death. In the case where positive staining was obtained there was a marked reduction in the number of cells with pyronin-positive cytoplasm, perhaps indicating less active antibody formation and perhaps leading to fixation of dengue antigen at the stage where there is antigen excess.

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Physiological Disturbance in Thai Haemorrhagic Fever *

SOMBODHI BUKKAVESA [1]

The physiological disturbance in Thai haemorrhagic fever begins with the virus or its products affecting the capillaries: the permeability of the capillary walls increases and the tourniquet test becomes positive. The erythrocytes can pass through the injured capillary walls to produce petechiae, purpura and ecchymoses on the skin and also haemorrhage in the internal organs. Involvement of the liver causes slight elevation of serum transaminases and slight enlargement of the liver. Involvement of the bone marrow causes arrest of the maturation of the megakaryocytes, thus producing thrombocytopenia.

Since the virus could rarely be isolated after shock or after the fourth day of disease and since the immunity response was very quick, it is probable that the virus dies after the fourth day of disease. Dying virus or its products may produce an endotoxin-like substance that causes constriction of the liver venules, thus leading to the pooling of blood in the splanchnic area. Shock develops because of the reduction in the circulating blood volume. Thereafter all the pathophysiological changes are similar to those of the septic-shock or the endotoxin-shock syndrome. As the blood pressure is low in the shock state, the tissues become toxic from anoxia and acidosis develops. The capillaries also suffer further injury, and intravascular fluid and low-molecular-weight colloids seep into the serous cavity. The plasma volume is thus reduced, while the red cell volume remains the same. The blood is concentrated, as shown by elevation of the haematocrit and haemoglobin values, and pooling of blood in the splanchnic area causes further enlargement of the liver. Anoxia of the liver causes further impairment of liver function—for example, deficiencies in the prothrombin complex (Factors II, VII, IX and X) and in Factor V, which aggravate haemorrhage, particularly in conjunction with thrombocytopenia and increased capillary permeability. Thus, a vicious circle is created and if it cannot be broken the patient will die from tissue anoxia and/or haemorrhage.

* Originally issued as document IR/Haem.Fever/Sem.1/WP/17.

[1] Department of Pediatrics, Faculty of Medicine and Siriraj Hospital, University of Medical Sciences, Bangkok, Thailand.

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Dengue Infection in Thai Children: A Pathophysiological Study *

MAYUREE BALANKURA,[1] AREE VALYASEVI,[2] CHAIYAN KAMPANART-SANYAKORN [3] & SANFORD COHEN [4]

Clinical material

117 patients, aged 5 months through 17 years, were admitted to the Thai Haemorrhagic Fever Study Centre with a tentative diagnosis of "Thai haemorrhagic fever". Of these 117 children, 94 had a serological diagnosis of acute dengue infection. Twenty-one of these dengue patients developed the shock syndrome during the course of the illness.

* A preliminary report from the Thai Haemorrhagic Fever Study Centre, Bangkok, Thailand. Originally issued as document IR/Haem.Fever/Sem.1/WP/28.

[1] Lieutenant-Colonel, Medical Corps, Royal Thai Army; Director, Thai Haemorrhagic Fever Study Centre, and Senior Paediatrician, Royal Thai Army Hospital, Bangkok, Thailand.

[2] Director, Thai Component, SEATO Clinical Research Centre, Bangkok, Thailand.

[3] Faculty of Public Health, University of Medical Sciences, Bangkok, and US Component, SEATO Medical Research Laboratory, Bangkok, Thailand.

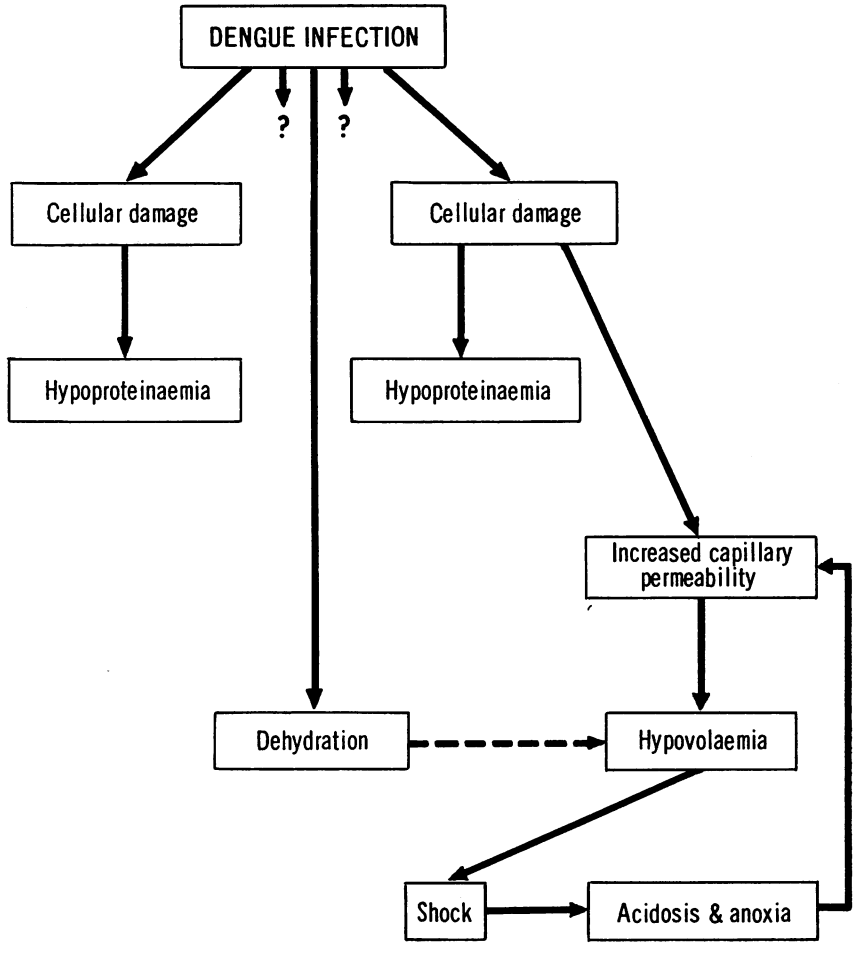
[4] Captain, Medical Corps, US Army; US Component, SEATO Medical Research Laboratory and SEATO Clinical Research Centre, Bangkok, Thailand.

This was defined as either an undetectable blood pressure or a pulse pressure lower than 20 Torr. The shock syndrome was invariably associated with tachycardia, cold clammy skin and either restlessness, stupor or semi-coma.

Laboratory studies

The laboratory investigations routinely carried out at the time of admission were studies of the blood chemistry; haematological, bacteriological, parasitological, and virus-isolation and serological studies; chest X-ray, electrocardiogram and urinalysis. The haematological, serological and chemical studies, along with urinalysis, were routinely repeated periodically while the child was under observation. The remainder were repeated only as indicated by the patient's condition.

THE EVOLUTION OF THE DENGUE SHOCK SYNDROME



MILD DENGUE SYNDROME DENGUE SHOCK SYNDROME

WHO 51428

Results

Three patients died during the course of the illness. All had shock associated with dengue infection, and all had mild hyponatraemia, elevated serum urea nitrogen (SUN), elevated SGOT and SGPT, low CO_2 and normal potassium levels and electrocardiograms when first examined. Each had abnormally low total serum protein concentrations during hospitalization and marked hyperkalaemia with serious electrocardiographic disturbance immediately prior to death.

Mild hyponatraemia and evidence of metabolic acidosis on admission occurred with significantly greater frequency among the patients with the dengue shock syndrome than among the other patients with dengue infection. None of the patients had either remarkable hyperkalaemia or the electrocardiographic disturbances associated with hyperkalaemia on admission.

Elevated SUN, SGOT and SGPT concentrations were significantly more frequent in the group with the shock syndrome than in the other dengue patients, and low total serum protein concentrations were also found more frequently in the former group. Low albumin : globulin ratios were not observed significantly more frequently in one group than in the other.

Bleeding, severe enough to lower the haematocrit value, occurred in only one patient, a child with gastrointestinal haemorrhage. The level at which the haematocrit stabilized while the patient was under observation was therefore used as an index of the patient's haematocrit prior to illness. The ratio

$$\frac{\text{highest haematocrit} - \text{index haematocrit}}{\text{index haematocrit}}$$

was computed for the 18 surviving shock cases and for the 49 mild cases in which the highest haematocrit value was higher than the index value. Significant haemoconcentration occurred with significantly greater frequency in the shock group than in the mild dengue group.

No abnormality was seen on admission electrocardiogram or chest X-ray and no bacterial complication was found in any case. Blood glucose and serum bilirubin concentrations were consistently within normal limits on admission.

Discussion

Patients with the mild dengue syndrome did not differ from those with non-dengue viral infections in respect of the incidence of hyponatraemia, metabolic acidosis, elevated SUN or haemoconcentration. However, the mild dengue group did differ from the non-dengue group in respect of the frequency of occurrence of abnormal total serum protein concentrations and SGOT levels. It appears that dengue infection caused hypoproteinaemia which did not seem to be associated with a specific lowering of the serum albumin concentration. Marked elevation of SGOT levels occurred more frequently in the mild dengue group than in the non-dengue group. This was not true of SGPT levels. Therefore, it seems unlikely that the elevated SGOT levels occur as the result of damage to liver cells only.

The accompanying figure depicts the probable evolution of the dengue shock syndrome. The mechanisms that lead to cellular damage are unknown, but it seems certain that dengue infection can initiate the cycle.

Along with the cellular damage and unknown effects of dengue infection in these children, dehydration occurs as a result of anorexia and vomiting. Cellular damage is probably responsible for the high SGOT values as well as for the abnormalities of the capillary wall that lead to a positive tourniquet test and to haemoconcentration and hypovolaemia. Dehydration causes the increase in SUN concentrations and contributes to the decrease in circulating blood volume.

When the circulating blood volume reaches a critical level, shock, with its attendant acidosis and cellular anoxia, occurs. Once established, this cycle is self-perpetuating. Acidosis and anorexia produce more cellular damage, which, in turn, tends to make the shock more severe. The final irreversible step, which occurs in fatal cases, is rapidly developing severe hyperkalaemia.