Clinical Features of Hospitalized Patients During Dengue-3 Epidemic in Far North Queensland, 1997-1999

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Abstract
Between December 1997 and March 1999, the Cairns and Mossman/Port Douglas regions of Far North Queensland, Australia, experienced an epidemic caused by DEN-3 virus. There were 496 confirmed cases over this period, 98 (20%) of this group were hospitalized. Additionally, 19 patients with probable dengue were hospitalized. The unusually high rate of hospitalization prompted an analysis of the clinical features of the hospitalized cases. The case records of 100 locally-acquired acute dengue cases hospitalized in the local regions were retrospectively examined. The mean age of the hospitalized cases was 42.5 years. In many cases admission was required for the management of severe rash, pain, or dehydration. Gastrointestinal symptoms were common. Other presentations included nephrotic syndrome, hepatitis and encephalopathy. One paediatric case of dengue haemorrhagic fever was recorded. The severity of illness observed in this epidemic is likely to be related to the virulence of the dengue strain.

Key words: Dengue fever, Dengue haemorrhagic fever, IgM IgG Elisa, Australia

Introduction
The city of Cairns (population 111,000) and the two adjacent towns (situated 60 km north of Cairns) of Port Douglas and Mossman (combined population 14,600) are two of the major population centres of Far North Queensland, Australia. The region is

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located in the wet tropical part of Australia and is a popular tourist destination. There are regular flights into Cairns from Papua New Guinea and South-East Asia.

Dengue fever is not endemic in north Queensland but the area is vulnerable to the introduction of the dengue virus. The city of Cairns experienced a major epidemic caused by DEN-1 in 1981-82 and a small epidemic caused by DEN-2 in 1996-97\(^1,2\).

In November 1997, a case of dengue fever, later identified as being caused by DEN-3, was recognized as being acquired in Cairns. A major epidemic ensued, moving briskly through a number of Cairns suburbs. The number of the notified cases fell during the cooler dry season (July-September) only to increase again as the temperature increased in the following summer, when the epidemic moved north to the Port Douglas/Mossman region. The last case of dengue fever during the epidemic was recorded in March 1999. Approximately 220 notifications of dengue fever were received from Cairns and 270 notifications from Port Douglas/Mossman. (Full details of this outbreak are to be presented elsewhere.)

Two hospitals provide inpatient services in the city of Cairns and there is one hospital in Mossman. Of the 496 notified cases, 98 (20%) were hospitalized and a general observation was made that the clinical manifestations of dengue fever during this epidemic were unusually severe. A retrospective analysis of the hospitalized cases was undertaken to record the clinical features.

**Methods**

Diagnostic laboratories or clinicians notified cases of dengue fever to the Tropical Public Health Unit. The cases were classified as ‘probable’ on the basis of a positive enzyme immunoassay test for IgM antibodies. Classification as definite cases required viral detection by either nucleic acid amplification or viral culture, or positive IgM antibodies against dengue as assessed by haemagglutination inhibition assay (HAI) on fractionated serum. Only the definite cases were notified. At the time of notification, instances of hospitalization were recorded.

Case records of all the notified cases admitted to any of the three hospitals in the region were analyzed. Additional hospitalized cases were included if there was probable dengue. Information extracted from the case notes included age, gender, reason for hospital admission, whether dengue fever was suspected as the cause of illness at the time of admission, the clinical features recorded during admission and laboratory data. Cases were classified as secondary infections if there was prior evidence of dengue virus infection (if the serum IgG ELISA was positive prior to the appearance of IgM), or primary (if IgM reactivity occurred first). If both IgM and IgG were reactive at the time of the initial serum collection, the cases could not be classified as either primary or secondary infections.

Statistics were performed on the tabulated data with ‘inStat’ and ‘Epi info, Version 6.04’ programs.
Results

A total of 117 hospitalized dengue fever cases were identified, 98 (84%) of which were confirmed. One hundred were admitted to the three hospitals in Far North Queensland, the remainder being hospitalized elsewhere.

Of the 100 patients, 35 acquired their illness in Cairns and 65 in the Port Douglas/Mossman region. The mean age of the patients was 42.5 (range 1 - 76) years. Seven (7%) were aged under 17 years and 13 (13%) were aged above 66 years. Forty-three (43%) of the hospitalized cases were male. The mean duration of hospital stay was 5.4 (range 1-44) days. The mean duration of symptoms prior to admission was 5 (range 1-35) days.

An admission diagnosis of dengue fever was made in 71 of the cases and viral illness in 11. In these cases admission to hospital was deemed necessary for complications such as dehydration or for symptom control. Other admission diagnoses included chest infection or asthma (5 cases), meningitis, encephalitis or psychosis (3 cases), gastro-enteritis (2 cases), pseudomembranous colitis (2 cases), and urinary tract infection (3 cases).

The symptoms recorded in the hospitalized patients are given in Table 1. Fever was documented in most cases. Eleven per cent had a maximum temperature of ≥40°C and 85% had a maximum temperature of ≥38°C. Patients who did not have a fever documented had been symptomatic 3-12 days prior to admission and it is likely that most had been febrile during that period.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number/Number recorded (%)</th>
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<tbody>
<tr>
<td>Fever (≥38°C)</td>
<td>85/100 (85)</td>
</tr>
<tr>
<td>Musculoskeletal ache</td>
<td>89/90 (99)</td>
</tr>
<tr>
<td>Headache</td>
<td>80/84 (95)</td>
</tr>
<tr>
<td>Rash</td>
<td>57/87 (66)</td>
</tr>
<tr>
<td>Any gastrointestinal symptoms</td>
<td>84/88 (95)</td>
</tr>
<tr>
<td>Nausea</td>
<td>81/88 (92)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>48/74 (65)</td>
</tr>
<tr>
<td>Altered taste</td>
<td>38/41 (93)</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>38/45 (84)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>10/22 (45)</td>
</tr>
<tr>
<td>Cough</td>
<td>23/47 (49)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>19/30 (63)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>20/23 (87)</td>
</tr>
</tbody>
</table>

Table 1. Symptoms and signs recorded for hospitalized patients with dengue fever in north Queensland 1997-1999

Headache and musculoskeletal pain were, as expected, very common, but gastrointestinal symptoms, especially nausea, were also very common. The presence or absence of other symptoms was recorded in less than half of the case records. Where recorded, the presence of altered taste, ocular pain and pruritis were common. Bleeding of any severity was noted in 19 patients. It is likely that for a dramatic symptom such as bleeding, occurrence would be reported but for a symptom such as altered taste under-reporting was likely.

Complications that were ascribed to dengue infection included ‘dehydration’ in 77 patients. The dehydration was, in most cases, not associated with evidence of
haemoconcentration or disturbed renal function. Treatment with intravenous fluids was often commenced as a consequence of nausea.

Rash was described as being particularly severe in 19 patients, with florid petechiae, frank haemorrhage and/or intense pruritis. Bleeding was listed as a complication for 13 of the patients. Amongst these patients the bleeding varied in severity from haematemesis or melaena to haemorrhagic conjunctivitis and vaginal blood loss. For 5 patients ‘collapse’ precipitated their admission. Eight patients had neurological symptoms that varied in severity from mild confusion and drowsiness to features suggestive of encephalitis. All patients made a full recovery.

There were 2 cases that fulfilled the World Health Organization criteria for dengue haemorrhagic fever (DHF)\(^3\). One case occurred in a child with haematemesis and melaena. The serological profile was that of a primary dengue infection. The other, an elderly man with a serological profile of secondary dengue infection, developed nephrotic syndrome.

Overall 80% of the hospitalized patients had a white cell count (WCC) <4 x 10\(^9\)/L (normal range (NR) 4-11 x 10\(^9\)/L); the lowest recorded WCC was 1.0 x 10\(^9\)/L. The neutrophil count was <2.0 x 10\(^9\)/L (NR 2-8 x 10\(^9\)/L) in 72% of the patients. Eighty-two percent of the patients were lymphopaenic (NR 1-4 x 10\(^9\)/L) and 81% had a thrombocytopenia (NR, 140-400 x 10\(^9\)/L). The lowest recorded platelet count was 8 x 10\(^9\)/L.

Ninety-three patients had measurements of hepatic transaminases and 90% of these patients had levels which exceeded the laboratory normal range for aspartate transaminase (AST) (NR <40U/L). Alanine transaminase (ALT) (NR <45U/L) was elevated in 77% and gamma glutamyltransferase (GGT) (NR <50U/L) was elevated in 60% of the 93 patients. AST was elevated in all of the patients with elevated hepatic transaminases, and three patients had AST levels that exceeded 1000 U/L.

Urinalysis results were recorded for 87 of the patients; blood was detected in 31% and protein in 74%. One patient (mentioned above) had clinical features of the nephrotic syndrome; urinary protein was quantified at 10.8 grams/24 hours.

Creatine kinase levels were measured in 15 patients; six patients had elevated plasma creatine kinase levels (NR <200 U/L).

ELISA was performed on serum from 99 patients and was positive in 85 patients. RT-PCR was performed on serum from 75 patients and was positive in 56. Viral culture was performed on serum from 49 patients and was positive in 22. For serum samples subjected to both viral culture and PCR testing, viral culture detected less than half of the PCR positive samples. There were, however, examples where viral culture was positive and PCR was negative. Three patients had serum without detectable IgM on ELISA, but detectable using HAI of the IgM fraction.
Fifty-five patients had probable primary dengue and 21 probable secondary dengue. Patients with secondary infections were older (p<0.01) and were less likely (p<0.01) to have a rash associated with their illness. The duration of stay in hospital (p>0.05) and other manifestations of illness, including the incidence of haemorrhagic phenomena (p>0.05), were similar in the two groups (Table 2).

Table 2. Clinical and laboratory features of patients with primary and secondary infections

<table>
<thead>
<tr>
<th></th>
<th>Primary infection (n=55)</th>
<th>Secondary infection (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>37.8 (1.5-71) years</td>
<td>51.7 (17-75) years</td>
<td>0.004</td>
</tr>
<tr>
<td>Duration of admission (range)</td>
<td>4.9 (1-13) days</td>
<td>7.0 (2-44) days</td>
<td>0.526</td>
</tr>
<tr>
<td>Rash (%)</td>
<td>39 (71%)</td>
<td>6 (29%)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>11 (20%)</td>
<td>5 (24%)</td>
<td>0.762</td>
</tr>
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</table>

Discussion

Severe clinical manifestations with a high hospitalization rate characterized the 1997/99 DEN-3 epidemic in the Cairns and Port Douglas/Mossman region of Far North Queensland. Previous epidemics in north Queensland have been associated with much lower hospitalization rates; 12% of the people with dengue fever were estimated to have been hospitalized during an epidemic in the city of Charters Towers in 1993⁴. Particular features of the epidemic included a very high incidence of gastrointestinal manifestations, and a high incidence of unusually severe rash, in those patients who were hospitalized. In most other regards the clinical features were typical of dengue fever. The apparently low reported rates of altered taste and pruritis are possibly a reflection on the retrospective nature of the study. A number of the hospital doctors were unfamiliar with the minor clinical features of dengue fever and did not enquire routinely about the presence of symptoms such as taste perversion and skin itch.

One case of DHF was documented in a child. This was the first case of paediatric DHF recorded in Australia since the early part of the 20th century. The serological profile in this case was consistent with a primary dengue infection.

One case of nephrotic syndrome was associated with dengue fever. This is an unusual complication of dengue fever. Immune complex deposition in renal tissue has been occasionally reported⁵. The high prevalence of urinary abnormalities in our study suggests that renal involvement is common in acute dengue although abnormal renal function itself is rare.

Liver involvement in the hospitalized cohort was also common. The AST was elevated more often than the ALT, which is a pattern that has been observed previously⁶. Hepatic disorders, in conjunction with bleeding and thrombocytopenia, have been proposed as an indicator of severe disease⁷. Several patients had a clinical picture dominated by their hepatitis.

The high prevalence of elevated CK levels in the small group actually tested suggests that myositis was common in this outbreak. This is no great surprise considering the prominent musculo-skeletal symptoms in classical acute
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dengue. Histological changes have been reported in muscle biopsies in acute dengue\(^8\)\(^9\) and clinical cases of dengue myositis have been reported\(^10\).

Patients with secondary dengue infection were older than those with primary infection. This is likely to have been the result of the previous major epidemics in the region that occurred ≥18 years ago\(^2\).

Primary and secondary dengue infections are currently classified according to serum antibody titres determined by haemagglutination inhibition assays. This test was not routinely performed and with the increasing use of ELISA worldwide it will become more difficult to estimate the proportion of dengue fever cases that are primary or secondary. The criteria used during this epidemic are readily assessable for many patients. Semi-quantitative determination of IgG levels is possible using immunochromatographic card tests and provides additional clues for the detection of secondary infection\(^11\). A need exists to modify the criteria for primary and secondary infections that take the evolving patterns of testing into account.

There have now been three major epidemics of dengue fever in north Queensland in recent years; Townsville/Charters Towers in 1992/93 (DEN-2), Torres Strait Islands in 1996/97 (DEN-2) and this most recent epidemic in Cairns and Port Douglas/Mossman. All of these epidemics have occurred in populations with a limited previous exposure to dengue infections. The severity of an average dengue illness is difficult to measure. The clinical impression that the dengue illness seen in this epidemic was more severe than in the other dengue epidemics was supported by the high rate of hospital admission. This supports the hypothesis that some dengue strains are intrinsically more virulent than others.

References