Management of meningococcal disease

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Abstract

In recent years remarkable progress has been made in the development of vaccines against the different disease-causing serotypes of *Neisseria meningitidis*. Despite this, invasive meningococcal disease (IMD) remains a life threatening illness with significant mortality, morbidity and long term sequelae. Prompt recognition and early treatment with antibiotics are the first steps in its management. Professionals looking after children with suspected IMD should be familiar with its clinical course, so that progression of the disease can be identified early, and its complications including septic shock, coagulopathy and raised intracranial pressure managed aggressively. This article summarizes the clinical features, presentation, pathophysiology and management of IMD focussing on its two common clinical presentations: septicaemia with associated shock and meningitis.

Keywords meningitis; meningococcus; sepsis; shock

Introduction

Meningococcal infection is a disease with significant mortality, morbidity and long term sequelae. *Neisseria meningitidis*, the responsible pathogen, is an exclusively human gram negative diplococcus that is a common commensal organism of the nasopharynx. It spreads from person to person via the respiratory route. There are 13 serogroups known to exist, some encapsulated and some unencapsulated. The polysaccharide capsule is associated with pathogenicity. The serogroups A, B, C, X, Y and W-135 are those implicated in invasive meningococcal disease (IMD).

The commonest age for disease is in children younger than 5 years, with the highest rate in infants 3–12 months. However, disease occurs throughout childhood, and the incidence increases again in adolescence and young adults.

While conjugate vaccines for serogroups A, C, W-135 and Y are available, the development of such a vaccine against serogroup B proved more challenging. The serogroup B meningococcal capsule is poorly immunogenic as it resembles mammalian neural cell adhesion molecules, a glycoprotein found on the surface of fetal neuronal cells. A novel Men B vaccine however has been developed and may be introduced into the UK schedule in the near future. At present serogroup B Meningococcal infection is responsible for the majority of IMD in the developed world. While initial data is encouraging, it is only following wide-scale introduction of the new Men B vaccine that we will be able to gauge its efficacy. Certainly there has been a dramatic reduction in the incidence of disease caused by serogroup C meningococcus in those countries which have introduced the Men C conjugate vaccine into their routine schedule.

Approximately 10% of the population are colonised with commensal, non-encapsulated *Neisseria meningitides*, some of which confer protection against encapsulated virulent strains. The progression from colonization to invasive disease is not fully understood. It is thought that meningococcal virulence factors, environmental conditions and host susceptibility play an important role. A recent (less than10 days) acquisition of a pathogenic strain in a susceptible host may lead to invasive disease. The clinical manifestation of IMD in an individual host is determined by the extent of activation of the immune system. This in turn is affected by bacterial factors, such as capsular serogroup, the amount of circulating endotoxin and bacterial load, as well as by genetic polymorphisms in constituents of the complement system, the inflammatory response and the coagulation cascade.

In some instances there may be rapid onset and progression of disease, and death may follow within hours. Even when diagnosis is made early and appropriate treatment is rapidly initiated case fatality is estimated at 5–10%. Of those who survive approximately 30% suffer severe sequelae of the disease, with one or more deficits in physical, cognitive and psychological functioning, including neurological defects, deafness, amputation of limbs or digits, or skin scarring. Prompt recognition and early aggressive treatment with antibiotics are paramount. Identifying complications such as shock, raised intracranial pressure (ICP) and seizures are imperative.

There are three main clinical manifestations of disease: meningitis, sepsis and pneumonia. Pneumonia is primarily a disease of the elderly and will not be discussed further.

Risk factors

Risk factors can be stratified into the following categories shown in Table 1.

Risk factors for invasive meningococcal disease

- ***Geographical location*** – e.g. meningitis belt in sub-Saharan Africa
- ***Seasonality***: winter season in moderate climate zones, dry season in sub-Saharan Africa
- ***Age (less than 5 and 15 – 24 years)***
- ***Overcrowding***: poor housing/military/university dormitories
- ***Active/passive cigarette smoking***
- ***Prior viral respiratory infection*** (e.g. influenza A virus, RSV infection)
- ***Inherited complement deficiency***
- ***Close (family/household) contact with index case***

Table 1

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In general meningococcal epidemiology can be divided into endemic infections and epidemic outbreaks. Endemic disease usually occurs in developed countries and has an incidence of 1—3 cases per 100,000. The highest prevalence of endemic disease occurs during the winter months, and is associated with increases in the rate of viral upper respiratory infection.

In the developing world, such as in sub-Saharan Africa, epidemic outbreaks occur with an incidence up to 10—100 times higher than that seen in endemic disease. The predominant organism in this region is Serogroup A. Epidemic disease usually occurs during the dry season.

The risk of meningococcal disease is inversely related to age. 49% of cases occur in children less than2 years of age. In epidemics, older children are more likely to be infected. Crowding especially among military recruits, or university students is considered a major risk factor.

An association between smoking and increased rate of meningococcal carriage has been demonstrated. Passive smoking has been implicated in increasing the risk of meningococcal disease in children. Recent infection with respiratory viruses has been documented to increase susceptibility to meningococcal infection. Respiratory viruses may disrupt the epithelial barrier and facilitate invasion of virulent meningococci.

In general, antibodies and complement are important in protection from meningococcal infection, and deficiency of either is associated with an increased risk of disease (see Table 2). Terminal complement component and alternative pathway deficiencies have been reported as predisposing to meningococcal disease.

Over the past twenty years much effort has gone into identifying individual genetic polymorphisms that may add to our understanding as to why some individuals experience invasive meningococcal disease while others remain carriers, as well as accounting for the different clinical presentations and varying severity of disease between individuals. Single nucleotide polymorphisms (SNPs) in genes controlling the host response to infection are thought to be important. The strongest associations found to date are in SNPs in genes involved in the fibrinolysis (SERPINE1) and cytokine (IL1B, IL1RN) pathways. A large Genome Wide Association Study has determined that variations in the complement factor H and factor H-associated proteins are important susceptibility factors. It is hoped that this area of research will allow us in the future to tailor treatment to individuals based on their genetic makeup.

Presentation

In the first few hours after disease onset the clinical picture is similar to one often seen in common viral infections. While the classical petechial/purpuric rash in a child with fever is highly suggestive of meningococcal disease, up to one fifth of children have no rash or a non-specific maculopapular rash on presentation. Less specific features such as: fever, cold peripheries, leg pain, tachycardia and abnormal skin colour present in the first 12 hours and must not be ignored. The characteristic haemorrhagic petechial/purpuric rash occurs much later and may present up to 24 hours after illness onset.

Clinical presentation with signs and symptoms of meningisim is more common in older children with meningococcal meningitis. The classical symptoms of fever, headache, photophobia, neck stiffness and altered mental status are often only partially present. A high level of suspicion is crucial to making an early diagnosis. The clinical features which are known to be associated with risk of mortality are outlined in Table 3.

Diagnostic workup

Microbiological confirmation is important for disease identification and institution of public health measures. Definitive diagnosis of meningococcal disease is established by isolation of *Neisseria meningitidis*, or its products from a normally sterile body fluid such as blood or CSF. Blood cultures are positive in 50—80% of cases, and CSF cultures are positive in 80—90% of cases. Meningococci are exquisitely sensitive to many antibiotics, with penicillin-resistant strains only rarely reported. Therefore, following administration of antibiotics, blood or CSF cultures are rarely positive. Some studies suggest that the CSF becomes sterile as soon as 2—8 hours after antibiotics are given. Polymerase chain reaction (PCR) assays in whole blood (using EDTA sample) or CSF detect nucleic acids of the pathogen and the test are highly specific (100% for blood, and near 100% for CSF) and sensitive (approx. 88% in different studies). PCR testing is useful up to 96 hours after antibiotics have been given, but early samples are more likely to be positive.

Non-specific laboratory tests such as white blood cell count (WBC) and C-reactive protein (CRP) may be elevated suggesting bacterial infection. The few studies looking at the diagnostic value of these markers found them to have insufficient specificity and sensitivity to distinguish IMD from other illnesses. They should therefore have a supportive role in the diagnostic work up, and they cannot be relied on to exclude IMD. A low/normal WBC and relatively low CRP are adverse prognostic factors in patients with diagnosed meningococcal disease.

Host factor susceptibility and severity

Complement deficiency
Hypogammaglobulinaemia
Hyposplenism
Various genetic polymorphisms in genes associated with the complement, inflammatory response and coagulation pathway

Table 2

Risk factors influencing fatal outcome

Rapidly progressing rash
Coma
Hypotension and shock
Low/normal peripheral white blood cell count
Low acute phase reactants
Low platelets
Coagulopathy
Absence of meningitis
Young age

Table 3