Early clinical clues to meningococcaemia

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ABSTRACT

- Meningococcal septicaemia has high mortality, especially when the diagnosis is delayed or missed.
- Early recognition is not always straightforward, as classic clinical features may be absent or overlooked at initial presentation.
- Septicaemia without focal infection accounts for 15%–20% of cases of meningococcal disease and is the most worrisome manifestation in terms of diagnosis and outcome; in contrast, meningococcal meningitis is usually straightforward to diagnose, with a relatively good prognosis.
- Useful early clinical clues to meningococcaemia include:
  - a haemorrhagic (petechial or purpuric) rash;
  - blanching macular or maculopapular rash that appears in first 24 hours of illness;
  - true rigors;
  - severe pain in extremities, neck or back; vomiting, especially in association with headache or abdominal pain; rapid evolution of the illness;
  - concern of parents, relatives or friends;
  - patient age (highest incidence at age 3–12 months, followed by 1–4 and then 15–19 years); and
  - contact with a patient with meningococcal disease.
- In addition to specific clues, clinicians should look at the whole pattern of the illness.
- Timely clinical review is essential if there is doubt about the diagnosis.
- In any acutely febrile patient, it is prudent to ask "Why is this patient seeking help now?", then "Could this patient have meningococcaemia?".

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DEATHS FROM MENINGOCOCCAEMIA in previously healthy children and young adults continue to occur in Australia. Newspapers and radio talkback shows regularly feature disturbing stories, and general practitioners and emergency departments are often blamed for delay in diagnosis and appropriate treatment. Is it true that we are poor in our recognition of meningococcal disease? If so, what can be done about it?

Guidelines on early management of meningococcal disease

Several recent Australian publications have highlighted this issue. An editorial by Hall in the Journal in June last year reminded us that "deaths from meningococcal septicaemia may be prevented by early antibiotic treatment".[1] All general practitioners are advised to be ready to administer benzylpenicillin immediately to a patient with an acute systemic febrile illness and either a petechial or purpuric rash. Likewise, the Department of Health Services, Victoria, has issued *Advice on meningococcal disease for medical practitioners* (modified January 2002), which stresses that "prompt diagnosis of meningococcal septicaemia and meningitis and preadmission treatment of presumptive cases can be life saving".[2] Common signs and symptoms of meningococcal disease are shown in Box 1.

In September 2001, the Communicable Diseases Network Australia published *Guidelines for the early clinical and public health management of meningococcal disease*.[3] They also urged immediate administration of benzylpenicillin in suspected cases of meningococcal septicaemia, and emphasised the importance of haemorrhagic rash as the most characteristic clinical feature. The authors pointed out that "less commonly, the rash has a maculopapular appearance, the discrete pink macules or papules blanching under pressure".

All three documents advocate early antibiotic treatment for suspected meningococcal septicaemia and stress the importance of a haemorrhagic rash. Unfortunately, the two government documents may not be commonly accessed by general practitioners. Even more importantly, only 40% of patients with invasive meningococcal disease present with a haemorrhagic rash; this usually does not appear until six to 12 hours after the first symptoms. About half the patients who die of meningococcal disease do so within 24 hours of the first symptoms.[4] Thus, to significantly reduce the risk of death, we need to suspect the presence of meningococcaemia in the first 12 hours of the illness. Can we do so, even in the absence of a haemorrhagic rash?

We would like to share our approach to early diagnosis of meningococcal disease, based on several decades' experience of teaching medical students and junior doctors about infectious diseases. We acknowledge that our advice is largely descriptive and is based on clinical observation and case reports and series.

Syndromes of meningococcal disease

First, we need to understand the varied nature of meningococcal disease. The rate of illness progression varies widely between individuals; it may be fulminant and cause death

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1: Common signs and symptoms of meningococcal disease*

In children and adults:

- Fever, pallor, rigors, sweats
- Headache, neck stiffness, photophobia, backache, cranial nerve palsy
- Vomiting or nausea, and sometimes diarrhoea
- Lethargy, drowsiness, irritability, confusion, agitation, seizures or altered conscious state
- Moaning, unintelligible speech
- Painful or swollen joints, myalgia, difficulty in walking
- While the absence of a rash does not exclude meningococcal disease, any haemorrhagic rash should be particularly noted.

In infants and young children the following may also occur:

- Irritability; dislike of being handled; unwillingness to interact or make eye contact
- Loss of interest in the surroundings
- Tiredness, floppiness, drowsiness, altered mental state
- Twitching or convulsions
- Grunting or moaning
- Turning from light
- Pallor despite a high temperature.

Note in particular:

- Rapid deterioration in clinical condition
- Repeat presentation to surgery or hospital
- Normally calm friends and relatives whose worry seems more extreme than the symptoms appear to justify.

*Modified from *Advice on meningococcal disease for medical practitioners* (Department of Human Services, Victoria, 2002 — modified January 2002).[2]

within 12 hours, or it may assume a chronic form that goes on for weeks. The determining factor is the clinical syndrome[5] (Box 2). The time elapsed between first symptoms and admission also correlates with the clinical syndrome.[4]

Meningitis is the most common clinical syndrome (80%–85% of cases). The diagnosis is relatively straightforward when the patient presents with the typical clinical picture (fever, headache, vomiting and change in conscious state), and treatment is not likely to be delayed. In most cases of meningococcal meningitis (as well as other bacterial meningitis), there is a non-specific illness one to three days before signs of meningitis appear. Rarely, the clinical picture is dominated by coma, which is both sudden and deep; this syndrome is sometimes referred to as fulminant meningococcal encephalitis.[6] Mortality of patients presenting with meningococcal meningitis is low (1%–5%), considerably lower than that of patients with invasive meningococcal disease without meningitis (up to 40%). Furthermore, prognosis of patients with bacterial meningitis (from all causes) was no worse in those whose disease was not recognised for as long as two to four days before admission than in those admitted when first seen.[7]

A few patients have less common syndromes, such as conjunctivitis, pneumonia, septic arthritis and pericarditis. Localising symptoms and signs ensure that diagnosis and treatment are unlikely to be delayed.

Meningococcaemia is another matter: between 15% and 20% of patients present with septicaemia unaccompanied by meningitis or other focal features. The illness in patients with pure septicaemia is generally more severe, progresses more rapidly, and has a high case fatality rate. Unfortunately, there is often confusion in the minds of the public, the media and even health professionals between meningitis and meningococcaemia; this may occasionally be a factor in delayed diagnosis.[8]

In most patients, the beginning of meningococcal septicaemia is marked by acute onset of fever, chills, and generalised muscle aches or pains in the back or thighs. There may be a transient clinical improvement after four to six hours; this is often the stage when patients are sent home from emergency departments. Six to 12 hours after onset, a rash typically appears, which may initially resemble a viral rash. The characteristic haemorrhagic rash appears soon after. How many patients suffer from meningococcal septicaemia without meningitis or a rash is unknown, as the diagnosis may well be missed in these cases. Similarly, every patient with fulminant meningococcaemia who lives long enough develops a haemorrhagic rash.

It is in this group with septicaemia but no obvious features of meningitis that the illness progresses most rapidly, has the most non-specific clinical features, and the highest fatality rate. Can we suspect meningococcaemia early? Several clues may help. Most of these also apply to sepsis caused by other bacterial pathogens, but meningococcal sepsis is the most fulminant.

Clinical clues to early diagnosis of meningococcaemia

Haemorrhagic rash: In Australia, the acutely ill patient with fever and haemorrhagic rash (petechial or purpuric) usually has bacteraemia, and the most common cause is meningococcaemia.[9,10] Typically, the rash begins within 24 hours of onset of illness — a useful clinical pointer. In the early stages, sparse petechiae can be easily missed unless specifically sought in body folds, groin and axillae, along flexor surfaces, on the ankles, or on the conjunctiva, sclera or oral mucosa. The rash evolves over time, and may become apparent on repeat examination.

2: Clinical syndromes associated with meningococcal disease*

- Meningococcal meningitis
- Meningococcal bacteraemia
- Meningococcaemia (purpura fulminans and the Waterhouse–Friderichsen syndrome)
- Respiratory tract infection
  - Pneumonia
  - Epiglottitis
  - Otitis media
- Focal infection
  - Conjunctivitis
  - Septic arthritis
  - Urethritis
  - Purulent pericarditis
- Chronic meningococcaemia

*Modified from Rosenstein et al.[5] Individual patients may have more than one syndrome.

3: Suggested strategies for family doctors and emergency departments

Treat immediately with benzylpenicillin or ceftriaxone and then admit to hospital all patients:

- With suspected meningococcal septicaemia or meningitis;
- With fever and a haemorrhagic rash; or
- With fever or pain at any site and a history of contact with meningococcal disease.

Refer and admit to hospital:

- Any patient, young or old, presenting with a true rigor;
- Any patient with fever and severe generalised muscle pain or bilateral anterior thigh pain; or
- A febrile patient seen for a second time within a 24–48-hour period.

Suspect meningococcaemia and observe closely:

- Any unwell patient with acute onset of fever and a non-specific "viral" rash appearing within the first 12 hours of illness; or
- A previously healthy child or young adult with an acute febrile illness whose family or friends are concerned about his or her condition.

Blanching macular or maculopapular rash: It is not commonly known that the early meningococcal rash may be diffuse macular or maculopapular (or rarely urticarial), a rash which blanches with pressure.[8] It mimics a non-specific viral rash and may completely disappear or dramatically evolve into the typical petechiae. Indeed, it may resemble the first day of a measles rash. However, measles rash is preceded by a prodrome of several days with prominent respiratory symptoms. Similarly the length of the prodrome and associated symptoms and signs would generally help identify other viral causes. Meningococcaemia should be considered if the rash is present in the first 24 hours of illness, and the patient appears unwell.

True rigors: A rigor is a shaking chill that cannot be stopped voluntarily. Onset is sudden, and duration may be 10–20 minutes. It should be distinguished from a sensation of chill or shivers that lasts only for seconds. Although rigors occur in some viral infections, they should generally be regarded as indicators of significant sepsis, in conditions such as bacteraemia, pneumonia, abscesses, endocarditis, cholangitis, and pyelonephritis.[11,12] We preach the "rigor rule" to our students: any patient, young or old, presenting with a rigor should be admitted to hospital for observation and investigation. This rule has not been popular with some colleagues in emergency departments.

Severe pain in extremities, neck, back or elsewhere: Severe muscle pain, even in the absence of overt fever, may be an early symptom of meningococcal, staphylococcal or streptococcal bacteraemia. It is also a feature of myositis and necrotising fasciitis. Anterior thigh pain and tenderness has been found to be a useful indicator of bacteraemia.[13] Children may refuse to walk because of pain in the extremities.[14] Muscle pain is more prominent in patients with meningococcal meningitis than in those with other forms of bacterial meningitis. It occurs in both adults and children.

Abdominal, chest and joint pains occasionally occur in patients with sepsis. When pain is prominent, it can dominate the patient's illness and become a false localising symptom. Although we do not know how common this is in meningococcal sepsis, we have anecdotal evidence of local pain leading clinicians and their patients to disaster. We pay a great deal of attention to any febrile patient with severe pain at any site.

Vomiting, especially in association with headache or abdominal pain: Vomiting is not a common symptom in previously healthy individuals. If it occurs without diarrhoea, it should not simply be dismissed as gastrointestinal infection, as it is a common symptom of central nervous system infection and occult sepsis. On the other hand, diarrhoea may also be a non-specific feature of bacteraemia.

Rapid evolution of illness: Rapid evolution of an illness is usually an indication of its severity. Previously healthy individuals tend not to seek medical attention unless something is seriously amiss. An abrupt change in health is a warning sign, and we take special notice of patients who present within 24 hours of onset or whose illness has progressed rapidly over 24–48 hours, especially from being up and about to being bedridden. Likewise, we view seriously anyone who presents to the doctor or emergency department more than once over a 24–48-hour period.

Concern of parents, relatives or friends: Parents are usually the best judges of the health of their children. We also take notice when relatives or friends are more worried than the patient's symptoms appear to warrant.[15]

Age: By itself, this is of little value in the diagnosis of meningococcal disease, which may occur at any age. The attack rate is highest among children aged three to 12 months (incidence in Victoria in 2001 was 32.5/100 000), followed by those aged one to four years (11.0/100 000).[16] The third-highest attack rate occurred in the age group 15–19 years (8.4/100 000). Fewer than 10% of cases of meningococcal disease occur in patients aged over 45 years.

In recent years, the incidence of group C meningococcal disease has increased in Australia. It is more severe than group B disease, and is most common in adolescents and young adults. This is the age group that goes to discos, smokes and lives communally and in military camps. Closeness, persistence of contact and cigarette smoking (active and passive) are known risk factors for infection and disease. As adolescents and young adults tend to shun doctors, it is wise to take seriously patients in this age group who present with a short history of fever and complaints of pains anywhere.

Contact with a patient with meningococcal disease: This history is seldom present when the infection occurs sporadically, as secondary cases constitute no more than 5% of the total. However, if a contact history is present, it must not be ignored.

Discussion

A major concern for doctors is missing the diagnosis of meningococcaemia when the patient does not appear very ill on initial presentation. Whether to give antibiotics is a perennial question. There are no reliable algorithms capable of directing management. The apparent improvement in some patients a few hours after the onset of illness makes the diagnosis even more difficult. This may be part of the disease process or the result of analgesic treatment or fluid replacement.

We have outlined nine clinical clues that are helpful in assessing febrile patients with no obvious focal signs. Of course, there are other relevant factors to consider, such as previous state of health, comorbid conditions, occupation, and travel history.[17]

- The first clue in our list gives rise to the golden rule: fever plus a petechial rash is meningococcaemia until proven otherwise, and immediate action is mandated.
- The related clue (a blanchable rash) is less categorical, but also urges us to consider meningococcaemia.[8]
- Individually, none of the other clues are indications for immediate antibiotic treatment and admission to hospital, and there are no data on their specificity or sensitivity. However, when one or more of these clues is present, meningococcaemia should be considered before the consultation is concluded. The message is to look at the whole pattern of the illness rather than exclusively at the presence or absence of any particular symptom or sign. It is not a matter of deciding whether the headache or shoulder pain is significant, or whether meningitis has been excluded by a normal cerebrospinal fluid examination, but why this patient is seeking help at this time.

Regrettably, there will always be a few patients whose meningococcaemia goes unrecognised, because they do not appear "toxic" on presentation, and their symptoms are non-specific. It is essential that all patients be advised to seek review if there is any clinical deterioration. As a final step, when assessing any febrile patient, it is prudent to ask ourselves these two questions: "Could this patient have meningococcaemia?" and "Why is he or she here now?".

Competing interests

None identified.

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