

Dengue Virus Infection-The Malaysian Experience

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Abstract

Since dengue was first documented in Malaysia in 1902 and made notifiable in 1973, the disease pattern has changed from major outbreaks every four years to one of increasing trend yearly. The largest outbreak was seen in 1996 with 14 255 dengue cases reported and 32 deaths. The case fatality rate varied from a high of 10.43% in 1985 when dengue type 3 was the predominant type to a low of 1.29% when dengue type 1 predominated. Severe disease patterns have been observed with dengue 2 and 3 serotypes in the country.

The clinical spectrum has also been changing and multisystem involvement with more severe manifestations are being seen. Liver involvement has been documented since 1987. Fulminant hepatitis with encephalopathy can resemble Reye's syndrome. Dengue type 3 has been isolated from liver biopsy specimens. Neurological manifestations can vary from irritability, convulsions, coma to peripheral neuritis. The isolation of dengue viruses from cerebrospinal fluids recently strongly suggests that dengue viruses can be neurovirulent. Adult respiratory distress syndrome was seen in three children admitted with shock. Deaths were more frequent in children in the early period but since 1982, over 50% of deaths have occurred in patients over the age of 15 years.

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Introduction

Dengue was first documented in Malaysia in 1902 and the disease was made notifiable in 1973. The first outbreak of dengue haemorrhagic fever (DHF) was reported in 1962, and major dengue outbreaks followed a four-yearly cyclic pattern since 1973/1974 until 1992. This cyclic pattern has been modified with large outbreaks occurring frequently. Cases are becoming more severe with involvement of several systems resulting in multiorgan failure, and a rise in the case fatality rate (CFR). Dengue infection was more prevalent in children than adults during the early 1970s but a change was noted in the 1980s. The proportion of cases in children under 15 years dropped from 64.7% in 1975 to 42.5% in 1982. Deaths were rare in adults but since 1982 over 50% of the deaths have occurred in patients over 15 years of age.

All four dengue serotypes were isolated since 1986 onwards except in 1993 and 1996 when dengue type 1 and type 4 were not found (Table I). One of the 4 serotypes has predominated each year, accounting for up to 80% of all isolates. Dengue type 3 predominated in 1985-1986 and type 1 in 1987-1988. During 1989-1991,

TABLE I: CIRCULATING VIRUS SEROTYPES IN MALAYSIA (1985 TO 1996)

Year	Virus Serotype			
1985	DEN 3*	DEN 4	DEN 2	
1986	DEN 3	DEN 1	DEN 4	DEN 2
1987	DEN 1	DEN 3	DEN 2	DEN 4
1988	DEN 1	DEN 2	DEN 4	DEN 3
1989	DEN 2	DEN 1	DEN 3	DEN 4
1990	DEN 2	DEN 1	DEN 3	DEN 4
1991	DEN 2	DEN 3	DEN 1	DEN 4
1992	DEN 3	DEN 2	DEN 4	DEN 1
1993	DEN 3	DEN 2	DEN 4	
1994	DEN 3	DEN 2	DEN 1	DEN 4
1995	DEN 3	DEN 2	DEN 1	DEN 4
1996	DEN 1/DEN 2	DEN 3		

* This column indicates the predominant strain

dengue type 2 was the prominent isolate. The CFR was 1.86%, lowest in those years dominated by dengue type 1. The rate increased to 3.99% during the dengue type 2 period, and to 4.18% during the period from 1992 to 1995 when dengue type 3 was the most common serotype. The CFR has further increased to 7.3% in 1995 compared

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to 5.1% in 1994. The major virus responsible for the outbreak was still dengue type 3 but there has been no significant increase in dengue type 2 activity towards the end of 1995. In 1996, dengue type 1 and type 2 were the predominant strains, displacing dengue type 3.

Materials and Methods

We present the clinical spectrum of dengue virus infection in Malaysia, with cases from 1973 to 1989 from the Kuala Lumpur Hospital. Laboratory confirmation was done at the Division of Virology, Institute for Medical Research, Kuala Lumpur.^{1,2} Cases described from 1990 onwards were from the Paediatric Intensive Care Unit, University Hospital, Kuala Lumpur. Laboratory confirmation was done at the WHO Collaborating Centre for Arbovirus Reference and Research, Department of Medical Microbiology, University Hospital, Kuala Lumpur.³⁻⁶

Results

The Period Prior to 1982

The first major outbreak of DHF in Malaysia occurred in Penang in 1964.^{7,8} Clinical features described were based on 61 laboratory-confirmed cases, and consisted of high fever which settled, in most cases, by the seventh day. In cases which developed shock, the temperature was almost normal on the fifth day; this was the period of more critical symptoms, coinciding in some cases with a shock-like state. Other gastrointestinal symptoms like vomiting, severe abdominal pain and diarrhoea were seen in a few cases. Hepatomegaly was common and although it was seen in some patients as early as the second or third day, this was observed as a significant finding after the seventh day of the disease. Bleeding tendencies were in the form of petechiae, melaena and ecchymoses. Some patients without skin manifestations had haematemesis, bleeding gums and epistaxes. These features can be described as the "Classical Dengue Syndrome". Forty-five per cent of cases presented as a

shock-like condition. The median age was 7.5 years and the CFR was 8.2%.

During the 1973 and 1974 period, two studies described the clinical features from laboratory-confirmed cases from the then General Hospital in Kuala Lumpur (Kuala Lumpur Hospital).^{9,10} During this epidemic which was mainly from Selangor, dengue fever was seen in young adults aged 18 to 25 years. However, the more severe grades of DHF occurred mainly in the 5 to 9 age group. There was only one affected child who was below the age of 1 year. The majority of the cases were among Chinese who lived in crowded urban areas, and the more severe and fatal cases also occurred among the Chinese. Hepatomegaly was seen in 55% of cases; massive pleural effusion causing respiratory distress and disseminated intravascular coagulation (DIVC) was also described in 2 cases. Convulsions occurred in 3 cases. The clinical features described were similar to those seen in 1964. Post-mortem was done in 3 cases and the histological picture was described as nonspecific and suggestive of virus infection with evidence of internal bleeding in the organs. The CFR during this epidemic was 5.6%.¹¹

The year 1978 saw a large nationwide outbreak of DHF. Many unusual manifestations were seen differing from the classical clinical presentation seen up until 1974. These caused problems in diagnosis, management and classification of the disease. However, during the period from 1974 to 1984, the unusual systemic manifestations were mild and did not cause much residual damage.¹²

Cardiac Abnormalities

Various forms of conduction defects and electrocardiogram abnormalities of non specific "ST" and "T" waves changes were noted frequently in 1973 and 1974. These changes were transient and complete recovery occurred after 4 to 6 weeks. However, from 1989 onwards, more severe cardiac manifestations occurred mainly in adults.¹³

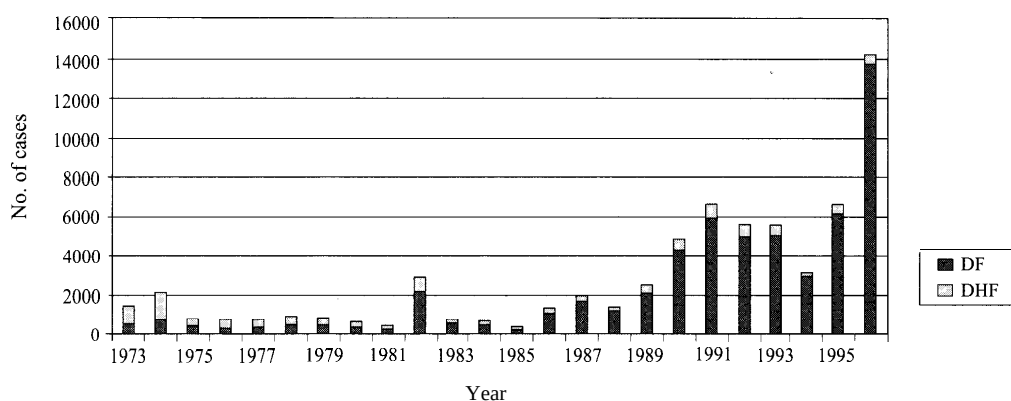


Fig. 1. Cases of dengue (DF) and dengue haemorrhagic fever (DHF) in Malaysia, 1973-1996.

Neurological Manifestations

Generalised convulsions and neck stiffness were documented in children, suggesting the possibility of raised intracranial pressure. Encephalopathy was also commonly seen in 1973 and 1974. A lumbar puncture was needed to rule out the possibility of meningitis and encephalitis but this was not encouraged due to the low platelet count and fear of bleeding complications. Para-infectious and post-infectious types of neurological disorders were also seen in a few cases. Peripheral neuritis with weakness of the lower limbs and sensory loss was seen in 3 cases, but they recovered completely with no residual sequelae. Only 1 child was left with sequelae of athetoid movements and mental retardation after one episode of generalised fits. This was seen in 1976.^{12,13} Intracerebral bleeding was suspected, but the lack of scanning equipment then made the diagnosis difficult.

Renal Complications

Acute renal failure was described as early as 1979 in a 4-year-old boy. This case was complicated with gastrointestinal bleeding and DIVC. This child, however, recovered completely after peritoneal dialysis and supportive therapy. Haemolytic uraemic syndrome was also seen in one child, but this complication proved to be fatal.¹²

Gastrointestinal Tract

Two children were admitted to the surgical ward with acute abdominal pain. Surgery was performed on one child with the mistaken diagnosis of an acute surgical problem. The severe gastrointestinal tract bleeding appeared only 48 hours later, when the possibility of DHF was suspected.^{12,13}

The 1982 Epidemic

Eighty-nine laboratory-confirmed cases were studied. Twelve cases showed features of typical dengue fever (DF) and the remaining 77 cases showed mild haemorrhagic manifestations. Only 2 cases developed shock. There was no fatality in this group. There was no significant difference in sex distribution, but there was a marked significant difference in the ethnic groups affected. Malays were more affected than the Chinese, which was markedly different from the earlier epidemic of 1973. This suggested that there was no real ethnic susceptibility to the disease. The rural to urban migration of Malays in recent years made them equally vulnerable to the infection. The age distribution showed some remarkable differences as compared to previous years. Sixty-two per cent of the cases were in the 16 to 30 age group and only 26.8% affected were below the age of 15 years. However, the two cases which manifested shock were children aged 7 and 8 years. The bleeding manifestations were mild with only a positive tourni-

quet test seen in 88.4%, petechiae in 45.5%, and epitaxes in 18.2%. Haemoconcentration and a high haemoglobin level were not common although thrombocytopenia affected 57.5% of the cases studied. The majority of the cases described seemed to fit into the newly defined category of "classical dengue fever with haemorrhage".¹²

The Period From 1989 Onwards

Severe clinical symptoms started to manifest in almost all the different systems. All age groups were affected; infants as young as 3 to 4 months as well as adults in the 40 to 50 age group. Unusual and severe clinical symptoms made diagnoses and management difficult.

In 1996, two cases of vertical transmission to infants from the mothers in late stages of pregnancy were documented.

Cardiac Abnormalities

Severe forms of myocarditis occurring in adult patients were documented from the University Hospital Kuala Lumpur. This mode of presentation has posed problems in diagnosis with a high CFR, as the typical bleeding manifestations may appear only on the third or fourth day of the illness.¹⁴

Liver Failure and Fulminant Hepatitis

George et al¹⁵ described four cases of confirmed dengue infection with fulminant hepatitis, encephalopathy and renal involvement. They all fitted into the WHO criteria of dengue fever, but the platelet count and haematocrit were normal. Eight cases of liver failure and encephalopathy were observed among twenty cases of grade 3 and grade 4 dengue haemorrhagic fever/dengue shock syndrome admitted to the Paediatric Intensive Care Unit of the University Hospital, Kuala Lumpur, from January 1990 to December 1991.¹⁶ Patients with deterioration of mental status showed a marked increase in liver enzymes (aspartate and alanine aminotransaminases) and severe coagulopathy, six patients needed cerebral protection including ventilation, intravenous sedation and muscle relaxant. There was one death during the period of study and one case of residual hemiparesis in a boy who had, in addition, intracerebral haemorrhage. All the survivors had complete recovery of liver and neurological functions. Seven patients had low fibrinogen levels, but the test for fibrinogen degradation product was negative, thus implying primary liver impairment. Three patients had clinical jaundice with their bilirubin levels ranging from 200 to 864 $\mu\text{m}/\text{L}$. Liver biopsy was done in a few cases showing histological features of extensive necrosis with residual viable hepatocytes, in contrast to the pathology of Reye's syndrome where the picture is that of fatty infiltration. Severe manifestations were seen in cases with primary as well as secondary infections. Dengue type 2 and dengue type 3 viruses were isolated from this series.

Neurological Manifestations

Mild neurological abnormalities were described in the 1973/ 1974 epidemic. However, almost all cases had complete recovery. From 1990 onwards, sign of cerebral oedema, raised intracranial pressure, encephalopathy and focal fits were more frequently seen and documented. Extensive intracranial haemorrhage has been detected in a few patients from institutions where sophisticated radiological investigation techniques are available. In a recent paper, Lum et al¹⁷ reported 6 children who were serologically confirmed as dengue infection with the clinical picture of encephalitis but there was additional evidence in the cerebrospinal fluid (CSF) of dengue virus invasion. All 6 cases had neurological symptoms on the second or third day of the disease. Clinical features of encephalitis were changes in the sensorium such as confusion, drowsiness, convulsions, abnormal behaviour, nuchal rigidity and focal neurological signs. Lumbar puncture was done in all cases within 24 hours of admission except in 1 case who was referred later. No red blood cells were seen on microscopic examination of the CSF.

Paired blood samples were also taken. Blood samples during the acute phase and the CSF were all sent for bacterial and viral cultures and tested by haemagglutination inhibition (HI) and dengue enzyme-linked immunosorbent assay (IgMELISA) against dengue antigens. These specimens were also tested for Japanese encephalitis virus and herpes simplex virus serologically. Virus isolation and detection, and identification by immunofluorescence using dengue-specific monoclonal antibodies were done in all cases. Dengue viral RNA detection and identification by the polymerase chain reaction (PCR) was carried out in both the CSF and acute blood samples. The youngest child in the series was a year old and the eldest was 11. The 11-year-old boy died on day 4 with liver failure complications, severe gastrointestinal haemorrhage and renal failure. Dengue type 3 was isolated from the CSF in 4 cases. In 2 cases, dengue virus was detected in the blood and CSF by PCR (dengue types 2 and 3). It is thus postulated that dengue type 2 and dengue type 3 viruses can cross the blood-brain barrier and invade the brain causing direct encephalitis. These preliminary findings have to be confirmed by virus isolation directly from the brain tissue in countries that have access to post-mortem specimens.

Dengue-associated Adult Respiratory Distress Syndrome (ARDS)

In adults, the adult respiratory distress syndrome which occurs as a result of increased permeability of the alveolar-capillary membrane causing oedema in the alveoli and interstitial spaces is often seen. This was seen in three children presenting with dengue shock syndrome.¹⁸ These were all serologically confirmed cases of

grade 3 or grade 4 shock syndrome. They were all serious cases with complications of intravascular coagulopathy and multiorgan failure. Treatment consisted of fluid resuscitation, correction of coagulopathy and mechanical ventilation. In spite of careful monitoring, 2 of the children died. The 1 survivor was well on discharge.

Gastrointestinal Bleeding

This may be initially occult and manifests as abdominal pain, abdominal tenderness, a firm distended abdomen, pallor, tachycardia or a drop in haematocrit without clinical improvement. Gastrointestinal haemorrhage leading to death in DHF has been described by George and Doraisamy.¹⁹ This was the commonest cause of death even in cases who initially presented with other clinical manifestations. A sudden drop in haemoglobin level and haematocrit heralded signs of internal bleeding and shock due to blood loss rather than due to plasma leakage.

Discussion

Dengue has become an important global problem in recent years and in 1993, the World Health Assembly passed a resolution asking member countries to increase their efforts at preventing the spread of the disease. The increasing trend in Malaysia is also seen and this is despite intensive efforts in vector control with strong government support. The much awaited dengue vaccine is still many years away and in the meantime, the only option is to continue with a more aggressive integrated vector control programme.

The classical clinical manifestation of dengue has been well documented by the World Health Organization. However, over the years, unusual features have been reported in several dengue endemic countries. The experience in Malaysia alone demonstrates this change quite remarkably in laboratory-confirmed cases presenting with cardiac abnormalities, renal complications, liver failure and fulminant hepatitis, neurological manifestations and even vertical transmission. It must be stressed that these unusual manifestations are relatively rare and would not have been attributed to dengue had it not been for the recent development of more sensitive and specific laboratory techniques. It is still debatable whether genetic changes in dengue viruses could account for this phenomenon and the study of viruses from these cases at the molecular level may help to provide an answer.

It is important to document atypical dengue as seen in Southeast Asian countries like Malaysia so that clinicians are put on the alert when they do encounter such cases for better patient management.

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