ORIGINAL ARTICLE

Thrombocytopenia in Dengue Hemorrhagic Fever

by

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Abstract

According to WHO thrombocytopenia is one of the diagnostic criteria of DHF. On the other hand many studies have reported DHF cases without evidence of thrombocytopenia.

One hundred fifty nine DHF out of 485 suspected cases were assessed for their platelet counts. Diagnosis of DHF was established based on the WHO criteria, and confirmed by the hemagglutination inhibition test. The platelet counts were done serially and intensively by phase contrast microscope from the first day of hospitalization until the patient's discharge.

In 77 patients thrombocytopenia appeared for the first time during hospitalization. Mild thrombocytopenia appeared in almost all of these cases before thrombocyte count of 100,000 reached. Seventy two patients had shown thrombocytopenia on the day of admission. No thrombocytopenia was found on the second day of illness, the earliest time of the detection of thrombocytopenia was on the 3rd and the latest was on the 8th day of illness. Thrombocytopenia lasted 1-5 days. It is concluded that many DHF diagnosis would have been missed if the thrombocyte investigation had not been done serially and intensively. Mild thrombocytopenia in DHF suspected patients should call attention to do platelet investigation intensively in those cases.

Introduction

Diagnostic criteria of dengue hemorrhagic fever (DHF) according to WHO are :

Clinical
1. Fever-acute onset, high, continuous and lasting 2-7 days.
2. Hemorrhagic manisfestation including at least positive tourniquet test. Any of the following may be present; petechiae, purpura, ecchymosis ; epistaxis, gum bleeding ; hematemesis and/or melena.
3. Enlargement of liver (observed at some stages of the illness).
4. Shock-manifested by rapid and weak pulse with narrowing of the pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness.[1]

Laboratory
1. Thrombocytopenia (100,000/ul or less).
2. Hemoconcentration; hematocrit increase by 20% or more of recovery value.

The first two clinical criteria plus thrombocytopenia and hemoconcentration are sufficient to establish a clinical diagnosis of DHF.

The severity of DHF is classified into four grades [1] :

Grade I   : Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test.

Grade II : Spontaneous bleeding in addition to the manifestations of Grade I , usually in the form of skin and/or other hemorrhages.

Grade III : Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness.

Grade IV : Profound shock with undetectable blood pressure and pulse.

In many studies it has been found that many of DHF cases showed no thrombocytopenia [2,3,4,5,6].

In this study we want to see the thrombocytopenia in DHF patients in relation to the diagnostic criteria.

Materials and methods

All patients admitted to Dr. Sardjito Central General Hospital, Yogyakarta and Empat Lima Children Hospital, Yogyakarta, suspected as suffering from DHF or fever of unknown causes were included to this study. The period of study was from June 1987 to June 1989.

Diagnosis of DHF was based on WHO criteria and confirmed by hemagglutination inhibition test, i.e. HI titer > 1280 in the acute stage or > 4 times rise of HI titer in the convalescence. Suspected cases which showed positive HI test but did not fulfill the WHO criteria were diagnosed as dengue fever (DF) and cases with negative HI test were diagnosed as fever of unknown origin (FUO).

Platelet counts were done daily at least two times, from the first day of hospitalization till the convalescent period when the patient was discharged, usually from the 2nd to the 9th day of illness, using phase contrast microscope and crossed checked by blood smear [7]. Platelet count less than 250,000/ul but more 100,000/ul was defined as mild thrombocytopenia. Duration of thrombocytopenia was counted from the day when the thrombocytopenia was for the first time detected to the day when the thrombocyte count was found more than 100,000/ul. Day of illness was based on the duration of fever according to the history.

HI test was done firstly on the first day of hospitalization and secondly in the convalescent period, i.e. more than 1 to 4 weeks after the first test.

Results

Out of 485 patients 159 were DHF, 204 were DF and 122 were FUO. The DHF patients were 47 DHF I, 44 DHF II, 46 DHF III dan 22 DHF IV.

Sixteen (13%) FUO patients and 32 (16%) DF patients showed evidence of thrombocytopenia in the course of their illness (Table 1).

Table 2 shows the number of DHF patients related to the day of illness. It revealed that no case was admitted on the first day of ilness, only 10 (6%) patients were admitted on the second day and the number was increasing on the following days. Most of the patients were admitted on the 4th and the 5th day of illness. On the 7th day of illness all but one patient was still hospitalized. Platelet investigations were carried out on all of the patients every day until they were discharged.

Table 1. *Thrombocytopenia in FUO and DF patients*

Diagnosis	Number of cases	Cases with thrombocytopenia	
		Number	(%)
FUO	122	16	13
DF	204	32	16

Table 2. *Number of patients related to the day of illness*

Diagnosis	Day of illness							
	2	3	4	5	6	7	8	9
DHF I (N)	3	9	23	43	46	47	43	32
DHF II (N)	3	9	23	41	44	44	44	32
DHF III (N)	2	6	26	35	43	43	43	36
DHF IV (N)	2	3	6	18	21	20	20	18
Total	10	27	78	137	154	158	150	118

Table 3. *Frequency of thrombocytopenia related to the day of illness*

		Day of illness							
		2	3	4	5	6	7	8	9
DHF I	(N)	0	1	2	22	25	31	17	3
	(%)	0	0	18	42	60	61	42	12
DHF II	(N)	0	0	4	17	26	27	18	4
	(%)	0	0	18	42	60	61	42	12
DHF III	(N)	0	2	13	24	37	35	21	9
	(%)	0	33	50	71	88	76	50	25
DHF IV	(N)	0	0	3	15	17	16	7	3
	(%)	0	0	50	83	81	76	35	17
Total	(N)	0	3	22	78	105	109	63	19
	(%)	0	11	28	57	68	69	42	16

.Table 4. *Beginning of thrombocytopenia during hospitalization*

Day of illness	DHF I (N)	DHF II (N)	DHF III (N)	DHF IV (N)	Total
2	0	0	0	0	0
3	1	0	0	0	1
4	1	2	3	1	7
5	10	5	6	3	24
6	8	11	9	2	30
7	9	8	3	0	20
8	0	2	0	0	2
9	0	0	0	0	0
Total	29	24	18	6	77

The frequency of thrombocytopenia during hospitalization (from the 2nd to the 9th day of illness) can be seen in Table 3.

On the 2nd day of illness it was observed that there was no thrombocytopenia among the patients of all grades of DHF while on the 3rd day of illness (the 2nd day of hospitalization) only 3 out of 27 cases (11%) of DHF patients showed thrombocytopenia. The number of cases with thrombocytopenia was increasing with the day of illness. It was observed that the highest frequency of thrombocytopenia was on the 6th and the 7th day of illness, in 105 out of 154 (68%) and 109 out of 158 (69%) respectively. On the 8th day of illness the frequency of thrombocytopenia decreased much, i.e. only in 63 out of 150 patients (42%). On the 9th day of illness 16% of cases (19 out of 118) still showed thrombocytopenia, although other clinical manifestations had subsided.

Table 4 shows the beginning of thrombocytopenia which for the first time appeared in the hospital related to the day of illness.

Seventy seven patients without thrombocytopenia on the day of admission developed thrombocytopenia during hospitalization: no thrombocytopenia developed on the 2nd day of illness; on the 3rd day of illness thrombocytopenia began to manifest in one case and the frequency of the thrombocytopenia increased with the course of the disease, to start to decrease afterwards on the 7th day of illness. There were 2 (1,7%) patients who began to suffer from thrombocytopenia on the 8th day of illness. On the 9th day no new thrombocytopenia appeared.

Before platelet count of 100,000/mm^3 or less was reached, 70 patients mentioned above had shown decreasing platelet counts (mild thrombocytopenia) in 1 to 3 days. Seven patients showed sudden thrombocytopenia (decreasing thrombocyte count from 250,000 on the previous investigation to 100,000 or less on the next). Table 5 shows the beginning of mild thrombocytopenia. On the 2nd day of illness six patients had shown mild thrombocytopenia.

Table 5. *Beginning of mild thrombocytopenia in the hospital*

Day of illness	DHF I Freq	DHF II Freq	DHF III Freq	DHF IV Freq	Total
2	2	2	2	0	6
3	4	4	0	1	9
4	11	10	9	2	32
5	7	10	3	0	20
6	0	2	1	0	3
7	0	0	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
Total	24	28	15	3	70

Table 6. *Number of patients with thrombocytopenia on the day of admission*

Day of illness	Number of cases
3	2
4	15
5	33
6	15
7	6
8	0
9	0
Total	7

Many patients (72 out of 159) had shown thrombocytopenia on admission, thus the exact beginning of thrombocytopenic manifestation could not be determined (Table 6). Of this group no one was admitted on the 2nd day of illness.

The duration of thrombocytopenia in all DHF patients (including patients with and without thrombocytopenia on admission) during hospitalization was from 1 to 5 days, with the peak of 1 to 2 days (Table 7).

Table 7. *Duration of thrombocytopenia*

	1 day	2 day	3 day	4 day	5 day	Total
DHF I	20	14	10	2	1	47
DHF II	26	11	6	1	2	44
DHF III	6	8	15	9	8	46
DHF IV	3	5	6	8	0	22
Total	55	38	37	20	11	159

Most patients of DHF I an DHF II showed thrombocytopenia only for one day, i.e. 20 out of 47 and 26 out 44 of patients respectively, while of DHF III the duration was mostly 3 days (15 out of 46 patients) and of DHF IV mostly 4 days (8 out 22 patients).

Discussion

Thrombocytopenia is one of the diagnostic criteria to establish the diagnosis of DHF[1]. Thrombocytopenia in DHF is defined as a platelet count of 100,000/ul or less. Platelet count is easily done from blood smear either with phase contrast microscope or by semiquantitative method [1,7]. This laboratory abnormality is actually easy to investigate, but in practice there are some problems.

Thrombocytopenia may occur in various infectious diseases, either due to bacteria, viruses or parasites. It is understandable therefore, that in DF or FUO cases thrombocytopenia may be found. Halstead (1989) said that bleeding should be regarded as part of a variable clinical spectrum of normal response toward infection by dengue virus[8]. On the other hand many studies found non thrombocytopenic DHF cases. Sumarmo and Widya (1973) reported 102 DHF cases, 65% out of which with thrombocytopenia, 15% with platelet count between 100,000 and 200,000/ul , and 19% with normal platelet count [2]. Again in 1975 Sumarmo et al. reported 180 cases, out of which 54% were with thrombocytopenia and 16% with platelet count between 100,000-200,000/ul[3]. Rosyid et al. (1981) reported 53 cases with platelets less than 150,000/ul and 3 cases with platelets more than 150,000/ul. Sumarmo (1983) reviewed 744 DHF cases, in which 64% of cases were with and the rest without thrombocytopenia [6]. Wong et al. (1973) reported 22 out of 129 patients showing platelet counts of 100,000 - 150,000/ul [9] , Songco et al, (1987) reported thrombocytopenia in 11,4% of 89 cases with secondary HI reaction [10]. Muzief Munir and Rampengan (1984) reported non thrombocytopenia in recurrent shock cases [11]. In most reports, it was not said on what day the platelet investigastions were done. In our study it was done serially, at least two times a day, sometimes more frequent necessary, from the first day of hospitalization till the patient's discharged. Many patients came to the hospital with manifestation of thrombocytopenia; in about half of our subjects the manifestation of thrombocytopenia occurred during hospitalization. As shown in Table 3, no thrombocytopenia was found on the

second day of illness, even in cases who later on developed into shock syndrome. On the 3rd, 4th, 5th, 6th, 7th, 8th and 9th day of illness the frequency of thrombocytopenia were 11% , 28% , 57% , 68% , 68% , 42% and 16% respectively. It means that causal platelet investigations will result in a great number of non thrombocytopenia among the DHF cases. The thrombocytopenia could be discovered only by serial intensive platelet investigations.

The duration of thrombocytopenia was variable. The shortest was 1 day and the longest 5 days, it was mostly 1 to 2 days (Table 7). So if the platelet investigation was not done serially, the thrombocytopenic period would not be detected and this means that those cases cannot be diagnosed as DHF according to the WHO criteria. Muzief Munir et al. (1982) reported thrombocytopenia on 74 cases by daily investigation, i.e. on the 2nd, 3rd, 4th, 5th and 6th day which revealed 18% , 22% , 30% , 32% and 19% respectively [5]. These figures show that the frequency of thrombocytopenia was less than ours. From the above mentioned we conclude that to detect the occurrence of thrombocytopenia in DHF cases, serial platelets investigations should be done routinely.

Some of our patients showed that the platelet count decreased abruptly, i.e. from a normal platelet count on the day before to 100,000/ul or less on the following day, but in patients with observed thrombocytopenia for the first time, almost all of them showed a gradually decreasing platelets count. As shown in Table 5, 70 patients firstly showed a mild decrease of platelet count and thrombocytopenia appeared thereafter on the following investigation. The mild thrombo-cytopenia lasted from 1 to 3 days. We believe that in patients with suspected DHF, mild thrombocytopenia should be regarded as a clue of on coming throm-bocytopenia and thus intensive thrombocyte counts should be performed on those cases.

Conclusion

Of 485 suspected DHF cases, 122 FUO, 204 DF and 159 DHF were discovered. Thirteen percent FUO and 16% DF cases showed thrombocytopenia during the course of the illness. Thrombocytopenia in DHF cases lasted for 1 to 5 days. No throm-bocytopenia was found on the second day of illness. The earliest time of the beginning of thrombocytopenia was the third day and the latest was the 8th day of illness. Most of them showed thrombocytopenia for the first time on the fifth or sixth day of illness. The highest frequency of thrombocytopenia during hospitalization was found on the sixth and seventh day of illness.

Thrombocytopenia and mild throm-bocytopenia were still observed on the 9th day of illness in some patients, although other clinical manifestations had subsided. We concluded that thrombocytopenia in DHF can only be found maximally if the platelet count is done serially and intensively at least from the third to the 8th day of illness. Otherwise, many DHF patients would be undiagnosed. Mild thrombocytopenia occurred before a platelet counts of 100,000/ul or less was reached. In DHF suspected patients mild thrombocytopenia should call attention to perform platelet counts serially/repeatedly.

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