Congenital Hypoproconvertinemia
A Report on 12 Cases with Total Deficiency and 19 Cases with Partial Deficiency

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Proconvertin (factor VII) takes part only in the extrinsic blood clotting system, i. e. clotting in the presence of tissue thromboplastin (Bergsagel [1955]; Hicks [1955]; Ackroyd [1956]; Waaler [1957]). According to Aas (1952) and Hjort (1957) proconvertin, tissue thromboplastin and calcium react together quantitatively, to form an active complex termed convertin. Recent discoveries indicate that this complex must also contain the Stuart-Prower factor. Convertin and accelerin form the final prothrombin converting principle in the extrinsic system, extrinsic prothrombinase (Hjort [1957]).

The first verified case of congenital proconvertin deficiency was published by Alexander et al. in 1951. Since then more than 50 patients with suggested proconvertin deficiency have been described. However, two years ago a hemorrhagic diathesis due to lack of the Stuart-Prower factor was described (Telfer et al. [1956]; Hougie et al. [1957]; Bachmann et al. [1957a]), and some of the previously reported "proconvertin" deficiencies have since been found to be deficiencies in this new factor. The two factors are rather similar in physico-chemical properties, but the Stuart-Prower factor acts both in the intrinsic and extrinsic blood clotting systems (Hougie et al. [1957]; Bachmann et al. [1957a]).

We have reinvestigated the two patients with proconvertin deficiency previously described by Aas (1952) and by Owren (1952; 1953). In addition this report describes 10 new cases with total deficiency and 19 patients with partial deficiency of proconvertin. We have not yet found a case of Stuart-Prower factor deficiency.

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Materials and Methods

Materials

Activated human serum. Whole blood was allowed to clot for 2 hours at 37° C, and then centrifuged for 15 minutes at 3,000 rpm (maximal g about 1,800). Glasswool was then added to the separated serum, and the mixture kept at room temperature for 30 minutes. After removal of the glasswool the serum was kept in ice-waer until used.

Barium sulphate adsorbed and dialyzed bovine plasma was prepared as earlier described (Waaler [1957]).

Barium sulphate adsorbed normal human plasma was prepared in the same way, but was not dialyzed. It was freshly prepared for each test.

Cephalin was prepared according to Hjort et al. (1955).

Dowex plasma was prepared by cation exchange with Dowex 50, 20—50 mesh (Serva, Heidelberg, Germany) (Hjort [1957]).

Platelet suspension was freshly prepared for each test from blood taken with 1/10 its volume of a 2.25 per cent solution (w/v) of EDTA (Komplexon III, B. Siegfried, Zofingen, Switzerland) and with silicone technic. The platelets were washed three times in saline containing 0.2 per cent Triton, and finally resuspended in 1/4 the plasma volume of normal saline. The suspension was frozen and thawed twice, and kept in ice-water until the start of the test.

Proconvertin-deficient plasma. Blood was taken with citrate (1/10 the blood volume of 3.1 per cent (w/v) of sodium citrate dihydrate) and perfect silicone technic from our first patient with congenital proconvertin deficiency (Am. M.). It was centrifuged for one hour at 30 000 rpm (maximal g about 80 000) and stored in siliconized stoppered tubes at — 20° C.

„Proconvertin reagent" was made from serum as described by Hjort (1957). It also contained Stuart-Prower factor and antihemophilic B factor.

Russell's viper venom in cephalin was prepared according to Hjort et al. (1955), but the crude cephalin was used in a 1 : 100 dilution, which was found to be optimal in the prothrombin assay.

Silicone. Glassware was siliconized twice with a 10 per cent solution of "siloxan" (Uddeholm, Sweden) in ethyl ether.

Stuart-Prower factor deficient plasma was kindly sent us (lypophilized) by Dr. J. Roos, Geneeskundige Universiteitskliniek, Utrecht, Holland.

Test plasmas were prepared from citrated blood (see proconvertin deficient plasma) taken with silicone technic, by centrifugation for 30 minutes at 2 500 rpm (maximal g about 1260). Some blood samples were sent to the laboratory in siliconized tubes by mail, and they were then tested the day after withdrawal. The results from such samples were very similar to those from freshly drawn blood specimens.

Methods

Antihemophilic B factor was estimated as described by Stapp (1958).

Bleeding time. The primary and secondary bleeding time were determined as described by Borchgrevink and Waaler (1958).

Cephalin time was performed as described earlier (Waaler 1957).

Clot retraction was measured by the method of Benthaus (1957), using test tubes with cm graduations, 1 cm being equal to 1 ml. The total content of the tubes amounted to 10 ml (10 cm), and the retraction has been expressed both in cm and in the amount of serum released.

PP estimations were done with the method described by Owren and Aas (1951).

Proaccelerin was estimated by a method using congenital proaccelerin-deficient plasma as substrate.

Proconvertin was estimated by a similar method, using congenital proconvertin-deficient plasma a substrate (Aas 1952).

Prothrombin was estimated both by the original method described by Hjort et al. (1955) and by a slightly modified method. The original method is sensitive to Stuart-Prower factor (Hougie 1956) as well, whereas the modified method is probably specific for prothrombin. In the modified method a mixture of 9 parts of $CaCl_2$ solution and one part of "proconvertin reagent" from normal serum (containing Stuart-Prower factor) is used for recalcification, instead of pure $CaCl_2$ solution.

Prothrombin consumption. Several 0.9 ml samples of whole blood were stored at 37° C. At varying intervals 0.1 ml of a 3.1 per cent sodium citrate dihydrate solution was added to one of the tubes, and the residual prothrombin in its serum was estimated by the specific prothrombin method.

Thromboplastin generation test was performed as described by Biggs and Douglas (1953), with the slight modifications that activated serum and the platelet suspension (frozen-thawed) from EDTA plasma were used.

Thromboplastin time (Quick time). Human brain thromboplastin was used instead of rabbit brain thromboplastin.

Whole blood clotting time was measured by a modification (Hjort and Stormorken 1957) of the original method of Lee and White (1913).

Results

Forty members of 9 different families in which proconvertin deficiency had been discovered were investigated. Twelve persons had a total (less than 3 per cent) deficiency and 19 had a partial deficiency of this factor. Table 1 shows the results of various clotting investigations in the individuals with deficiencies. Family members with normal proconvertin levels (75 to 125 per cent) are not listed in the table.

Cephalin time and proaccelerin content are not listed, since all values were within the normal range.

Only the 12 patients with total deficiency had any history of hemorrhagic tendency. None of the persons with partial deficiency had experienced any abnormal bleeding tendency. The types of bleeding episodes in the totally deficient patients and the age at the time of the first pathological hemorrhage are listed in Table 2. Epistaxis, bleeding after tooth extraction, and development of ecchymosis on slight trauma were the most common bleeding manifestations. Some of the females had prolonged menstrual bleeding and 8 of the patients had had one or more probable joint hemorrhages. Only 2 or 3 patients had had repeated bleeding into joints. Marked ankylosis was not observed in any of the patients. One patient with hypertension had had a cerebrovascular accident and many of her relatives had died from stroke.

Some of the family trees are shown in Figs. 1 and 2.

Tab. 1: Findings in laboratory clotting tests in patients with total or partial proconvertin deficiency.

	Age	Sex	Clotting factors per cent of normal				PP-value, per cent	Thrombo-plastin time, seconds
			Pro-convertin	Prothrombin		Anti-hemophilic B factor		
				I	II			
Normal range			75—125	75—125		75—125	75—125	12—14
Family I.								
K., E.	45	f	45	115	112	110	68	16.0
K., T.	15	m	37	105	102	85	65	15.5
K., S.	10	f	<3	95	102	80	5	59.6
Family II.								
E., M.	62	f	32	92	95	78	68	16.7
K., El.	34	f	<3	95	95	150	8	84.8
S., T.	28	f	35	100	100	60	60	14.8
E., H.	20	f	64	87	90	115	62	15.2
Family III.								
M., K.	56	m	42	100	100	70	55	15.6
L., L.	55	f	55	92	92	150	55	14.3
M., An.	52	m	60	90	90	95	60	14.0
M., R.	47	f	40	100	100	80	75	15.1
M., Am.	44	m	<3	125	125	95	12	81.1
M., P.	43	m	<3	95	95	75	6	66.0
M., O.	41	m	60	85			89	16.3
Family IV.								
S., B.	56	f	<3	95	95	95	8	56.2
D., J.	52	f	<3	105	105	102	10	45.5
Family V.								
U., R.	63	m	40	105	105	70	60	13.8
U., H.	41	f	35	105	105	90	55	14.2
U., Mag.	26	m	<3	78	78	85	7	61.2
U., Mal.	23	m	<3	88	88	90	7	68.5
U., E.	18	m	32	80	80	80	45	15.2
U., T.	12	m	61	96				79.0
Family VI.								
H., K.	65	f	3.5	98	98	83	20	70.8
H., T.	37	m	37	75	75	76	60	16.1
H., J.	34	m	25	104			45	17.1
H., F.	23	m	35	78	78	80	55	18.8
Family VII.								
N., B.	29	f	<3	90	90	95	22	45.6
Family VIII.								
T., I.		f	47				65	
T., T.	11	f	<3	112			7	78.7
T., E.	9	m	40				53	
Family IX.								
J., P.	15	m	<3	85	85	80	8	77.7

Tab. 2: Hemorrhagic histories in the 12 patients with total proconvertin deficiency.

Name	Sex	Age at first bleeding episode (years)	Types of bleeding observed
K., S.	f	4	Epistaxis, bleeding after tooth-extraction, circumarticular bleeding
K., El.	f	20	Bleeding after tooth-extraction, menorrhagia, ecchymosis
M., Am.	m	early childhood	Epistaxis, ecchymosis, joint hemorrhage (after trauma)
M., P.	m	childhood	Epistaxis, bleeding after tooth-extraction, joint hemorrhages (?)
S., B.	f	childhood	Epistaxis, bleeding after tooth-extraction, joint hemorrhages
D., J.	f	early childhood	Epistaxis, menorrhagia, ecchymosis, joint hemorrhages, cerebrovascular accident
U., Mag.	m	childhood	Epistaxis, ecchymosis, joint hemorrhages
U., Mal.	m		
H., K.	f	(?)	Epistaxis, bleeding after tooth-extraction, joint hemorrhages, ecchymosis
N., B.	f	2½	Ecchymosis, circumarticular bleeding
T., T.	f	2	Epistaxis, bleeding after tooth-extraction, ecchymosis, joint hemorrhages
J., P.	m	14	Joint hemorrhages (after trauma)

Plasma from one particular patient was used as substrate in all proconvertin assays. These tests can thus be considered as cross-matching experiments. The substrate plasma (from patient Am. M.) was also cross-matched against a plasma with a known deficiency in Stuart-Prower factor (Table 3). The two plasmas normalized one another almost completely and must thus represent different deficiencies. The normalizing effect of the Stuart-Prower factor deficient plasma on the proconvertin deficient plasma was slightly poorer than that seen with

normal plasma. The lyophilization of the Stuart-Prower plasma may account for this.

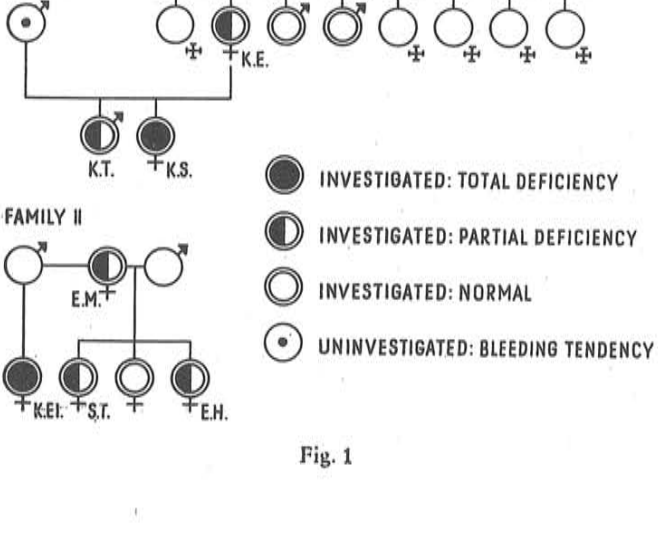

Fig. 1

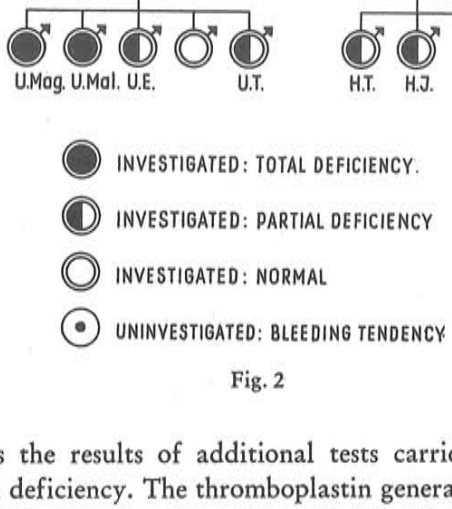

Fig. 2

Table 4 shows the results of additional tests carried out on some of the patients with total deficiency. The thromboplastin generation test, the prothrombin consumption test and the clot retraction test all had completely normal

Tab. 3: Mixing experiments using proconvertin deficient plasma (M., Am.) and Stuart-Prower factor deficient plasma.

	Cephalin time in seconds
Stuart-Prower factor deficient plasma	253
Stuart-Prower factor deficient plasma + proconvertin deficient plasma (diluted 1 : 10)	118
Stuart-Prower factor deficient plasma + normal plasma (diluted 1 : 10)	108
	Thromboplastin time in seconds
Proconvertin-deficient plasma	80.5
Proconvertin-deficient plasma + Stuart-Prower factor deficient plasma (diluted 1 : 10)	20.5
Proconvertin-deficient plasma + normal plasma (diluted 1 : 10)	14.8

Tab. 4: Additional tests in some patients with total proconvertin deficiency. Patient K., S.: Thromboplastin generation test: normal result (10.2 sec. after 4 min.) Prothrombin consumption test: normal result (Residual prothrombin in serum 11 per cent after 2 hours)

Bleeding time:

Patient	Primary (normal range: ♂ < 10 min., ♀ < 11 min.)	Secondary (normal range: < 6 min.)
K., S.	13.5 min.	6 min.
K., El.	4.5 min.	5 min
M., Am.	6.5 min.	5.5 min.
J., P.	7.5 min.	

Whole blood clotting time (normal: < 5 min.):

Patient	
K., S.	4.5 min.
M., Am.	4 min.
J., P.	3 min.

Clot retraction test:

Patient	cm retraction (normal: > 6.5)	Amount of serum in ml (normal: > 9.5 ml)
K., S.	8.1	9.9
M., Am.	7.2	9.8

values in the patients investigated. Bleeding time was found to be normal in 3 patients and slightly prolonged in one (S. K.). The reason for this last finding could not be determined. Neither the tourniquet test, capillary microscopy, test for platelet adhesivity (Hellem 1958), clot retraction test, nor microscopic examination of platelet morphology revealed any abnormality.

Discussion

In his review of 1956 Ackroyd considered the data for 38 previously reported cases of "hypoproconvertinemia" and concluded that the group was heterogeneous. Following the description of Stuart-Prower factor deficiency (Telfer et al. 1956; Graham et al. 1956; Hougie et al. 1957; Bachmann et al. 1957a) it became clear that some cases which had been described as "hypoproconvertinemia" might have been deficiencies in this new factor, as pointed out by Hougie et al. (1957). The patient Stuart, investigated by them, had previously been considered by Lewis et al. (1953) to have a congenital proconvertin deficiency. Bachmann et al. (1957b) have critically reviewed reports of 59 cases of so-called factor VII deficiency. They concluded that some of the cases were undoubtedly deficient in factor VII, a few were surely deficient in Stuart-Prower factor, but the large majority were not sufficiently analyzed for conclusions to be drawn. Burmeister et al. (1958) and Dann et al. (1958) have recently described additional cases of proconvertin deficiency.

Proconvertin acts only in the extrinsic blood clotting system whereas Stuart-Prower factor is necessary for both clotting systems. One important difference to be expected in the laboratory findings, therefore, is in the whole blood clotting time, which should be normal in proconvertin deficiency and prolonged in Stuart-Prower factor deficiency. Other differences in the results of various clotting tests in the two types of deficiency are listed in Table 5.

A review of the published cases of "hypoproconvertinemia" suggests that nearly half of them, having signs of a deficient intrinsic clotting system, might have been Stuart-Prower factor deficiencies.

As shown by the tests in the proconvertin assay system, all the patients of this report lack the same clotting factor since they all fail to correct the clotting defect in the same single substrate plasma. The deficient factor must be proconvertin since the whole blood clotting time, the thromboplastin generation test, and the prothrombin consumption test all show that the intrinsic clotting system functions normally in these patients. That the factor lacking in these cases is different from Stuart-Prower factor is evident from the mutual correction seen between our substrate plasma and plasma from a patient with a proved Stuart-Prower factor deficiency.

Tab. 5: Comparison of results in laboratory tests on patients with Stuart-Prower factor deficiency and patients with proconvertin deficieny.

Type of test	Proconvertin deficiency	Stuart-Prower factor deficiency
Whole blood clotting time	normal	prolonged
Thromboplastin time	prolonged	prolonged
Prothrombin consumption	normal	reduced
Russell's viper venom in cephalin time (Prothrombin assay, Stuart-Prower factor sensitive)	normal	prolonged
As above, with addition of "proconvertin reagent"	normal	normal
PP-time	prolonged	prolonged
Thromboplastin generation test	normal	serum defect
Cephalin time	normal	prolonged
Recalcification time	normal	prolonged

The pattern of heredity illustrated by Figs. 1 and 2 permits the conclusion that this deficiency is transmitted by a defective autosomal gene and that the gene in single dose causes a partial deficiency, in double dose a total deficiency. Thus the patients seem to fall into two clearly distinguished groups. The first have between 25 and 65% of the normal proconvertin level and no abnormal bleeding tendency. The second have an almost total deficiency of proconvertin and yet even in these cases the bleeding tendency is far less pronounced than that which occurs with defects of the intrinsic blood clotting system, as in hemophilia A or B, for example.

Summary

Investigations on 12 patients with a total and 19 patients with a partial deficiency of proconvertin (factor VII) are reported. All patients proved to have the same deficiency and it was distinguishable from Stuart-Prower factor deficiency. The differentiation between proconvertin deficiency and Stuart-Prower factor deficiency is discussed.

Résumé

Les auteurs ont étudié 12 patients avec une déficience totale et 19 patients avec une déficience partielle en proconvertine, (facteur VII). Tous les patients ont le même défaut, différent d'un manque en facteur Stuart-Prower. La distinction entre un défaut en facteur VII et un défaut en facteur Stuart-Prower est discutée.

Zusammenfassung

Es wurden 12 Patienten mit vollständigem und 19 Patienten mit teilweisem Mangel an Proconvertin (Faktor VII) untersucht. Bei allen Patienten ließ sich der gleiche Mangel nachweisen, und es ließ sich zeigen, daß es sich nicht um den Stuart-Prower-Faktor-Mangel handelt. Der Unterschied zwischen Proconvertin-Mangel und Stuart-Prower-Faktor-Mangel wird diskutiert.

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