THAI HAEMORRHAGIC FEVER

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Haemorrhagic fever is one of the great problems of infectious diseases in Western Pacific and south East Asia. An epidemic of haemorrhagic fever in children was first reported in Manila in 1954. This disease probably first appeared in Thailand as early as 1935 (5). In 1958, a serious epidemic occurred in Bangkok.

Since then, haemorrhagic fever becomes a common paediatrics problem in the big cities of Thailand. It is an annual endemic but more children are affected in every two years (6). In 1958, nearly 2,500 patients were hospitalized with a mortality rate of 10 per cent (11). The name Thai haemorrhagic fever (T.H.F.) was introduced by Tuchinda (12). In 1960, 2,000 cases had occurred widely through out Thailand, as far as 400 kms. north and 700 kms. south of Bangkok (6).

Etiology

It has been established that Aedes Aegypti is the primary vector of dengue and chikungunya viruses in areas where haemorrhagic fever has been reported. Diagnosis of T.H.F. by using complement fixation and haemagglutination inhibition tests are highly accurate (6,7,12,14). Dengue virus type 1,2,3,4, and chikungunya virus are detected both in the patients and in Aedes Aegypti. The following criterias are recommended for Complement-fixation (CF) and haemagglutination inhibition (HI) test :-

1. Positive dengue infection, if during the course of clinical disease HI and/or CF antibodies to dengue viruses exhibit a four fold or greater increase in titre, or if both specimens are collected after the fifth day of the onset and show rather high antibody titre to dengue viruses (i.e., HI. titre $>$ 1 : 2,560 : CF titre $<$ 1 : 64) with-out demonstration of a significant rise.

2. Positive chikungunya infection, if during the course of clinical disease HI and/or CF antibodies to chikungunya virus exhibit a four fold or greater increase in titre.

3. Positive dengue and chikungunya infections, if during the course

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of clinical disease HI. and/or CF. antibodies to both dengue and chikungunya virus simultaneously show a four fold or greater increase in titre.

4. Negative, if HI. and CF. antibodies to dengue or chikungunya are not demonstrable throughout the course of illness.

5. Inconclusive: If both acute and convalescent sera show some degree of antibody (HI. titre $>$ 1: 1,280, or CF. titre $<$ 1: 64) without demonstration of an increase.

Pathology

Several pathological findings in T.H.F. have been reported [2,8,9,10]. Gross autopsy findings were petichial haemorrhage and effusion with high protein content in serous cavities. Haemorrhage was noted in the stomach, intestine, subendocardium, subcapsular region of the liver, lungs and soft tissue.

The most important lesion in Thai haemorrhagic fever patients appeared to be generalized capillary damage. It was manifested by haemorrhage and edema of the wall of small blood vessels.

Reticuloendothelial System: Changes consisted of marked proliferation of lymphocytoid and plasmocytoid cells.

Liver: Changes in the liver were cellular infiltration in the portal area, formation of acidophilic cells in sinusoids, acidophilic necrosis of the Kupffer's cell and liver cell.

Heart: Petechiae were observed on the pericardium and endocardium of the heart. The most striking feature was the presence of irregular patches of subendocardial haemorrhage in the interventricular septum of the left ventricle.

Lungs: Petechiae were frequently seen in the pleura, and pleural effusion was common. The alveoli showed focal edema, haemorrhage and atelectasis.

Brain: There was no evidence of necrosis but hyperemia of the blood vessels of the meninges and brain was prominent.

Adrenal glands: A constant feature in all cases was hyperemia of the cortical capillary plexus, medullary venous plexus and periadrenal blood vessels. Marked edema was always present in the periadrenal fatty tissue and was associated with haemorrhage in some cases. Small foci of haemorrhage were also noted in the medulla. None of the adrenal glands showed haemorrhage comparable to that seen in the Waterhouse–Friderichsen syndrome.

Gastrointestinal tract: The entire gastro–intestinal tract showed focal congestion of blood vessels, sometimes associated with haemorrhage. The small intestine often revealed cellularity in the lamina propria of the mucosa and hyperplasia of lymph follicles of the Peyer's patches.

Pathophysiology:

Pathophysiological changes have

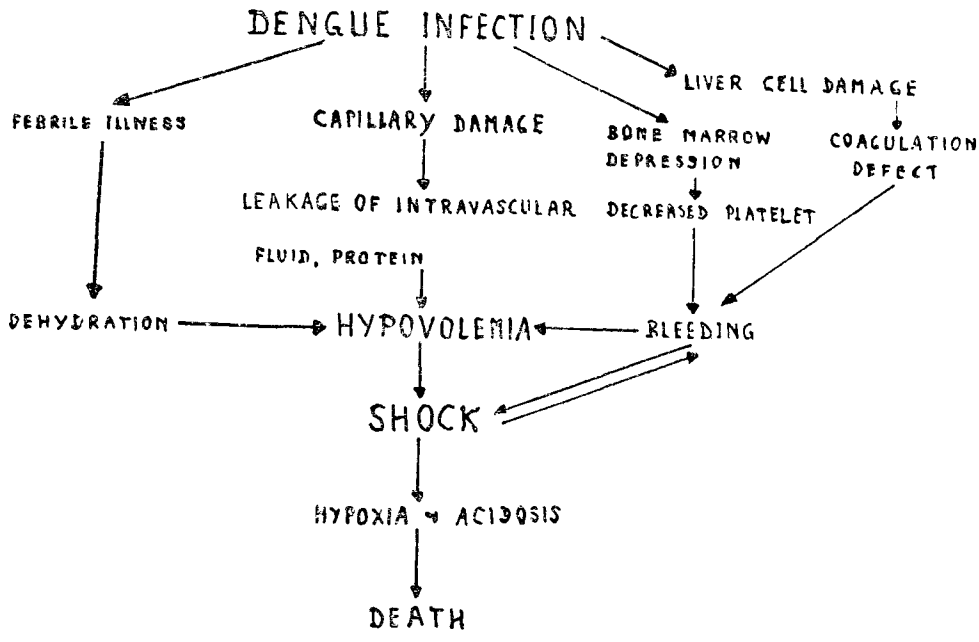

Figure I. Summarized Pathophysiological changes in Thai Haemorrhagic Fever.

been reported [11,12]. It can be summarized as in figure I.

1. Mild cases of dengue and Chikungunya infection are self-limited acute febrile disease. No profound physiological disturbance has been observed in these cases.

2. Dengue infection with haemorrhagic syndrome is characterized by abnormal permeability of the vascular system, liver enlargement and thrombocytopenia. Coagulation defect was quite common.

3. Dengue infection with shock syndrome occurs in about 30 per cent of admitted cases. It is still unclear why some patients develope mild symptoms while others manifest severe bleeding and shock (about 30 per cent of admitted cases). Serological studies on patients with shock syndrome are indicative of previous dengue infection, therefore a hypersensitive response may be the cause of shock syndrome in hemorrhagic fever. More studies are needed to confirm this hypothesis.

In severe dengue infection we observed more lethargy, vomiting and anorexia and subsequent dehydration. With capillary damage, the intravascular fluids, proteins and some red blood cells leak in to the extravascular compartment and serous cavities causing hypovolemia and shock syndrome. At this point, there are hypoproteinemia, hemoconcentration and signs of poor tissue perfusion. The blood pressure may not be measurable or the pulse pressure becomes narrow. Liver cell damage

creating coagulation defect in combination with bone marrow depression and reduction in platelets ultimately results in severe bleeding in the gastrointestinal tract, endocardium and other organs. This bleeding complicates shock syndrome. Tissue perfusion becomes poorer. Heart function becomes more impaired. Hypoxia and acidosis are followed by death.

Haematology

The hemoconcentration, through damaged capillaries, is usually observed, as high as 87 per cent of cases with shock syndrome. Leukopenia with depression of neutrophilic granulocytes is seen in about half of mild cases. It occurs between the third and eighth day of illness. Leukocytosis, 12,000 per culic millimeter or sometimes may be up to 20,000 to 40,000 per culic millimeter with absolute neutrophilia is noted in about half of shock and fatal cases. Thrombocytopenia also occurs during the third and eighth days of the disease, 49 per cent of mild cases, 90 per cent of shock and 84 per cent of fatal cases respectively. This lasts only three to four days and is followed by spontaneous and rapid rise. The degree of depression is directly related to the severity of illness.

Bone marrow injuries are manifested in both thrombocytopenic and nonthrombocytopenic patients. In the thrombocytopenic ones, the abnormalities may be divided into three phases. During the prethrombocytopenic stage, between the second to the fourth days of illness, the marrow shows moderate hypocellularity. Both erythroid and myeloid series are decreased in number with maturation arrest. The megakaryocytes are normal in number and function. The number of lymphocytes, monocytes, reticulum cells and plasma cells are increased. There are vacuoles in some of granulocytes, monocytes and megakaryocytes. The thrombocytopenic stage is between the fifth to the eighth days of illness. There is moderate increase of cellularity with arrest of maturation. The megakaryocytes are also increased, both mature and immature ones, but they poorly produce platelets. Other changes remain the same. In the convalescent stage, during the tenth to the fourteenth days, the cellularity returns to normal. Megakaryocytes and all marrow elements start functioning normaly.

In non-thrombocytopenic group the presence of vacuoles in myelocytes and megakaryocytes and the arrest of maturation of erythroid cells are noted in some cases.

Impaired haemostasis, though it is one of the severe and fatal symptoms of the disease, its underlying mechanism, however, remains obscured. Factors contributed to haemostatic disturbance that could be detected are vascular damage, thrombocytopenia and deficiency of coagulation factors. The last one is usually due to mild to moderate deficiency of

factors II, V, VII, IX and X which is detected between the second and eighth days of illness.

Laboratory findings in haemorrhagic fever are not diagnostic. The haematocrit almost always is high during the course of illness in severe cases. The serum is sodium usually normal or low normal with normal potassium and low serum carbon dioxide. Increase blood pH and low PCO_2 indicate respiratory alkalosis and are observed in most of the patients.[15] All patients who had profound shock had hyponatremia, low blood pH and low carbon dioxide and high serum potassium level. Electrocardiogram also showed low voltage in limb lead with ST & T waves change in seriously ill patients.

Elevated BUN., SGOT and SGPT concentrations are significant and frequently found in the group with shock syndrome. The total serum protein concentration is also low in this group.

Clinical manifestation :

As in any other infectious diseases, there appears to be a spectrum ranging from mild to fatal infection, Clinical syndromes caused by dengue and chikungunya viruses in Thailand could be classified as.

1. Acute undifferentiated respiratory disease.
2. Undifferentiated fever.
3. Dengue fever.
4. Haemorrhagic fever without shock.
5. Haemorrhagic fever with shock.

Clinically, we could divide Thai hemorrhagic feurt into three phases.

1. Febrile phase
2. Hypotensive phase
3. Recovery phase.

Febrile phase or the first stage of the disease may have a gradual or a sudden onset of fever. General malaise, sorethroat, nausea and headache are common. This phase can not be differentiated from other viral infections. This stage usually lasts for 2–3 days.

Hypotensive stage or second stage. After the fever, the patient may become progressively worse with severe abdominal cramps and manifestation of haemorrhage such as epistaxis, haematemesis and melena.

The skin manifestations (Petechial or intracutaneous haemorrhage) are quite common, and do not indicate severity of illness. On the fourth day the temperature begins to fall. In severe cases after or simultaneously with the haemorrhagic manifestations, patients rapidly lapse into shock. The skin becomes cool and blotchy. The pulse pressure becomes narrow and then imperceptible. The liver is usually enlarged; pleural effusion and ascites are not uncommon. Reports of fatality in shock cases vary from 15–30 per cent.

Recovery phase or the third phase. Convalescence, when occurs is usually very prompt and uncomplicated both in mild case or in shock syndrome. At present, there appears to be no available clinical or laboratory method to predict the severity of the disease in febrile phase. History of a severe form of haemorrhagic fever in the sibling or neighbour, the symptoms of abdominal pain, anorexia, vomiting, lethargy and haemorrhagic manifestation suggest severity of haemorrhagic fever.

Management:

The management of Thai haemorrhagic fever is based on the pathophysiology of this disease. [13] In mild case, only symptomatic treatment is justified. Early administration of corticosteroid and or antipyretics does not alter the course of the disease.

In haemorrhagic fever with shock syndrome, the principle of treatment is to bring the patient back to normal homeostasis as soon as possible. When the patient shows the early signs of shock, infusion of half strength nor-

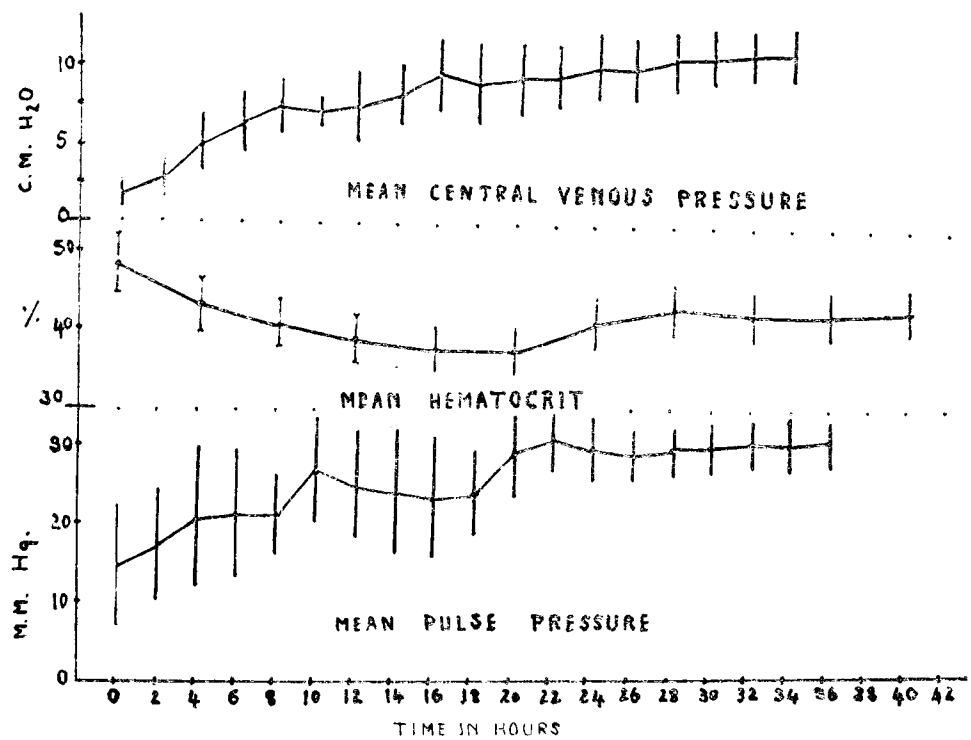

Figure II. Correlation of central venous pressure, haematocrit and pulse pressure in Thai haemorrhagic fever with shock. The patients recieved $\frac{1}{2}$ N S.S. in 5% Dextrose water 10—20 cc./Kg/Hr. in the First 6 hours, then maintain on $\frac{1}{2}$ N.S.S. in 5% Dextrose water 100 cc./Kg. in the next 24 hours.

mal saline, 10–20 cc/kg in 5 percent dextrose water for 6 hours is usually adequate to bring hematocrit, Central venous pressure and blood presure closely to normal. (Figure II) Administration of hydrocortisone 25–50 mg/kg/24 hours (or other equi valent corticoids) in severe shock is advised. The rate of infusion following 6 hours of initial therapy depends on hematocrit, and clinical response. In most instances, maintenance fluid therapy is enough to correct hemoconcentration and hypovolemia. Plasma transfusion is not generally needed in case of which fluid therapy alone can maintain good tissue perfusion. Plasma transfusion is indicated when there is lack of prompt response or when there is evidence of abnormal coagulogram. Blood transfusion is not recommended in hypotensive phase of the dieases when haematocrit value is high.

Thai haemorrhagic fever with haemorrhage is one of the serious problems, expecially when associated with profound shock. Early plasma transfusion or fresh plalelet transfusion is indicated in severe haemorrhage. If there is a rapid falling of haematocrit or early low hematocrit, blood transfusion should be given. Metabolic acidosis may be seen in severe and prolong shock. Seven per cent sodium bicarbonate may be given intravenous 3–5 milliequiv. per kilogram of weight.

Administration of heparin, aldosterone [13] and phentolamine [14] are under studies. Some observers stated that the results are promising but the number of cases is yet small.

Extreme irritability is usually seen in shock patient, these patients need sedation and chloral hydrate is the drug of choice. In cases with hyperpyrexia, hydrotherapy and antipyretics should be given especially when there is convulsion. For anticonvulsant intravenous short acting barbiturate is the drug of choice. Oxygen administration is helpful in cases with shock.

Antibiotic is recommended when there is evidence of bacterial infection and severe shock. All intramuscular injections should be avoided because of haemorrhagic tendency.

Despite all these active and vigorous treatments in shock cases, there is still a large number of fatality. This is due to lack of complete knowledge of the pathophysiologic changes in Thai haemorrhagic fever. More studies are required to answer the problem.

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