CONGENITAL FACTOR V DEFICIENCY—REPORT OF A CASE

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In 1947 Owren described a patient whose blood had a long one stage prothrombin time which was restored to normal by the addition of plasma from which the prothrombin had been removed. Owren named the condition "parahemophilia", Owren (1947), and the substance lacking from this patient's blood "Factor V" also known as "proaccelerin" Owren (1950). Since then other reports, Stohlman et al (1951); Brink and Kingsley (1952); Alexander and Goldstein (1952); Lewis and Ferguson (1955); Sacks and Raccuglia (1955); O'Brien (1958), have appeared on the same condition, a number of which have been summarised by Biggs and Macfarlane (1962).

The defect is an extremely rare disorder. It may be familial and affects either sex. Clinically they present with a history of a tendency to bleed easily. Epistaxis, bruising, and menorrhagia are some of the common features. The condition is diagnosed by the prolonged one-stage prothrombin time using either brain extract or Russell's Viper Venom as thromboplastin. The long one stage prothrombin time is restored towards normal by the addition of normal adsorbed plasma but not by normal serum.

Because of the rarity of the disease this case is being reported. At the same time studies made on the fate of Factor V in fresh plasma transfused into the patient are recorded.

CASE HISTORY

The patient, T.S.G. an eleven year old school girl, first presented in 1961 with a history of recurrent episodes of spontaneous bleeding from the gums since the age of 4. In addition, she had prolonged and excessive bleeding from tooth sockets following dental extractions. She also has a tendency to bleed and bruise easily following minimal trauma and has had several episodes of epistaxis. She has never had a hemarthroses or bleeding from any of the other systems of the body. She is the eldest in the family with three brothers and three sisters, all of whom are well and healthy with no history suggestive of a bleeding tendency. There is no history of consanquinous marriage in her parents, both of whom are well with no haemorrhagic symptoms.

A detailed inquiry did not reveal any history suggestive of a haemorrhagic diathesis among any of the relatives of both the parents.

Patient had been labelled as a case of "hypoprothrombinemia of unknown etiology" because of the persistently prolonged clotting times with Russell's Viper Venom ranging from 28 to 55 seconds. She has been treated with large doses of Vitamin K with no beneficial effect on the bleeding or prolonged clotting times. She has never received any blood or plasma transfusion for the bleeding.

On clinical examination, the only significant findings were a few small generalised ecchymosis and a marked gingivitis with very carious teeth. No abnormalities referable to any of the other systems were found. There was no hepato splenomegaly or lymphadenopathy. There were no congenital defects.

LABORATORY INVESTIGATIONS

METHODS

The methods used in general were those recommended by Dacie and Lewis (1962) and Biggs and Macfarlane (1962).

Two tests, the estimation of prothrombin time by the Quick One-Stage method and the thromboplastin generation test are used to a great extent in the investigation of this case and it might be useful at this stage to mention the principles underlying the tests.

ESTIMATION OF PROTHROMBIN TIME BY QUICK ONE STAGE METHOD

A potent preparation of human brain emulsion is added to citrated plasma. The mixture is then recalcified and the clotting time estimated.

Introduced originally as a test of prothrombin activity—hence the name, the test is now known to measure in addition and more importantly, Factors V, VII and X. There are many modifications of this test, one of which, the substitution of the brain emulsion with Russell's Viper Venom as a source of thromboplastin, has been used in some of the investigations of the case.

THROMBOPLASTIN GENERATION TEST

In this test three reagents, adsorbed plasma containing Factors V and VIII; serum, containing Factors VII, IX and X, and platelets are prepared separately and then recombined in the presence of calcium. The mixture is then tested for thromboplastin production by taking sub samples from the mixture at one minute intervals and adding to tubes containing prothrombin and fibrinogen. The clotting times of the second mixture are then noted as an index of thromboplastin formation.

By interchanging the source of the reagents, between the patient and a normal control, presumptive evidence of the coagulation component which is defective may be obtained.

INVESTIGATION

Preliminary screening tests gave the following results:—Haemoglobin 13.3 gm.%. Platelet count 250,000/c.mm. Peripheral blood picture and platelet morphology was normal. Whole blood coagulation time (Lee and White at 37°C) 5 mins. Bleeding Time (Ivy's Method) 2 mins. Prothrombin Time (Russell's Viper Venom) 27-38 seconds, normal control 14 seconds. Tourniquet Test (Hess's) negative. Clot retraction normal. Fibrinogen 180 mgm%. Liver function tests gave uniformly normal results.

It will be seen from the above that the only abnormal finding was a prolonged prothrombin time. The whole blood coagulation time and bleeding times were always within normal limits on a number of occasions.

PROTHROMBIN TIME STUDIES

Tables I-V show the detailed prothrombin time studies making use of various reagents. The results shown are the average values of tests carried out in triplicate.

TABLE I: The patient's prothrombin time using an extract of rabbit brain (Difco) as a source of thromboplastin, was always prolonged to between 22-26 seconds. The same results were obtained when human brain thromboplastin (Stayne) and Russell's Viper Venom were substituted for rabbit brain.

TABLE II: The prolonged times were shortened to almost normal values by the addition of 20% normal adsorbed plasma (as a source of Factor V). Addition of 20% normal serum failed to shorten the prolonged time, showing that there is no deficiency of serum factors.

TABLE III: Aged plasma is deficient in Factor V and has a prolonged prothrombin time. Addition of 20% normal plasma restored the prolonged prothrombin time of aged plasma to almost normal values, but addition of the patient's plasma failed to do so. This is presumptive evidence that the deficiency in aged plasma and the patient's plasma are similar.

TABLE IV: Plasma from patients on anticoagulant therapy is deficient in prothrombin, Factors VII, IX and X. Patient's plasma was found to be as effective as normal plasma in shortening the lengthened one stage prothrombin time of plasma from a patient on dicoumarol therapy showing that the patient's plasma does not lack any of the factors reduced by anticoagulant therapy.

TABLE V: Aluminium hydroxide adsorbed haemophilic plasma contains Factor V only. Addition of 20% of this plasma to the patient's plasma resulted in the return of the prolonged prothrombin time to normal values confirming that the patient's plasma is deficient in Factor V.

The above studies were carried out in parallel using both human brain extract and Russell's Viper Venom. The results obtained with Russell's Viper Venom were very similar to that using brain extract.

THROMBOPLASTIN GENERATION TEST STUDIES

Table VI shows the details of the thromboplastin generation test studies.

It will be seen that slightly prolonged clotting times were obtained when using patient's adsorbed plasma and normal platelets as a source of phospholipid (Expt. 2). The clotting times were made more prolonged when a combination of patient's adsorbed plasma and patient's own platelets were used (Expt. 3). The

TABLE I

ONE STAGE PROTHROMBIN TIME

	CLOTTING TIME (SECS.)	
	Brain Ext.	**Russell's Viper Venom**
Normal Plasma - - -	12	14
Patient's Plasma - - -	22	34

TABLE II

EFFECT OF NORMAL PLASMA & SERUM ON PATIENT'S PLASMA

	CLOTTING TIME (SECS.)	
	Brain Ext.	**Russell's Viper Venom**
Patient's Plasma - - -	22	34
Patient's Plasma + 20% N. Ad. Plasma	14	17
Patient's Plasma + 20% N. Serum -	22	34

TABLE III

EFFECT OF NORMAL & PATIENT'S PLASMA ON AGED PLASMA

	CLOTTING TIME (SECS.)	
	Brain Ext.	**Russell's Viper Venom**
Aged Plasma (Factor V Deficient) -	55	58
Aged Plasma + 20% N. Ad. Plasma -	19	20
Aged Plasma + 20% Patient's Ad. Plasma - - -	55	58

TABLE IV

EFFECT OF NORMAL & PATIENT'S PLASMA ON DICOUMAROL TREATED PLASMA

	CLOTTING TIME (SECS.)	
	Brain Ext.	**Russell's Viper Venom**
Dicoumarol Treated Plasma - -	26	30
Dicoumarol Plasma + 20% N. Plasma	13	15
Dicoumarol Plasma + 20% Patient's Plasma - - -	13	15

TABLE V

EFFECT OF HAEMOPHILIC PLASMA ON PATIENT'S PLASMA CLOTTING TIME (SECS.)

	Brain Ext.	Russell's Viper Venom
Patient's Plasma - - -	22	34
Patient's Plasma + 20% Ad. Haemophilic Plasma - -	12	15

TABLE VI

THROMBOPLASTIN GENERATION STUDIES

Mixture of Reagents	Incubation time at 37°C. (minutes)					
	1	2	3	4	5	6
	CLOTTING TIME SECONDS					
Expt. 1: Normal Ad. Plasma - - Normal Serum Normal Platelets	30	13	12	12	11	11
Expt. 2: Patient's Ad. Plasma - - Normal Serum Normal Platelets	45	24	20	20	21	17
Expt. 3: Patient's Ad. Plasma - - Normal Serum Patient's Platelets	35	30	25	23	22	20
Expt. 4: Normal Ad. Plasma - - Patient's serum Normal Platelets	35	17	17	14	11	11
Expt. 5: Normal Ad. Plasma - - Normal Serum Patient's Platelets	30	11	11	11	11	11
CORRECTION TESTS						
Expt. 6: Patient's Ad. Plasma - - +20% normal Ad. Plasma	32	24	18	13	12	11
Expt. 7: Patient's Ad. Plasma - - + 20% Haemophilic Ad. Plasma	35	22	20	13	12	12

TABLE VII

INVESTIGATIONS OF PARENTS

	Father	Mother
Prothrombin Time (Brain ext.) - -	13 secs.	12 secs.
Prothrombin Time (R.V.V.) - -	14 secs.	14 secs.
Bleeding Time (Ivy) - -	3 mins.	2 mins.
Coagulation Time (Lee & White) - -	7 mins.	6½ mins.
Thromboplastin generation test - -	Normal	Normal
Assay of Factor V Activity (% of normal)	100%	110%

prolonged times were equally corrected by the addition of 20% normal adsorbed plasma (Expt. 6) and 20% haemophilic adsorbed plasma (Expt. 7). No defect was demonstrated in the patient's serum (Expt. 4) or platelet (Expt. 5).

FACTOR V CONTENT

An Assay of the factor V activity of patient's plasma was carried out using the method described in another report (192) The assay made on a number of separate occasions always showed a Factor V level of between 10-15% of normal with a mean of 12.5%. The normal range found in 41 normal blood donors was between 75%-216% with a mean of 132%.

FAMILY STUDIES

It was not possible to carry out the full family studies as the parents strongly objected to blood being taken from their children. However, it was possible to carry out some studies on both parents, all of which gave normal results.

THE EFFECT OF FRESH PLASMA TRANSFUSION

The clot promoting effect in parahaemophilia of fresh normal blood or plasma was clearly shown in Owren's original case and in studies carried out by Brink and Kingsley (1952), Alexander and Goldstein (1952). Studies on the Factor V level following transfusions of fresh frozen plasma were made on the patient

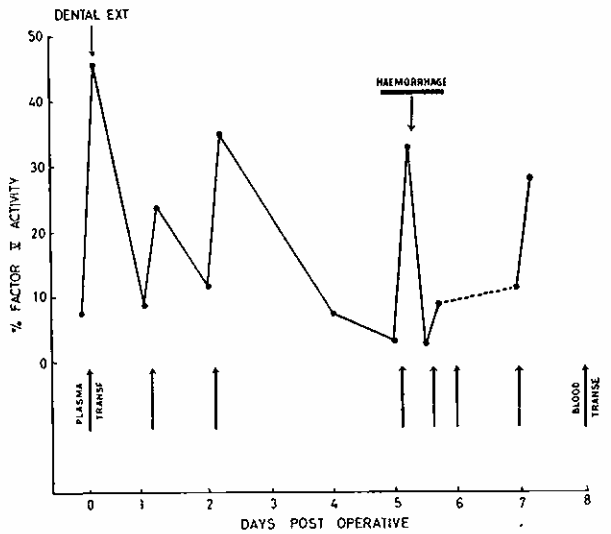

Fig. 1. Factor V levels in the patient following transfusions of fresh frozen plasma.

who had to undergo dental extraction for carious teeth. Prior to the extraction special acrylic dental splints were made.

On the morning of the operation the patient was given a transfusion of fresh frozen citrated plasma, 10 ml./kg. body weight, total volume 350 ml. rapidly over 1½ hours. The Factor V levels immediately before and after the transfusion were assayed. This showed levels at 7.5% and 45.5% respectively (Fig. 1).

Thereafter the patient was submitted to the dental extraction. Three adjoining teeth were extracted under general anaesthesia, one from the upper and two from the lower jaw. Gelatine sponge soaked in thrombin solution was placed in the tooth sockets and the dental splints applied in position. There was no undue bleeding during the extraction.

24 hours after the dental extraction the Factor V level had fallen to 8.7% and this was raised to 23.5% following a second transfusion of fresh frozen plasma.

On the 2nd. postoperative day, the Factor V level was 11.2% and this was raised to 35.0% following a 3rd transfusion.

There had been no bleeding from the sockets during the past 48 hours.

No transfusion was given on the 3rd and 4th postoperative days as haemostasis was well maintained. The Factor V level on the 4th day was 7.2%.

On the 5th postoperative day, patient began bleeding and the level of Factor V at this stage was 3.0%, the lowest ever recorded.

Patient was given a 4th transfusion of fresh plasma and this raised the Factor V level to 33.0% with some slight improvement in the bleeding. However, 12 hours later with persistent bleeding, the level had again fallen to 3.0% and a further (5th) transfusion of fresh plasma was given raising the level to 9.0% only.

The following morning patient received a further transfusion of fresh plasma (6th) but no Factor V assays were made due to inability to obtain sufficient blood.

On the 7th postoperative day, the level of Factor V was 11.5% and then following a further transfusion of fresh plasma patient had the dental splints removed.

Thereafter the convalescence was uneventful. Patient received a transfusion of whole blood

on the 8th postoperative to correct an anaemia of 7.69 gm.% (her pre-operative haemoglobin level was 13.17 gm.%).

Patient was discharged on the 10th post-operative day with a well healed wound and a haemoglobin level of 11.84 gm.%.

DISCUSSION

It is now accepted that parahaemophilia is due to a congenital deficiency of a single coagulation factor—Factor V, which is the same thing as Quick's labile factor and Seeqer's ac-globulin, Alexander and Goldstein (1952). Clinically the degree of disability varies, the case appears not unlike mild haemophilia and other related conditions, although hemarthrosis is said to be uncommon, Wintrobe (1961), Ratnoff (1960). Menorrhagia is fairly common in females, Brink and Kingsley (1952) some of whom have bled to death at their first menstrual period. Factor V deficiency has occasionally been described in association with other deficiencies, like combined deficiencies of Factors V and VIII, Iversen and Bastrup-Madsen (1956); Seibert, Margolius and Ratnoff (1958).

An acquired defect Factor V deficiency may be associated with the defibrination syndrome, with advanced carcinomatosis, particularly of the colon, and with haemorrhagic scarlet fever, Biggs and Macfarlane (1962). It has also been described in cases of liver poisoning, advanced liver disease, Alexander and Goldstein (1950) and leukaemia.

The distinguishing feature of Factor V deficiency from heamophilia and Christmas Disease is the prolonged one stage prothrombin time. However, the prolonged prothrombin time would include in it the group of disorders known as the hypoprothrombinemias, which term includes such conditions as prothrombin, Factors VII and X deficiency. Other conditions which could give rise to a prolonged prothrombin time are fibrinogen deficiency and circulating anticoagulants or inhibitors.

Fibrinogen deficiency has been excluded by direct chemical quantitation of the substance in the plasma. The presence of circulating inhibitors has been excluded by the fact that addition of 20% normal plasma to patient's plasma could return the prolonged prothrombin time to normal values.

Deficiency of prothrombin and factor VII has also been excluded by the fact that addition of adsorbed normal plasma, which is devoid of prothrombin and factor VII, could correct the prolonged prothrombin time, thus strongly suggesting a defect not based on prothrombin or factor VII deficiency. Furthermore factor VII deficiency will result in a prolonged prothrombin time with brain extract only, whereas factor V deficiency is reflected in prolonged times with both brain extract and Russell's Viper Venom, Rapport, Aas and Owren (1954). Further, failure of correction of the patient's defect by addition of stored normal plasma excludes Factor VII deficiency.

The laboratory tests carried out show that the factor deficient in the patient's plasma appears to be identical in its behaviour with Factor V. Unlike most of the cases described, Biggs and Macfarlane (1962), the coagulation time in this patient was always within normal limits. This is not of great significance as the whole blood coagulation time test is a relatively insensitive non specific test and the coagulation mechanism may be grossly impaired without necessarily raising the coagulation time above the normal range.

Another point of interest is the observation that the minimum times obtained with the patient's adsorbed plasma and patient's own platelets in the thromboplastin generation test (Expt. 3), are much more prolonged than when using patients adsorbed plasma and platelets from a normal donor. (Expt. 2). This does seem to suggest that normal platelets exhibit some Factor V activity, an observation agreeing with those made by Hjort, Rapaport and Owren (1955) and O'Brien (1958).

The presence of symptoms from a young age and the lack of evidence of coexisting disease indicates that the deficiency in this patient is probably congenital. None of the liver function tests showed a deviation from normal and it could be presumed that liver disease was not responsible for the prolonged prothrombin time. It is also interesting to note that doses of Vitamin K failed to correct the prothrombin time or control the bleeding.

Congenital Factor V deficiency has been observed in both sexes. Its mode of inheritance appears to be that of an autosomal recessive. In some instances, parents or children of an affected patient have had partial deficiencies of Factor V, Wintrobe (196M1), acfarlane and Biggs (1962).

In this instance it is also interesting to note that both parents were normal with no haemorrhagic symptoms. Factor V activity was normal in both of them. It was unfortunate that the siblings could not be examined, but a detailed inquiry from the parents did not reveal any symptom suggestive of a defect in any of the 6 siblings. Macfarlane and Biggs (1962) state that in some instances all other members of the family are normal.

In the studies on Factor V activity made following transfusions of fresh frozen plasma it will be seen that with a single exception, each transfusion of fresh plasma was able to raise the Factor V level from about 10% to between 25% to 45%. The single exception was with the 5th transfusion when for some unexplained reason the level was raised from 3% pretransfusion to 9% posttransfusion. It is possible that the presence of haemorrhage meant a rapid utilization of Factor V thus preventing the build up of high Factor V levels. However, Brink and Kingsley (1952) found that the rate of disappearance of the deficient factor, when supplied by transfusion, was independent of the presence of haemorrhage.

Other points of note are that even in the absence of haemorrhage there is a rapid utilization of Factor V so that 24 hours after a transfusion the Factor V activity was down to the pretransfusion level. In similar studies, Fantl (1957) found a half-life of approximately 20 hours.

Further, during the first few postoperative days hemostasis was well maintained with no bleeding with Factor V levels of as low as 7.5%. When bleeding occurred on the 5th postoperative day, the Factor V level was 3%. This low level was recorded twice during the bleeding episode suggesting that the levels were insufficient to maintain hemostasis. It would therefore appear that the critical level was in the region of 5% below which bleeding was likely to occur. This level appears to be lower than that found by Fantl (1957) when he stated that abnormal haemorrhage was likely if the factor level is less than 30% of normal.

SUMMARY

An isolated case of congenital Factor V deficiency has been studied and the findings of previous workers confirmed. This is the first case of Factor V Deficiency described in Singapore and probably also the first to be recorded in Asia. The laboratory findings are similar to cases described by workers in earlier reports. The level of Factor V in the body following transfusions of frozen plasma have been studied. Our experience confirms the observations that minor surgery can be undertaken in these cases if an adequate supply of fresh frozen plasma or blood is available.

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REFERENCES

1. Alexander B. and Goldstein, R. (1952): "Parahaemophilia in three siblings (Owren's Disease)". Amer. J. Med., 13, 255.
2. Alexander, B. and Goldstein, R. (1950): "Coagulation defect with hepatic disorders: deficiency of prothrombin conversion accessory substance". J. Clin. Investigation, 29, 795.
3. Biggs, R. and Macfarlane, R.G. (1962): "Human blood coagulation and its disorders". 3rd Edn. Blackwells Scientific Publications, Oxford.
4. Brink, A.J. and Kingsley, C.S. (1952): "A Familial disorder of blood coagulation due to deficiency of the labile factor". Quart. J. Med., 21, 19.
5. Dacie, J.V. and Lewis, S.M. (1963): "Practical Hematology" 3rd Edn. J. & A. Churchill Ltd., London.
6. Fantl, P. (1957): "Parahaemophilia (Proaccelerin Deficiency) Occurrence and Biochemistry" in Haemophilia and Haemophiloid Diseases. Chapel Hill, 19, 79.
7. Hjort, P., Rapaport, S.I. and Owren, P.A. (1955): "Evidence that platelet accelerator (platelet factor I) in adsorbed plasma proaccelerin" Blood, 10, 1139.
8. Iversen, T. and Batrup-Madsen, P. (1956): "Congenital familial deficiency of factor V (parahemiphilia) combined with deficiency of antihemophilic globulin." Brit. J. Haemat., 2, 265.
9. Lewis, J.H. and Ferguson, J.H. (1955): "Hypoproaccelerinemia" Blood, 10, 351.
10. O'Brien, J.R. (1958): "Factor V in blood coagulation in vitro and a report of a case of Factor V deficiency." Brit. J. Haemat., 4, 210.
11. Owren, P.A. (1947): "Investigation of a new clotting factor". Acta Med. Scand., Suppl. 194.
12. Owren, P.A. (1950): "The prothrombin activating complex and its clinical significance." Proc. 3rd Int. Congr., Int. Soc. Haemat., Cambridge, Groinc & Stratton. New York. pg. 379.
13. Ratnoff, O.D. (1960): "Bleeding Syndromes" Charles C. Thomas, Springfield, Illinois.
14. Rapaport, S.I., Aas, K. and Owren P.A. (1954) "The clotting reaction of Russel's Viper Venom". Blood 9, 1185.

15. Sacks, M.S. and Raccuglia, G. (1955): "Hereditary deficiency of proaccelerin (parahemophilia) a family study." J. Lab. Clin. Med., 46, 89.

16. Seibert, R.H., Margolins, A. and Ratnoff, O.D. (1958) "Observations on Hemophilia, parahemophilia and coexistent hemophilia and parahemophilia. Alterations in the platelets and thromboplastin generation test." J. Lab. Clin. Med., 52, 449.

17. Stohlman, F., Harrington, W.J. and Moloney, W.C. (1951) "Parahemophilia (Owren's Disease). Report of a case of a woman with studies on other members of her family." J. Lab. Clin. Med., 38, 842.

18. Wintrobe, M.M. (1961) "Clinical Hematology" 5th Edn. Henry Kimpton. London.