CONGENITAL·FACTOR VII DEFICIENCY

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

BY

H. B. W. GREIG, H. C. FALCKE, M. SIMON and H. COHEN

From the Department of Haematology, South African Institute for Medical Research, and the Department of Paediatrics, Coronation Hospital, Johannesburg

(RECEIVED FOR PUBLICATION MARCH 5, 1956)

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 absorbants as prothrombin, i.e., BaSO₄, Al(OH)₃, Ca₃(PO₄)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 BaSO₄ 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 BaSO₄. These latter findings are difficult to reconcile with present concepts.
Owen 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. per cent. 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.
CONGENITAL FACTOR VII DEFICIENCY

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**

<table>
<thead>
<tr>
<th>Incubation Time (min.)</th>
<th>Patient's Alumina Plasma 1:5 Patient's Serum 1:10 Normal Platelets (sec.)</th>
<th>Patient's Alumina Plasma 1:5 Normal Serum 1:10 Normal Platelets (sec.)</th>
<th>Normal Alumina Plasma 1:5 Patient's Serum 1:10 Normal Platelets (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>39</td>
<td>41-5</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>17-5</td>
<td>32-0</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>10-5</td>
<td>23-5</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>11-0</td>
<td>18-5</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>11-0</td>
<td>20-0</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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.

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**

<table>
<thead>
<tr>
<th>Tube (ml.)</th>
<th>Normal citrated plasma</th>
<th>Patient's citrated plasma</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0</td>
<td>1-0</td>
<td>0-9</td>
<td>0-5</td>
</tr>
<tr>
<td>1:5</td>
<td>0-1</td>
<td>0-5</td>
<td>0-9</td>
</tr>
<tr>
<td>1:10</td>
<td>Nil</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

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.

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.

![Fig. 2.—Prothrombin content tests performed according to the 2-stage method of Biggs and Douglas (1953).](http://adc.bmj.com/.../10.1136/adc.31.8.295)
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 haemorr-
ragic 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 haemorr-
ragic 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**

<table>
<thead>
<tr>
<th>Patient's Plasma</th>
<th>Normal Serum 1/10</th>
<th>Normal Alumina 1/10</th>
<th>Thrombin Topical (0·5 μ/ml)</th>
<th>Thrombin Topical Absorbed with Al(OH)₃</th>
<th>Serum from Patient Treated with Tromexan†</th>
<th>Factor VII Preparation 1/10</th>
<th>Patient's Serum 1/10</th>
<th>Brain Thromboplastin Time (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·09</td>
<td>0·01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·09</td>
<td></td>
<td>0·01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·05</td>
<td></td>
<td></td>
<td>0·05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·05</td>
<td></td>
<td></td>
<td></td>
<td>0·05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In each case 0·01 ml. brain and 0·1 ml. M CaCl₂ 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 K$_1$ 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.

REFERENCES


Congenital Factor VII Deficiency: A Review with a Report of a Case in an Indian Infant


Arch Dis Child 1956 31: 293-297
doi: 10.1136/adc.31.158.293

Updated information and services can be found at:
http://adc.bmj.com/content/31/158/293.citation

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/