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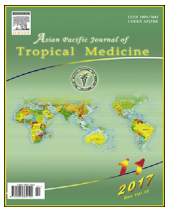

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Meningococcal disease, a clinical and epidemiological review

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ABSTRACT

Meningococcal disease is the acute infection caused by *Neisseria meningitidis*, which has humans as the only natural host. The disease is widespread around the globe and is known for its epidemical potential and high rates of lethality and morbidity. The highest number of cases of the disease is registered in the semi-arid regions of sub-Saharan Africa. In Brazil, it is endemic with occasional outbreaks, epidemics and sporadic cases occurring throughout the year, especially in the winter. The major epidemics of the disease occurred in Brazil in the 70's caused by serogroups A and C. Serogroups B, C and Y represent the majority of cases in Europe, the Americas and Australia. However, there has been a growing increase in serogroup W in some areas. The pathogen transmission happens for respiratory route (droplets) and clinically can lead to meningitis and sepsis (meningococcemia). The treatment is made with antimicrobial and supportive care. For successful prevention, we have some measures like vaccination, chemoprophylaxis and droplets' precautions. In this review, we have described and clarify clinical features of the disease caused by *N. meningitidis* regarding its relevance for healthcare professionals.

1. Introduction

Meningococcal disease (MD), known for more than 200 years, is recognized as a worldwide public health problem due to its cosmopolitan distribution, potential to cause outbreaks or epidemics, the greater impact on children and teenagers (especially during epidemics), high mortality rates and significant morbidity represented by complications of the disease, especially permanent neurologic damage [1–4]. Furthermore, MD is associated with high financial costs both in patient treatment and rehabilitation, thus, the investments in prevention of this disease through use of conjugated antimeningococcal vaccines appears to be a cost-effective public health measure [5–9].

Neisseria meningitidis (*N. meningitidis*) is a pathogen capable of causing extremely severe conditions in humans, especially meningococcal meningoencephalitis (MM) and meningococcemia [10]. With regards to meningitis, *N. meningitidis* was the primary etiology of acute bacterial meningitis (ABM) in Brazil during the period of 2010–2013 (Ministério da Saúde/SVS), and the second most common cause of community-acquired bacterial meningitis among adults in the United States [11]. With regards to meningococcemia, it is probably the infectious condition most rapidly fatal to a human being, with 92% of deaths reported within the first two days of hospitalization [1]. However less severe clinical conditions caused by meningococci can occur in less than 5% of cases [12].

The presence of fever and cutaneous alterations petechia or purpura in an acutely ill patient should mandatorily evoke in the physician, the hypothesis of MD [1]. Because it is an infectious

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emergency, on considering this diagnostic hypothesis the time between suspicion and institution of antimicrobial therapy should not be greater than half an hour [13–15]. Under no circumstances should therapeutic delays, for collection of exams or for transfer of the patient to larger healthcare units, be allowed [1,14].

In this article we present a review of the principal microbiological, epidemiological, pathophysiological, diagnostic, therapeutic, and preventive measures of MD.

2. Etiology

Microorganisms of the species *N. meningitidis* are gram-negative cocci grouped in pairs (diplococcus) with typical morphology (bean or kidney-shaped), with humans as their sole natural host. They neither form spores nor possess flagella, but have fimbria (pili) [1]. They are aerobic agents, catalase-positive, oxidizing glucose and maltose with acid production and without gas formation. They grow well in chocolate and blood agar at temperatures between 35 °C and 37 °C, requiring an atmosphere of 5%–10% carbon dioxide [16]. *N. meningitidis* is a frequent colonizer of the human naso- and oropharynx, but can be found in other areas of the body such as the anal mucosa, the conjunctiva and the urogenital tract [17].

The main virulence factors of *N. meningitidis* include:

(1) The polysaccharide capsule: a structure that protects the etiologic agent from complement-mediated phagocytosis and lysis [18], and is important for the differentiation of serogroups (total of 13) [10,12,17]. In human illness notable serogroups include A, B, C, W, X and Y [16,19];
(2) Lipopolysaccharide is an endotoxin (so-called because it presents in the bacterial wall), and very important to *N. meningitidis*, responsible for toxic shock, meningococcal adhesion and activation of the innate immune system [17]. *N. meningitidis* can be divided into 13 immunotypes (according to lipopolysaccharide structure) [16,18];
(3) Adherence factor: type IV pilus, that binds to CD46 receptors, is a complex protein structure, located on the external plasma membrane, which plays an important role in pathogen adherence to epithelial and endothelial cells of *Homo sapiens sapiens* and also in the "capture" of DNA molecules from the human host, diversifying and incrementing the meningococcal genome [6,18];
(4) External membrane proteins belonging to the porine class, believed to participate in adhesion and invasion of the host cell, which induces calcium influx and apoptosis of epithelial and phagocytic cells, in addition to activating Toll-like 2 receptors [16,12,46];
(5) Iron incorporation: when there is reduced iron in the extracellular medium, the bacteria express proteins present on its external membrane that capture iron from lactoferrin and transferrin in the medium and internalize it [16–18].

3. Epidemiology

Epidemics are historically common in sub-Saharan Africa (known as the African meningitis belt) since 1905, with periodicity every five to ten years [19]. The annual incidence of MD during these epidemics can reach 1 200 cases per 100 000 inhabitants [19–21]. In developed nations (North America, Europe and Australia), the disease tends to be endemic, with an estimated incidence ranging from 0.3 to above 3 cases per 100 000 inhabitants [20,21].

MD is also endemic in Brazil, with a periodic occurrence of epidemics in some cities [22]. In Brazil, there are records of four epidemic "waves" involving MD: a) 1920 to 1925 (serogroup A); b) 1945 to 1951 (serogroup A); c) 1971 to 1977 (serogroups C and A) and d) 1988 to 2002 (serogroups B and C). Of these, the epidemic that emerged in the 1970's was the most catastrophic in Brazil's history [23].

Serogroup A was the predominant MD etiology in Europe before and during the First and Second World Wars. While serogroup B was dominant in Europe in the 1970's and in South America in the 1980's, in the XXI century epidemics arose associated with serogroups W and Y. There was a deviation in the age range affected by MD with an increased incidence in the elderly, a fact associated with serogroup Y [24]. Additionally, there was a decline in MD cases caused by serogroup C in adolescents, due to implementation of routine vaccination against meningococci of this serogroup, leading to a reduction in the number of healthy carriers as well as the incidence of MD, with consequent emergence of collective immunity [24,25]. Recent epidemics caused by serogroup W occurred in some South American countries, but serogroups B and C are still responsible for most cases of MD on this continent [26]. The epidemiologic tendency of MD has remained relatively constant in Africa, with serogroup A the primary etiologic agent, although recently serogroups X and W were responsible for a large proportion of morbi-lethality of MD in that continent [24]. Serogroup A conjugate vaccine (MenAfriVac) began distribution to millions of 1–29 years old in Mali, Niger, and Burkina Faso. Benefits were immediate, with a drop in incidence rate of meningococcal A meningitis of 99% in Burkina Faso within the first year [27]. Serogroup A carriage was eliminated in both vaccinated and unvaccinated populations for up to 13 mo after the mass vaccination campaign [28]. In Asia, large epidemics caused by serogroup A occurred historically in China, India, Nepal and Russia, more recently serogroups B and C were responsible for the majority of MD cases on this continent. Since the 1990's, serogroup W is the principal etiology of MD in Hajj pilgrims and their close contacts [16].

In Brazil, according to Sistema de Informação de Agravos de Notificação data, from 2010 to 2013, the number of confirmed MD cases varied between 2 083 and 3 003 and its incidence (per 100 000 inhabitants) varied between 1 and 1.5 (Ministério da Saúde/SVS). According to SIREVA II (conducted by the Pan-American Health Organization), in 2012 the distribution of MD cases in Brazil, by identified serogroups, was as follows: 71% from serogroup C, 19% from serogroup B, 6% from serogroup W and 4% from serogroup Y [29].

Lethality rates ranging from 10% to 20% were reported in recent years in several Latin American countries: Chile (14% in 2010), Argentina (7%–15%), Panama (13%), Mexico (18% between 2005 and 2008) and Uruguay (15%) [30]. However, a high lethality rate (21%–22% between 2010 and 2013) is still reported in Brazil (Ministério da Saúde/SVS), despite increased availability of intensive care units and improvements in healthcare [30]. During the recent MD epidemics, which were associated primarily with serogroup C, a very high lethality rate was reported (approximately 40%). Usually the MD associated lethality rate averages 10% (without important differences observed worldwide) that is lower than the rate