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Review

Meningococcal pneumonia

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ABSTRACT

Neisseria meningitidis remains the most important cause of bacterial meningitis worldwide, particularly in children and young adults. The second most common and a potentially severe end-organ manifestation of invasive meningococcal disease (excluding systemic sepsis) is meningococcal pneumonia. It occurs in between 5% and 15% of all patients with invasive meningococcal disease and is thus the second most common non-systemic end-organ manifestation. To establish the diagnosis requires a high level of clinical awareness – the incidence is therefore very likely underreported and underestimated. This review of 344 meningococcal pneumonia cases reported in the Americas, Europe, Australia, and Asia between 1906 and 2015 presents risk factors, pathogenesis, clinical manifestations, diagnostic approaches, treatment, and prognosis of meningococcal pneumonia.

Contents

1. Introduction

Invasive meningococcal disease (IMD) is feared for its rapid progression from health to death or permanent disability within as little as 24 h [1]. The disease is caused by infection with a Gram-negative diplococcus, *Neisseria meningitidis* (meningococcus), member of the phylum ß-proteobacteria and of the bacterial family *Neissericaceae*. IMD occurs worldwide and year-round. The annual incidence of IMD varies between 0.4 and 1000 cases/100,000 population with low rates in North America and Europe and epidemics occurring particularly in sub-Saharan Africa [2–5]. IMD may, however, be underreported as well as underdiagnosed even in European countries [6]. The majority of cases are noted during winter and early spring and in children and teenagers although all age-groups may be affected [7]. The rates of disease are highest among infants in whom protective antibodies have not yet developed; the rates drop after infancy and then increase again during adolescence and early adulthood [7]. In these two age groups, meningococcal meningitis is the leading cause of bacterial meningitis, and in adults, it is the second most common cause of community-acquired bacterial meningitis [2,8]. In a survey conducted in the Netherlands between June 1999 and 2011

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only 8% (69 of 874) of all cases were reported in patients aged ⩾65 years [9].

In the pre-antibiotic era, the mortality of meningococcal infection was 70–90% [10]. The prognosis of the disease improved dramatically with the advent of antimicrobial treatment options. Still, overall case-fatality rates decreased only to 10–15% percent by the late 1960s and remained at this level despite further major advancements in supportive care [2,11,12]. Moreover, 11–19% of survivors have long-term sequelae including neurologic disability, limb or digit loss, and hearing loss [13,14].

Meningitis is one of the most severe manifestations of IMD, particularly in children and young adults, and affects about 50% of patients [7,15]. At the onset of symptoms, clinical manifestations may be difficult to distinguish from other acute neurological diseases. Symptoms include sudden onset of fever, nausea, vomiting, headache, decreased ability to concentrate, neck stiffness, and myalgias in an otherwise healthy patient. In severe cases, purpura fulminans, disseminated intravascular coagulopathy, or vasculitis may be noted. IMD may also present clinically without neurological involvement as bacteremia, arthritis, pericarditis, pharyngitis, urethritis, conjunctivitis, or immune complex disease. Nevertheless, the second most common end-organ disease of IMD remains widely neglected despite accounting for 5–15% of cases – meningococcal pneumonia [15–17]. This review aims to highlight the clinical relevance, as well as the diagnostic and management challenges related to this disease. Increasing awareness for meningococcal pneumonia may result in more frequent diagnosis of the disease, earlier institution of targeted therapies, and improved prognosis.

2. Pathogenesis of meningococcal pneumonia

Meningococci may invade the lower respiratory tract hypothetically via three different modes of infection. First, *N. meningitidis* colonizes the nasopharyngeal mucosa of 4–10% of young, asymptomatic adults and carriage rates may range in selected cohorts between 4% and 59% [18–22]. Invasion of the loco-regional blood supply results in bacteremia and secondary dissemination of the bacterial pathogen from the oropharynx to multiple body sites, including the lungs, where a favorable micro-environment sustains bacterial replication. In concordance with a clinical significance of this pathway, 23% (10 of 44) of patients with blood cultures that are positive for *N. meningitidis* also have an infiltrate evident on a chest radiograph [7,23]. In these cases, meningococci may have entered the lungs via the blood stream [7]. Second, large airborne droplets that are generated during coughing and contaminated with microbial nuclei may be inhaled. Third, meningococci colonizing the oropharynx may be transmitted to the lower respiratory tract by microaspiration following biofilm formation. *N. meningitidis* infection in the oropharynx requires adherence of bacteria as microcolonies on nonciliated nasopharyngeal epithelial cells. Consecutively, re-organization of host cell actin and formation of membrane protrusions by bacterial mechanisms protect bacteria from shear stress by biofilm formation. Post-translational modification of bacterial pilin lead to the disassembly of bacteria and spread to other sites such as the lungs [24,25]. Viral or other bacterial infections may further reduce resistance to meningococcal infection of the lower respiratory tract as well-documented for IMD [26,27].

3. Meningococcal pneumonia

In 1907, Jacobitz described for the first time cases of meningococcal pneumonia that could be diagnosed by demonstration of *N. meningitidis* in sputum samples [28]. In this case series, thirteen soldiers living in the same barracks suffered from IMD. Four of these soldiers had meningitis and pneumonia and seven had a respiratory tract infection only including two with mixed infection by meningococci and pneumococci. The source of infections could be traced back to a single index patient who presumably had contracted the disease in the nearby town of Colmar, where IMD was endemic. Jacobitz noted already more than a century ago that asymptomatic individuals may also carry *N. meningitidis* in their oropharynx, and hence, demonstration of the pathogen in these samples does not confirm the clinical diagnosis [28]. Large outbreaks of meningococcal pneumonia were noted during the 1918–19 influenza pandemic [29]. In 1948 the first two cases of meningococcal pneumonia in the antibiotic era were systematically studied and previous case series reviewed [30]. Brick noted in this analysis that "It has been known for some time that extrameningeal meningococcal infections are not uncommon, but the attention directed to the respiratory phase of such infections is very scant"[30]. Based on a review of contemporary evidence Putsch et al. suspected in 1970 a significant role of *Neisseria meningitis* in community-acquired pneumonia [31]. Since then, multiple reports of individual cases and case series indicated the clinical relevance of IMD of the respiratory tract (Table 1) [32]. We could identify a total of 344 cases of meningococcal pneumonia that were observed in the Americas, Europe, Australia, and Asia and published over a period of more than a century (1906–2015). The largest proportion of meningococcal isolates (142 cases) identified in this review of published IMD cases were of serogroup Y (Table 1). National surveys on the incidence of IMD indicate that meningococcal pneumonia is the most common non-neurological end-organ disease of IMD and occurs in about 17% (61 of 364) of patients (Table 1). This is consistent with the previously published range of 5–15% [15–17,23,33–35]. Still, the incidence of meningococcal pneumonia is very likely underestimated as discussed in more detail in "Microbiological diagnosis of meningococcal pneumonia" below.

4. Risk factors for meningococcal pneumonia

Meningococcal pneumonia is considered to affect mostly older adults (>50 years) in contrast to meningococcal meningitis which affects predominantly children and teenagers, based on epidemiological surveys [16,32,34,36]. In patients aged >65 years, pneumonia is even the most common manifestation of IMD [34,36]. Nevertheless, recent reports and our present revision points to a bimodal age distribution of cases with peaks in incidence in patients aged <30 years and those aged >60 years [32]. Accordingly, factors other than patient age or serogroup may contribute more significantly to a predisposition for meningococcal pneumonia.

The second relevant predictor for respiratory disease in IMD may be the infecting bacterial strain type. Several outer membrane components have been linked to meningococcal virulence, such as outer membrane proteins and lipooligosaccharid subtype; the capsular polysaccharides, however, are the major virulence factor of *N. meningitidis* and the main target of humoral immunity [1,37]. Genetic differences within the gene coding for capsular polysaccharides of *N. meningitidis* translate into antigenic differences that allowed differentiation between thirteen meningococcal serogroups so far. More recently, genomic typing, i.e. multilocus sequence typing (MLST) and whole-genome sequencing have allowed for grouping of meningococcal strains with even higher discriminatory power [38]. These analyses revealed that five *N. meningitidis* serogroups (A, B, C, W, and Y) are responsible for the majority of meningitis cases. In contrast to meningococcal meningitis, pneumonia is caused mostly by otherwise rare serogroups – particularly serogroup Y followed by serogroup W