal colonization [2, 3]. Some settings, such as schools, university dormitories and barracks, are at high risk for *N. meningitidis* transmission. Moreover, low socioeconomic status, minority ethnicity, immune deficiencies and asplenia predispose individuals to meningococcal infection [2, 3].
The serogroups causing IMD vary geographically, mostly likely due to differences in population immunity and environmental factors. Meningococcus serogroup A (MenA) occurs in Africa and some areas of Asia, whereas serogroups B (MenB), C (MenC) and Y (MenY) are predominant in the other continents, including Europe and North America [2, 4]. In the 13 countries included in the African "meningitis belt", MenA was responsible for the majority of cases in 2007-2009, while meningococcus serogroup W135 (MenW135) predominated in 2010 and 2011 [4]. Although MenC is rare in Africa, in 2013 and 2014 two outbreaks due to a novel strain of MenC were reported in Nigeria and Kebbi, respectively [7]. Moreover, during 2006-2010 outbreaks of MenX were described in Niger, Togo, Kenya, Uganda, and Burkina Faso [8]. In Europe, MenB is the main cause of IMD, followed by MenC and MenY [4]. In countries with established MenC vaccination programs, the incidence of MenC disease has significantly declined [2, 4]. In comparison with the US, IMD caused by MenY is rare in

Europe. However, an increase in this serogroup has been reported in recent years, particularly in the Nordic European countries [9].

Clinical manifestation and sequelae

The most common clinical manifestations of meningococcal infection are meningitis and septicemia, although in some cases both clinical pictures are present [3, 10-12]. However, signs and symptoms at the onset of the disease, such as coryza and sore throat, may resemble those of common respiratory viral infections [11]. The incubation period varies from 1 to 14 days, although it usually lasts less than 2 days [11].
The clinical pattern can differ according to age, and it is not infrequent for children to be initially misdiagnosed. The clinical manifestations may be more insidious in young children, with non-specific signs; thus, diagnosis may be more difficult than in older children or adolescents. Irritability and lethargy are common features at this age. In some cases, seizures with focal onset may occur at the beginning of the disease. Moreover, neck stiffness is rare in children younger than 2 years of age [3, 10-12]. Bulging anterior fontanalle may occur in infants <18 months of age. In general, infants exhibit a more rapid progression of the disease compared to older children [12]. Similar to adults, in older children the most common symptoms are fever, nausea, vomiting, photophobia, headache, agitation, decreased level of consciousness and neck stiffness. However, seizure and focal neurological signs are less common [3, 10-12]. Septic shock is more common in children and progresses rapidly, with multiple organ failure and death occurring within 24 hours [3, 10-12]. Often, non-specific symptoms such as fever, drowsiness, nausea and vomiting, irritability and poor feeding are present within 4-6 hours from the onset of the disease [3, 10-12]. One of the most common symptoms associated with sepsis is a rapidly progressive hemorrhagic rash that usually starts on the lower extremities, although mucous membranes and sclera may be involved [3, 10-12]. Skin lesions include macules, maculopapules, urticaria, petechiae, purpura and ecchymoses. The purpuric rash may progress to purpura fulminans, a cutaneous manifestation of disseminated intravascular coagulation. These cases are often associated with septic shock and skin necrosis, ischemia, or infarction of digits or limbs that usually require amputation [3, 10-12]. Three clinical signs of early sepsis have been identified in children and adolescents: leg pain, cold hands and feet, and abnormal skin color. These features may suggest that the vital signs are compromised [11]. Some authors reported chronic meningococcemia that consisted of recurrent attacks of fever, arthralgia and/or arthritis associated with a rash and headache [3, 11].
IMD is a life-threatening disease with a very high rate of severe sequelae among survivors. In a recent article, Sadargani et al. evaluated the outcomes of IMD in 868 subjects (52% adults and 48% children) in Canada between 2002 and 2011. The mortality was lower in children than in adults, but 21% of children (particularly those < 5 years of age) had at least one complication compared with 15% of adults. The highest complication rates occurred in children with septic shock without meningitis, and the most common sequelae were hearing loss, deafness, seizure, amputation and skin scarring [13]. In a study that evaluated the outcome of IMD in 181 children < 15 years of age, the case fatality rate was 11.6% and at least one long-term sequelae was reported in 33% of patients: learning academic difficulties (22.6%), hearing impairment (7%), and neurological (12.2%), behavioral (14.8%) and motor (10.4%) deficits [14].
The duration of illness prior to admission and the presence of seizures, focal neurological deficits, depressed level of consciousness and low levels of cerebrospinal fluid glucose may be associated with a high risk of sequelae [11]. Wang at al. demonstrated that sequelae occurred in all children <1 years of age with IMD and a history of prematurity [15].

Treatment

Due to the severity of meningococcal disease including its high case fatality rate and possibility of sequelae, early clinical and laboratory diagnosis is very important. Lumbar puncture must be performed in all suspected cases with clinical signs and symptoms of IMD. In most cases, cerebrospinal fluid (CSF) reveals high opening pressure, pleocytosis, high protein levels and low glucose levels [10]. *N. meningitidis* should be detected in the CSF or blood by Gram staining, standard culture and/or polymerase chain reaction (PCR) [10, 11]. These examinations must be performed very quickly to avoid delays in the administration of therapy. Sometimes standard cultures may result in false negatives due to prior administration of oral antibiotic treatment that reduces the sensitivity of the exam. In these cases, PCR could be useful [10]. Lumbar puncture can be hazardous in patients with prolonged seizures, immunocompromised patients, in the presence of signs of space-occupying lesions and in patients with severe impairment of consciousness and shock [10].
Prompt and adequate intravenous antibiotic treatment is essential to stop the proliferation and kill *N. meningitidis*. Local antibiotic resistance should guide the choice of the antibiotic. In most cases, an intravenous third-generation cephalosporin (e.g., 100 mg/kg/day ceftriaxone administered i.v. in one daily dose or 100 mg/kg/day cefotaxime administered i.v. divided into three daily doses) should be used as the first choice of treatment. If these antibiotics are not available, intravenous penicillin should be started [10, 11]. If available, the result of antibiotic sensitivities could guide the continuation of the antibiotic therapy. The recommended duration of treatment is 7-10 days, although recent studies demonstrated that CSF sterilization may occur within 3-4 days [10, 11].
Prophylaxis is indicated and recommended only for close contacts of the index case (i.e., subjects who remained with the index case for more than 4 hours during the 7 previous days). In these cases, oral rifampicin

or ciprofloxacin are the drugs of choice according to age [11].

Meningococcal vaccines

Vaccination remains the best strategy to prevent meningococcal disease due to the high fatality rate and the significant sequelae that can result from the infection despite prompt antibiotic treatment. Recently, new meningococcal vaccines have been introduced worldwide, resulting in a reduction in the overall burden of the disease.

Since the introduction of the meningococcal serogroup C conjugate vaccine, the incidence of MenC disease has significantly declined [16]. Commercially available monovalent conjugate vaccines include Menjugate (MCC-CRM197), Meningitec (MCC-CRM197) and NeisVac (MCC-TT). Quadrivalent vaccines containing the meningococcal ACWY serogroups conjugated with different proteins have also been produced. Those available in the market are Menactra (ACWY-DT) licensed for children aged 2-55 years, Menveo (ACWY-CRM197) licensed in Europe and the US for children ≥2 years of age and Nimenrix (ACWY-TT) licensed in Europe for infants ≥12 months of age. These conjugated vaccines have proven to be safe and effective in protecting individuals against meningitis; moreover, these vaccines have demonstrated herd immunity by interrupting carriage transmission [17-19]. The quadrivalent polysaccharide vaccines Menomune and Mencevax have also proven to be safe and elicit bactericidal antibodies in older children and adults; however, they are not used in routine vaccination programs due to their poor immunogenicity in young children, short-term protection and inability to produce herd immunity [16, 18]. Unfortunately, quadrivalent ACYW meningococcal vaccines (conjugated or polysaccharide) are not widely used in developing countries due to high costs. An effective and safe conjugate vaccine against MenA (MenAfrivac) first licensed in India in 2009 was introduced into the African "meningitis belt" in 2010 for subjects between 1-29 years of age; this vaccine is being implemented in these regions with the goal of protecting the entire population at risk by the year 2016 [18].

Considering the high incidence of MenB disease in developed countries, the production of a vaccine effective against this serotype was a priority. However, vaccines against MenB were difficult to produce. Because the external polysaccharide capsule of MenB resembles the adhesion molecules on the surface of neural cells, conjugate vaccines were not protective against MenB disease and moreover could induce an autoimmune response [5, 20]. The first vaccine that showed a partial efficacy against MenB disease was produced in Cuba, New Zealand and Norway, but it was strain specific and therefore was used only to control the epidemics [5]. For these reasons, this vaccine could not be considered effective against the different MenB strains that cause epidemics worldwide. After several attempts, a multicomponent MenB vaccine (4CMenB, Bexsero) that covered different strains was produced using reverse vaccinology [5, 21]. 4CMenB was composed of four components: the first component was the factor H binding protein (fHbp) fused with the GNA 2091 protein, the second was Neisseria adhesion A (NadA), the third was the Neisseria heparin binding protein (NHba) fused with the GNA 1030 protein, and the forth component was OMV NZ98/254, which has several antigen components (the major component is PorA). The three antigens fHbp, NadA and NHba evoke serum bactericidal antibodies, while the two antigens GNA 2091 and GNA 1030 improve the immunogenicity of the major antigens when fused with them [5, 20]. In January 2013, 4CMenB was licensed in the European Union and thereafter in Australia and Canada for use in subjects older than 2 months of age [5, 20]. Considering the low incidence of IMD, it is quite difficult to evaluate the impact of any meningococcal vaccine through randomized controlled clinical studies. Although serological methods could be used to evaluate the protection of other meningococcal vaccines, these methods could not be used for 4CMenB due to the high number of genetically different MenB strains that cause IMD. To overcome this problem, the vaccine's manufacturer used a new method called the meningococcal antigen typing system (MATS) that uses a unique vaccine antigen-specific ELISA capable of detecting qualitative and quantitative differences in the fHbp, NHba, and NadA antigens; then, the results are combined with PorA typing information [5]. The results from the analysis of 1,052 MenB strains isolated from different countries in Europe showed that 4CMenB could protect against 68%-88% of MenB strains [5]. A bivalent fHbp recombinant vaccine (also known as LP2086; Trumenba) has been developed since 2006 and has now been approved by the US Food and Drug Administration for use in 10- to 25-year olds [26]. This vaccine appeared to be safe in a phase 3 study in approximately 5,600 healthy individuals aged 10 through 25 years and was immunogenic and safe when co-administered with routine meningococcal A, C, Y, and W and tetanus, diphtheria and pertussis (Tdap) vaccines in a phase 2 study in more than 2,600 healthy individuals aged 10 through 12 years [26]. Studies on this vaccine are ongoing in Europe, and approval from the European Medicines Agency is expected in 2017.

In the future, optimal preventive strategies necessitate a unique vaccine against MenA, B, C, W, and Y. A recent phase 2 study assessed the immunogenicity, safety and reactogenicity in healthy adolescents of an investigational formulation of a meningococcal ABCWY vaccine consisting of recombinant proteins (rMenB) and OMV components of a licensed serogroup B vaccine combined with components of a licensed quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) [23]. The authors showed that the investigational MenABCWY formulation containing OMV components elicited a high response against all strains with an acceptable safety profile [23].

Due to the emergence of MenX in Africa in the last decades, it is extremely important to develop a new vaccine that is effective against this serotype. No licensed vaccine

is available at present, but interesting data were reported in a recent study conducted in mice that evaluated the immunogenicity of the MenX outer membrane vesicles (X-OMV) or MenX polysaccharide (X-PS) combined with a bivalent AW-OMV vaccine previously demonstrated to be immunogenic in mice [24]. The authors demonstrated that a high antibody response was induced after two doses of X-OMV alone or combined with AW-OMV. In contrast, X-PS was not immunogenic alone but was immunogenic in combination with AW-OMV.

Conclusions

IMD represents a severe and life-threatening problem for the worldwide community. Early recognition of children with meningococcal infection is mandatory in order to immediately start systemic antibiotic therapy and avoid death or long-term sequelae. Vaccination represents the best strategy to prevent meningococcal disease. Recently, the introduction of new conjugate vaccines that are effective in very young children has significantly reduced the incidence of IMD in many countries. Moreover, the availability of new vaccines against MenB will permit a further increase in preventive possibilities against IMD. The goal of the next few years should be to increase vaccination coverage against meningococcal diseases, continue to monitor IMD and develop a unique vaccine able to cover all of the main meningococcal strains.

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■ Correspondence: Susanna Esposito, Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Commenda 9, 20122 Milano, Italy - E-mail: susanna.esposito@unimi.it

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