"SINGAPORE HAEMORRHAGIC FEVER" — CLINICAL REVIEW

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Haemorrhagic Fevers have been known in the East as far back as the 1930's. These were known as "Epidemic Haemorrhagic Fevers" and were first recognised by the Russians in far eastern Siberia and shortly after by the Japanese in Manchuria and subsequently appeared among United Nations personnel in Korea in 1951. The fever was characterised by an abrupt onset associated with headache, backache, myalgia and haemorrhagic manifestations varying from a mild petechial rash to frank gross haemorrhage (e.g. haematuria, malaena, haemoptysis, haematemesis). The outstanding feature was the involvement of the kidneys early in the disease giving rise to a proteinuria and changes in the urine closely resembling those of acute glomerular nephritis. In favourable cases recovery occurred within 14 days of the onset. Death was due to peripheral vascular collapse and the mortality rate was between 10-15%. The cause is generally considered to be a virus transmitted to man by the mite, the host of which is a field mouse.

A new group of haemorrhagic fevers have been reported over recent years in South East Asia. These include the epidemics reported in the Philippines in 1956, in Thailand in 1958 and in Singapore in 1960. In the Philippines and in Thailand the diseases were similar in that they occurred as an acute febrile illness in children chiefly below 6 years of age and fatality rates around 10% were reported. The haemorrhagic manifestations were predominant and were associated with one or more of the following: - bronchopneumonia or other respiratory manifestations, hepatomegaly or gastrointestinal symptoms. Four types of dengue virus, chikungunya virus and another virus yet to be identified were isolated from the blood of patients who lived mainly in urban areas infested with Aedes aegypti mosquitoes.

The Haemorrhagic fever epidemic in Singapore was recognised in 1960. It initially affected young adults again living in urban areas infested with Aedes aegypti mosquitoes. There were no fatalities. The presenting feature was the abrupt onset of fever associated with symptoms of classical dengue, e.g., headache, backache, myalgia. The haemorrhagic manifestations were very mild. The fever lasted about a week and complete recovery occurred within a fortnight. Three types of dengue virus have so far been identified in the blood of patients. This paper records a clinical review of such patients seen over the past three years (1960, 1961 and 1962) in Medical Unit I of the Singapore General Hospital.

CLINICAL MATERIAL AND METHOD

The patients observed were over the age of 10, admitted into one of the two Medical Units of the General Hospital, Singapore and presenting with symptoms suggestive of dengue fever, that is, cases with fever, headache, backache, generalised muscle and bone pains. Virus studies were undertaken during the acute phase of the illness and also during convalescence two to four weeks later. 80 patients were studied in 1960; 66 in 1961 and 50 in 1962 — a total of 196 cases in all.

CLINICAL FEATURES

All the patients observed have belonged to the indigenous population and there have been no fatalities.

The fever was of abrupt onset associated with chills and severe malaise. Temperatures rising as high as 104-105°F at the onset have been recorded and in most instances have lasted for 5-7 days. Unfortunately all these patients were discharged from hospital (owing to the acute shortage of beds) as soon as they became afebrile so that any secondary rise of temperature (the so-called saddle-back temperature) was not observed apart from one case. Variations in the duration and course of the fever are shown in Fig. 1.

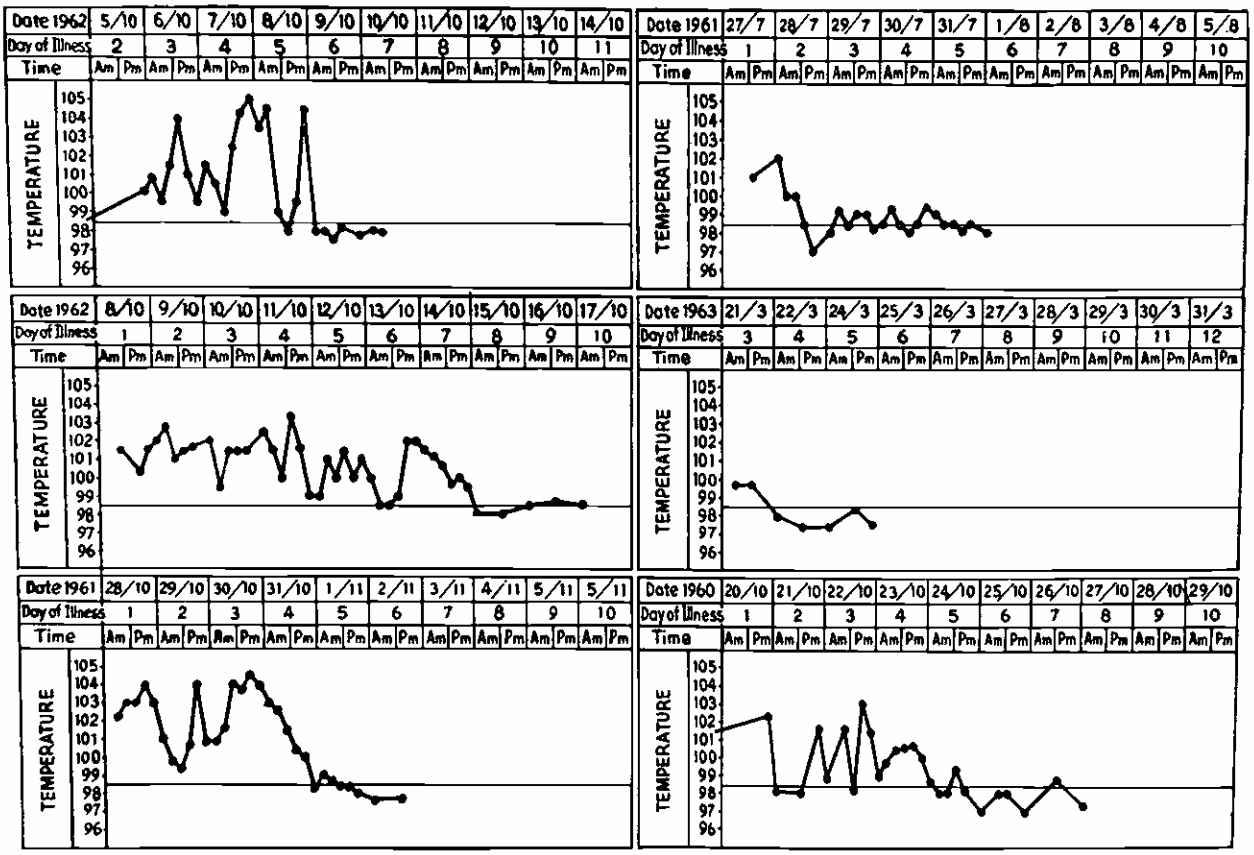

Fig. 1. Fever Charts in six cases.

Headache, dizziness, backache, bone and muscle pains were common features. However, the typical eyeball pain so common in classical dengue was exceedingly rare in the observed cases.

Gastrointestinal symptoms were the next common. These included nausea, vomiting and abdominal pain. There was no marked alteration in appetite or bowel habits. The abdominal pain was colicky in nature, unrelated to food and usually generalised but sometimes confined to the epigastrium or right iliac fossa. On a few occasions a mistaken diagnosis of appendicitis was made.

Haemorrhagic manifestations were observed in about two thirds of the cases. In the majority of the fair skinned patients a generalised rose red flush was noted, which paled easily on digital pressure and was most marked on the face, the palms of the hands and the soles of the feet. The next common skin change was a red flush with fine petechiae superimposed on it. In some of these cases the whole surface of the body showed this flush with petechiae leaving islets of pallor which were areas of normal skin (Fig. 2). In some cases only few petechiae could be demonstrated usually over the cubital fossa and in the oral mucosa. A few patients had a mobilliform rash simulating measles. In some cases where no petechiae were observed increased capillary fragility could be demonstrated by Hess's tourniquet test (Fig. 3). These cases were usually associated with a thrombocytopoenia.

Gross frank haemorrhage was not noted in any of these cases. However, over the past 3 years, 2 cases had haemoptysis, 4 complained of bleeding from their gums and 8 presented with epistaxis.

Mild hepatosplenomegaly and lymphadenopathy particularly the cervical group were observed in a little over half the cases.

Motor weakness of the limbs was complained of by 25% of the patients but no objective evidence could be demonstrated. Only four cases had signs of meningitis, and although the C.S.F. pressure was a little raised on lumbar puncture, examination did not reveal any abnormalities in the fluid.

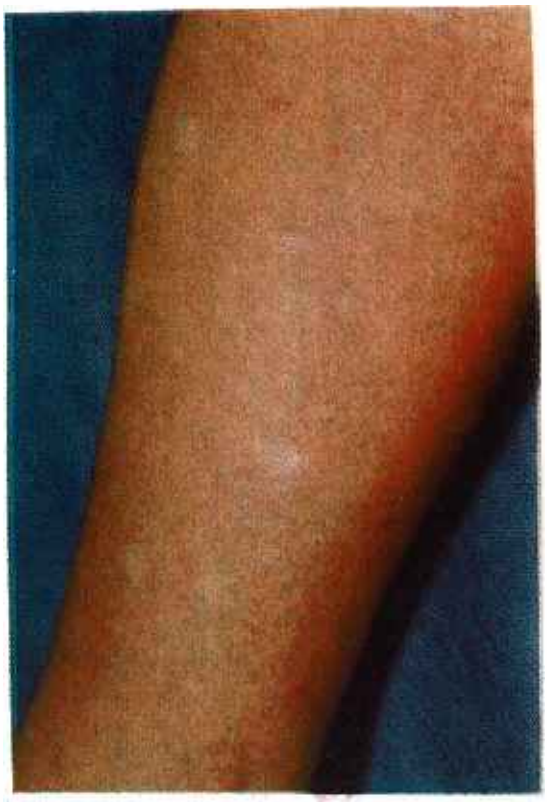

Fig. 2. Petechial rash with islets of pale normal skin.

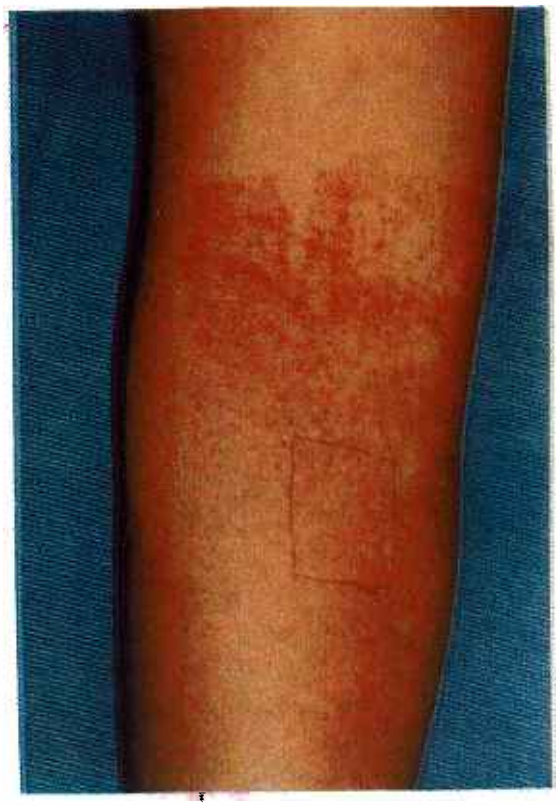

Fig. 3. Positive tourniquet test for capillary fragility.

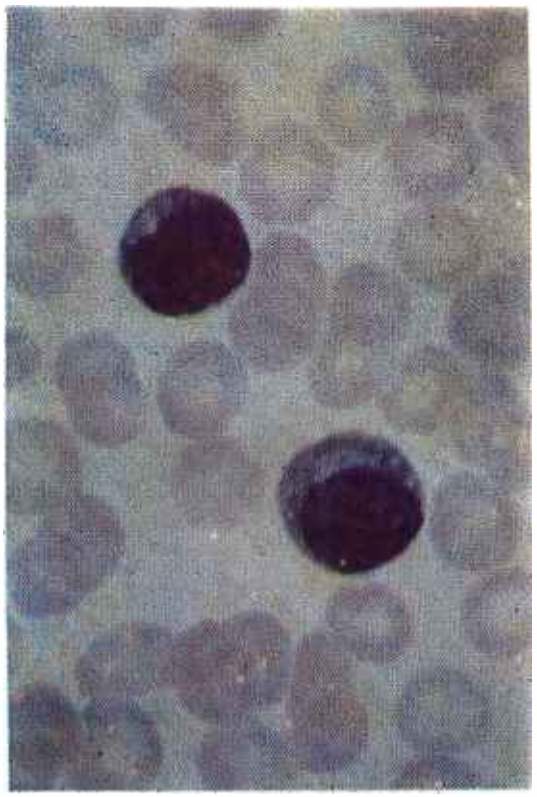

Fig. 4. Atypical mono-nuclear cells in the peripheral blood film.

PLATE I

LABORATORY STUDIES

No alteration was observed throughout the febrile period in the haemoglobin and red cell count. The leucocyte count was normal at the onset but a leucopoenia (below 4,000 cells/c.mm.) developed during the latter half of the febrile period returning to normal when the fever subsided usually in about a week. The lowest white blood cell count noted was 1100 cells/c.m. A further feature of the leucocytes in the peripheral blood was the presence of atypical mononuclear cells resembling the Turk cell, slightly larger than a lymphocyte with abundant basophilic cytoplasm and rather coarse nuclear chromatin (See Fig. 4). These cells were chiefly seen between the 5th-8th day of illness and the highest number noted was 40% in 2 cases.

The platelet counts were below 100,000 per cu.mm in 75% of the cases and figures as low as 5,000/c.m. have been noted. The thrombocytopoenia appeared around the 3rd-4th day of the fever but counts returned to normal in a fortnight. In 4 patients the bone marrow was examined at the time when there was a leucopoenia and thrombocytopoenia in the peripheral blood and was found to be normal. The bleeding time was prolonged by about one and a half times the normal in 25% of the patients and the prothrombin time in a few patients. All these alterations returned to normal by the end of a fortnight. No changes were noted in the clotting time.

No changes were noted in the urine. The Widal and Weil Felix reactions were negative or of insignificant titre in those cases tested as were the Paul Bunnel test for glandular fever and the blood Kahn test.

INCIDENCE

Age: Patients admitted into Medical Unit I, Singapore General Hospital do not include children under 10 so that the cases observed were all adults and the majority affected were below 35. Subsequent to the outbreak in 1960 pediatric cases have been noted.

Sex: There was no particular predominance of either sex.

Ethnic group: All the affected patients belonged to the indigenous population and the majority affected were the Chinese who also form the largest group in the normal population.

Season: June to November were the months during which most of the hospital cases were noted.

AETIOLOGY

In this series viruses have been isolated in 10 cases where blood was obtained within the first 3 days of the fever. These have been identified as Dengue type one, two and four. In most of the cases serological studies showed a rise of antibody titre in suitably spaced paired specimens in a combination of complement fixation and neutralisation tests.

DIAGNOSIS

The diagnosis was based on a clinical picture of dengue fever associated with a haemorrhagic rash, leucopoenia and thrombocytopoenia at some stage of the fever. Because of strong serological relationships between the dengue and other viruses such as that of Japanese encephalitis which also occurs in Singapore, serological tests are not always adequate for diagnosis. Only isolation of the virus gave full proof of the diagnosis. In some instances a mistaken diagnosis of idiopathic thrombocytopoenic purpura was made because of the petechial rash and the bleeding tendency, but the presentation of these cases is that of a febrile condition. Before the virus aetiology of this fever was established many of the earlier cases presenting with purpura were thought to be due to drug sensitisation. In a few cases presenting with abdominal pain particularly referable to the right iliac fossa appendicitis was the provisional diagnosis. The rash and/or the absence of leucocytosis were differentiating points.

TREATMENT AND PROGRESS

No specific therapy was required. In the majority of cases the temperature became normal by the end of the week and at the end of a fortnight all haematological changes were normal. Convalescence was not prolonged and no sequelae were noted.

COMMENT

The cases studied closely resemble classical dengue which is endemic in Singapore. How-

ever, the haemorrhagic manifestations, the splenomegaly, the thrombocytopoenia and increased capillary fragility which were commonly seen in this outbreak are rare observations in classical dengue. Notable too was the absence of pain on movement of the eyes, and the prolonged convalescence.

A very interesting feature which has arisen from this study is the entirely different clinical picture reported in the epidemics of haemorrhagic fever in Thailand and the Philippines yet caused by the same group of Dengue viruses. In these two epidemics the haemorrhagic manifestations were predominant and were associated with bronchopneumonia or other respiratory manisfestations, hepatomegaly or gastrointestinal symptoms. Children under the age of six were chiefly involved, and there were 10% fatalities.

The epidemic haemorrhagic fever seen in North East Asia appears to be a different clinical entity from the recent epidemics in the Philippines, Thailand and Singapore. Adults are chiefly affected and in addition to the haemorrhagic manifestations, renal involvement is striking. The aetiologic agent is thought to be a virus though this has not yet been isolated.

SUMMARY

A clinical review of a dengue-like fever with haemorrhagic manifestations which was first noted in 1960 is recorded. 196 cases were clinically observed and investigated in 1960, 1961 and 1962. There were no fatalities. Dengue virus type 1, 2 and 4 have been isolated in 10 cases.

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