CONGENITAL FACTOR VII DEFICIENCY

A REVIEW WITH A REPORT OF A CASE IN AN INDIAN INFANT

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The presence of a factor, present in serum and capable of accelerating the conversion of prothrombin to thrombin, was postulated by Mann, Hurn and Magath (1947), Owen and Bollman (1948), and MacMillan (1948), as a result of experiments with plasma from patients treated with dicoumarol. Subsequently several groups of investigators have described factors with similar properties, and, as is customary in the field of blood coagulation, a like number of synonyms have appeared in the literature. Thus it seems likely that the co-thromboplastin of Mann, Barker and Hurn (1951), serum prothrombin conversion accelerator of de Vries, Alexander and Goldstein (1949), and of Alexander, de Vries, Goldstein and Landwehr (1949), convertin of Owren (1951a and b), prothrombin conversion factor of Jacox (1949), and factor VII of Koller, Loeliger and Duckert (1951), and the factor lacking in the chicks poisoned with dicoumarol of Dam and Søndergaard (1948), are all the same factor. Koller's (1954) term factor VII has gained considerable currency in the British and Continental literature and seems the most satisfactory term for our present state of knowledge.

Factor VII is found in normal serum; the demonstration of a plasma precursor has not yet been conclusively shown. It is stable on storage which immediately distinguishes it from factor V, the other prothrombin conversion accelerator, which is labile. It is readily absorbed by the same absorbents as prothrombin, i.e., BaSO_4 , $\text{Al}(\text{OH})_3$, $\text{Ca}_3(\text{PO}_4)_2$, asbestos, etc., and can be eluted from them by sodium citrate solution.

The role of factor VII in the coagulation process appears to be two-fold. First, Biggs, Douglas and MacFarlane (1953) showed it to be essential for the evolution of plasma thromboplastin, while Koller *et al.* (1951) and Owren (1951b) have demonstrated its role as a prothrombin conversion accelerator, and as a co-factor for tissue thromboplastin, being

essential for the normal reaction of brain emulsion and prothrombin.

Factor VII deficiency may be either congenital or acquired. In the acquired category may be grouped deficiency resulting from therapeutic administration of the coumarin group of drugs, deficiency in hepatic disease, and in the newborn.

Cases of congenital deficiency of factor VII are rare; before 1950 they were reported in common with cases of factor V deficiency as hypoprothrombinaemias on account of the misconception then prevailing that the single-stage prothrombin time was a measure of plasma prothrombin.

A total of 14 cases designated as a deficiency of a serum factor, and probably corresponding to factor VII deficiency, have been found in the literature. Biggs and MacFarlane (1953) give some details of three probable cases of factor VII deficiency described before the factor itself was adequately characterized. These were the cases of Giordano (1943), Crockett, Shotton, Craddock and Leavell (1949) and Landwehr, Lang and Alexander (1950). Frick and Hagen in 1953 review a case previously described as a hypoprothrombinaemia by Hagen and Watson in 1948. This case was a 24-year-old woman whose defective single-stage 'prothrombin' time was wholly corrected by the addition of small amounts of serum. Alexander, Goldstein, Landwehr and Cook (1951) described the condition in a 4-year-old girl as 'an unrecognized coagulation defect rectified by serum and serum fractions' and showing that the missing factor was one readily absorbed by BaSO_4 from normal plasma or serum, but found that dicoumarol plasma, i.e., plasma from a patient under dicoumarol therapy, was efficacious to a considerable extent in correcting the defect and that its correcting power was little diminished by absorption with BaSO_4 . These latter findings are difficult to reconcile with present concepts.

Owren in 1952 gave details of a similar case in a 38-year-old man, and Beaumont and Bernard (1953) described a case in a newborn baby. Lewis, Fresh and Ferguson (1953) describe two cases, one in a girl who died of haemorrhage at the age of 14 years, and one in a man of 32 years, and Jenkins (1954) a further case. Bell and Alton (1955) describe a case in a 29-year-old man in whom the condition was associated with Christmas disease, while de Vries, Kettenborg and van der Pol (1955) report three patients, in one of whom also Christmas disease and factor VII deficiency were found in association. These authors stress attaching significance to very small prolongations of the single-stage prothrombin time.

Clinical Details of Present Case

An Indian male child was admitted to the Paediatric Division of the Coronation Hospital on October 24, 1954, when he was 10 days old.

His mother stated that the infant had been bleeding from the mouth for six days and that she had noticed a change in the colour of the stools. He had also been vomiting after meals.

He had been delivered at full term at home by a midwife after an uneventful pregnancy. Labour was normal and lasted about six hours. The child appeared to be perfectly well at birth, and weighed 9 lb.

On the fourth day of life the mother first noticed bright red blood issuing from the child's mouth. He was seen by a general practitioner who gave him an injection of vitamin K. The next day he continued to bleed from the mouth and the mother also noticed that his stools now appeared black. The following day he vomited after his feeds and on one occasion the mother noticed bright red blood mixed with the vomitus. The bleeding persisted intermittently until the tenth day when he was admitted to hospital.

The mother was a healthy Indian woman aged 18 years and was born in Johannesburg. The father was aged 30 years and was born in India. The parents were first cousins. A previous sibling had died at the age of 4 days from 'haemorrhage'.

On admission the child appeared to be fairly well nourished weighing 8 lb. He did not appear to be unduly pale but he was slightly jaundiced. His hydration was good.

The head measured $14\frac{1}{2}$ in. in circumference. The anterior fontanelle was open and admitted four fingers. There was no craniotabes or separation of sutures. The eyes were normal although the conjunctivae were slightly icteric. The fundi were normal. Fresh blood was seen on the tongue which in its middle third appeared to have several small purplish spots. Similar lesions were seen at the junction of the soft and hard palate. The chest was normal in shape, moved freely on respiration, and the breath sounds were normal in character. The heart was not enlarged clinically and the heart sounds were normal. No masses were felt in the abdomen. The

spleen was not palpable. The umbilical stump was still present; it was dry and the umbilicus appeared to be normal. No petechial haemorrhages were seen. The examination of the central nervous system did not reveal any abnormality. In view of the nature of the death of the previous sibling as well as the presence of haemorrhagic lesions on the tongue and palate in the patient a tentative diagnosis of hereditary telangiectasia was made.

The haemoglobin was 13 g. per 100 ml. The bleeding time was 4 minutes. The coagulation time was 6 minutes.

The umbilical stump separated and this was accompanied by haemorrhage from the umbilicus. The haemoglobin level dropped to 9 g. %. A blood transfusion of fresh blood was given. The patient had no further bleeding and was discharged on November 2, 1954.

On January 10, 1955, the patient was again brought to hospital with a history that he had been quite well until the day before admission when he again vomited his food which contained bright red blood. He appeared to be very sleepy and refused to take his feeds. On examination the baby was stuporose, the limbs flaccid and he was extremely pale. The anterior fontanelle was tense and bulging. He had no neck stiffness or head retraction. The eyes were deviated to the right. The mucous membranes of the mouth were pale and haemorrhagic purplish spots were again seen on the soft palate. The examination of the heart, chest and abdomen did not reveal any abnormality. He was generally hypotonic, and the reflexes were absent. A lumbar puncture was performed and the cerebrospinal fluid was blood stained. The patient had obviously had a cerebral haemorrhage.

In view of the persistence of the haemorrhagic tendency the blood clotting mechanism was investigated and the diagnosis of factor VII deficiency was established as described below.

After the establishment of the diagnosis an attempt was made to correct the deficiency by the administration of intravenous serum. Daily estimations of the thromboplastin time were performed but did not provide a satisfactory indicator of the efficacy of the treatment or of the amounts of serum required. Clinically, the bleeding appeared to be controlled by the administration of serum. On August 3, 1955, the patient died suddenly as a result of a fresh cerebral haemorrhage.

Post-mortem examination revealed a recent cerebral haemorrhage in addition to a large haemorrhagic cyst from a previous haemorrhage which occupied the whole of the left parietal lobe. Nothing of significance was found in the other organs.

Investigations

All the methods used are as described by Biggs and MacFarlane (1953). The bleeding time: (method of Ivy) was 1 minute. The clotting time (method of Lee and White) averaged 1 minute 45 seconds. Platelets numbered 400,000 per c.mm. (method of Kristensen, modified by Lempert), and appeared morphologically normal on stained smears.

Capillary resistance (tourniquet test) was normal. The thromboplastin time (single-stage 'prothrombin time') was performed on numerous occasions. It ranged from 3 minutes 55 seconds to 1 minute 5 seconds. Addition of 10% 'alumina plasma', i.e., normal plasma absorbed with aluminium hydroxide as described by Biggs and MacFarlane, did not result in any diminution of the thromboplastin time, but on the addition of 10% of normal serum, the time was reduced to normal (12 seconds).

The times recorded in a typical thromboplastin generation test are recorded in Table 1 and Fig. 1. A defect is clearly demonstrated in the patients' serum.

TABLE 1
THROMBOPLASTIN GENERATION TEST

Incubation Time (min.)	Patient's Alumina Plasma 1:5 Patient's Serum 1:0 Normal Platelets (sec.)	Patient's Alumina Plasma 1:5 Normal Serum 1:10 Normal Platelets (sec.)	Normal Alumina Plasma 1:5 Patient's Serum 1:10 Normal Platelets (sec.)
1	65	39	41.5
2	38	17.5	32.0
3	28	10.5	23.5
4	23	11.0	18.5
5	20	11.0	18.5
6	20	—	20.0

The test was performed as described by Biggs and MacFarlane (1953). 0.3 ml. amounts of each reagent were incubated together as the reaction mixture and 0.1 ml. transferred to 0.1 ml. normal citrated plasma. The clotting time of this substrate is given in seconds.

FIG. 1.—Results of thromboplastin generation tests. The composition of the incubation mixtures is as follows:

- 0.3 ml. 1:10 dilution of normal serum.
- 0.3 ml. 1:5 dilution of patient's alumina plasma.
- 0.3 Suspension of patient's platelets.
- 0.3 ml. dilution of patient's serum.
- 0.3 ml. 1:5 dilution of patient's alumina plasma.
- 0.3 ml. Suspension of patient's platelets.
- 0.3 ml. 1:10 dilution of patient's serum.
- 0.3 ml. 1:5 dilution of normal alumina plasma.
- 0.3 ml. Suspension of normal platelets.

The possibility of a thromboplastin inhibitor being present was considered. To exclude the presence of such a factor, the recalcification time of various mixtures of the patient's and normal plasma was determined before and after incubation for two hours at 37° C. The results are shown in Table 2.

TABLE 2
TEST FOR THROMBOPLASTIN INHIBITOR

	Tube (ml.)				
Normal citrated plasma	1.0	0.9	0.5	0.1	Nil
Patient's citrated plasma	Nil	0.1	0.5	0.9	1.0
Recalcification Time (sec.) of these Mixtures					
Before Incubation	175	110	94	100	146
After incubation at 37° C. for 2 hours	270	240	230	220	392

The prothrombin content of the patient's plasma was determined by the two-stage method (Biggs and Douglas, 1953), with comparison of the areas. The curves of the patient and a normal are shown in Fig. 2, and the area of the normal is 17 sq. cm.; of the abnormal 21 sq. cm.

FIG. 2.—Prothrombin content tests performed according to the 2-stage method of Biggs and Douglas (1953).

The effect of the patient's serum on the thromboplastin time of a patient under treatment with 'tromexan', whose thromboplastin time was 40 seconds, was tested by the addition of 10% of the patient's serum; the time of the mixture was 46 seconds.

The addition of a small amount (0.1% final concentration) of a preparation of factor VII (Biggs and MacFarlane, 1953) to the patient's plasma used in the thromboplastin time test completely corrected the defect.

The prothrombin consumption test was carried out as described by Merskey (1950). The plasma time was 50 seconds and the serum time 8 minutes, giving a prothrombin consumption index of 11%. This test was repeated after the addition of 10% of normal serum which had been incubated at 37° C. for two hours and aged at + 4° C. for 48 hours to ensure prothrombin

conversion and destruction of thrombin. The plasma time was in this case 19.5 seconds and the serum time 5 minutes, giving an index of 6.6%.

It is clear from the foregoing data, summarized in Table 3, that the patient's deficiency was one of factor VII.

It was found that the patient's own serum (after incubation for three hours at 37° C.) was to some extent efficacious in correcting the defective thromboplastin time. This anomaly was also noted by Crockett *et al.* (1949), Jenkins (1954) and de Vries *et al.* (1955, case 2) in their cases.

The addition of a very small amount of thrombin (Parke-Davis 'topical thrombin') to the single-stage thromboplastin time resulted in complete correction. After absorption of the thrombin solution with $Al(OH)_3$ there was no correction, suggesting that commercial thrombin may be contaminated with factor VII, a possibility supported by the work of Frick and Hagen (1953).

Spontaneous activation of the patient's plasma on standing was noted; and the thromboplastin time was longest when performed without delay. After two to three hours the time fell to about 65 seconds, about which level it then remained stable for some time.

Tests were carried out on the mother, father, paternal grandmother and grandfather, but no abnormality was found in any of these.

Discussion

Congenital factor VII deficiency is a rare condition; 10 of the 15 published cases have occurred in males. It seems very probable from the published cases that it is familial. In the present case the presumption is strong, although no tests were performed on the elder brother, that he suffered from a similar deficiency. Whether the fact that the parents are first cousins is of import is not known; neither shows any evidence of a factor VII deficiency, and there is no clear history of haemorrhagic diathesis in the family. The similarity of the case presented here with that described by Landwehr *et al.* (1950) is very striking. Both cases are the second children of first cousin marriages, and in both cases the previous child died of haemorrhage shortly after birth.

On the clinical side, manifestations of the haemorrhagic state became apparent at birth or very soon after in the majority of the published cases. Of the sites of haemorrhage, gastro-intestinal bleeding is reported in eight of 15 cases, haemarthroses in seven, epistaxes in six, haematuria and menorrhagia twice each and cerebral haemorrhage once. The prognosis would not seem to be duly bad from the

TABLE 3

SUMMARY OF LABORATORY FINDINGS ON RASHID

Bleeding time: Normal
 Coagulation time: (Lee and White) Normal
 Hess's Test: Normal
 Platelets: Normal quantitatively and morphologically
 Brain thromboplastin time (Quick's one-stage prothrombin time): Greatly prolonged, but corrected by addition of 10% normal serum
 Factor V (Biggs and MacFarlane's method): Normal
 Factor VII: (Biggs and MacFarlane's method): Greatly diminished
 Prothrombin content (Biggs and Douglas's method): Normal
 Thromboplastin generation test showed the presence of a defect in the patient's serum factors.

ADDITIONAL TESTS

Patient's Plasma	Normal Serum 1/10	Normal Alumina 1/10	Thrombin Topical (0.5 u/ml.) *	Thrombin Topical Absorbed with $Al(OH)_3$	Serum from Patient Treated with Tromexan†	Factor VII Preparation 1/10	Patient's Serum 1/10	Brain Thromboplastin Time (sec.)
0.1								65-234
0.09	0.01							12- 18
0.09		0.01						185-206
0.05			0.05					12- 13
0.05				0.05				50- 57
0.09					0.01			36
0.09						0.01		14- 16
0.09							0.01	32- 37

In each case 0.01 ml. brain and 0.1 ml. $\frac{M}{40}$ $CaCl_2$ solution added and the clotting time recorded.

* Clotted patient's plasma without brain and Ca in 80-100 sec.

† Thromboplastin time of 'tromexan' plasma 40 sec.

published cases: nine out of 15 were apparently still alive at the time of reporting and had survived to adult life, three had died. The remaining three were alive, but still in childhood.

Treatment can only be by serum, plasma or blood transfusion, logically the first. Correction of the abnormal thromboplastin time is found, but it seems (Beaumont and Bernard, 1953) to be extremely shortlived, only a matter of hours. Similar treatment, intravenous or intramuscular injections of normal serum, in the present case produced no lasting alteration of the abnormal laboratory tests, but appeared to have a beneficial effect on the duration of haemorrhage clinically.

The injection of synthetic vitamin K and K₁ preparation has been uniformly unsuccessful in the reported cases, and was tried in this case without any benefit either clinically or as shown by laboratory tests.

Summary

A case of congenital factor VII deficiency in an Indian child is described, with laboratory findings. The literature of these cases is reviewed, and the clinical features, prognosis, treatment and laboratory findings discussed.

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