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Problems in diagnosis and classification of dengue virus infection

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INTRODUCTION

The earliest report of a dengue epidemic in the Malay Peninsula was from Singapore in 1901.[1] However, the first report of the sinister dengue fever with haemorrhagic manifestations was made only in 1962 from Penang Island.[2,3] The term "Dengue Haemorrhagic Fever" (DHF) brings to mind the image of a child bleeding all over. However, it must be emphasized that this picture is not always seen. The virus can cause infection with symptoms varying from a mild nonspecific febrile episode to severe shock syndrome with multiorgan failure. The fact that there are four strains of the virus and possible variations within each strain may explain the alterations in clinical manifestations.

The clinical observations reported here are made from laboratory confirmed cases seen in the General Hospital Kuala Lumpur and the University Hospital.

The dengue syndromes include dengue fever, dengue haemorrhagic fever and dengue shock syndrome (Fig. 1). The World Health Organization (WHO) has classified DHF into four grades[4] with the severe cases in the category of dengue shock syndrome (DSS).

WHO CLASSIFICATION OF DHF

The severity of DHF is classified into four grades:

Grade 1: Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test.

Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin and/or other haemorrhages.

Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness.

Grade IV: Profound shock with undetectable blood pressure and pulse.

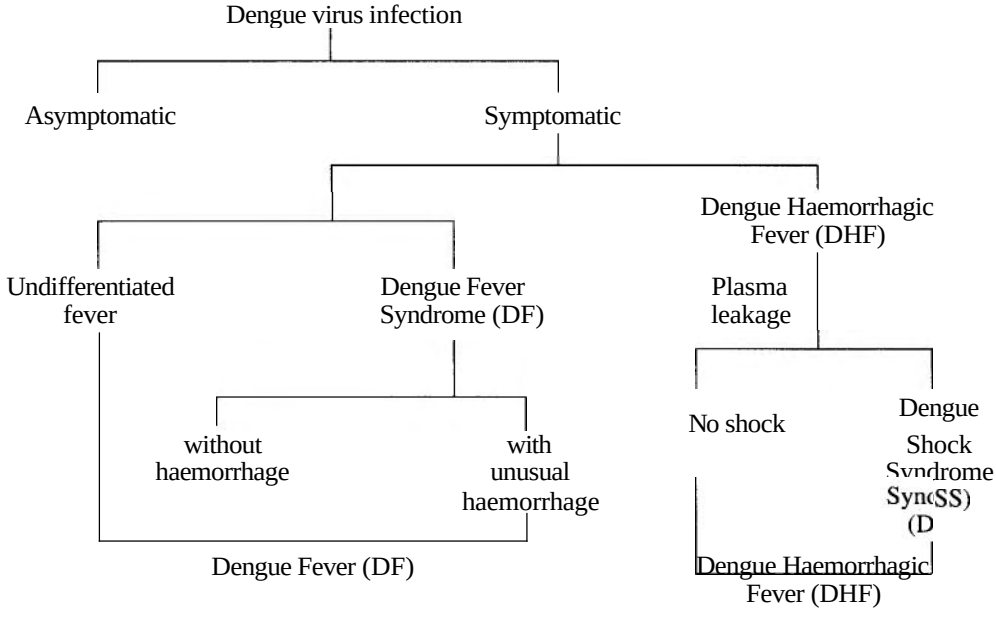

FIG. 1: The dengue syndromes.
Source: Dengue haemorrhagic fever: diagnosis, treatment and control. WHO Geneva, 1986.

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Due to the changing pattern in the clinical presentation and the presence of bleeding manifestations and unusual haemorrhages in some cases of DF, it has become difficult for the clinician to easily fit the cases into the correct classification. This may result in delay in giving the correct management and also cause confusion in documentation.

THE HISTORY OF DENGUE INFECTION

The history of dengue infection in this region can be described as follows:-

1901	DF in Singapore
1962	DHF documented in Penang
1973/4	Major outbreak of DHF in Malaysia (Selangor)
1978	Nationwide outbreak of DHF
1982	Outbreak of DF in young adults in Selangor
1986	Outbreak of DF/DHF nationwide
1987/8	Outbreak with features of encephalopathy
1990-1992	Outbreak with severe and unusual manifestations.

THE EARLY PERIOD OF DENGUE VIRUS INFECTION

1962-1974.

Sinister manifestations with haemorrhage and plasma leakage were first described in Penang by Pararneswaran[2] and Rudnick *et al.*[3] During this period the features described can be classified as the "Classical Dengue Syndrome". Clinical features comprised high fever which subsided in most cases by the seventh day. In cases that developed shock, the temperature came down to almost normal about the fifth day during the period of the more critical symptoms, coinciding with a shock-like condition. Other features described were gastrointestinal symptoms like vomiting and severe abdominal pain. Hepatomegaly was common and was a significant finding when it was also associated with raised liver enzymes, usually observed after the seventh day of disease. Bleeding tendencies were in the form of petechiae, melaena and ecchymosis. The classical maculopapular rash which is aptly described as "islands of white in a sea of red" was commonly seen. The median age of patients was 7.5 years, and initially, the case fatality rate was high as clinicians were not aware about the clinical features and correct methods of management. During the first major epidemic in 1974, a few postmortem examinations were performed. The histopathological features were non-specific but "suggestive of virus infection with evidence of internal bleeding in the liver, lungs, spleen, kidney, which could be brought about by haemorrhagic fever."

1974-1986.

This was the period of the second decade. Several unusual manifestations started appearing as described by George *et al.*,[5] making the diagnosis difficult in some cases unless there was a high index of suspicion. However, these unusual features were mild and only few residual manifestations were recorded. The features included cardiac arrhythmias, transient ST and T wave changes. These changes were no longer seen after 4-6 weeks.

Neurological manifestations included generalised fits, transient weakness of the lower limbs with sensory loss and athetoid movements. These were also transient. Acute abdominal pain simulating acute abdomen was also seen, and as the haemorrhagic manifestations appeared only after 48 hours, some cases were first admitted into the surgical wards.

The 1987-1990 period.

Features of liver involvement started to appear. George and Lam[6] described four cases of confirmed dengue infection with fulminant hepatitis, encephalopathy and renal involvement. The interesting feature in these cases was that they all fitted into the WHO criteria of dengue fever. Patients were also seen with severe encephalopathic features, generalised seizures, deteriorating conscious levels and coma. These patients also had evidence of severe liver dysfunction with grossly elevated liver enzymes as well as coagulopathy. Liver biopsy was done in a few cases and showed histological features of extensive necrosis and infiltration with lymphocytes, neutrophils and plasma cells. This picture is different from that seen in Reye's syndrome, where the picture is that of microvesicular fatty infiltration. Massive intracranial bleeds and multiorgan failure were also seen, needing careful monitoring and management in the intensive care unit.

Clinical features in 1992

Many cases were seen in the paediatric wards, presenting with massive plasma leakage which manifested as severe ascites and massive pleural

effusion. The bleeding manifestations were significantly less.

THE AGE INCIDENCE

Early epidemics mainly affected children with very few cases in adults. However, in 1982, young adults were mainly affected but with low case fatality. From 1987 onwards, all age groups were affected, including infants below *6* months of age and adults above 50 years of age. The case fatality rates were high in adults, in some cases due to delay in recognising the diagnosis.

The problems in diagnosis and classification have been further complicated by the recognition of cases of DF with unusual haemorrhagic manifestations like gastrointestinal bleeds, haematuria, and hypermenorrheoa.

In the early epidemics before clinicians became familiar with the manifestations of dengue shock syndrome, severe shock due to drug allergic reaction was suspected.

Several diseases have been "mimicked" by the dengue virus. The clinical presentation keeps changing rapidly creating more confusion.

The systems affected are:-

Neurological:	Poliomylitis, meningitis, encephalitis
	Behaviour disorder
Cardiac:	Arrhythmias
	Myocarditis
	Infarction
Renal:	Acute renal failure
	Haemolytic uraemic syndrome
	Nephrotic syndrome
Surgical:	Acute abdomen
Obstetrics and Gynaecology:	Septic shock syndrome
	Abortion
	Menorrhagia
Liver:	Reye's syndrome
	Hepatitis "A" or "B"

The most important feature to look for in classifying the disease is evidence of plasma leakage. This is the most important criterion that differentiates DF from DHF. The presence of serous effusion and a rising haematocrit confirm the evidence of plasma leakage.

Early recognition and correct management can save lives. The DF syndromes are usually mild whereas DHF and DSS can be very severe and will need careful monitoring and intensive care.

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