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Meningococcal Meningitis: Etiology, Diagnosis, Epidemiology and Treatment

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Abstract Scientific knowledge of meningococcal infection has increased greatly since the epidemic nature of the illness was first described by Vieusseux at the dawn of the nineteenth century (1805). Meningococcus is a pathogenic member of the *Neisseria* genus and classified in the family Neisseriaceae. It is a Gram-negative coffee bean shaped, aerobic, diplococcus, naturally inhabiting the human pharynx. Meningococcal disease occurs worldwide as an endemic disease with seasonal variations. The incidence varies in the human population from rare to over 1000 per 100,000 in different parts of the world, outbreaks occur every 8 to 12 years, frequently resulting in attack rates of 500 to 1000 cases per 100,000 population. However, the most common manifestations of meningococcal disease are meningitis, where the bacteria can be found in the cerebrospinal fluid (CSF), and septicemia, where the bacteria are found in the blood. The overall mortality in patients suffering from meningococcal disease is about 10%. The clinical course of severe septicemia is rapidly progressive, where the time from onset of fever until death can be as short as 12 hours. In meningitis patients, 8 to 20% of the survivors suffer from neurological sequelae, varying from deafness and mental retardation to concentration disturbances. The gold standard for definitive diagnosis of meningococcal disease is isolation of meningococci from a normally sterile body fluid. Effective antibiotics immediately stop the proliferation of meningococci.

Keywords Meningococcus, Identification, Epidemiology, Treatment

1. Introduction

The meningococcus is a pathogenic member of the Neisseria genus and classified in the family Neisseriaceae along with the genera Kingella, Eikenella, Simonsiellaand Alysiella. The family is placed in the β-subgroup of the phylum Proteobacteria. The Neisseria genus contains two human pathogens, N. meningitidis and N.gonorrhoeae (the gonococcus). Several other Neisseria species such as N. lactamica, N. sicca, N. subflava, N. mucosa, N. flavescens, N. cinerea, N. polysacchareaand N. elongataare also found inhuman but are considered primarily non-pathogenic [1].

The meningococcus is a Gram-negative coffee bean shaped aerobic diplococcus, naturally inhabiting the human pharynx. It can be encapsulated or unencapsulated [2]; the polysaccharide capsule of the meningococcus is an important virulence factor for the bacterium and plays a crucial role in invasive meningococcal disease. The capsule promotes transmission and colonization, it protects the bacterium from dehydration, phagocytic killing, opsonisation, and complement mediated killing [3]. Only encapsulated meningococci regularly cause invasive disease. Based on the biochemical composition of the capsule, meningococci can be divided into 13 serogroups, but only six of these (A, B, C, W-135, Y and X) are currently associated with significant pathogenic potential [4, 5].

In non-epidemic settings approximately 10% of healthy individuals, carry meningococci in their upper respiratory tract [6], however bacteria spread from person to person by direct physical contact or airborne by droplets that contain viable organisms [1, 7]. Rates of transmission and carriage increase in closed and semi-closed populations, such as military recruits, university students and in household contacts of a case of meningococcal disease [4). Carriage is an age dependent phenomenon; it increases from less than 3% in young children 0-4 years, peaking to (24-33%) carriage in the ages 15-24 years, thereafter declining steadily [6]. The duration of carriage can differ substantially, from a chronic state to an intermittent or transient state [8]. In addition to asymptomatic carriage, the meningococcus can cause a spectrum of diseases, from a benign self-limiting infection to fulminant septic shock. The common manifestations of meningococcal disease are meningitis, where the bacteria can be found in the cerebrospinal fluid (CSF), and septicemia, where the bacteria are found in the blood. Meningitis alone is present in 30 to 50% of patients, with a relatively low mortality

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(approximately 5%). About 10% of the patients present with septicemia alone. In these patients the mortality rate can be considerably higher, (5 to 40%). Finally, 40-60% of the cases display a mixed picture of both meningitis and septicemia. The clinical course of severe septicemia is rapidly progressive, where the time from onset of fever until death can be as short as 12 hours; if the disease is not treated early, patients with septicemia may progress to hemodynamic collapse and multi-organ failure [9]. In meningitis patients, 8 to 20% of the survivors suffer from neurological sequelae, varying from deafness and mental retardation to concentration disturbances [10]. The symptoms of meningococcal meningitis include: headache, fever, vomiting, photophobia, neck stiffness and lethargy. Septicemia is characterized by fever, rash, vomiting, headache, flu-like symptoms and abdominal pain [11].

A recent study on clinical recognition of meningococcal disease in children and adolescents noted that the classical features developed later on disease progression (median time of onset 13-22 hours after symptoms began), whereas less specific features (such as fever, headache, loss of appetite and nausea) developed early and lasted for about 4 hours in younger children and up to 8 hours in adolescents [12]. Despite today's intensive care, overall mortality in patients suffering from meningococcal disease is about 10% [9].

2. Identification and Characterization of Meningococci

The gold standard for definitive diagnosis of meningococcal disease is isolation of meningococci from a normally sterile body fluid, CSF or blood. After culturing, the colonies should be examined microscopically by Gram-staining and tested for rapid oxidase production and sugar degradation. Meningococci degrade glucose and maltose, but not sucrose, fructose or lactose. Glucose- or maltose-negative isolates may, however, be isolated occasionally [1]. The presence of meningococci in CSF may also be confirmed by antigen detection with, for example, direct latex agglutination, a method often used in Africa [13]. Negative culture results due to antibiotic treatment prior to sample collection are common. For this reason, several non-culture methods based on PCR technique and DNA sequencing for identification of meningococci has been developed [14]. The cell surface components of meningococci display high levels of variation and can be used for characterization and classification of the bacteria. Traditionally, differentiation of divergent meningococcal strains has been performed by the use of monoclonal or polyclonal antibody panels against phenotypic markers, such as the capsular polysaccharide for serogroup, the PorA and PorB proteins for subtype and type, respectively, and lipooligosaccharide for immunotype. In addition, antibiogram of the different meningococcal strains has been used. The agar dilution method is the "gold standard" for antibiotic susceptibility testing. The minimum inhibitory concentration (MICs) of several different antibiotics is determined and the susceptibility pattern can be used for differentiation of isolates [15].

3. Epidemiology of Meningococci Disease

Meningococcal disease occurs worldwide as an endemic disease with seasonal variations. The incidence varies in the human population from rare to over 1000 per 100,000 in different parts of the world [3, 16]. The epidemics usually start in the beginning of the dry season and end quickly when the rains start, only to break out again when the subsequent dry season starts. The reason for this pattern is not fully understood, but environmental factors, such as absolute humidity, dust concentrations and a higher number of respiratory tract infections due to the cold nights, have been confirmed as important factors [17]. However; early research noted the occurrence of epidemics during the dry, dusty season, and it is hypothesized that high temperatures coupled with low humidity may favor the conversion of benign meningococcal meningitis bacteria in the nose and throat to a pathogenic bacteria by damaging the mucosa and lowering immune defense [18].

The rates of meningococcal disease are highest in young children because of their reduction of protective maternal antibodies and then increasing again for adolescents and young adults [19]. Certain lifestyle factors common among adolescents and young adults increase their risk. Everyday adolescent activities can lead to increased risk. Sharing a bite of food, a drink, utensils, or any activity where respiratory secretions, throat secretions, and saliva are exchanged can definitely spread the disease.But other lifestyle factors may also contribute, including crowded conditions at college dormitories.

In endemic situations serogroup B is most common in infants, serogroup C in adolescents and serogroup B and Y in older adults [3]. Risk factors for meningococcal disease include young age, winter or dry season, close contact with a case of meningococcal disease, overcrowding, active or passive smoking and co-infections of respiratory pathogens [20]. In addition, complement deficiencies, defects in sensing or opsonophagocytic pathways, combinations of inefficient variants of Fc"-receptors and immune suppression predispose for invasive meningococcal disease [21].

The first clearly described outbreak of invasive meningococcal disease was in Geneva, Switzerland in 1805 [22], on following year, typical cases of meningococcal meningitis (cerebro-spinal meningitis) were seen in New England [23] and epidemics occurred across Europe and North America throughout the nineteenth century. In 1840, the first outbreak in Africa was reported among French troops based in Algiers [24] and during the latter half of the 19th century several outbreaks occurred in Egypt and the

Sudan [25]. However, it was not until 1905 that the first major epidemic in West Africa was reported [26]. The most severe epidemic of meningococcal meningitis experienced by Africa was in 1996, with more than 150,000 reported cases and 16,000 deaths. In 2002, Burkina Faso was the first country to experience a major serogroup W135 epidemic, with 13,000 reported cases, and 1,400 deaths. [27] During the 2012 epidemic season, 19 African countries using enhanced surveillance reported a total of 22 673 suspected meningitis cases including 1931 deaths (case-fatality rate [CFR], 8.5%). The epidemicactivity was concentrated in 2 foci, one in West Africa, which affected mainly Burkina Faso, Benin and Ghana (plus, to a lesser extent, Côte d'Ivoire), and the other in Central Africa, in Chad [28].

Epidemic meningococcal disease remains a major public health challenge in the African meningitis belt [1]. The concept of a meningitis belt was first described by Lapeyssonnie in 1963. The belt stretches over Africa from Senegal in the West to Ethiopia in the east and is bounded to the North by the Sahara and to the South by the areas of tropical rainforest [29]. This zone comprises 22 countries and a population of >400 million. The burden of the disease in this area is considerable, owing to hyper endemic meningococcal disease and intense recurring large-scale epidemics with annual incidence reaching 1000 cases per 100 000 population. During 1993–2012, nearly 1 million (947 000) suspected meningitis cases were reported, including an estimated 100 000 deaths. The most recent large-scale meningitis epidemic in the African meningitis belt occurred in 2009, when nearly 80 000 cases were reported and the epidemic threshold was crossed in 210 districts, mostly in Nigeria. Subsequent epidemic seasons have been milder [28]. A statistical analysis of cases and meteorological conditions across this belt during 2009–2011 showed that dry conditions are conducive to meningitis epidemics, and that the epidemics end with the high humidity associated with the onset of the rainy season [18]. In this belt the rates of meningococcal disease were several times higher than in industrialized countries, and the reported mortality was usually approximately 10 percent, a rate similar to that in industrialized countries. However, the estimated figures are most likely an underestimation, which is due to both a breakdown of the normal reporting systems and the fact that many patients with septicemia die before they reach a hospital [30]; outbreaks occur every 8 to 12 years, frequently resulting in attack rates of 500 to 1000 cases per 100,000 populations [18, 31]. In 1996, the largest outbreak ever reported occurred in the meningitis belt; the total number of cases reported to the World Health Organization (probably a substantial underestimate) was 152,813 with 15,783 deaths [32]. In Africa, meningitis belt, epidemics of acute meningitis can reach incidence rates of 1000 cases /100,000 inhabitants and, in individual communities, attack rates as high as 1:10 of the population have been reported [30].

Serogroups A, B, and C account for most cases of meningococcal disease throughout the world, with serogroups B and C responsible for the majority of cases in Europe and the Americas and serogroups A and C predominating throughout Asia and Africa [31]. Israel and Sweden are the only countries, other than the United States that have reported an increase in serogroup Y disease [33].

During recent years, strains of other serogroups, such as serogroup C, W-135 and X, have also been involved [33]. Several studies have shown that while there is enormous diversity in the meningococcal population, and especially within isolates from asymptomatic carriers, most cases of invasive meningococcal disease globally are caused by strains from a limited number of clonal complexes, i.e. hyper-virulent lineages. However, in the 1970s and 1980s different serogroup B strains, caused epidemics in Norway, Cuba and Chile [35]. Another Serogroup B isolates, were also responsible for the NewZeeland epidemic that started in 1991s [36].

During the 1990s, a serogroup C variant spread throughout Europe and resulted in an increase of disease and outbreaks among teenagers [37]. The serogroup W-135 isolates were responsible for outbreaks of disease among Hajj pilgrims in Mecca, Saudi Arabia, in 2000 and 2001s. This clone spread worldwide and caused disease in returning pilgrims and their close contacts [38]. Perhaps as a result of this, the first large epidemic caused by serogroup W-135 occurred in Burkina Faso in 2002s, resulting in 12,000 cases [39]. In Niger, meningococcal isolates of serogroup X were responsible for about 50% of the confirmed cases during 2006, and in the south west parts of the country for as much as 90% [40]. In 2007 meningitis killed nearly 2,000 people in four African countries; Sudan, Burkina Faso, Uganda and the Democratic Republic of the Congo [41].

In recent years, there has been an increase of serogroup Y in the USA, Sweden and Israel [4, 33]. The rates of endemic disease in Europe in 2004 varied from 0.3 to 4.9 cases per 100,000 inhabitants while in recent years, the incidence of meningococcal disease has mainly decreased in the Western world. In Sub-Saharan Africa and in Asia, large epidemics, due mainly to serogroup A, are still common [42]. Meningococcal disease affects both males and females with similar incidence, but some studies reported increased incidence in males [43].

4. Treatment and Prophylaxis

The continuously increasing antimicrobial resistance in many bacterial pathogens is a serious public health threat worldwide. However the meningococcus has mostly been an exception that in general has remained susceptible to the antibiotics used for treatment and prophylaxis [44].

Effective antibiotics immediately stop the proliferation of meningococci [45]. All meningococci in cerebrospinal fluid are killed three to four hours after initiation of intravenous treatment with an appropriate antibiotic in an adequate dose [46] and the concentrations of meningococcal endotoxin in plasma decrease by 50% within 2 hours [45].

In Africa the general recommendations for treatment

during endemic periods are: ceftriaxone (2 gX1, IV for 5 days), in multiple doses to provide effective treatment also of other presumptive etiological agents of bacterial meningitis, such as *Streptococcuspneumoniae* and *Haemophilus influenzae*or multiple doses of penicillin. During meningococcal epidemics, the recommended treatments are: single dose of chloramphenicol in oil [3, 34]. The recommended treatment for adults with suspected acute bacterial meningitis patients in industrialized countries is usually an extended-spectrum third generation cephalosporin: for example, in Sweden, cefotaxime (3 g X4, IV) or ceftriaxone (2 g X2 or 4 g X1, IV) in combination with ampicillin (3 g X4, IV) alternatively monotherapy with meropenem (2 g X3, IV) [47]. After identification of meningococci, the antibiotic treatment should be continued with penicillin G or a third generation cephalosporin. The treatment is recommended efficiently eradicate meningococcal isolates from the nasopharynx and ceftriaxone is the first choice prophylaxis for pregnant women [48]. In African meningitis belt, chemoprophylaxis to close contacts of patients is rarely used and is not recommended by the WHO [49], because of the problem with logistic, costs and the danger of enhancing emergence of resistance strain while in the western world, on the other hand, chemoprophylaxis is often used, and ciprofloxacin and rifampicin are recommended antimicrobial agents [3].

During the past decades, there have been reports of emerging resistance in the meningococcal; increased levels of reduced susceptibility to penicillin have been reported worldwide [44, 50, 51]. This reduced susceptibility has been mainly due to alterations in the penicillin-binding protein 2 (PBP2), encoded by the *penA*gen [44, 50]. Furthermore, resistance to chloramphenicol has been reported from Australia, France and Vietnam [52]. This resistance is considered to be mainly due to the presence of the *catP*gene, encoding the enzyme chloramphenicol acetyltransferase. Resistance to ceftriaxone has been reported from India [53]. However, in recent years, there have been reports of reduced susceptibility to ciprofloxacin [54) and rifampicin from several countries worldwide [55].

Today, many meningococcal isolates are resistant to sulfonamide and hence this drug is no longer used for prophylactic treatment. Instead, mainly ciprofloxacin and rifampicin are used [3].

In addition to antibiotic treatment, aggressive management of raised intracranial pressure reduces mortality. Management of shock through the use of volume expansion, intensive care monitoring, inotropic support and correction of haemostatic metabolic abnormalities can also reduce the fatality rates of meningococcal septicemia from over 30% to less than 5% [3, 11]. Another way to prevent mortality and morbidity following meningococcal disease in a longer perspective is by vaccination. Today, there are protective vaccines available against serogroup A, C, W-135 and Y, as well as against certain specific types of 27 serogroup B meningococci. The protective effect of vaccination is good and immunity is presumed to last up to three years with polysaccharide vaccine and longer with the new conjugate vaccine. However, there is still no broad vaccine available that covers all serogroup B strains [48]. Until 2010, the primary strategy for managing meningitis outbreaks was reactive vaccination with the bivalent (A, C) or trivalent (A, C, W135) polysaccharide vaccines. [18] Introduction of the meningococcal A conjugate vaccine (MACV) in the African meningitis belt began in 2010; by the end of 2012, more that 100 million people in 10 countries had been vaccinated. This campaign, which is planned to cover >300 million persons aged 1–29 years in 26 countries by the end of 2016, is expected to have a significant impact on the epidemiology and burden of meningitis in this region [28].

Anticapsular antibodies play a major part in the protection against meningococcal disease, and the capsule forms the basis for both the licensed polysaccharide vaccines and the new conjugate-polysaccharide meningococcal vaccines [56]. However, meningococcal vaccines remain underutilized globally, particularly in resource-limited countries outside the African meningitis belt [57].

5. Conclusions

Neisseria meningitidis is one of the leading causes of bacterial meningitis globally and can also cause sepsis, pneumonia, and other manifestations and if untreated, may be fatal with case fatality rates reaching 5- 10%. Vaccines are available for the majority of serogroups that cause disease and have proven effective in reducing the disease incidence in countries that have applied them at the population level.

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