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Meningococcal disease

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Abstract

Meningococcal disease, caused by *Neisseria meningitidis*, is a rapidly progressive, potentially life-threatening infection. The organism, an encapsulated Gram-negative diplococcus, is classified into at least 13 serogroups, with A, B, C, W, X, and Y being responsible for most invasive cases. Host susceptibility is increased in individuals with complement deficiencies, asplenia, or immature immune systems. Transmission occurs via respiratory droplets, and asymptomatic carriage is common. Clinical presentation ranges from meningitis and fulminant septicaemia to less common manifestations such as pneumonia, arthritis, and pericarditis. Timely recognition and empirical treatment with third-generation cephalosporins are critical for patient survival.

Diagnosis is confirmed by blood and cerebrospinal fluid cultures, supported by polymerase chain reaction and other ancillary investigations. Vaccination remains the most effective preventive measure, with conjugate vaccines available for the virulent serogroups. However, in Sri Lanka, meningococcal vaccination is not included the routine immunisation program, except for high-risk groups and during outbreak situations. Public health measures such as notification, chemoprophylaxis for close contacts, and implementation of droplet precautions are essential to control and prevent further transmission. The lack of serogroup-specific surveillance in Sri Lanka hinders effective outbreak management and policy development. Enhanced diagnostic capacity, routine surveillance, and context-specific vaccination strategies are essential to reduce the burden of meningococcal disease and improve outcomes in affected populations.

Key words: meningococcal disease, *Neisseria meningitidis,* meningitis, septicaemia

Introduction

Meningococcal disease is caused by Gram-negative diplococcus *Neisseria meningitidis*. It can present in various forms including meningitis, septicaemia, and other invasive syndromes and may progress to a life-threatening disease. Despite advances in diagnosis and treatment, meningococcal disease remains a major public health concern in both developing and developed countries, due to its unpredictable outbreaks and potential for rapid and severe clinical deterioration.

Microbiology and pathophysiology

N. meningitidis is an encapsulated bacterium which can be classified based on its polysaccharide capsule into at least 13 serogroups. The six serogroups (A, B, C, W, X, and Y) are primarily responsible for invasive disease. *N. meningitidis* is an obligate commensal residing in the respiratory tracts of humans. The pathogen is transmitted through aerosols. The capsule with its lipopolysaccharide (LPS) capsular antigen plays a crucial role in immune evasion and virulence. Other virulence factors include the presence of IgA1 protease activity, pili, endotoxins and outer membrane proteins. Along with the colonization of bacterium in the nasopharyngeal mucosa, there is a possibility of invasion into the bloodstream and dissemination to sterile sites, even crossing the blood-brain barrier. The organism may also have a direct spread from the nasopharynx to the subarachnoid space through the cribriform plate via perineural sheaths of olfactory nerves.[1,2]

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Host factors of immunosuppression including complement deficiencies (C5-C9, properdin and factor D), functional and anatomical asplenia (including sickle cell disease), and genetic predispositions increase the disease susceptibility. Persons possessing specific complement-dependent antibodies to capsular antigens are protected. However, young children aged between 3 months to 3 years with waning humoral antibodies and immunologically naïve adolescents are at increased risk. Furthermore, patients on humanised monoclonal antibody eculizumab which inhibits complement activation by binding to C5 are also susceptible to meningococcal disease.[3] The inflammatory response triggered by lipo-oligosaccharide endotoxins (lipid A moiety) contributes to the characteristic features of septic shock and meningitis. Certain lineages of *N. meningitidis* are highly invasive and strongly associated with the development of the disease.

Epidemiology

The incidence of meningococcal disease varies widely by geography, age, and vaccination coverage. It is estimated that up to 500,000 cases of meningococcal disease occur globally each year. Most countries experience a sporadic case distribution of 0.3-5 per 100,000 population. Data in Sri Lanka is limited, consisting of few case reports and case series, with a reported case fatality of 1 out of 3.[4-6]

The highest risk is seen among infants, adolescents, and young adults. The disease is hyperendemic in Sub-Saharan Africa or the 'meningitis belt' (Senegal to Ethiopia), with periodic epidemics of serogroup A and more recently W-135 and X. The serotypes B, C and Y tend to predominate in the more developed regions. Peaks usually occur during dry seasons and in winter months in temperate climates. Asymptomatic carriage can be present in up to 10% of the population.[7] Smokers appear to carry meningococcal more often than non-smokers. Overcrowding is an important factor in the transmission of the organism. Places of confinement such as refugee camps, prisons, asylums, barracks, and dormitories contribute to increased frequency of infection due to overcrowding and close contacts.[1] Global incidence has declined significantly with the introduction of conjugate vaccines. However, outbreaks still occur, particularly in unvaccinated populations and during mass gatherings (e.g., Hajj pilgrimage and Mela in India).

Clinical manifestations

Meningococcal disease presents with a wide range of clinical manifestations such as meningitis, meningococcaemia (septicaemia), pneumonia, septic arthritis, pericarditis and osteomyelitis. The incubation period is 1-3 days. Meningococcal meningitis presents with characteristic features of fever, headache, neck stiffness, and photophobia. Altered mental status and seizures may manifest in severe cases.[8] Kernig's and Brudzinski's signs although being classical signs of meningism, may not appear in infants or older adults. Meningococcaemia or septicaemia may present as a sudden onset of fever, chills and fatigue leading to hypotension with a characteristic non-blanching petechial or purpuric rash. Purpura may evolve into purpura fulminans, leading to skin necrosis due to microvascular coagulation. A severe form of meningococcaemia can lead to shock, multiorgan failure, and death within hours of symptom onset.[1]

Miscellaneous presentations include pneumonia which occurs in about 15% of cases. Less common manifestations include monoarticular arthritis, osteomyelitis, purulent pericarditis and non-invasive forms such as conjunctivitis and uveitis.[9,10] Chronic meningococcaemia is also a well-recognised entity with intermittent fever, rash, and arthralgia.[11] Fulminant meningococcal disease may lead to Waterhouse-Friderichsen syndrome, characterized by bilateral adrenal haemorrhage leading to adrenal insufficiency, hypotension, and death.[12] Despite nasopharyngeal carriage, meningococcal pharyngitis is rarely reported.[1]

The use of antibiotics has reduced the mortality. However, even with prompt and appropriate interventions of resuscitation and chemotherapy, the case fatality ranges from 0-15% even rising to 40% in meningococcaemia.[9] Unfavourable prognostic signs include the presence of coma on presentation, rapidly coalescing rash and shock. Death usually occurs due to shock, associated occasionally with raised intracranial pressure. Up to 20% of survivors have long-term sequelae, highlighting the importance of prevention. Complications of meningitis include hearing loss, cognitive impairment and seizures. Acute limb ischaemia, including digital gangrene has been reported, along with skin scarring and disseminated intravascular coagulation.[13,14] Both survivors and caregivers of individuals who were ill have been found to develop post-traumatic stress disorder.[15]

Diagnosis

Rapid diagnosis is essential given the aggressive and rapidly progressive nature of the disease. Quick pattern recognition based on clinical presentation and risk factors (heuristic or type 1 clinical reasoning) is essential. Cultures from blood, cerebrospinal fluid (CSF) and skin swabs from lesions when present are

cornerstone tests of confirmation although treatment should not be delayed. Lumbar puncture should not be delayed after starting antibiotics as it may affect the accuracy of CSF analysis and hinder detection of the organism. CSF analysis will demonstrate elevated opening pressure (above 20 mmHg) indicating increased intracranial pressure, along with neutrophilic pleocytosis, low glucose and elevated protein levels. Additionally, Gram staining of the CSF may show intracellular Gram-negative diplococci. Samples of CSF are cultured on blood agar and chocolate agar for isolation of the organism. Sugar utilisation tests and commercial identification kits are employed to identify *N. meningitidis*. A rapid diagnostic option is slide agglutination using specific antisera on colony suspensions.[16] This test allows for quick presumptive serogroup identification of *N. meningitidis*, often within minutes, which is helpful in outbreak settings or when rapid public health decisions are needed.

Polymerase chain reaction (PCR) is a highly sensitive diagnostic tool, particularly valuable when antibiotic treatment has been initiated prior to sample collection. Serological tests for antibodies to meningococcal antigens are not validated for clinical use in diagnosing acute meningococcal disease and should not be used to guide treatment decisions. However, they can be useful in retrospective studies or when other methods are unavailable. While antigen tests such as immunochromotographic test (ICT) can provide quick results, they are generally less sensitive and specific than PCR and culture, particularly in cases where prior antibiotics have been used. Other ancillary tests include full blood count, coagulation profile, serum electrolytes, and renal and liver function tests. Imaging such as CT or MRI may be needed if raised intracranial pressure is suspected.[16]

Management

Initial resuscitation, particularly in cases of shock or impending shock, is critical by stabilising the airway, breathing, and circulation. Aggressive administration of intravenous fluid for oligaemia, initiation of inotropes for shock and oxygen supplementation for hypoxia need to be considered. Metabolic derangements such as hypoglycaemia, acidosis, hypokalaemia, hypocalcaemia, hypomagnesaemia along with anaemia and coagulopathy may be anticipated.[1]

Empirical antibiotics should be commenced without delay. The first line antibiotics include ceftriaxone (75-100 mg/kg/day or 2 g twice daily) or cefotaxime (200mg/kg/day or 2 g eight hourly) to cover potentially penicillin-resistant strains. In resource-limited settings, high-dose penicillin G or chloramphenicol are alternatives. Third-generation cephalosporins and penicillin easily cross the inflamed blood-brain barrier.[1] Once culture results are obtained, treatment should be adjusted according to the sensitivity profile. Antibiotics should be continued for 7 days for confirmed meningitis and 7-10 days for septicaemia.[17,18] Single dose of ceftriaxone will clear nasopharyngeal carriage effectively. If other third-generation cephalosporins are used, eradication of nasal carriage requires rifampicin (4 doses over 2 days) or a single dose of ciprofloxacin or ceftriaxone before discharge.[2]

The use of steroids as an adjunctive treatment remains controversial, as no study to date has had sufficient power to conclusively determine their efficacy. High-dose dexamethasone given at the onset of suspected bacterial meningitis has proven benefits in pneumococcal meningitis; however, should be discontinued once meningococcal infection is confirmed.[17] Therapeutic doses of glucocorticoids are not recommended in meningococcal septicaemia, although they may be beneficial in cases of refractory shock caused by involvement of adrenal glands. Other adjunctive therapies being studied include the development of antibodies to LPS, and the usage of recombinant bactericidal/permeability-increasing protein ($rBPI_{21}$) and activated protein C.(15,19,20). Level 3 support may be needed for organ failure, coagulopathy, or shock.[1]

Vaccination

Conjugate tetravalent vaccines are available for protection against serogroups A, C, W, and Y (MenACWY) and serogroup B (MenB). Polysaccharide vaccines are no longer widely used globally as they do not induce adequate immunological memory and poor efficacy in children of 3-5 years of age. The MenACWY-D vaccine is licensed for use from age of 9 months to 55 years while the MenACWT-CRM is recommended for 2 months to 55 years as it is known to induce T-cell response. The MenBFHbp vaccine is developed upon surface-exposed lipoprotein factor H while MenB-4C has 4 antigenic components. Both are protein-based recombinant vaccines and are recommended in countries with high serogroup B burden. The efficacy of these vaccines varies between 85-93%.[21]

Although meningococcal vaccines are not included in routine immunisation programme in Sri Lanka, they are administered in epidemic outbreaks, to protect travellers to endemic countries (including pilgrims to Mecca and Medina) and for at-risk laboratory workers. Additionally, vaccines are recommended for individuals with complement deficiencies, anatomical

or functional asplenia, and those living with HIV (irrespective of stage or CD4+ cell count), recipients of stem cell transplants and those to be commenced on eculizumab. Meningococcal vaccination is not recommended for post-exposure prophylaxis following exposure to a single case.[21]

Vaccination is contraindicated in individuals with acute febrile illness or known hypersensitivity to any vaccine components. In addition to common adverse effects, syncope can occur following vaccination with adolescents and young adults being most commonly affected.

The MenACWY vaccine is recommended for 11 to 12-year-old adolescents, with a. booster dose advised at the age of 16 years due to waning of immunity. The selection of these ages is based on the period in life at when individuals are at the highest risk of contracting infection. The MenB vaccines are specifically used in outbreaks for adolescents and young adults. Two doses of this vaccine should be administered with an interval of 6 months. Individuals at risk of infection who are more than age 2 months old should receive 2-4 doses as primary series with regular booster doses.[21]

Public Health Measures

Meningitis as a generic condition is listed under group B notifiable diseases in Sri Lanka. However, meningococcal disease is not included in statutory reporting as in most other countries.[6] However, prompt identification and information to epidemiological services will help to trace contacts and contain the disease. Contacts need to be actively tracked. These include household dwellers, inmates and healthcare contacts. Monitoring of serogroups and antibiotic resistance patterns through surveillance systems has helped to guide vaccination policy decisions.

A considerable escalation of invasive meningococcal disease outside the meningitis belt than usually expected is considered as an 'outbreak', by the World Health Organisation. This could be even two cases from the same serogroup in a population.

Chemoprophylaxis in the form of rifampicin (600 mg b.d. for 2 days) or ciprofloxacin (500 mg single dose) is advocated. Ceftriaxone 250 mg intramuscular or azithromycin 500 mg orally as a single dosage are also used. These need to be commenced as soon as possible.[22] For patients with confirmed or suspected disease, standard and droplet precautions should be maintained until 24 hours after the initiation of effective antibiotic therapy. Post-exposure chemoprophylaxis is recommended for household contacts and healthcare workers who have been exposed to the patient's respiratory secretions. Post-exposure vaccination is advised only in the context of outbreak control.[23]

In Sri Lanka, the unavailability of serotyping capabilities significantly hinders the ability to link individual cases and detect potential outbreaks. There is a need to strengthen early case identification, implement surveillance systems, and establish prompt protocols for treatment and chemoprophylaxis. The decision to vaccinate the general population should be made cautiously, after a thorough assessment of the disease burden.[6]

Key Messages

- Meningococcal disease is rapidly progressive and life-threatening and can present mainly as meningitis and septicaemia with or without the characteristic rash.
- Higher risk is observed among children, individuals living in overcrowded conditions, those with poor socioeconomic status and immunocompromised persons. Asymptomatic carriage of pathogen is also common.
- Early recognition and prompt initiation of empirical antibiotic therapy are crucial for survival. Ceftriaxone or cefotaxime are the preferred initial agents.
- Vaccination with conjugate preparations is the cornerstone of prevention.
- Chemoprophylaxis with rifampicin, ciprofloxacin, or ceftriaxone for close contacts and health care workers is effective in preventing secondary transmission.
- Sri Lanka faces challenges in surveillance and serogroup typing, indicating the need to strengthen laboratory capacity and public health infrastructure.

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