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ON HEMOSTATIC STUDIES IN HEMOPHILIA

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ABSTRACT

In order to elucidate the factors which account for hemorrhagic diathesis of hemophilia, hemostatic studies were carried out in 55 hemophiliacs, consisting of 39 of hemophilia A and 16 of hemophilia B. These patients were classified into severe group (18 cases), moderate group (25 cases) and minimum group (12 cases), according to clinical severity without regard to the data of coagulation test. The results were summarized as follows;

1) The clinical severity in hemophilia did not necessarily coincide with data of coagulation test. Moreover, when hemostatic tests were conducted for prolonged period on severe cases fluctuations were seen in their hemorrhagic manifestations, but, during same observational period, there showed no variations in the grade of the amount of their congenitally deficient clotting factor.

2) On the other hand, changes in fibrinolytic activity of these hemophiliacs had a definite relationship not only with the grade of clinical severity but also the fluctuations of hemorrhagic manifestation.

Based on the above results, it became clear that the hemorrhagic disorders seen in hemophilia can be influenced by fluctuation in the fibrinolytic system.

I. INTRODUCTION

Although the theory of deficiency of the blood clotting factor in hemophilia is commonly supported today, Tocantins[1] has resurrected the circulating-anticoagulant theory, by stating that the antihemophilic factor is deficient in hemophilic plasma, but it can be revealed on uncovering with prolonged shaking with ether. Seegers *et al.*[2] also obtained results that helped to support this latter view. However, the diversity of the clinical manifestations of hemorrhage and the occurrence of long term remissions seen in hemophilia can not be wholly accounted for from both theories. In this paper, the author tried to elucidate such factors which account for the hemorrhagic manifestations in this disease.

II. MATERIALS AND METHODS

A) Thirty nine patients with hemophilia A and 16 with hemophilia B, totalling 55 patients were examined.

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B) Method of examination

a) Blood was obtained between 11.00 A.M. and 12.00 noon by the two syringe method. 3.8% sodium citrate solution was used as anticoagulant. To obtain citrated plasma siliconized glassware was used in all cases.

b) The hemostatic tests carried out and the methods employed were as below.

1) Whole blood clotting time: Lee-White's method.

2) Thromboplastin generation test: Biggs-Douglas' method[3].

3) Factor VIII activity: Pitney's method[4].

4) Factor IX activity: Fukui-Umegaki's method[5].

5) Fibrinolytic activity (Euglobulin fraction, Streptokinase-activated euglobulin fraction and Antiplasmin): Fibrin plate method[6].

III. OUR CLASSIFICATION OF HEMOPHILIA ACCORDING TO GRADE OF CLINICAL SEVERITY

As the clinical manifestations of hemorrhage in hemophilia do not necessarily coincide with the data of coagulation tests, the total of 55 hemophilic patients, consisting of 39 of A and 16 of B, were classified into three groups according to clinical severity, based mainly on hemorrhagic manifestations, without regard to the data of coagulation test; namely, into i) severe group (18 cases, consisting of 13 A and 5 B types) characterized by hemorrhages occurring on more than half the days of a month and high grade disturbance of daily life; ii) minimum group (12 cases, consisting of 11 A and 1 B types) presenting only abnormal hemorrhagic manifestations at external injuries or surgical operations and scarcely any obstacle in conducting a normal life; and iii) moderate group (25 cases, consisting of 15 A and 10 B types) lying in between the above two groups.

IV. RESULTS

1) The blood clotting system and the grade of clinical severity

The following relationships were recognized between blood clotting system and clinical severity.

As shown in Fig. 1, whole blood clotting time was 13–191 (mean, 91.6) minutes in the severe group, 15–306 (mean, 101.6) minutes in the moderate group and 11–85 (mean, 19.9) minutes in the minimum group. In the first two groups there were thus seen cases with whole blood clotting time of 10 minutes, while in the minimum group a case of 85 minutes. The activity of intrinsic thromboplastin was 2–32 (mean, 11.9) % in the severe group, 3–36 (mean, 13.7) % in the moderate group and 5–54 (mean, 34.1) % in the minimum group. The activity of congenitally deficient factors was 0–5.0 (mean, 0.99) % in the severe, 0–3.8 (mean, 0.64) % in the moderate and 0.9–50.0 (mean, 20.2)

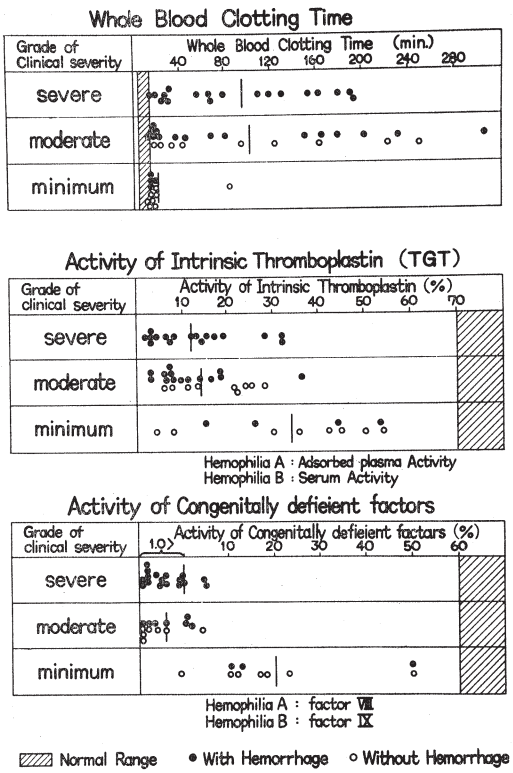

FIG. 1. Relation between blood clotting system and clinical severity in hemophilia.

% in the minimum cases. For reasons stated above, the difference was hardly seen between severe and moderate groups as regards blood coagulability. While the majority of the minimum group were mild cases by the data of coagulation tests.

Next, hemostatic tests were conducted for prolonged periods on 16 severe cases, but, as shown in Fig. 2, no definite relationship was found to exist between the fluctuation in whole blood clotting time and the variation in hemorrhagic manifestation. And during same observational period, the author failed to reveal variations in the grades of the amount of Factor VIII in hemophilia A and Factor IX in hemophilia B respectively.

Thus, it was suggested that clinical severity of hemophilia does not necessarily coincide with data of coagulation tests. That is to say, the variations in hemorrhagic manifestation can not be explained merely by the fluctuations in the blood clotting system, and it seems that the occurrence of hemorrhage in hemophilia is caused by certain factors other than deficiency of the blood clotting factor.

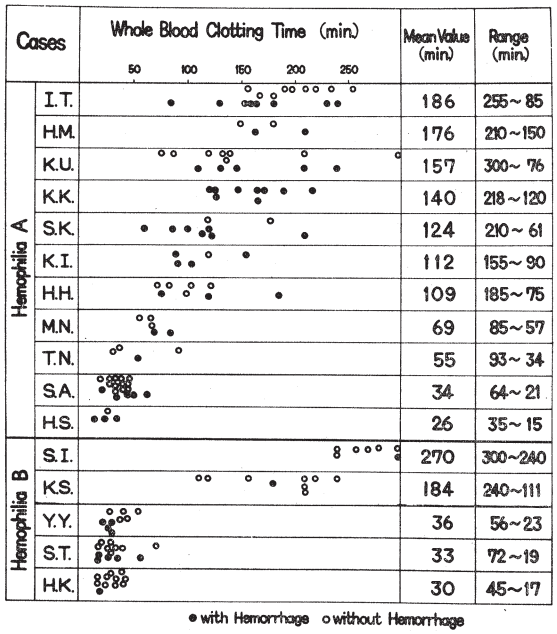

FIG. 2. Changes in whole blood clotting time in hemophilia —in relation with hemorrhagic manifestation—

2) The fibrinolytic system and the grade of clinical severity

The following relationships were recognized between the fibrinolytic system and clinical severity. As shown in Table 1, the fibrinolytic activity of euglobulin was 0-340 (mean, 95.0) MSD units/ml in the severe group, 0-280 (mean, 54.8) MSD nnits/ml in the moderate group and 0-110 (mean, 37.5) MSD units/ml in the minimum group, indicating a tendency for increased fibrinolytic activity in cases with severe hemorrhagic manifestations. Streptokinase (SK)-activated euglobulin activity was 200-4 840 (mean, 1 610) MSD units/ml in the severe group, 500-6 300 (mean, 2 590) MSD units/ml in the moderate group and 200-3 060 (mean, 1 630) MSD units/ml in the minimum group, and showed a

TABLE 1. Relation between Clinical Severity and Fibinolytic Activity in Hemophilia

Grade of clinical severity	Number of cases	Fibrinolytic activity (mean values: MSD units/ml)			Cases with increased fibrinolytic activity
		Euglobulin	SK-eug.	Antiplasmin	
severe	18	95	1 610	7 500	12
moderate	25	55	2 590	10 600	16
minimum	12	37	1 630	8 900	4
normal range		0-70	200-2 400	6 000-13 000	

difference with statistical significance between the moderate and the other two groups. Antiplasmin activity was 4 800-12 400 (mean, 7 470) MSD units/ml in the severe group, 6 500-15 100 (mean, 10 600) MSD units/ml in the moderate group and 6 000-12 700 (mean, 8 930) MSD units/ml in the minimum group, indicating decrease in antiplasmin activity only in the severe cases. The difference seen between severe and moderate group was statistically extremely significant. When now the results of tests on euglobulin, SK-activated euglobulin and antiplasmin are summarized, the cases with increased fibrinolytic activity were seen in 12 out of 18 severe cases (67%), in 16 out of 25 moderate cases (64%) and in 4 out of 12 minimum cases (33%), indicating a tendency to increased fibrinolytic activity in groups with severer hemorrhagic manifestations.

When hemostatic tests were followed up in a case of hemophilia A (I. T. aged 16, male, severe group) at his clinical progress, it was found that though no definite relationship was seen between variations in hemorrhagic manifestations and whole blood clotting time or fluctuations in Factor VIII (as shown in Fig. 3), euglobulin activity already rose to the high level of 140 MSD units/ml on the day before occurrence of hemorrhage, and with worsening of hemorrhagic manifestations continued to increase to levels exceeding 200 MSD units/ml Fig. 4 shows another severe case (S. A. aged 13, male, hemophilia A)

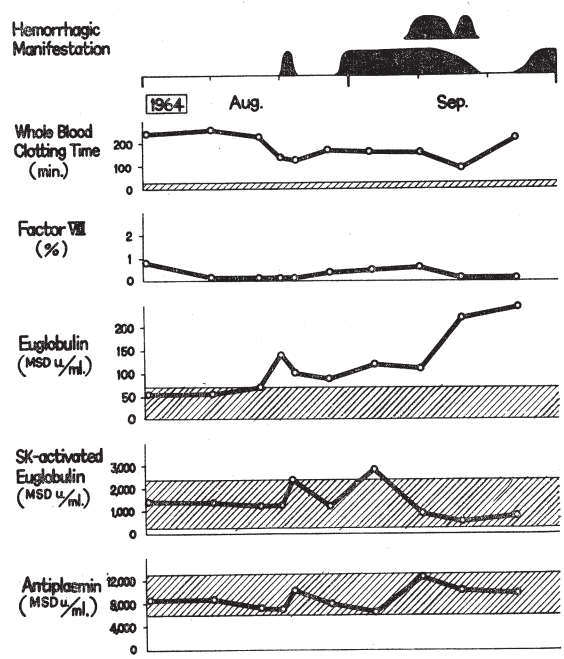

FIG. 3. Hemophilia A, age 16, male (I. T.).

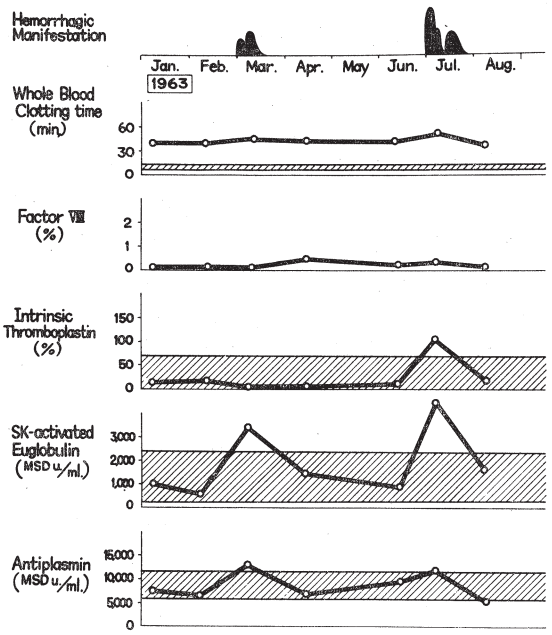

FIG. 4. Hemophilia A, age 13, male (S. A.).

examined. The whole blood clotting time and activity of Factor VIII showed practically no fluctuations during the observational period, but the fibrinolytic activity of euglobulin and SK-activated euglobulin rose synchronously with occurrence of hemorrhage. We conducted tests for hemorrhage totalling 63 made during progress of 5 severe cases consisting of 2 hemophilia A and 3 hemophilia B, and found increase in fibrinolytic activity in 21 out of 27 tests made at the time of hemorrhage, but only 6 out of 36 tests made during non-hemorrhagic states.

Based on the above results it became clear that a definite relationship exists between fluctuations in fibrinolytic activity and variations in hemorrhagic manifestations.

V. DISCUSSION

Absolutely unrelated to the results of hemostatic tests Waaler[7] (1959) classified hemophilia A patients into some groups, and stated that efficiency of the hemostasis in hemophilia A patients is not solely determined by the plasma level of antihemophilic A factor. Regarding such a phenomenon, Biggs[8] (1962) stated also that there are undoutedly difficulties in accepting the simple deficiency theory of hemophilia. While, there have been reports on experiences of cases where the clinical manifestations in hemophilia are influenced by emotional disturbances as well as changes in climate.

Astrup (1960[9], 1961[10]) studied the hemostatic effect of peanut factor reported by Boudreaux and Frampton[11] in hemophilia, and suggested that the occurrence of hemorrhage in hemophilia is probably influenced by break down of the dynamic equilibrium between fibrin formation and fibrin resolution. The present findings that a relationship exists between fibrinolytic activity and hemorrhagic manifestations in hemophilia, in part may account for the efficacy of the antiplasmic substance ε-aminocaproic acid in hemophilia, that has been developed by us (1962, 1963)[12][13][14], Abe *et al.* (1962)[15][16] and Reid (1964)[17]. By thus introducing the idea that fibrinolysis plays a role in the hemorrhagic disorders in hemophilia it is believed that the relationship between emotional disturbances and clinical manifestations of hemophilia can be more easily apprehended.

VI. CONCLUSION

Fifty five cases of hemophilia were classified into three groups by the clinical severity, and it was found that the hemorrhagic disorders seen in hemophilia can be influenced by fluctuation in the fibrinolytic system.

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