Hereditary Hemorrhagic Disorders
Excluding Hemophilia Group

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The purpose of this paper is to present clinical and hemostatic studies on our patients with hereditary hemorrhagic disorders excluding the hemophilia group. Some additional observations concerning to the platelet thrombi formation in connection with hemostatic mechanism will be described.

I. Coagulation defects

1. Congenital deficiency of factor V (Parahemophilia)

Congenital factor V deficiency is a very rare hemorrhagic disease. Since Owren reported the first case with this disease in 1947, under the name of Parahemophilia, about 35 additional cases have been found in various parts of the world. Only two instances have been reported in Japan, including one by us which seemed to be the first case in this country.

The condition affects both males and females. Hemorrhagic tendency is noted in early life. Bleeding episode may be manifested by nasal bleeding, easy bruisability, hemorrhage from gastrointestinal and urinary tracts, and excessive bleeding after dental extractions or surgical procedures. Except for the absence of hemarthrosis, these symptoms do not differ qualitatively from those of classic hemophilia.

The severity of bleeding varies from case to case. Profuse and prolonged menstruation has been reported, and one girl bled to death at the time of first menstrual period. Surprisingly, a delivery was not accompanied and followed by any unusual bleeding in whom menorrhagia were frequently observed.

Accordingly, the prognosis of this disease seemed to be reasonably good with regard to life.
CASE. B. O. 33yrs. old, male.

Family history: The parents of the patient are first cousins. His elder sister had had a hemorrhagic diathesis very similar to the patient's since her childhood, but she passed a delivery without being accompanied by any marked postpartum bleeding. The patient and his wife are also first cousins. There are one boy and one girl, and the former has a hemorrhagic tendency characterized by easy bruising.

Past history: From early childhood, he has frequently developed ecchymoses after slight trauma. Also, massive and persistent bleeding had been observed following cuts. After tooth extraction and tonsillectomy, he was very close to death by large blood loss. Hemarthrosis of right knee was recognized following a traffic accident, but never thereafter.

Present status: Normally developed, but rather anemic pale. Physical examinations of the chest and abdomen were almost entirely negative. There was no ecchymotic area on the extremities. His joints showed none of the changes to be expected in hemophilia.

Diagnostic studies: The results of the tests on blood coagulation show that the hemorrhagic diathesis is due to a specific deficiency of factor V.

The thromboplastin generation test was abnormal when the reacting mixture consisted of normal platelet, normal serum, barium sulfate adsorbed plasma obtained from the patient and calcium. It was observed that the abnormality was exaggerated when the patient's platelets were used instead of normal platelets together with patient's adsorbed plasma in the reacting mixture. This observation suggests that the patient's platelets are deficient in the factor V-like (platelet factor 1) activity, since the thromboplastic factor (platelet factor 3) activity seemed to be normal if determined by thromboplastin generation test. The platelet factor 1 activity was thus estimated, and it is proved that the platelet factor 1 activity of the patient's platelet was markedly reduced. Furthermore, the fact that the defect in platelet factor 1 was correctable by exposing the abnormal platelets to normal plasma was reconfirmed. From these observations we believe that the platelet factor 1 and factor V of plasma are closely related, and platelet factor 1
of platelets perhaps results from the adsorption of plasma factor V from plasma.

The coexistence of deficiencies of factor VIII and factor V has been reported in four instances. The present case represents no such abnormality.

Two children had a prolonged one-stage prothrombin time and had a deficiency in factor V.

The exact mode of inheritance of parahemophilia is not clear. In this respect, the author's case seemed to supply a very valuable data.

2. Congenital deficiencies of the stable factors, factor VII and factor X

In the 1940's, a number of patients, in whom the one stage prothrombin time had been prolonged through life-long, were reported to have hereditary prothrombin deficiencies.

In 1951, Alexander et al. found in a case the prolongation of prothrombin time was corrected by the addition of serum. Alexander assumed that the patient's plasma lacked some additional substance, and they named a such substance serum prothrombin conversion accelerator (SPCA). Since then, many cases have been described. But the results of hemostatic studies revealed not uniform, and they seem to fall into two general groups, those which seem to coincide to Alexander's case of Factor VII deficiency and those which seem to have a defect described by Telfer and by Hougie and Graham as deficiency of Factor X.

3. Hereditary deficiency of prothrombin

There are number of patients who were reported to have hereditary deficiency of prothrombin, but an isolated deficiency of prothrombin itself is most exceptional; according to Ratnoff only the patients described by three authors have congenital deficiency of prothrombin.

4. Congenital afibrinogenemia

In 1920, Rabe and Salomon described a boy aged 9 years who had no fibrinogen in his blood under the name of congenital afibrinogenemia. Since then, about 30 additional cases were found. In our country, three additional cases were found after our report of the first case in Japan in 1955.
The bleeding manifestations of congenital afibrinogenemia is relatively severe. Patient may bleed firstly from the umbilicus at birth, and the prognosis of this disorders is moderately poor; many patients died either in infancy or in childhood.

CASE. N. Y. 7 yrs. old, female.

Family history: The family history showed nothing relevant. There is no known consanguinity of the parents.

Past history: Since her early life she had a history of profuse umbilical bleeding for 10 days beginning 6 days after birth, and she suffered from uncontrollable bleeding from injuries. She continuously had several ecchymoses on her extremities resulting from the slightest trauma. She had had no gum-bleeding, petechie or hemorrhothsis.

Present status: Physical examination was almost entirely negative. No abnormalities were noted except the presence of several ecchymotic areas on the outer aspect of both legs, which were attributed definitely to involuntary contusion.

Diagnostic studies: Laboratory examinations were negative except for the complete incoagulability of the blood. Furthermore, some chemical analysis, electrophoresis of the plasma, etc. demonstrated a complete lack of fibrinogen in her blood. Other studies on the various clotting factors involved in the formation of thrombin have revealed no abnormalities.

It is believed that congenital afibrinogenemia is hereditary disease, transmitted as a recessive and non sex-linked characteristic. Some heterozygous carriers are said to have moderate hypofibrinogenemia. The patient's mother had had no evidence of hemorrhagic tendency, and her blood clotted and retracted normally, her plasma fibrinogen concentration being entirely normal.

II. Vascular defect

There are two congenital vascular defects with hemorrhagic diathesis; they are hemorrhagic diathesis of Willebrand-Jürgens type and hereditary hemorrhagic teleangioectasia.

The nature of the bleeding symptoms of the latter is quite different one compared with that seen in hemophilia. Thus the author will discuss the former.
Hemorrhagic diathesis of Willebrand-Jürgens type

In 1926, von Willebrand described a new congenital hemorrhagic diathesis found in a family living on the Åland Island, under the designation of “Pseudohemofili”. Later he and Jürgens found an abnormality in the platelets, and changed the name to “Konstitutionelle Thrombopathie”. Many cases similar to his original report have been reported, and the entity of the hemorrhagic condition with characteristic manifestations is now generally accepted.

This is a hereditary bleeding disease transmitted by and occurring in both males and females.

It is characterized by a prolonged bleeding times, despite the presence of normal number of platelets, with normal coagulation time and clot retraction.

We have observed four typical cases of Willebrand-Jürgens’ hemorrhagic diathesis, one 16 year-old male and three unmarried females, 25, 24 and 20 years in age, respectively.

Family history disclosed that the mothers of two of the patients had a bleeding diathesis similar to that of the patients, but this tendency disappeared spontaneously after the age of 30 years.

The bleeding manifestations in all these cases are quite similar, the initial symptoms being massive epistaxis in all. Although ecchymosis and easy bruising are rather common, no petechie has been observed. Severe menorrhagia has been observed in one case.

All clinical findings are in accord with those usually accepted as being characteristic of hemorrhagic diathesis of Willebrand-Jürgens type.

Coagulation studies made on the blood of these patients disclosed no abnormalities regarding platelet count, clot retraction and plasmatic clotting factors. The only exception was the striking prolongation of bleeding time. Thrombelastogram revealed completely normal.

Platelet morphology was carefully examined on stained films and isolated samples. The size of the platelets do not always show a constant pattern. Platelet fragility test disclosed normal. Capillaroscopic observation of the skin and retinæ gave negative results.

No treatment which is unexceptionally effective with this hemorrhagic diathesis is unknown. Administration of various hemo-
statics and fresh blood transfusion were ineffective. However, a new adrenochrome derivative, sodium-1-methyl-2,3,5,6-tetrahydro-5-semicarbazo-6-oxyindole-3-sulfonate, gave a satisfactory therapeutic response; the patients have been free from abnormal bleeding for one year by its continuous administration, and the bleeding time has also been markedly shortened. Thus, we believe that the basic defect of this disease may be attributed definitely to the abnormality in capillary walls.

In 1953, Alexander and Goldstein reported a new hemorrhagic disease wherein a prolonged bleeding time and a reduced factor VIII were demonstrable, though clinical manifestations were indistinguishable from those of hemorrhagic diathesis of Willebrand-Jürgens type. These new bleeding disorders are now understood to have dual hemostatic defect, i.e. deficiency in plasma thromboplastic factor and abnormal capillary walls, and has been designated as 'Vascular hemophilia'. Ever since the presence of vascular hemophilia was postulated, interpretation of these two diseases seemed to be in utter confusion. Biggs et al. showed the evidence that some of their patients with von Willebrand's disease showed a moderate lack in factor VIII in the blood. Jürgens re-examined the Åland Island bleeders, and discovered that their titer of factor VIII was often moderately low. Thus some investigators have postulated the opinion that the hemorrhagic diathesis of Willebrand-Jürgens type and vascular hemophilia are the same disease. But other authorities stressed that so called "thrombopathia of Willebrand-Jürgens type", "vascular hemophilia", "angiohemophilia" and "pseudohemophilia" are varieties of the same disease, and classified into 5-8 different subgroups according to the laboratory data.

III. Defect in platelet

*Thrombasthenia of Glanzmann*

There is a rare disease which shows nearly the same hemorrhagic tendency as the thrombocytopenia inspite of the platelet count of the patient being normal. It is called "Glanzmann's thrombasthenia". And the defect seems to be transmitted as a dominant trait.

We have observed 5 typical cases of this disease. They are 38,
5 and 7 years old males and 36 and 11 years old unmarried females, respectively.

Familial appearance of hemorrhagic tendency was seen in 2 cases. The parents of a patient are first cousins.

Hemorrhagic manifestations appeared in early childhood in all cases, and continued thereafter. They have had petechiae, epistaxis and gum bleeding. Severe menorrhagia has been observed in female patients.

Physical examinations revealed almost negative, except the slight degree of splenomegaly.

Hematologic examinations revealed a slight decrease in platelet count in two cases, which is presumed to be a splenic thrombocytopenia. In any way, the thrombocytopenia in this degree never causes the hemorrhagic diathesis. In other patients, platelet count disclosed normal or rather increased.

There was no sign of platelet agglutination on the smeared film. And, furthermore, no clot retraction was observed. Also a prolonged bleeding time and a positive Rumpel-Leede phenomenon were demonstrated. No abnormalities were found in various coagulation factors. As far as our studies concerned, the morphological abnormalities were found only under the electron microscope on ultra-thin sectioned platelet samples.

The author has studied the change in blood platelets and their relation to the fibrin strands on various hemorrhagic diseases during blood clotting, under the phase contrast microscope. On the addition of calcium chloride solution to citrated normal platelet-rich plasma, the platelets clumped together and from conglomerates within a short time. Platelet conglomerates observed here are moderately firm, and suggest the important role of platelet thrombi in hemostasis.

In the congenital afibrinogenemia, the changes of the platelets seemed to be normal. From this observation, the author believes theunnecessity of fibrin to form platelet thrombus. Platelet clumping, in the blood of parahemophilia, hemorrhagic diathesis of Willebrand-Jürgens type, occurred quite normally. Platelet-rich plasma of the thrombasthenia, however, showed no platelet conglom-
erates formation during the clotting. This fact may indicate the platelets of thrombasthenia do not form platelet thrombi in case of vascular damage. And the author believes that this is one of the causes of prolonged bleeding in this disease.

When the fibrin filament began to appear the fibrin net exhibits a radial formation adhering to the platelet conglomerates at their center in normal blood samples. To the platelets of the thrombasthenia, however, most of fibrin filaments did not adhere. This looks as if there are some qualitative abnormalities in the patient's fibrin. But the fibrin net produced by the recalcification of the patient's platelet-poor plasma containing normal platelets seemed to be quite normal.

Consequently, it may be concluded that the significant abnormality is present in the platelets of the patients.

This finding has been firstly reported by Prof. Morita as the characteristic and important abnormality found in this disease. We believe that the deficient adhesiveness of the patients' platelets to the fibrin induces a impaired clot retraction of the thrombasthenia.

Recently, some workers reported the change in ATP concentration of the platelets during blood clotting. And some other investigators found a diminution of ATP level in the platelets of the thrombasthenia. The author estimated the platelet ATP concentration by the method of Cohn & Carter. In two cases of thrombasthenia, we found a uniform decline of ATP concentration. But this diminution was rather slight than reported previously. By the present time, whether the diminution of ATP in platelets is the key to thrombasthenia and impaired clot retraction, is difficult to answer.