Dengue fever and dengue haemorrhagic fever

A diagnostic challenge

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The number of cases of dengue fever in returning travellers is increasing worldwide. In Australia, two mosquito vectors exist and the *Aedes aegypti* mosquito has already been responsible for local transmission within Queensland. For these reasons, general practitioners need to be able to recognise dengue fever and its complications: dengue haemorrhagic fever (DHF) and dengue shock syndrome. Infections can vary from severe to asymptomatic. The incubation period, duration of fevers, presence of rash and relative bradycardia can assist in the diagnosis of dengue. Dengue haemorrhagic fever is a severe form of dengue fever associated with plasma leakage and specific risk factors. The risk of DHF to most travellers previously infected with dengue is probably low. Serology and reverse transcriptase polymerase chain reaction are useful tests for diagnosing infection, although both have limitations. Vaccine design is a promising strategy to prevent infection.

Case study

A woman in her 30s presented to an emergency department with fevers after returning from East Timor. She had spent 10 days in East Timor working for a nongovernment organisation and had also visited there previously. All but 2 days were spent in the capital, Dili. Her immunisations were up-to-date and she took no malaria prophylaxis during this trip. Her previous medical history was unremarkable.

She became unwell 24 hours before presenting to the emergency department; 3 days after returning from East Timor. She described the insidious onset of a 'cap-like' headache, feeling hot and cold, generalised myalgias and arthralgia. She recalled being bitten by mosquitoes while in Dili. Her physical examination revealed fever of 38.9°C and relative bradycardia (ie. the heart rate was inappropriately slow for the degree of fever). The remainder of the examination was normal. Specifically no rash, conjunctival injection, jaundice or neck stiffness was noted.

Her blood tests revealed the following abnormalities: leukopaenia (2.2 x 10^9/L) with lymphopaenia, thrombocytopaenia (144 x 10^9/L) and bilirubin 25 µmol/L. The blood film showed mild toxic changes. A chest X-ray was clear. Three malaria films were negative.

On the following day (day 3 of her illness), she was reviewed by the infectious diseases team. Her symptoms were present but improving. The fevers and relative bradycardia persisted. A diffuse erythematous rash was noted on the back and shoulders. Blood tests showed a worsening leukopaenia (1.5 x 10^9/L), now with neutropaenia as well as lymphopaenia, and worsening thrombocytopaenia (79 x 10^9/L). A provisional diagnosis of dengue fever was made. She was not commenced on antibiotics. Serum for dengue antibodies was collected and sent to an interstate reference laboratory.

The patient was discharged on day 5 of her illness. Her rash and fevers had largely resolved. Three malaria films and blood cultures were negative. The leukopaenia had reached a plateau and the thrombocytopaenia was resolving. The next day, she developed a new pruritic rash over the arms, back, palms and soles of her feet. However, this resolved within 3 days.

The following week, she was completely well apart from resolving lethargy. The haematological parameters were now normal. The dengue serology from day 3 of her illness was IgG and IgM negative; however, a repeat enzyme immunoassay from day 7 demonstrated positive IgM and IgG, consistent with primary dengue infection.

Dengue fever is becoming increasingly relevant to general practitioners in Australia. It is a common cause of hospitalisation in travellers returning from tropical destinations.[1] Outbreaks of dengue fever have occurred in North Queensland in recent years.[2,3] Between 2003–2005 there were 1429 dengue notifications compared to only 392 notifications in 2000–2002. In 2005, there were 217 notifications of dengue infection compared to no cases of Japanese encephalitis, 53 cases of typhoid fever, 321 cases of hepatitis A infection, and 817 cases of malaria.[4]

Dengue belongs to the family of viruses, Flaviviridae, and consists of four serotypes (DENV-1–4). The word 'dengue' is Spanish and presumably refers to the mannerisms related to the patient's stiff gait and fear of motion. However, the term may have originated from the Swahili phrase 'Ki denga pepo' (a sudden cramp-like seizure from an evil spirit or plague).[5]

Vector and transmission

Dengue is a mosquito borne arbovirus. The principal vector, *Aedes aegypti*, is found in most parts of the world, including Australia. The mosquito feeds during the day and has a propensity for man made habitats containing water.[1] Other mosquitoes from the Aedes genus, such as *A. albopictus* and *A. polynesiensis*, can also transmit infection.[6] This is relevant to Australia as *A. albopictus* is now established in islands of the Torres Strait and has the potential to spread to southern Australia.[7] Even in regions where these vectors are not established, there are constant risks of invasion through the importation of goods. Between 1997 and 2005, port and quarantine authorities in Australia have intercepted *A. albopictus* on almost 30 occasions.[7] While mosquito borne transmission accounts for almost all cases of dengue fever, transmission to health care workers through exposure to infected blood has rarely occurred.[8]

Clinical features

Classic dengue is recognised as a syndrome of severe myalgias and arthralgia (hence the name 'break bone fever'), fevers, retro-orbital pain, headaches and rash. There are three types of rash typically described: a petechial rash, diffuse erythematous rash with isolated patches of normal skin, and a morbilliform rash. However, the majority of dengue infections, especially in children under the age of 15 years, are minimally symptomatic or asymptomatic.[9] Accompanying clinical features can include conjunctivitis, facial flushing, lymphadenopathy, sore throat, and respiratory and gastrointestinal symptoms. Rare clinical manifestations include severe hepatitis, rhabdomyolysis and neurological presentations such as encephalopathy, neuropathy, and Guillain-Barré syndrome.[1,10]

Clues that might help GPs diagnose dengue fever include:

- the incubation period
- the duration of fever, and
- the presence of relative bradycardia.

The incubation period of dengue is typically 4–7 days (range 3–14 days). Therefore, an illness beginning more than 2 weeks after returning from an endemic region is unlikely to be dengue. The fever of dengue usually lasts for 5–7 days; fevers persisting beyond 10–14 days suggest another diagnosis.[1] Relative bradycardia refers to the absence of an expected relationship between heart rate and temperature. Normally, the heart rate will increase with increasing temperature. However, this relationship is lost in certain infections and the heart rate is slower than expected.[11] Such infections include typhoid fever, Legionnaire disease, pneumonia due to chlamydia species, and dengue and sandfly fever.[12] Before a finding of relative bradycardia can be made, the presence of cardiac pacemakers and medications that slow the heart rate must be excluded. The expected relationship between fever and heart rate is shown in *Table 1*. In any patient where a diagnosis of dengue is being considered, it is always worth discussing the case with an infectious diseases physician or microbiologist.

Table 1. The usual relationship between temperature and heart rate[21]

Temperature	Beats per minute
38.3°C (101°F)	110
38.9°C (102°F)	120
39.4°C (103°F)	120
40°C (104°F)	130
40.6°C (105°F)	140
41.1°C (106°F)	150

Dengue haemorrhagic fever/dengue shock syndrome

Dengue fever is usually a self limiting condition and death as a result is uncommon. The main concern is the development of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) which occur in up to 1% of cases.[3] The mortality rates of DHF and DSS can be up to 10–20% and 40% respectively.[1] Dengue haemorrhagic fever is often a poorly understood term because it implies that haemorrhage is the major feature. However, many patients with uncomplicated dengue fever have haemorrhagic manifestations, such as epistaxis, petechiae and gum bleeding. The World Health Organisation case definition for DHF is shown in *Table 2*.

The first three components can be seen in uncomplicated dengue fever – it is the fourth component, 'objective evidence of plasma leakage', which differentiates the two conditions. For this reason, it has been suggested that the term 'DHF' no longer be used, instead referring to 'severe dengue' in patients with objective evidence of plasma leakage. Deterioration during DHF tends to occur around the time the fever subsides. Dengue shock syndrome is a severe form of DHF. Clinical indicators of impending DSS include severe abdominal pain, change from fever to hypothermia, restlessness, sweating, prostration and tender hepatomegaly.[9] Risk factors for the development of DHF include:

- age – 95% of DHF/DSS cases occur in children under 15 years of age;[14] young adults have the lowest risk. Physiological changes in microvascular permeability seen with age seem to parallel the susceptibility of young children to DHF[15]
- repeat dengue infections – pre-existing antibodies from an earlier dengue infection prevent reinfection with that same serotype. However, they are not capable of neutralising infection with a different serotype. These pre-existing antibodies can still generate an immune response, which can be deleterious to the host
- viral genotypes with increased pathogenicity – in general, the Asian strain (genotype) of

Table 2. WHO definition for dengue haemorrhagic fever[22]

- Current or recent fever
- Platelet count ≤100 000/mm3
- Haemorrhagic manifestations
- Objective evidence of plasma leakage caused by increased vascular permeability manifested by at least one of the following:
  - elevated haematocrit (≥20% over baseline or a similar drop after intravenous fluid replacement)
  - pleural or other effusion (eg. ascites)
  - low protein

Table 3. Common differential diagnoses for dengue fever in a returning traveller[1]

Malaria
Typhoid fever
Leptospirosis
Epstein-Barr virus
Cytomegalovirus
HIV seroconversion illness
Measles
Rubella

DENV-2 is supposedly more virulent than its American DENV-2 counterpart, causing more DHF[16]

- genetic factors – studies on southeast Asian populations show that HLA class I alleles influence the outcome of further dengue infections in individuals previously infected with another serotype.[17] Afro-American people are less susceptible due to the presence of a resistance gene[15]
- nutritional status – probably due to reduced cellular immunity, malnourished children are less likely to develop dengue fever or DHF. Conversely, obese children are more prone. However, if malnourished children do develop DHF, they are more likely to experience a severe form, ie. DSS.[18]

Laboratory features and diagnosis

Laboratory abnormalities commonly seen in dengue infections include leukopaenia, thrombocytopaenia, elevated liver transaminases and hyponatraemia.[1,19] Many of the laboratory and clinical features of classic dengue are nonspecific and can be attributed to other infections, which comprise the differential diagnosis (*Table 3*). In potential dengue patients who have returned from malarious areas, it is essential to have at least three negative blood films before excluding malaria.

The laboratory diagnosis of dengue fever is based on serology or the detection of virus, both of which have their limitations. These tests are performed in Australia but at few centres; therefore, specimens may have to be sent interstate for analysis.

Serological techniques for dengue include enzyme immunoassay, haemagglutination inhibition, complement fixation, dot-blot immunoassays and neutralisation. Primary dengue infection is relatively easy to diagnose. IgM is detectable in large amounts after 4–5 days of infection, peaking at about 2 weeks.[1,20] Low levels of IgG are produced just after the IgM. Therefore, patients with primary infection will seroconvert from IgM/IgG negative to IgM positive, and eventually IgG positive (as with the patient presented in the case scenario). In the early stages of primary infection, the infecting serotype of dengue can be determined as the IgM is serotype-specific.[20] One disadvantage of serology in primary infection is that the IgM can persist for months, making it difficult to distinguish a new infection from one contracted months earlier. Also, false positives can occur in patients with rheumatoid factor.[1]

A second dengue infection or exposure to other flaviviruses (eg. yellow fever, Japanese encephalitis), through immunisation or previous infection, result in a secondary antibody response. This makes a serological diagnosis more difficult to make because the IgM response is much lower, sometimes not even detectable. In fact, the IgG response occurs earlier, is higher, and lasts longer than the IgM response. This means that serology will often give a nonspecific diagnosis in patients with a secondary antibody response, eg. acute flavivirus infection.[20]

Dengue virus can be detected through culture, antigen detection and genome detection (using nucleic acid hybridisation and reverse transcriptase polymerase chain reaction [RT-PCR]). However, of these techniques, RT-PCR is the most commonly used in Australia. It is more sensitive and faster than viral culture techniques, and can be used as an epidemiologic tool to rapidly detect infecting serotypes.[20] Dengue RT-PCR is over 90% sensitive in detecting the dengue virus in serum early in the disease; however, after 1 week the sensitivity plummets to around 10%, presumably due to clearing of the viraemia.[1] Some laboratories may first use a screening RT-PCR to detect flaviviruses. If positive, further examination will be performed to see if the virus is dengue.

While both RT-PCR and serology will be positive relatively early in the course of disease, this advantage may be reduced by delays if the specimen has to be sent interstate.

Advice to infected travellers returning to endemic regions

- Dengue infection with one serotype provides lifelong immunity against that serotype, however, they are still susceptible to infection with the other three serotypes
- DHF is rare in travellers[13]
- Reinforce the need to properly use antimosquito measures (insecticides, protective clothing and repellents) while travelling. These may not prevent infection, but they do reduce the risk
- If the traveller is an adult, this further reduces the risk of DHF.

Therapy

There is no specific pharmacotherapy for dengue fever apart from analgesia and medications to reduce fever. There is no evidence in vivo to support the use of antiviral agents, corticosteroids, or drugs that reduce vascular permeability. The management of DHF and DSS is purely supportive.[1]

Immunisation

Unlike flaviviruses such as yellow fever and Japanese encephalitis, there is no dengue vaccine commercially available. Two live attenuated vaccines are in the advanced stages of testing, and have produced 80–90% seroconversion rates in human subjects. However, given the complexities of the immune response in dengue fever, ongoing research in vaccines is required.[14]

Conclusion

Doctors in Australia are likely to see more dengue in returning travellers and during outbreaks in North Queensland. The potential movement of the mosquito vectors increases the likelihood of more widespread local transmission within Australia. A combination of clinical, epidemiological and laboratory features can point toward a provisional diagnosis of dengue which can be confirmed with serology and/or RT-PCR. When considering a diagnosis of dengue, it is extremely important to rule out other serious infections, particularly malaria.

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