Dengue or Kokobera? A case report from the Top End of the Northern Territory

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Abstract

In early April 1998, the Centre for Disease Control in Darwin was notified of a possible case of dengue which appeared to have been acquired in the Northern Territory. Because dengue is not endemic to the Northern Territory, locally acquired infection has significant public health implications, particularly for vector identification and control to limit the spread of infection. Dengue IgM serology was positive on two occasions, but the illness was eventually presumptively identified as Kokobera infection. This case illustrates the complexity of interpreting flavivirus serology. Determining the cause of infection requires consideration of the clinical illness, the incubation period, the laboratory results and vector presence. Waiting for confirmation of results, before the institution of the public health measures necessary for a true case of dengue, was ultimately justified in this case. This is a valid approach in the Northern Territory, but may not be applicable to areas of Australia with established vectors for dengue. *Comm Dis Intell* 1998;22:105-107

Introduction

Dengue fever is a flavivirus infection transmitted by the mosquito *Aedes aegypti.* After an incubation period of 7-10 days, a flu-like illness develops with high fevers, chills, myalgia and headaches. Distinctive features include retro-orbital headache and bone pain ('breakbone fever'). Following repeat infection with a heterologous serotype it can be a severe, occasionally fatal illness, causing haemorrhage and shock. The last documented cases of dengue fever in Darwin occurred in 1955. Surveys since 1974 have found no *Ae. aegypti* mosquitoes in the Northern Territory.[1] Proven locally acquired dengue in 1998 would necessitate an expensive program of enhanced human and entomological surveillance, Northern Territory quarantine, and vector control measures.

Case study

On 2 April 1998, the Centre for Disease Control in Darwin received a notification from a local doctor of a suspected case of dengue in a Darwin resident. A 20 year old male had presented to his general practitioner on 17 March 1998 complaining of a two day history of fevers, chills, myalgia, pharyngitis and headache. The illness was short lived; his temperature returned to normal after three days, but he had persistent myalgia and remained tired for a week. He made a complete recovery.

The patient gave a history of recent travel to New South Wales and Queensland, from which he had returned 22 days prior to the onset of symptoms. He denied travelling further north up the Eastern seaboard than suburban Brisbane during this trip. He had not been overseas since 1989 and had not been north of Rockhampton since 1993. Extensive questioning failed to reveal any other recent source of exposure to the vector.

Diagnosis

Dengue serology was ordered because of his travel history. However, on epidemiologic grounds, the illness was most likely to have been locally acquired in the Northern Territory. The clinical illness was not consistent with classic dengue, as there was no bone pain or retro-orbital headache. As the diagnosis was not confirmed, it was decided to repeat the serology results, to ascertain whether there was a fourfold rise in total antibody, prior to implementing a full scale search for a possible vector.

On both 17 March and 2 April 1998, the patient's screening flavivirus IgG by haemagglutination inhibition test showed a titre of 1:160, with a positive dengue IgM and negative Murray Valley encephalitis and Kunjin IgMs by immunofluorescence. However, given the highly variable persistence of flavivirus IgM[2], it was considered that this could have been evidence of old infection, either from 1993 in Queensland or (as an unlikely possibility) from India before 1989. There was no fourfold titre rise in total antibody to support an acute infection, and it was unlikely that, at presentation to his doctor on day two of the illness, the IgM would be already positive.

A more likely possibility was that his test results were due to another flavivirus infection giving a false positive dengue result, as has been documented previously[3]. No serum was left from the first bleed to undertake polymerase chain reaction testing or virus culture. In order to exclude other flaviviruses, the remaining second, and a third specimen were sent to Queensland Health Scientific Services for further testing (Table 1).

The twofold rise in Kokobera IgG titre alone was not significant. However, the presence of moderate levels of Kokobera IgG and Kokobera specific IgM indicated probable Kokobera infection. Virus neutralisation tests were not undertaken.

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Table 1. Results of flavivirus testing from the case in Northern Territory[1]

Test	Date of specimen collection	
	2 April 1998	20 April 1998
Enzyme immunoassay		
Flavivirus IgG	Detected	Detected
Dengue IgM	Not detected	Not detected
Encephalitic flavivirus IgM[2]	Not detected	Not Detected
Non-encephalitic Australian flavivirus IgM[3]	Detected	Detected
Ross River IgG, IgM		Not detected
Barmah Forest IgG, IgM		Not detected
Haemagglutination inhibition (HAI)		
Murray Valley encephalitis	40	20
Dengue 1	80	80
Dengue 2	40	20
Dengue 3	20	20
Dengue 4	20	20
Alfuy	160	80
Kunjin	40	80
Kokobera	80	160
Stratford	80	160
Japanese encephalitis	80	80
Ultra-centrifugation and HAI		
Kokobera IgM		Detected
Stratford IgM		Not detected

1. From the Queensland Health Scientific Services
2. Japanese encephalitis, Murray Valley encephalitis, Kunjin
3. Kokobera, Stratford

Vector monitoring

A vector survey is costly because *Ae. aegypti* is not readily caught in the usual CO_2 baited traps, and time consuming house to house searches of water containers with larvae and adult biting catches are required. While the serological results were pending, overall mosquito activity was monitored by three CO_2 traps set around the patient's house on two occasions in mid April, and the results of ongoing ovitrap surveillance for exotic mosquito species were reviewed. No *Ae. aegypti* or *Ae. albopictus* (another recognised vector of dengue) were detected, and the overall numbers of adult mosquitoes caught at the residence were low.

Discussion

On the basis of these results a presumptive diagnosis of Kokobera infection was made. This flavivirus is known to cause occasional human infection[4] and the clinical illness may resemble dengue, although it has more often been associated with arthralgia.[5] Kokobera has been isolated from *Culex annulirostris* mosquitoes in the Northern Territory[6] and these were the predominant mosquitoes trapped around the patient's house. In addition, there have been ten Kokobera isolates from *Culex annulirostris* during recent mosquito surveys in northern Queensland (D. Phillips, personal communication).

Specific flavivirus serology results, particularly IgM results, are unreliable. They may be elevated for a period of some years following infection, or falsely elevated because of cross reactivity with related but distinctly different flavivirus, or other arbovirus infections, each with very different public health implications. If significant public health action is dependent on a flavivirus result, every effort should be made to confirm the diagnosis, rather than rely on a positive IgM result alone. A fourfold rise in antibody level over the acute phase of illness, with sera tested in parallel to ensure a consistent reading under identical conditions, is required for diagnosis. It is, therefore, very important to obtain repeat blood samples. This approach is suitable in the Northern Territory, but may not be applicable to areas of Australia with established vectors for dengue, where immediate public health action is required. In these areas, other tests, such as polymerase chain reaction, or viral culture may be used to establish the diagnosis quickly.

Conclusions

Because of the high rate of cross reactivity in flavivirus serology, a positive screening test should be interpreted with caution. Specific tests for other flavivirus infections such as Kokobera are not routinely requested. If the patient had had a travel history consistent with vector contact in Queensland, he would have been notified as a case of dengue. However, if he had not travelled to Queensland dengue serology would not have been requested in the first place. This case is a reminder to consider a wide range of diagnostic possibilities when determining the cause of an arboviral infection.

This case also reinforces the importance of ensuring that all factors; laboratory tests, clinical symptoms and epidemiologic data, are consistent before making a diagnosis that has considerable public health implications. This case of 'dengue' was suspect because the clinical illness was inconsistent and there was no entomological evidence that the vectors were present in Darwin. The assumption that this was not dengue was borne out by reference laboratory testing. In the Northern Territory it justified the approach of waiting for the results before vector surveys and control strategies, including human health service alerts, were implemented.

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