Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 38 (1981)
Heft: 1

Artikel: Bleeding manifestations of dengue haemorrhagic fever in Malaysia
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DOI: https://doi.org/10.5169/seals-312806

Acta Tropica *38*, 71–78 (1981)

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Bleeding manifestations of dengue haemorrhagic fever in Malaysia

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Summary

Analysis of the bleeding manifestations of 130 cases of dengue haemorrhagic fever admitted into the Children's ward of the General Hospital, Kuala Lumpur from May 1973 to September 1978 has been done. Petechial skin rash, epistaxis and gum bleeding were seen most commonly in mild and moderately severe cases. However, blood stained gastric aspirates, and severe haematemesis were seen in severe or very severe cases. Though with better vector control and preventive measures, a marked reduction in the incidence of the cases has been noted, severe cases were seen with symptoms of shock and gastrointestinal bleeding. These symptoms carried a bad prognosis. Among 15 children that died 10 had gastrointestinal bleeding and 2 had a disseminated intravascular coagulation defect.

Lymphocytosis with atypical lymphocytes, low platelet count, low reticulocyte count and raised packed cell volume were the main haematological features seen in all these cases. All these features reverted to normal within a week. Mild evidence of disseminated intravascular coagulation was seen in a number of cases, but severe features were seen only in four. Two cases improved as a result of heparin therapy.

Key words: dengue haemorrhagic fever; shock; gastrointestinal haemorrhage; atypical lymphocytosis; thrombocytopenia; disseminated intravascular coagulation defect

Introduction

Dengue fever (DF) has been reported in Malaysia as early as 1902, but the sinister dengue haemorrhagic fever (DHF) in epidemic proportions was seen

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only as late as 1962. At that time 61 cases occurred in Penang Island, and there were 14 virus isolates which were identified as dengue type II (Rudnick et al., 1965). The second major epidemic occurred in 1973, and the majority of cases occurred in the Selangor State. A study of the clinical features and laboratory results of 98 laboratory confirmed cases admitted into the Paediatric wards of the General Hospital Kuala Lumpur was described in 1976 (George and Lim, 1976).

In this paper the clinical features with main emphasis on the bleeding manifestations of 130 clinically diagnosed and laboratory confirmed cases are being described. This covers a period from May 1973 to September 1978. Though the total number of cases being admitted has been significantly reduced, cases being admitted in the stages of shock or impending shock have shown severe bleeding manifestations. An attempt has been made in this paper to correlate the laboratory findings with the bleeding manifestations. Our management of these cases has also been presented.

In this study it has been attempted to isolate the viral agent from the acute phase sera of the patients. The method used for the isolation of virus was by inoculation of acute serum into the brains of 1–2-day old suckling mice (Lennet and Schmidt, 1969). By this method 8 positive isolates were identified in 1973. It was significant that 6 of these isolates were identified as dengue type III virus whereas in 1965, the significant strain isolated was dengue type II (Rudnick, 1965). Unfortunately the virus recovery rate in mice during the following study was low as the main mouse colony used by the laboratory was affected by an epizootic of reovirus. More recently the technique of identification of dengue viruses using the mosquito as the host is under investigation (Kuberski and Rosen, 1977), however, the results are not complete.

Patients and methods

Patients. All clinically diagnosed and laboratory confirmed cases of DHF admitted into the Paediatric wards from May 1973 to July 1978 have been included. Only children below the age of 10 years are admitted into the Paediatric wards of the General Hospital.

Serology. All acute and convalescent sera were tested using the haemagglutination-inhibition (HI) prodecure of Clarke and Casals (1958) modified for the microtiter technique. Suckling mouse brain antigens were prepared by the sucrose-acetone method. A 4-fold rise in titre between acute and convalescent sera constitute a positive response, and a titre of 1 : 1280 or greater in a single serum was considered a presumptive positive response. Both responses indicate current infection. When the rise in titre between sera was less than 4 fold or when the titre in a single specimen was 1 : 640 or less the result was considered inconclusive. Serological diagnosis was confirmed in 115 cases. However, in the 15 cases that died, only one specimen during the acute phase could be sent. It was felt justified to include these cases in the study because of strong clinical evidence and manifestations of DHF, including the presence of shock in all these cases.

Entomology. Regular mosquito surveys are being carried out in this area. Investigations carried out strongly indicate that this was an *Aedes aegypti* transmitted disease.

Table 1. Age distribution. Age in years

Year	<1	1	2	3	4	5	6	7	8	9	10	Total
1973	Nil	1	2	2	3	5	5	18	7	Nil	Nil	45
1974	Nil	4	2	2	3	3	3	3	Nil	Nil	Nil	24
1975	Nil	2	2	Nil	2	2	3	Nil	1	Nil	Nil	14
1976	Nil	3	3	Nil	2	Nil	5	Nil	Nil	Nil	1	15
1977	Nil	3	3	2	1	4	1	Nil	2	Nil	2	18
1978	1	2	2	3	1	2	Nil	2	Nil	Nil	1	14
Total	1	15	14	9	12	16	17	23	10	Nil	3	130

Table 2. Distribution according to race and sex

Year	Chinese	Malays	Indians	Total	Male	Female
1973	42	Nil	3	45	19	26
1974	17	3	4	24	15	9
1975	11	2	1	14	5	9
1976	9	4	2	15	6	9
1977	9	4	5	18	10	8
1978	5	3	6	14	7	7
Total	93	16	21	130	62	68

Results

Age distribution (Table 1). 68 of the 130 children (60%) were between 4 to 7 years old. There was only one positive case recorded below the age of one year who was only 3 months old. This child showed all the classical features of DHF but made a complete recovery.

Racial and sex distribution (Table 2). There was a significant predominance among Chinese children. The Chinese prefer to live in crowded semi-urban and urban localities which are ideal for the multiplication of the vector mosquito. The Malays and Indians tend to live in more rural surroundings with less over-crowding and this may explain the racial distribution. There was no significant difference in the sex distribution.

Seasonal distribution of cases. In the 1973 epidemic the peak incidence occurred during the rainy months May to August. This pattern was maintained during the following 4-year period as well. However, since 1978 onwards, there has been a shift in the peak incidence to the later part of the year.

Table 3. Main clinical features seen during the period of study

	1973	1974	1975	1976	1977	1978	Total	%
Fever	45	24	14	15	18	14	130	100
Bleeding tendency	30	21	6	16	7	12	84	64.5
Skin rashes	27	15	8	12	10	8	80	62
Hepatomegaly	25	9	6	8	6	4	58	40.5
Vomiting	22	12	5	5	3	2	49	30.7
Abdominal pain	21	15	4	4	3	2	49	30.7
Cough	15	10	6	8	2	2	42	30.7
Lethargy	16	10	1	6	3	3	39	30
Infected throat	22	1	3	2	3	2	35	27
Haematemesis and melaena	11	5	3	3	4	1	27	20
Shock	11	5	3	3	2	2	26	20
Lymphadenopathy	10	4	4	3	1	1	23	10.7
Neck stiffness	6	2	1	2	2	0	13	10
Generalised fits	3	4	1	2	1	1	12	10
Cardiac abnormalities	9	1	Nil	Nil	1	Nil	11	8.4
Disseminated intravascular coagulation	1	Nil	1	1	1	1	5	4
Other clinical signs	2	1	Nil	2	2	1	8	5

Grading of the cases

The cases have been graded according to the WHO specifications (1975).

Grade I. Fever accompanied by non specific constitutional symptoms, the only haemorrhagic manifestation is a positive tourniquet test – 14 cases.

Grade II. Spontaneous bleeding from any site. Skin and/or other haemorrhages – 70 cases.

Grade III. Circulatory failure manifested by rapid and weak pulse, narrowing of pulse, pressure (20 mm Hg or less) or hypotension, with the presence of cold clammy skin and restlessness – 31 cases.

Grade IV. Profound shock with undetectable blood pressure and pulse – 15 cases.

Clinical features (Table 3)

Fever. This was the commonest manifestation and was present in 100% of the cases.

Hepatomegaly. The liver is usually palpable in the early febrile period. The size of the liver did not correlate with the disease severity and its size varied from just palpable to 2–4 cm below the costal margin. However, it was found that if hepatomegaly was associated with serological evidence of hepatocellular damage, it was a bad prognostic sign. The liver may be tender but jaundice was not usually observed even in patients with a big tender liver. The stretching of the capsule of the liver could explain the presence of epigastric and generalised abdominal pain in about 30% of the cases.

Table 4. Bleeding manifestations

	1973	1974	1975	1976	1977	1978	Total
Positive tourniquet test	22	21	6	16	7	12	84
Petechial rash	16	11	7	19	6	8	69
Epistaxis	12	10	5	5	1	1	34
Gum bleeding	13	3	Nil	6	4	4	30
Melaena	11	8	3	2	1	1	27
Haematemesis	11	5	3	3	4	1	27
Blood stained gastric aspirate	3	5	2	3	1	3	17
Ecchymotic skin lesions	3	1	1	3	1	2	11

Haemorrhagic manifestations (Table 4). Detailed analysis from 1973–1978 showed that bleeding manifestations varied from mild features like epistaxis and gum bleeding to severe and fatal gastrointestinal haemorrhage. A positive tourniquet test was the commonest sign of haemorrhagic manifestation seen. The standard method using a blood pressure cuff (Bell et al., 1940) was used. It is emphasised that in classical dengue haemorrhagic fever, the test usually gives a definitely positive result, i.e. more than 20 purpuric spots per square inch, but this test may be negative or only mildly positive during the phase of profound shock. It usually becomes strongly positive again, if looked for during the stage of recovery from shock. Epistaxis and gum bleeding, though they may not be serious, should always be looked at with caution, during the "dengue season", as they may herald more sinister manifestations.

Neurological manifestations. Neurological manifestations are being encountered more frequently in the recent years. Three cases presented with motor paresis of both the lower limbs, with partial sensory loss. Haemorrhagic features developed only about 48 hours later, and they all fitted into grade III of the WHO classification. The CSF was essentially normal, and complete neurological recovery was made in all three cases. The possibility of intraspinal petechial haemorrhages which resolved later is suggested in these cases. However, one child was brought in coma and in shock, with generalised convulsions. This child also recovered, but became mentally retarded and developed athetoid movements as a result of the possible initial intracranial bleeding.

Haematological profile. The full blood picture was done where possible, on admission and after the acute phase was over. The *total white cell count* did not show any definite pattern, and if the count was done within the first three days of the illness the patients usually showed a low or normal white cell count. 82.76% of the cases showed the presence of atypical lymphocytosis. *The platelet counts* were analysed in 32 patients. 30 cases showed a platelet count of less than 200,000. 87.5% showed a low platelet count below 150,000. The platelet counts and haematocrit values were useful indices in diagnosis and management of these cases. If the counts were done within the first three days of the illness, a

Table 5. Analysis of deaths (1973–1978). Total number of deaths = 15

Salient features seen	No. of cases	%
1. Shock	15	100
2. Thrombocytopenia (platelet count below 100,000/mm^3)	15	100
3. Haematocrit above 40%		93
4. Severe G.I.T. bleeding	10	66
5. D.I.C.	2	13
6. Hemolytic uremic syndrome	1	6

low platelet count and a high haematocrit value was found. Very low platelet counts heralded a bad prognosis, and served as a warning for the development of severe bleeding and shock. If these cases recovered, and the haematalogical profile was repeated after the 4th day of the illness, these values usually tended to be normal.

Other associated features

Pleural effusion. Though pleural effusion has been reported as being a common feature, extensive effusion which needed pleural tapping to relieve respiratory distress was seen only in two cases. One of these cases also showed the features of the haemolytic uremic syndrome. Peritoneal dialysis had to be done to bring down the blood urea, and this child made a complete recovery however.

Skin lesions. The skin lesions were varied, from a mere generalised flushing to large ecchymotic patches which later ulcerated.

Analysis of fatal cases (Table 5)

Shock was found to be present in all the cases that died. Severe gastrointestinal haemorrhage was seen in 66%. Though haemorrhage is not a serious problem in most cases, in the severe cases, who are admitted in the advanced stage of the disease i.e. in grade III and grade IV with shock and metabolic acidosis, gastric haemorrhage was found to be a very grave and life threatening problem. The bleeding was intractable and death occurred. The exact cause of the bleeding could not be determined in all the cases. In two cases, however, there was definite evidence of disseminated intravascular coagulation defect. This feature was confirmed by laboratory data showing increased FDP (fibrin degradation products) more than 100 μg/mm and also other features including.

1. bleeding continuously from venipuncture sites,
2. extensive ecchymotic patches all over the body,
3. fresh bleeding from mouth and frank blood from gastric aspirates,
4. low platelet count, below 40,000/mm^3,
5. irregularly contracted and fragmented red cells on the peripheral blood film. Presence of anisopoikilocytosis.

It must be mentioned here that a full recovery was made in one case who presented with frank DIC, where intravenous heparin therapy was used. In conclusion, though evidence of mild DIC was encountered in many cases, severe DIC as a cause of severe gastrointestional bleeding was seen only in a small proportion of cases. The value of heparin is controversial, but it may be tried in a desperate situation. In most cases, the DIC was a self limiting process.

Discussion

Dengue fever has been reported in Malaysia as early as 1902, but the sinister dengue haemorrhagic fever has been seen in epidemic proportions only as late as 1962. This pattern is seen throughout South East Asia, and why this change in the disease pattern has occurred has posed a puzzling problem. Extensive epidemiological studies have convincingly demonstrated that dengue haemorrhagic fever and the dengue shock syndrome occur more frequently where two or more dengue serotypes are simultaneously endemic or sequentially endemic and where ecological conditions favour efficient virus transmission by the vector mosquitoes. It is significant that in Malaysia the type II virus was being isolated in 1962, but the type III virus is being mainly isolated from 1973 onwards.

Thrombocytopenia and moderate depression of several clotting factors do occur in DHF, but at present there is no adequate single explanation for the severe haemorrhagic diathesis. Although lowered plasma fibronogen levels during DHF have been interpreted as evidence for disseminated intravascular coagulation, the relative importance of the latter as a major pathogenic mechanism is controversial (Srichakul et al., 1977). Although the activation of the complement system in the dengue shock syndrome has been well established its role in the pathogenesis of massive haemorrhage rests on indirect evidence. Death resulting from severe gastrointestinal blood loss has been reported from other regions as well, as also the difficulties faced on the management of these cases (Summarmo, 1976). Massive haemorrhages severe enough to cause death is infrequent, despite the very low levels of platelets commonly found in shock cases, but severe gastrointestinal haemorrhage has been seen in cases that present with prolonged irreversible shock and they invariably have a bad prognosis.

Recent fibrinogen metabolism studies in DHF have revealed increased fibrinogen consumption and haemostatic changes indicating occurrence of DIC even in non shock cases of DHF (Srichakul et al., 1977). It is likely that parallel to the formation of immune complexes and complement activation; the clotting mechanisms are also activated to the extent that DIC develops. It seems most likely that DIC does not play a significant role in the early stages and in mild cases, as compared with the role of plasma leakage. As the disease progresses to a certain extent that shock develops, DIC is then aggravated to play a significant

role. DIC and shock will then perpetuate each other, if shock is not corrected and acidosis develops leading on to a stage of irreversibility multiple organ involvement and death. It has been our observation as well that prolonged uncontrolled shock was found in all the cases that ended fatally. Severe gastrointestinal haemorrhage was found in 66% of fatal cases. Prolonged uncontrolled shock, often complicated with acidosis, gives rise to a more complicated course with severe gastrointestinal haemorrhage. In these cases DIC does seem to play an important role in producing this serious complication.

Acknowledgments. (1) Dr. S. C. E. Abraham, Senior Consultant Paediatrician, General Hospital, Kuala Lumpur; (2) Dr. C. G. Lopez, Senior Consultant Haematologist, General Hospital, Kuala Lumpur; (3) Staff members of the Paediatric Unit and Blood Bank for help in typing the manuscript and tabulation; (4) Director, General Hospital, Kuala Lumpur; (5) Head and Staff, Virology Division, Institute of Medical Research, Kuala Lumpur.

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