

Don't forget dengue! Clinical features of dengue fever in returning travellers

ABSTRACT – **Background:** Dengue virus infection is an increasingly important cause of imported fever, but many cases remain unrecognised. This study reviews the clinical features of dengue fever in patients seen at a regional department of infection and tropical medicine.

■ **Subjects:** All patients with dengue fever presenting to the Department of Infection and Tropical Medicine in Leicester over a three year period.

■ **Results:** The diagnosis of dengue fever was confirmed in 15 patients. The age range of patients was 19–61 years, and 80% were immigrants returning from a visit to their country of origin. In 11 (73%) patients, infection was associated with travel to India; others had gone to South-east Asia, Barbados and Uganda. All patients presented within three weeks of their return to the United Kingdom. The clinical manifestations of infection were often non-specific. They included fever, nausea, headache, cough and diarrhoea; 5 (33%) patients had a macular rash. Thrombocytopenia was seen in 7 (47%) patients, but only one had evidence of dengue haemorrhagic fever. Dengue infection was confirmed by serology in 14 (93%) patients. In one, dengue virus type 1 was identified by polymerase chain reaction, and the virus was subsequently isolated in tissue culture.

■ **Conclusions:** Dengue virus infection should be considered in all febrile travellers who have recently returned from areas where the disease is endemic and in whom tests for malaria are negative.

Dengue fever is an arbovirus infection that is widely distributed throughout the tropics and subtropics. Many millions of cases are believed to occur annually worldwide, and large epidemics of infection have been reported in Central and South America during recent years¹. Dengue fever is a relatively common but frequently unrecognised cause of fever in travellers returning from abroad².

Dengue is a flavivirus, four distinct serotypes of which have been described. The *Aedes aegyptii* mosquito is the vector of transmission. Two clinical presentations are recognised – classic dengue fever and dengue haemorrhagic fever. Classic dengue fever is a relatively mild illness that occurs in non-immune individuals and is characterised by

fever, headache, transient macular rash and joint pains that may be severe ('breakback fever'). The illness may run a biphasic course with recurrence of fever and a more extensive rash, but recovery is otherwise uncomplicated. In contrast, dengue haemorrhagic fever is a serious illness that usually occurs in people who are partially immune and is associated with hypotension, increased vascular permeability, thrombocytopenia and haemorrhagic manifestations³.

Dengue fever is diagnosed relatively infrequently in the United Kingdom. However, many doctors treating patients who have the disease are probably unaware of the possibility of dengue infection and fail to request specific diagnostic tests.

Methods

The study included all adults admitted to the Department of Infection and Tropical Medicine in Leicester over a three year period with a confirmed diagnosis of dengue fever infection. We extracted from the patients' case notes information on the following: symptoms, the length of illness, and any complications; the countries they had visited and for how long; the results of laboratory investigations and the diagnostic methods used to identify dengue virus infection. The total number of specimens sent for dengue virus diagnostic tests over the study period was determined from records kept in the virology department of the Leicester Public Health Laboratory. Case records were also obtained from patients who had suspected dengue fever but whose virological tests were negative. Clinical features in the patients with confirmed and suspected disease were then compared to determine whether any presentations were particularly associated with dengue fever.

Results

Diagnostic tests for dengue virus infection were requested for 59 patients over the study period, and 15 cases of dengue fever were confirmed. This represented approximately 0.5% of all admissions to the department during the three years.

The median age of the patients with confirmed dengue was 38 years (range 19–61 years) and 8 (53%) were male. Eleven patients (73%) had visited India, 2 (13%) had been in South-east Asia, one had been in Uganda and one Barbados. Twelve of the 15 patients (80%) were immigrants who had visited their country of origin. The mean duration of travel was 4.4 weeks (range 1–12 weeks). The mean time from

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Table 1. Symptoms and signs of dengue fever.

Symptom/sign	Patients with proved infection (n=15)		Patients with negative serology (n=38)	
	No.	%	No.	%
Fever	14	93	34	89
Headache	8	53	23	61
Nausea/vomiting	6	40	11	29
Rash	5	33	5	13
Joint aches	2	13	3	8
Dry cough	2	13	10	26
Diarrhoea	1	7	12	32

return to the United Kingdom to the first symptoms was 3.9 days (range -2-14 days), and the mean time between return and admission to hospital was 7.1 days (range 1-21 days).

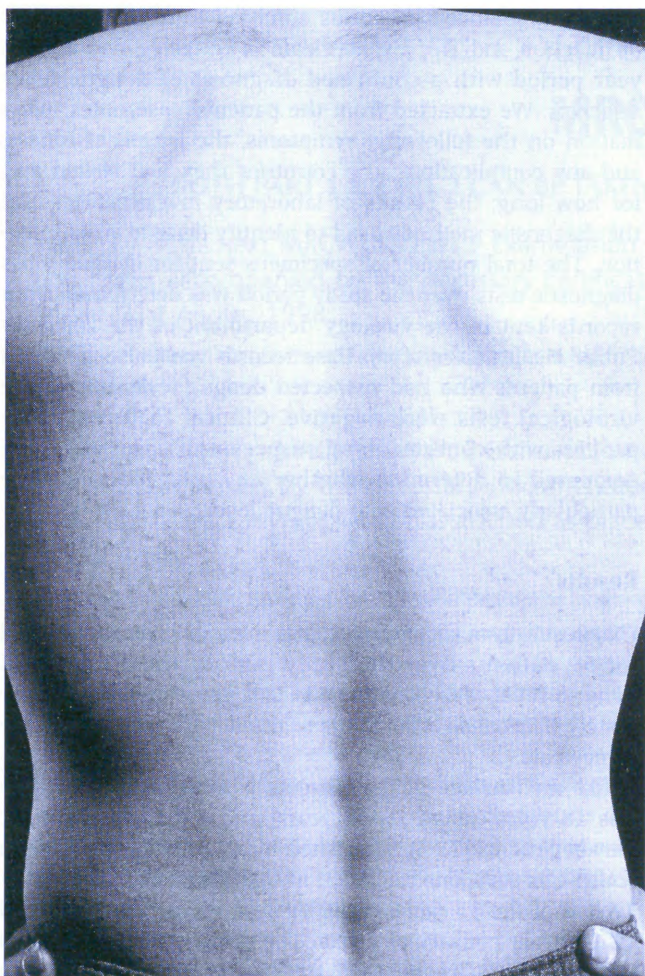
The patients' symptoms on admission to hospital are summarised in Table 1. All but one had fever, and other common presenting symptoms were headache and nausea.

A macular rash was noticed in 5 (33%) of the patients (Fig 1).

Investigations undertaken showed a mean white cell count of $5.9 \times 10^9/l$, (range $3.1-11.8 \times 10^9/l$). The mean platelet count on admission was $178 \times 10^9/l$ (range $20-379 \times 10^9/l$), however 7 (47%) of the 15 patients had thrombocytopenia (platelet count $<150 \times 10^9/l$). Abnormal liver function tests were noted in 4 (27%) patients. Repeated examination of blood smears did not show malaria in any of the patients.

Major complications included clinically severe thrombocytopenia with mucosal bleeding in one patient (whose platelet count reached a minimum of $11 \times 10^9/l$), renal impairment (serum creatinine $>150 \mu\text{mol/l}$) in 3 (20%) patients and hypotension (systolic blood pressure of 80 mmHg) in one patient. All the patients survived and the abnormal laboratory test results returned to normal in all cases. Other complications or coexistent problems included staphylococcal septicaemia after an infected insect bite, salmonella gastroenteritis, severe iron deficiency anaemia

Fig 1. Rash associated with dengue fever. The characteristic macular rash is seen on the back with a haemorrhagic area on the front of the chest.



(haemoglobin 63 g/l), urinary tract infection and exacerbation of asthma and rheumatoid arthritis. The mean stay in hospital was 5.9 days (range 2–15 days).

The diagnosis was confirmed by serology in 14 (93%) patients. In the remaining patient, viral RNA was detected in blood by reverse transcriptase polymerase chain reaction (RT-PCR). Dengue virus was subsequently isolated in tissue culture from this patient.

Case records were obtained for 38 (86%) of the 44 patients in whom dengue fever was suspected but test results were negative. There were no appreciable differences in the presenting symptoms and signs in patients with confirmed or suspected dengue fever (Table 1; proportions compared by χ^2 analysis with correction for small numbers).

Discussion

Dengue virus infection should be suspected in patients who have returned recently from endemic areas showing rather non-specific symptoms of flu-like illness with fever and headaches. A characteristic macular rash was seen in only a third of patients.

Fifteen cases of dengue fever were confirmed in Leicester over a three year period. After malaria, dengue is one of the most commonly diagnosed causes of fever in travellers and military personnel recently returned from visiting tropical or subtropical regions^{2,4,7}. During 1994, 465 cases of dengue fever were diagnosed serologically in England and Wales, and the Centre for Applied Microbiology and Research has noted an increase in the numbers of cases over recent years¹.

The fact that 73% of our patients had returned from visiting India reflects the ethnic background of the population in Leicester. Dengue is most frequently found in urban and suburban areas of the tropics and is associated with households harbouring large numbers of female *Aedes aegyptii* mosquitoes¹⁰. Although no vaccine against dengue infection is yet available, simple precautions to avoid mosquito bites, including covering bare skin, use of insect repellents and mosquito nets, would give some protection. Travellers visiting their country of origin seldom seek advice, however, and are often unaware of these simple measures¹¹.

It is clearly essential to exclude other treatable causes of fever in this group of patients. Repeated blood films for malaria should be performed as well as blood cultures to identify enteric fever and other causes of septicaemia.

Results of investigations were often non-specific. The white cell count was usually in the normal range or slightly low, and nearly half of the patients had thrombocytopenia. Although liver function tests were mildly abnormal in 27% of patients, this was not associated with any clinical problems. Abnormal liver function tests are a well recognised feature of dengue, and the infection is occasionally associated with more severe lobular hepatitis or fulminant hepatic failure in patients with dengue haemorrhagic fever¹². Three patients had renal impairment at the time of admission, but this improved rapidly. The cause of acute

renal insufficiency was uncertain. Analysis of urine showed mild proteinuria and red and white cells were seen on microscopy, but renal biopsies were not performed.

Only one definite case of dengue haemorrhagic fever was seen in a patient with a haemorrhagic rash associated with hypotension and renal impairment. The patient had no recollection of previous dengue fever, but had lived in India for many years. Thrombocytopenia responded to platelet transfusion and conservative treatment.

In the acutely ill patient, rapid diagnosis of dengue is possible by virus isolation in tissue culture or by RT-PCR^{8,9}. However, the diagnosis is most often made by comparing titres of antibody in specimens taken during the acute and convalescent phases of the illness.

In conclusion, dengue virus is rapidly spreading throughout much of the tropics. Dengue infection is one of the more common causes of fever in travellers who have recently returned from abroad and should be suspected if malaria has been excluded or if the patient has a macular rash. General physicians may be unaware of the possibility of dengue fever and undoubtedly some cases are currently unrecognised. Complications of classic dengue virus infection are rarely seen, but dengue haemorrhagic fever is a serious medical emergency.

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