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Meningococcal disease: Clinical presentation and sequelae

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ABSTRACT

The clinical spectrum of invasive meningococcal disease is diverse with meningitis and/or septicaemia being the commonest modes of presentation. The severity of manifestations of meningococcal infection ranges from bacteraemia, associated with mild non-specific symptoms, to fulminant sepsis with multiorgan failure and death in approximately 10–15% of cases. Localised infections (such as conjunctivitis or septic arthritis) as well as chronic disease may be the sole clinical manifestations but can also lead to disseminated fulminant disease. Among survivors, disabling long-term sequelae can complicate meningococcal disease and result in potentially devastating effects on the quality of life of survivors, most of whom are infants, children and adolescents. The only rational approach to the prevention of meningococcal disease and the associated human suffering is through vaccination.

1. Introduction

Neisseria meningitidis is an obligate human pathogen that has been known to cause meningitis and septicaemia since the 19th century. Invasive meningococcal disease (IMD) is of major public health importance due to its global distribution, epidemic potential, predominant disease burden in children and adolescents and fulminant clinical manifestations. The majority of the global disease burden is caused by *N. meningitidis* serogroups A (MenA), B (MenB), C (MenC), W-135 (MenW-135), Y (MenY) and more recently X (MenX) [1–4]. Although the last two centuries have been marked by major improvements in the management of IMD, overall mortality rates still stand at 8–14% [5,6]. Meningococcal meningitis is associated with 5–15% mortality, a rate that has remained relatively unchanged since the 1930s [7]. Devastating long term sequelae such as amputations, hearing loss and neurodevelopmental disabilities are seen in 11–19% of IMD survivors [8]. Recognition of IMD and its timely treatment is critical in managing and reducing complicated and fatal disease.

2. History

The first descriptions of meningitis epidemics were published in Europe and the US at the beginning of the 19th century. Although no diagnostic tools existed at that time to attribute such epidemics to the meningococcus, the clinical manifestations were highly indicative of meningococcal disease. Gaspard Vieussuex, a Swiss physician, was the first to describe a meningitis epidemic occurring in 1805 in Eaux Vives, a small suburban town of Geneva. He documented 33 deaths from 'spotted fever', which was accompanied by meningitis in the majority of cases, over a period of 3 months [9]. In the following year two American physicians: Lothario Danielson and Elias Mann independently described another outbreak in Medfield, Massachusetts in the US [10]. It was not until 1887 when the causative organism was identified by the Austrian pathologist Anton Wiechselbaum [11]. The intracellular nature of the paired diplococci within white blood cells in the cerebro-spinal fluid (CSF) led to the name *Diplococcus intracellularis meningitidis*, whose nomenclature was later changed to *Neisseria meningitidis*. In 1896, the differentiation of *N. meningitidis* from the gonococcus in the throat of asymptomatic carriers by Kiefer, a German microbiologist, shed light on the mode of transmissibility [12]. Throughout the 19th century meningococcal epidemics occurred in Europe and North America and outbreaks were also reported, largely in the military, in Algiers, Egypt and Sudan [13,14]. The first major epidemic of meningococcal meningitis to be reported in West Africa was in Zungeru and Yola in northern Nigeria during 1905 [15,16]. Over the subsequent 2–3 years the epidemic had spread to involve several neighbouring countries in West Africa with an estimate of 20,000 cases and several thousands of deaths [17].

Mortality rates during meningococcal outbreaks in the early 1900s reached 70–80% [18]. The intrathecal infusion of equine derived anti-serum, developed by Flexner and Jobling in 1908 [19], resulted in a reduction of mortality to 30% [18]. However, the efficacy of serum therapy was questioned during the 1920–25 epidemics when mortality in treated patients reached 50% [20]. Serum

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therapy was abandoned in the 1930s following the discovery of sulphonamides [21]. The emergence of sulphonamide resistance in 1963 [22] has since then led to the preference of β-lactam antibiotics for the treatment of meningococcal disease.

3. Carriage and transmission

Asymptomatic nasopharyngeal carriage provides a reservoir for meningococcal transmission which occurs through close contact with infected upper respiratory tract droplets or secretions. In non-epidemic settings the overall carriage prevalence in adults is 10% [23] but may increase to 18–35% during epidemics [24]. Carriage rates increase progressively with age, from 0.71% in children <4 years old [25] to 25% in 15–19 year olds [23] and up to 32% in 25 year olds [26], probably as a result of changes in social behaviour. Besides age, overcrowding as in military barracks [27] and during the Hajj pilgrimage [28], intimate kissing or close contact as in pubs and discotheques [29], as well as damage to the nasopharyngeal mucosa from active/passive smoking [30] or from co-infection with influenza and *Mycoplasma* species [31], increase the risk of carriage.

4. From carriage to disease

The mechanisms that lead from colonisation to invasive disease, which occurs only in a small proportion of carriers, are still incompletely understood but are thought to be a result of meningococcal virulence factors, environmental conditions and host susceptibility. The expression of the polysaccharide capsule, which inhibits opsonisation and phagocytosis [32], can lead to bloodstream invasion. Furthermore, certain meningococcal clones, such as the ST-11 complex MenC or MenW-135 strains, are known to be hyperinvasive [33,34]. Damage to the nasopharyngeal epithelium from changes in temperature and humidity, as may occur with a high relative humidity and low temperatures in winter in temperate climates [35] or from increasing temperatures, low humidity and sand particles blown by Harmattan winds in Africa [36], is associated with a higher incidence of meningococcal disease. Infancy and adolescence [5], social behaviour [37], exposure to *N. meningitidis* [38], and specific immune defects, such as hypo/asplenia [39] and terminal complement deficiency [40] are all risk factors for meningococcal disease.

5. Clinical spectrum

Disease manifestations may appear within the first week (range 1–14 days, but at times weeks later) following the acquisition of a pathogenic meningococcal strain within the nasopharynx [41–43]. The clinical spectrum of IMD is diverse and may vary from a mild febrile illness to septicaemia or meningitis or a mixed expression of both [44]. The initial mild clinical presentation may progress to fulminant disease, multi-organ failure and death within hours. The principal determinant of the manifestations of IMD is the extent of activation of the host innate and acquired immune response (Fig. 1), which in turn is affected by bacterial factors, such as the amount of circulating endotoxin (meningococcal lipopolysaccharide) and bacterial load [45], as well as by genetic polymorphisms in constituents of the complement system, the inflammatory response and the coagulation and fibrinolytic cascades that affect susceptibility, severity and outcome of the infected individual [46].

5.1. General symptoms

Upper respiratory tract symptoms, such as coryza and pharyngitis, fever, loss of appetite, nausea and vomiting, irritability in children <5 years and headaches in older children are common

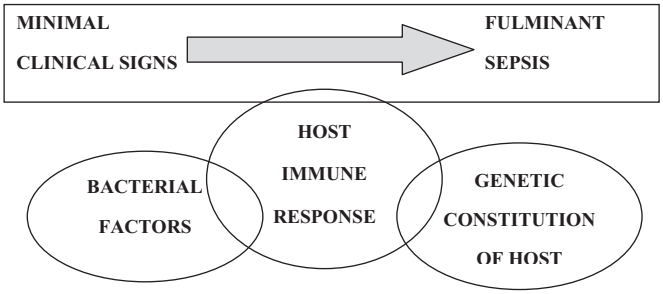

Fig. 1. Interplay of factors contributing to the manifestations of meningococcal disease.

symptoms that manifest in the first 4–6 h from disease onset [47]. Specific clinical features suggesting sepsis or meningitis would eventually follow and are often present at the time of presentation. The initial non-specific manifestations mimic the symptoms of common viral infections and may create a diagnostic conundrum for the examining clinician.

5.2. Meningitis

The most common presentation of IMD is meningitis, a reflection of the characteristic meningeal tropism of *N. meningitidis* [48], that affects 30–60% of infected individuals [1,49]. The relatively compartmentalised inflammatory response triggered within the subarachnoid space is responsible for the symptoms and signs of meningitis [50]. Fever, vomiting, headache, photophobia, irritability, agitation, drowsiness and neck stiffness are typical manifestations of meningitis in children >5 years of age [51–54]. A rash may be present in up to 26% of cases [55], but is more likely to be absent, scanty or atypical than in septicaemia. Seizures develop in less than one third of affected children [56,57]. By contrast, most children <2 years of age lack specific features of meningitis and may present predominantly with irritability/lethargy [51,58]. Signs of meningeal irritation, such as neck stiffness, Kernig's or Brudzinski's sign might not be present in the under 2s [51,57,58]. Infants may present with unconsolable crying, poor feeding, and a bulging fontanelle [58]. Meningococcal meningitis may also present as part of early or late onset sepsis in neonates [59]. In children neck stiffness and photophobia, and a bulging fontanelle in infants, are rather late signs occurring at a median of 12–15 h from disease onset, with unconsciousness, delirium and seizures occurring after an average of 15 h in infants and at 24 h in older age groups [47]. Raised intracranial pressure, caused by cerebral inflammation and oedema, is a recognised complication of meningococcal meningitis that may lead to cerebral herniation and death [60]. Meningococcal meningitis has a mortality of 5–18% [1].

5.3. Septicaemia

Septicaemia is the predominant presentation in 20–30% of cases of IMD [1,49]. Lower limb pain, cold peripheries and skin pallor are early indicators of sepsis in children and adolescents, occurring within 12 h of disease onset [47]. Drowsiness, fast or laboured breathing and at times diarrhoea are additional symptoms seen in younger children [47]. The appearance of a petechial or purpuric rash, a classical sign of meningococcal septicaemia (Fig. 2), is seen in 40–80% of cases [47,61]. A maculopapular blanching rash is commonly present early in the disease, even among those who later develop a petechial or purpuric rash and persists in 13% [62] potentially leading lead to misdiagnosis of a viral infection (Fig. 3). Confusion and delirium, secondary to hypotension and cerebral hypoperfusion, are late signs [47]. Meningococcal replication within the bloodstream results in the release of large quantities