PLASMA THROMBOPLASTIN COMPONENT DEFICIENCY —CHRISTMAS DISEASE: A REPORT OF 3 CASES

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Plasma thromboplastin component (PTC) deficiency is a constitutional disorder of blood coagulation which like haemophilia is inherited as a sex linked recessive Mendelian trait, transmitted by the female and usually seen only in males. The first description of this disorder was published in America by Aggeler and associates, 1952. At about the same time, Biggs and associates described similar cases from England. The condition has also been called Christmas Disease after the surname of the first patient investigated, Biggs et al., 1952 and is also sometimes referred to as haemophilia B, Quick and Hussey, 1959. Since these reports, many cases thought to be classical haemophilia due to antihaemophilic globulin (AHG) deficiency have been reinvestigated and a number of additional cases have been recorded, Aggeler et al., 1954; Fantl and Sawers, 1954; Harmon et al., 1957; Biggs and Macfarlane, 1958; Quick and Hussey, 1959.

Clinically, PTC deficiency is indistinguishable from haemophilia. Spontaneous haemorrhage or haemorrhage following trauma from an early age being a common presentation. Haemorrhage characteristically occurring into muscles, subcutaneous tissue, and joints being the commonest symptoms; whilst less commonly bleeding occurs from the gums and mucous membranes of the mouth and from the gastro intestinal and urinary tracts. It is generally believed that the condition tends to be milder than haemophilia, Rosenthal, 1954; Biggs and Macfarlane, 1962; Quick and Hussey, 1959.

The incidence of PTC deficiency relative to haemophilia varies from country to country. Haemophilia has been recorded as being about ten times more frequent than PTC deficiency in England, America, France and Australia, whilst a higher incidence of Christmas Disease ranging from 27 to 32% of all cases of haemophilia have been found in Canada, Germany, Holland and South Africa, Biggs and Macfarlane, 1958.

This paper reports on the clinical features and haematological findings in three patients with PTC deficiency. They are the first cases to be described in Singapore.

TECHNICAL METHODS

The laboratory methods followed in general are those described by Biggs and Macfarlane, 1962, and Dacie and Lewis, 1963. The details of the methods employed and the normal range of values obtained in our laboratory have been described in another paper.

CASE REPORTS

Case No. 1: T.Y.S., an 11 year old schoolboy was first seen in April 1965 with a complaint of swelling of the right knee of 4 months duration. His parents noticed a tendency to bruise and bleed easily from young. At the age of 10 months, he bled persistently from an abscess for which he had to be hospitalised and given transfusions of blood. He has had occasional episodes of epistaxis and bleeding from the gums. Transient swellings involving both elbows. wrists and ankles have occurred occasionally, Slightly prolonged bleeding on shedding of his decidous teeth was also noted.

Patient comes from a family of 10 with 6 sisters and 3 brothers all of whom are apparently well and healthy with no symptoms suggestive of a bleeding tendency. There was no history suggestive of a bleeding tendency in any of the maternal relatives all of whom are away in Sarawak.

Clinically the only positive findings were a number of ecchymoses on the thigh, a definite hemarthroses of the right knee with some limitation of movement, and mild hemarthroses of the left elbow.

Case No. 2: K.C.S., a 9 year old schoolboy was first seen in June 1964 for bleeding after a tooth extraction 5 days before admission. He was noticed to have a tendency to bruise and bleed easily from the age of ten months and to develop large hematomas after injection. He has had an occasional epistaxis and a chronic swelling of the right ankle for the past few years. At an early age he accidently cut his thumb which had to be sutured, but because of the severe and persistent bleeding, he had to be admitted for transfusion.

Patient comes from a family of 7 with five brothers and 1 sister all of whom are apparently well and healthy. There was a negative history of a bleeding tendency in any of the maternal relatives all of whom are in China.

Clinically, apart from some ecchymoses all over the body and an ankylosed right ankle, there was nothing else of note. He had a very carious set of teeth and was bleeding actively from a tooth socket.

Case No. 3: L.Y.K. a 4½ years old male was first seen in March 1963 at the age of 16 months because of persistent bleeding from the gums following a fall three days previously. From the age of 1 year, his parents have noticed him to bruise easily. He has had a number of admissions into hospital for prolonged bleeding from lacerated wounds on the fingers and forehead, and for a retrobulbar haemorrhage following a knock against a table.

Patient comes from a family of 11 with 4 brothers and 6 sisters. Two of his elder brothers were reported to have died from haemorrhage, one due to a "persistent nose bleed" and the other due to "bleeding into the brain". Two other children, a male and a female, were believed to have died from non-haemorragic causes. Apart from this, there was no other history suggestive of a bleeding tendency in the maternal relatives, all of whom are away in China.

Clinically the only abnormalities found were marked pallor, bleeding from the gums with some bruises over the legs.

LABORATORY FINDINGS

The results of the haematological investigations carried out on the 3 patients are shown in Table I and II.

TABLE I

RESULTS OF PRELIMINARY SCREENING TESTS

	Case 1	Case 2	Case 3	Normal
Platelet /c.mm.	200,000	205,000	300,000	150 - 300,000
Whole blood clotting time (min.)	14	8	120	5 - 10
Bleeding time (min.)	3	3	2½	3 - 7
Prothrombin time (sec.)	14	14	13	12 - 15
Partial thromboplastin time (sec.)	200+	200+	200+	< 100
Prothrombin consumption index (%)	63	33	120	0 - 30

TABLE II

THROMBOPLASTIN GENERATION STUDIES—SHOWING MINIMUM CLOTTING TIMES IN SECONDS WHEN USING PATIENT'S ADSORBED PLASMA, SERUM AND MIXTURES OF NORMAL AND HAEMOPHILIC SERUM WITH THE PATIENT'S SERUM

REAGENT	Case 1	Case 2	Case 3	Normal
Expt 1 Adsorbed plasma	6	6	7	8
Expt 2 Serum	20	18	22	9
Expt 3 Addition of 20% normal serum	8	6	9	-
Expt 4 Addition of 20% haemophilic serum	8	8	10	-
Expt 5 Addition of 20% adsorbed normal plasma	20	18	21	-

The thromboplastin generation studies showed normal minimum clotting times when using aluminium hydroxide adsorbed plasma from all three patients. The minimum clotting times were prolonged in all three patients when serum from the patients were used. These prolonged times were restored to normal by the addition of 20% by volume of normal serum and serum from a known haemophiliac patient, but not by normal adsorbed plasma.

The presence of circulating anticoagulants have been excluded by the normal times in plasma (Expt. 1) and by the normalisation of the clotting time by addition of small volumes of normal serum (Expt. 3).

FAMILY STUDIES

It was only possible to carry out limited family studies of the three patients as some of the brothers or sisters were not in Singapore and therefore not available for study. In all three cases no other maternal relatives were staying in Singapore.

Case No. 1: Only the mother, two sisters and one younger brother of this patient were available for study. The other members of the family being away in Malaya. All the preliminary screening tests and the thromboplastin generation studies were found to be normal in the younger brother and the other members studied.

Case No. 2: The mother, five brothers and one sister of this patient were available for study. The investigations including the thromboplastin generation studies gave uniformly normal results in all the five brothers studied as well as the sister and mother.

Case No. 3: Only 1 brother, 4 sisters and mother of the patient were available for study. All screening tests and the thromboplastin generation studies gave normal results.

DISCUSSION

All the patients had the characteristic history of a tendency to bruise and bleed easily from an early age. Hematoma formation, epistaxis, bleeding gums and hemarthroses were complained of by all the cases.

It is interesting to note that only one of the 3 cases gave a positive family history suggestive of a bleeding tendency. This was further confirmed by the normal findings in the family studies carried out. In Case No. 2, all five brothers were found to be absolutely normal with no evidence of any deficiency of PTC.

Clinically all 3 cases were of mild to moderate severity with recurrent spontaneous bleeding into skin, subcutaneous tissue and joints.

The results of the preliminary screening tests in PTC deficiency are the same as in haemophilia with normal bleeding time, platelet count, one stage prothrombin time and tourniquet test.

The whole blood clotting time which is usually slightly prolonged was found to be normal in Case 2, slightly prolonged in Case 1 and greatly prolonged to beyond 120 minutes in Case 3.

The prothrombin consumption index which is usually abnormal in these cases was found to be just outside of the normal range in Case 2, whilst in Case 1 and 3, the index was definitely abnormal.

The only diagnostic test is the thromboplastin generation test, T.G.T. which in PTC deficiency gives abnormal or prolonged minimum clotting times when using patient's serum, whereas in haemophilia abnormal results are obtained when patient's adsorbed plasma is used. In all three patients, the minimum clotting times were prolonged when using patient's serum whereas using the patient's adsorbed plasma, normal times were obtained.

Deficiency of Factor X will also give abnormal results in the T.G.T. when using the patient's serum, but this deficiency also causes a prolongation of the one stage prothrombin time test.

In addition, it was possible to demonstrate the normalisation of the T.G.T. of all three patients by the addition of 20% by volume of normal serum but not by adsorbed normal plasma which is deficient in PTC.

The addition of 20% by volume of serum from a known haemophiliac patient was also able to normalise the abnormal T.G.T. in all these cases thereby showing that the deficient factor in the 3 patients and in haemophilia are not the same.

The AHG level in all these patients were assayed and found to be normal. The PTC level was not assayed. No circulating anticoagulants were demonstrated in any of these patients. The fibrinogen and prothrombin levels were normal and no deficiency of any other coagulation factor could be demonstrated.

The characteristic history of a bleeding tendency from an early age coupled with typical T.G.T. studies are considered sufficient to confirm the diagnosis of PTC deficiency in the 3 cases.

It is interesting to note the relative incidence of PTC deficiency and haemophilia. These three cases were detected during a 2 year period of study when 36 cases of haemophilia were recorded thus giving a relative incidence of 1 to 12 or 8%.

SUMMARY

The clinical and haematological findings in 3 cases with PTC deficiency believed to be the first cases recorded in Singapore or Malaya are described. The clinical features are indistinguishable from classical haemophilia due to AHG deficiency. The results of the laboratory investigation are in agreement with similar cases reported by other workers.

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