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Dengue Hemorrhagic Fever in adolescents and young adults in the Department of Internal Medicine, Gadjah Mada University Hospital in Yogyakarta

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INTRODUCTION

Dengue fever, a well known disease in the tropical and sub-tropical parts of the world, was first described by David Beylon, a municipality surgeon in Batavia, in 1779 (Kouwenaar, 1951). A year later Banjamin Rush gave its well known colloquial name "break bone fever" (Nelson, 1964). It also has other names as five-day fever or van der Scheer's fever or seven-day fever (Kouwenaar, 1951).

Hemorrhagic fever was first reported by Quintos *et al.* (1954), in Manila. Hammon (1956) established the causative relation of Dengue infection to dengue hemorrhagic fever (Halstead, 1969).

The disease is caused by dengue virus, of which there are at least four and probably six types as well as chikungunya virus. Dengue virus type 2, 3, and 4 were isolated from sera of patients of Phillippine H.F.; dengue virus type 1, 2, 3, 4, 5, 6, and chikungunya virus were found in Thai H.F.; and type 1, 2, 3, and 4 in Singapore H.F. (Gajdusek, 1962; Dasaneyavaja *et al.* 1963; Halstead, 1966).

I. Dengue virus 1, 2, 3, 4, (5, 6) = Arbovirus group B.

II. Chikungunya virus = Arbovirus group A.

Snijder *et al.* (1931), Denger *et al.* and Mertins *et al.* (Kouwenaar, 1951) stated that *Aedes aegypti* and *Aedes albopictus* were the vectors of this disease. Vectors of importance are also *Aedes polynesiensis* and probably members of the *Aedes scutellaris* complex (WHO, 1969).

Clinically, dengue and Chikungunya virus manifest itself as:

I. UNDIFFERENTIATED FEVER

This is a very mild febrile illness, frequently considered to be of respiratory origin.

II. **DENGUE FEVER SYNDROME.**

This includes febrile disease characterzed by myalgia, and/or arthralgia and leukopenia, with or without rash or lymphadenopathy, but including many of the following biphasic fever, severe headache, pain on moving the eyes, positive tourniquet test and a few spontaneous petechiae.

III. **HEMORRHAGIC FEVER.**

A. Without shock,

This includes fever, usually without prominent myalgia or arthralgia, usually becoming more severe after the first two days, positive tourniquet test, leukopenia or rash present or absent, but usually with several or all of the following: epistaxis, hematemesis, melena, thrombocytopenia, prolonged bleeding time, elevated prothrombin time, and maturation arrest of megakarycytes.

B. Without shock.

The pulse pressure is 20 mm Hg. or less, or systolic and diastolic pressures unobtainable, with collaps of the patient. Shock may occure without the hemorrhagic manifestation described above but with most of the following associated with serious disturbance of the hemostastic mechanism as essential criteria if hemorrhagic fever has been diagnosed: positive tourniquet test, thrombocytopenia, prolonged bleeding time and maturation arrest of megakaryocytes.

For all of the above catagories, the etiology should be stated when known, or stated as unknown. (WHO, 1969).

Dengue Hemorrhagic Fever (DHF) is thought to represent a hypersensiti vity to a second or succeeding infection with dengue virus. Non immune foreigners, adults as well as children, exposed to dengue virus during an outbreak of hemorrhagic fever have classic dengue fever or even a milder disease.

This disorder is almost exclusively a disease of children. Somchitt Iamsaard (1966) found 9 cases of DHF in Thailand (Bangkok) from June 1962 to June 1964, their ages ranging from 15 to 22 years; 8 cases were of Thai and one case of Chinese origin.

CASE REPORTS

Case 1. A 13 years old boy, Indonesian, was examined at the "AURI - Maguwo polyclinic on March 23, 1970 and consulted to the Department of Internal Medicine, Gadjah Mada University at Pugeran, Yogyakarta, because of 2 days fever, cephalgia, substernal and abdominal pain, anorexia and vomiting, diarrhea, melena and petechiae. Body temperature was 40.2°C, pulse 120/min., regular and equal. Blood pressure (BP) 110/40 Hg., positive tourniquet test, liver not palpable. Lab. exam.: Hgb. 12.2 gr%, WBC 5200 ESR 6/15, diff. count : eos 9, stab.–, segm. 64, lymph. 27; very few platelets on slide. Slight proteinuria with leukocyturia and hematuria. Patient recovered and discharged on the 11th day after admission.

Diagnosis : Hemorrhagic Fever without shock (Dengue?).
No serological test done.

Case 2. Patient was a 14 years old boy, P., Indonesian, admitted to Kadipolo Hospital in Sala on May 27, 1970 and consulted to the Department of Internal Medicine, Gadjah Mada University Hospital, Pugeran Yogyakarta, because of 7 days fever and cephalgia, anorexia, nausea, vomiting, diarrhea, melena, petechiae and ecchymoses, skin rash, myalgia and arthralgia. Bleeding on lips and gums. Patient was in a state of shock with positive tourniquet test, liver was palpable 2 fingers below the costal margin. Lab. exam. : Hgb. 3 gr / WBC 5200 with 57% of lymphocytes. Thrombocytes 28.000 – 64.000. Bleeding time longer than 30 min., clotting time was normal.

Widal : negative. Hemagglutination Inhibition test :

D_I 1/20 — 1/40

JBE 1/20 — 1/80

Patient died on the 38th day after admission.
Diagnosis : Dengue Hemorrhagic Fever with shock.
Serologically proved.

Case 3. Patient was an 10 years old boy, K., Indonesian, admitted to the Department of Internal Medicine, Gadjah Mada University Hospital Pugeran, Yogyakarta, on Juni 12, 1970, because of 4 days fever, retroorbital cephalgia, myalgia, arthralgia, anorexia, nausea, vomiting, melena, skin rash, petechiae, ecchymoses, bleeding on lips and gums. Body temperature was 39.5° C, pulse 90 / min. which was regular and equal, BP. 100 / 75 Hg., liver not palpable and a positive tourniquet test. Lab. exam. Hgb. 12 gr%, Hct. 44%, WBC 6000 with 42% of Lymphocytes. Thrombocytes 180.000, prolonged bleeding time and prothrombin time was 54%.

H.I. test : D_I 1/5.120 — 1/20.480

JBE 1/10.240 — 1/20.480

Diagnosis : Dengue Hemorrhagic Fever without shock.
Serologically proved.

Case 4. S. was a 13 years old girl, Indonesian, admitted to the Department of Internal Medicine, Gadjah Mada University Hospital, Pugeran, Yogyakarta, on January 29, 1971 because of fever for 10 days, anorexia, nausea, vomiting, diarhea, petechiae and ecchymoses. Liver was palpable and patient was in a state of shock. Lab. exam. : Hgb 10 gr%, WBC 10.400 with 23% lymphocytes. Widal : negative.
Bone marrow revealed an increased number of megakaryocytes 10 per low power field with dyssynchronism between cytoplasm and nucleus, with a few platelets around.

Diagnosis : Hemorrhagic Fever with shock (Dengue).
No serological test done.

Case 5. Patient was a 25 years old female, B., Indonesian was admitted to Kadipolo Hospital in Sala on February 5, 1971 and consulted to the Department of Internal Medicine, Gadjah Mada University Hospital,

because of fever, headache, anorexia, nausea, arthralgia, bone pain, some bloody vomiting and melena, petechiae, ecchymoses. Liver was not palpable and BP. was normal.

H.I. test: D_I 1 / 640

JBE 1 / 1260

Diagnosis: Dengue Hemorrhagic Fever without shock.
Serological proved.

Case 6. A 22 years old male student, B.P., Indonesian, was examined at the outpatient department of the Department of Internal Medicine, Gadjah Mada University Hospital, Pugeran, Yogyakarta, on March 8, 1971, because of 2 weeks fever, epigastric and abdominal pain, anorexia, nauses, myalgia, arthralgia, petechiae, ecchymoses, skin rash.

Liver not palpable and a normal Bp. and negative tourniquet test.

Lab exam.: Hgb. 13 gr%, WBC 8700 with diff. count: eos 1, stab. 2, segm 84, lymph. 12 and mono. 1%. Thrombocyte 190.000, prothrombin time 88,5%, normal bleeding time, clotting time 8 min. 17 seconds.

Bone marrow revealed an increased number of megakaryocytes 10 per low power field, with nucleus-cytoplasmic dyssyncronism and a few platelets around.

H.I. test : D_I 1/10.240

JBE 1/5.120

Diagnosis : Dengue Hemorrhagic Fever without shock.
Serologically proved.

Besides these patients, there were another two patients aged 12 yrs., diagnosed as DHF admitted on February 7 and 11, 1970; no serologi cal test were done on these two patients.

DISCUSSION.

The chief complains of the 9 patients reported by Somchitt Iamsa-ard were fever (100%), petechial hemorrhage (70%) and headache (60%). Bone marrow studies in 4 of his cases showed an increased number of megakaryocytes 10 or more per low power field, while other hemopoietic cells were normal in cellularity.

Dyssynchronism between cytoplasm and nucleus of megakaryocytes, with no or a few platelets around was found by other authors. Clasmatocytes histiocytes phagocytizing leukoytes and or erythrocytes were reported to be significant.

Nelson *et al.* (1960, 1964 and 1966) found 3 characteristic phases with different pictures in the bone marrow in Dengue virus infection; the early phase (days 1 – 4) with hypocellularity and almost absent megakaryocytes; while Supa Na-Nakorn (1966) found in this phase normal of number megakaryocytes with younger forms in some in all of their cases. The recovery phase (days

5 – 8) with hypercellularity and increased number of megakaryocytes, 10 – 20 per low power field with dyssynchronism between cytoplasm and nucleus and a few platelets around. Clasmatocytes phagocytizing leukocytes and erythrocytes were also reported. The convalescence phase (after 10 days) is normocellular.

Wether the relative lack of cases in adults in most countries is related to immunity or age–related factors is not known. Two theories were offered to explain the pathogenesis of DHF, the disease was thought to be due to 1). virulence factors of the virus and 2). an unusual reaction in the host. Some type of hypersensitivity reaction induced by prior dengue virus infection in a host with possible inherited factors and/or nutrional states was thought to be present.

Our own cases represent DHF in adolescent and young adults of Indonesian origin, their ages ranging from 13 to 25 years, a total of 6 patients, 4 males and 2 females. 4 cases serologically proved and 2 cases clinically diagnosed. One case had a fatal end. Besides these another two cases aged 12 yrs., one male and one female were diagnosed as DHF clinically.

The bone marrow findings are in accordance with those found in the literature. The marked increased number of megakaryocytes, is significant. Clasmatocytes, phagocytizing leukocytes and erythrocytes, and megakaryocytes showing dyssynchronism between cytoplasm and nucleus are important findings in DHF.

Summary.

A short history of Dengue, the etiology of Dengue Hemorrhagic Fever and the vectors are reviewed. A classification and nomenclature for diseases suspected to be of dengue or chikungunya virus etiology, as suggested by WHO is given.

Six cases and two additional cases of Dengue Hemorrhagic Fever in adolescents and young adults are reported.

The bone marrow findings in our cases compared with those found in the literature.

The pathogenesis of Dengue Hemmorrhagic Fever is reviewed in short.

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