NEW ASPECTS IN THE PATHOGENESIS OF HAEMORRHAGIC DIATHESIS IN DENGUE HAEMORRHAGIC FEVER

by

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We had the opportunity to study the haematological aspects of dengue haemorrhagic fever in 1 119 children in our department during the last 14 years. All these children, varying in age from 4 months to 13 years, conformed to the WHO criteria of DHF. Viral isolation was positive in about 25 per cent of the cases examined, type III being predominant in 47.0 per cent, type I in 18.7 per cent, type II in 29.9 per cent and type IV in 4.5 per cent.

With regard to the severity of the disease, out of a total of 1 129 children, 311 belonged to dengue grade I (27.6 per cent), 450 (49.9 per cent) to grade II and 358 cases (32.5 per cent) to grades III and IV. These children were referred to our department with fever of unknown origin of a few days' duration; haemorrhages (DHF) or shock (DSS) were observed in about half of the cases on admission. In general, the clinical picture of these children according to frequency were respectively: fever 100.0 per cent, vomiting 69.6 per cent, epigastric pain 46.8 per cent, U.R.I. 44.3 per cent, hepatomegaly 41.9 per cent, neurologic signs 39.4 per cent, shock 37.5 per cent, cyanosis 19.7 per cent, diarrhoea 17.2 per cent and dyspnoea 10.3 per cent. Haemorrhagic manifestations without shock were observed in only 30.0 per cent of these children on admission, being melaena 45.6 per cent, haematemesis 36.8 per cent, epistaxis 27.1 per cent, ecchymosis 16.6 per cent, gum bleeding 4.8 per cent and haematuria 0.7 per cent.

In order to find out the explanation for the pathogenesis of haemorrhages in these children, routine haemograms and screening tests of haemostasis were done; CBC, tourniquet test, bleeding time, clotting time, recalcification time, prothrombin time, thrombin time, activated partial thromboplastin time, thromboplastin generation test, fibrinogen and fibrinogen degradation products in blood and urine, clot retraction, platelet function tests, the presence of patelet antibodies in the serum, and circulating anticoagulants, while bone marrow aspiration was done in some cases.

The evaluation of the results of this laboratory examination revealed the possibilities of the bleeding tendency in DHF to be as follows:

(1) Increased fragility of the vascular walls. The positive tourniquet test found in the early stages or during hospitalization in all these children revealed a tendency to increased fragility of the capillary walls (Kho et al, 1969).

(2) Decreased coagulation factors as concluded from the tests mentioned above, being decrease of fibrinogen, F II and other clotting factors needed for coagulation. (Kho et al, 1976, Mitrakul et al, 1977, Srichaikul, 1979, Funahara et al, 1983).

(3) Severe DIC and consequently consumption of platelets and coagulation factors were found in 35.4 per cent of all cases (Kho et al, 1976) with the following findings: thrombocytopenia, prolonged PTT, prolonged PT, disturbed TGT, increased FDP and the finding of burr cells in the blood fils. DIC as one of the most serious complications of DHF was for the first time put forward by the author during the 13th SEAMEO Seminar on Tropical Medicine and Public Health in Saigon in 1974 (Kho et al, 1976). Most of the investigators present were sceptical about this finding. However, later on, Srichaikul et al (1977) and Funahara (1983) confirmed the presence of DIC in DHF. Srichaikul (1979) mentioned a figure of as high as 83 per cent DIC in shock patients and 12 per cent in non-shock patients, while Funahara found signs of DIC in all children with DHF examined.

(4) Thrombocytopenia alone without DIC was found in about half of the cases. This could be the consequence of hypoplasia of the bone marrow in the early stages of the disease (Kho et al, 1972) or due to its destruction by platelet antibodies found in 52 per cent of all cases of thrombocytopenia. (Kho et al, Medika, in Press 1984).

(5) Alterations of platelet function (thrombopathia) were observed among others in Thailand and Japan (Mitrakul et al, 1977, Okamoto et al, 1968).

(6) Decrease of Alpha 2 - antiplasmin levels was observed by Funahara (1983). He made studies on hemostasis of 11 children suffering from DHF in Jakarta (8 with DHF grade II, 2 with grade III and 1 with grade IV) and found in all these children manifestations of the acute type of DIC, i.e., prolongation of APTT, PT; decreased levels of platelet count, fibrinogen, prothrombin, F VIII, plasminogen, and antithrombin III activities were observed transiently during the acute stage of DHF.

(7) In serious cases circulating anticoagulants were present in the blood (under study).

According to many investigations, in the field of DHF the increased fragility of the capillary walls is the consequence of toxic agents produced by antigen-antibody complement reactions, and/or allergic or anaphylactic reactions (anaphylatoxins). We also found decreased concentration of complement C3 and C4 in DHF patients (Kosin et al, 1978). Immune complex and anaphylactic reactions give rise to the production of agents as histamin, SRS-A and Serotonin from the platelets that are known to cause damage of the capillary walls. Leakage of fluid through the capillary walls occurred, followed by haemoconcentration and shock. Circulatory disturbances give rise to anoxemia and increase of acid metabolic products as amino acids, fatty acids, which are also damaging for

the vascular walls. In our opinion, the initiation of the pathological process of hemostasis begins with the increased fragility of the capillary walls in dengue fever, resulting in small damages throughout the whole body resulting in leakage of tissue fluid containing phospholipids in combination with the exposed collagen and extravasation of endothelial factor VIII : vWF initiates the aggregation of the platelets on the damaged places. Extrinsic as well as intrinsic coagulation occurs due to the interaction of factors mentioned above with the cooperation of prekallikrein and kininogen mechanism. Due to the fact that this reaction occurs throughout the whole body within a short period, the liver and bone marrow could not compete with the increased consumption of coagulation factors and platelets.

Complications of dengue fever such as haemorrhages, circulatory disturbances, shock and encephalopathy occur only in a few cases from thousands of dengue viral infections. These complictions occur especially in the age-group between 2 and 6 years. Why this is the case is still unknown.

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