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HÆMOPHILIA DUE TO FACTOR VIII DEFICIENCY IN AN INDIAN BOY

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Hæmophilia is a well-known inherited disease in Europe, but it is thought to be very rare in Asian countries.

It is a disease characterized by a life-long tendency to prolonged hæmorrhage and markedly delayed coagulation time in affeced males. It is due to a plasma factor deficiency, factor VIII, also called "anthihaemophilic globulin (=AHG). It is inherited as a recessive Mendelian trait and is sex-linked.

Recently, similar inherited coagulation defects were described, resembling hæmophilia. They were due to a deficiency in other factors or due to circulating anticoagulants. These conditions were given different names such as pseudohæmophilia, parahæmophilia, etc. A disease resembling almost completely the classical hæmophilia, is factor IX deficiency, called hæmophilia B. Much confusion has arisen from this variety of names and it has therefore been proposed to designate the conditions by the name of the coagulation factor which is lacking. Since it is of great importance for the treatment and management of the disease to know exactly what is lacking, attempts should always be made to arrive at an accurate diagnosis as regards the deficiency state.

In this paper a case of classical hæmophilia due to deficiency of factor VIII in an Indian boy is described.

METHODS

Routine hæmatological examinations were carried out according to standard methods.

The blood for study was obtained from the antecubital vein with a new disposable Monoject needle without traumatisation in order to prevent contamination with tissue thromboplastin. The two syringes technique was employed and all syringes were siliconized in order to prevent the activation of certain coagulation factors by contact with glass. The quantity of blood was calculated in advance and all necessary equipment was kept ready in order to avoid undue delay.

As a control, the blood of a normal healthy person was used whose blood was known to us by previous examinations.

Bleeding time was studied by the method of Ivy (1935). With this method the normal bleeding time is 1 to 9 minutes.

Capillary fragility test was that of Rumpel Leede, using a tourniquet to study the resistance of the capillaries.

Coagulation time was done by the method of Lee and White (1913), using glass and siliconized test tubes. Our normal values obtained with this method are 6 to 12 minutes in glass and 25 to 35 minutes in siliconized tubes.

Clot retraction. The simple qualitative (Budtz-olsen 1951) and the quantitative test of Didisheim (1961) were employed.

Clot lysis was evaluated as recommended by Wintrobe (1961), by tilting the tubes, used for the estimation of coagulation times, 90 degrees at 8, 24, 48 and 72 hours. If a clot was found initially and subsequently the blood has become completely fluid, lysis has taken place. This does not occur within 72 hours in normal blood.

Prothrombin time. The one-stage plasma prothrombin time of Quick (1945) was employed, using a commercial thromboplastin made from rabbit brain (Difco-Bacto-Thromboplastin).

Plasma fibrinogen was estimated as described by Ratnoff and Menzie and modified by Holburn (1955).

Thromboplastin generation test. The rapid screening test for disorders of thromboplastin generation as modified by Hicks and Pitney (1957) and the modified thromboplastin generation test of Biggs and Douglas (1953) using inosithin instead of platelets were employed. This test reveals any deficiency due to factor V, VIII, IX and X as well as Hageman factor and PTA.

Test for anticoagulants was performed as described by Wintrobe (1961).

CASE REPORT

Prak., a 5½ year old Indian boy has suffered from easy bruising and a tendency to prolonged haemorrhage since 6 months of age. In 1960 when he was 1½ years old, following a cut on his tongue, the bleeding was so prolonged that a blood transfusion had to be given. However, after a transfusion of 2 pints of blood, the bleeding did not stop and the condition became critical. He was transferred from Kuantan to Penang where plasma and another blood transfusion were given before the bleeding stopped. He had never had joint bleeding. He was the only son in the family, a younger sister was healthy and had no bleeding tendency. No other members were known to suffer from easy bleeding. On December 11, 1963, we saw a resonable well nourished boy, who did not look anæmic but who showed bruises on body, arms and legs. According to the father these bruises were obtained from slight knocks and bumping. Other physical findings were normal. Spleen and liver were not enlarged. Hæmatological findings were as follows. Hb 14.3g%, RBC 6.04 per cmm, WBC 9600 per cmm, PCV 41.5%, MCV 68.7, MCH 23.7 uug, MCHC 34.5%. Platelets 270000 per cmm. Reticulocytes 4.2%, differential count of the leucocytes normal.

Specialized studies. The bleeding time was 6 min. Tourniquet test of Rumpel Leede was negative. Coagulation time was very much prolonged, it was 47 minutes in glass and 7 hours in siliconized tubes. The normal control showed a coagulation time of 10 minutes

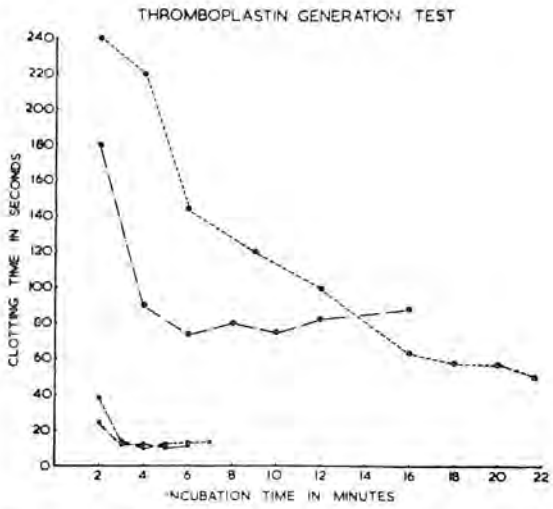

Fig. 1. Showing the abnormal thromboplastin generation test in patient Prak. when patient's absorbed plasma was incubated either with his own serum or with normal serum.

o - - - - - - o Normal absorbed plasma + normal serum.

o - · - · - o Normal absorbed plasma + Patient's serum.

· · · · · · · · Patient's absorbed plasma + Patient's serum.

· - · - · - · Patient's absorbed plasma + normal serum.

in glass and 30 minutes in siliconized tubes. Clotting time of recalcified plasma was 11 minutes and that of the normal control was 3 minutes. Clot retraction was normal. Although the clotting time was very much prolonged, the clot retraction was satisfactory once the clot was formed. Clot lysis was also normal, taking place only after 72 hours. Prothrombin time was 13.6 seconds (75%), normal control 13.7 seconds (75%). Fibrinogen content of the blood was 276.5mg% (normal range 200—400mg%). Protrombin consumption was very poor. The rapid screening test for disorders of thromboplastin generation of Hick and Pitney was found to be grossly abnormal, so the thromboplastin generation test of Biggs and Douglas was carried out to determine the exact nature of the deficiency. This last test showed that thromboplastin formation was deficient when patient's absorbed plasma, patient's or normal serum, inosithin and Ca Cl_2 were incubated together (see fig.). It was normal when patient's serum or normal serum and normal absorbed plasma, inosithin and Ca Cl_2 were incubated. This test points

to a deficiency of either factor V or factor VIII. No circulating anticoagulants were detected.

DISCUSSION

The thromboplastin generation test showed that either factor V or factor VIII was deficient. Since the prothrombin time was normal, factor V was not deficient. Therefore the deficiency was in factor VIII. In agreement with this, is the abnormal prothrombin consumption test. No deficiency of any other coagulation factors could be demonstrated and the platelet number and capillary resistance were normal. The patient is therefore a classical type of hæmophilia due to factor VIII deficiency. Recently cases of hæmophilia were reported which were due to circulating anticoagulants directed against factor VIII. (Horowith and Fujimoto 1962, Ehrenworth, 1963). However, no circulating anticoagulant could be demonstrated in the patient. A condition resembling almost completely the classical type of hæmophilia is that due to factor IX, (Aggeler *et al* 1952), also called hæmophilia B or Christmas disease, (Biggs *et al* 1952). Factor IX, also called PTC (plasma thromboplastin component) is found in serum. Our patient's serum incubated with normal absorbed plasma, inosithin and Ca Cl_2 showed normal thromboplastin generation, which demonstrated that factor IX was not deficient in the patient. The father and mother did not show prolonged coagulation times. It is a pity that no maternal uncles could be included in the study.

This is the first case of hæmophilia due to factor VIII deficiency described in Malaya.

Up to now no therapy has been found which can cure hæmophilia. However, once it is known exactly which factor is lacking in the patient, the management and symptomatic treatment can be carried out more effectively. The patient must of course be protected from wounds and abrasions and he should be warned not to cut or bruise himself. However, it is important that the patient lives normally and does not become an invalid. Operations should be avoided. If this can not be avoided the factor VIII level in the blood should be raised before operation takes place. In a bleeding crisis the basis of therapy should be the administration of a sufficient quantity of antihæmophilic factor to restore the normal coagulation of the blood. This should be maintained until the crisis has passed. Factor VIII should be given intravenously. It can be administered as a transfusion of fresh whole blood if the patient has anæmia, otherwise fresh plasma, freshly frozen or freshly lyophilized plasma should be given. This has to be given frequently or by continuous drip, since the effect of factor VIII lasts only a few hours. It may take some time before the bleeding stops. Bleeding in the region of the throat should be treated vigorously since asphyxation may be the result of swelling of the soft tissue. Also acute joint bleeding should be treated intensively.

Factor VIII has been produced in purified form but it is still very difficult to obtain and these preparations are only available in small amounts.

Bleeding from accessible places can be treated by applying thrombin to the exposed bleeding points. The care of teeth is very important. Special precautions have to be taken in case dental surgery is required.

A paper by Boudreaux (who himself was a hæmophiliac) and Frampton in 1960 reported that the ingestion of peanuts or peanut flour gives symptomatic improvement of bleeding tendency. However, this observation has not yet been confirmed on scientific basis.

A complication of repeated administration of blood or plasma is the development of a circulating anticoagulant directed against factor VIII rendering the patient refractory to therapy. This makes prevention of bleeding the more important.

SUMMARY

A case of classical hæmophilia due to factor VIII (Antihæmophilic globulin) in an Indian boy is described. The diagnosis was revealed by the finding of an abnormal thromboplastin generation test and an abnormal prothrombin consumption, while other factors than factor VIII were found not to be deficient. No circulating anticogulants were detected. This is the first case of hæmophilia due to factor VIII deficiency described in Malaya.

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