THE TRANSITORY ABSENCE OF SEVERAL CLOTTING FACTORS IN A NEWBORN BABY*

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Haemorrhagic diathesis of the newborn is usually characterized by a physiological deficiency of prothrombin and probably also by a deficiency of proconvertin (van Creveld, Paulssen, Ens, Mey, Versteegh and Versteeg, 1954). Sometimes a third clotting-factor, pro-accelerin, is also lacking. We found a simultaneous deficiency both of prothrombin and pro-accelerin in some cases of intra-uterine melaena and of haemolytic disease of the newborn; it is also found in severe congenital damage of the liver (van Creveld, Paulssen and Teng, 1952). We do not know how far in such permanent congenital haemorrhagic diatheses as haemophilia, fibrinopenia and Christmas disease other clotting factors are transiently lacking after birth, as well as a temporary shortage of prothrombin and a permanently deficient specific clotting factor. Except in these instances we can say that no cases of a haemorrhagic diathesis in the newborn are known where a deficiency of more than three clotting-factors is found.

We were able to observe a transitory haemorrhagic diathesis in a young infant in whom four clotting-factors were simultaneously deficient. It was remarkable that this deficiency involved just those clotting-factors which are necessary for the whole second phase of the coagulation process.

Case Report

The infant P. was the third child of healthy parents. Apart from a case of diabetes no specific diseases were found in the family history, in particular no diseases of the blood. The mother's pregnancy was normal. Delivery was normal; neither mother nor child lost an abnormal amount of blood, and the child was not asphyxiated. The birth weight was 4,500 g.

Soon after birth the child took feeds poorly and at the age of 11 days refused breast and bottle feeding; he vomited after feeds. At the same time he became dyspnoeic and appeared to be in pain. At the age of 15 days the child was admitted to the Children's Clinic, Amsterdam,

on account of feeding difficulties and a bulging fontanelle.

On examination the infant was moderately ill, without dyspnoea, cyanosis or anaemia, but with slight jaundice. The anterior fontanelle was wide and distinctly bulging. No stiffness of the neck or abnormalities of the lungs were found. The heart was not enlarged on percussion; the heart sounds were pure, the pulse was rapid. The abdomen was not protruding and could easily be palpated. The liver was palpable just below the costal margin, the spleen was not enlarged. The femoral arteries could be palpated weakly on both sides. No abnormal reflexes were found. Lumbar puncture produced clear, colourless cerebrospinal fluid, with 17 cells per c.mm. and no excess protein. After the lumbar puncture the level of the fontanelle was normal and consequently did not bulge any more.

Some hours after admission (one hour after the first feed) the child became suddenly cyanotic and respiration became irregular. His condition remained the same for the next few hours and in that time he twitched slightly and occasionally shrieked. Notwithstanding the administration of oxygen and subcutaneous injection of 1 ml. of nikethamide 25%, the colour did not improve. An E.C.G. showed biphasic complexes in all leads, with notching of the QRS complexes. In the meantime the liver rapidly increased to 4 cm. below the costal margin in the right mid-clavicular line. Acute heart failure was diagnosed and digitalis administered. A radiograph showed an enlarged heart with slight congestion of the lungs.

The day after the admission the child's condition improved remarkably: the cyanosis disappeared, but he vomited haemorrhagic mucus. The liver was still greatly enlarged; a rough systolic murmur could be heard in the third and fourth intercostal spaces to the left of the sternum. The femoral arteries could not now be felt clearly. We suspected heart failure caused by coarctation of the aorta.

During the first few days the child received intramuscular injections of vitamin K, and later on vitamin K orally. As 'digalen' was not taken by mouth it was injected intramuscularly. In the next days the condition remained stationary. The child, however, developed general oedema. The systolic murmur also remained

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clearly audible. New E.C.G.s showed increased myocardial anoxia. The pulsations of the femoral arteries varied greatly from day to day. One month after admission the child was still dyspnoeic and took no feeds by mouth, but was fed by tube. The condition seemed to improve and the liver decreased in size.

Seven weeks after admission pyrexia and symptoms of gastro-enteritis developed. The respiration rate increased, the child groaned, and died within 24 hours.

The pathological findings (Dr. van Dam) showed an infantile type of coarctation of the aorta with a wide patent ductus arteriosus. The heart muscle was hypertrophic. Under the epicardial surface and on the pericardium haemorrhages were visible. No endocardial fibrosis was seen.

Investigation of the Clotting Factors. The clotting factors were investigated because the child vomited haemorrhagic mucus shortly after admission. With the one-stage prothrombin time test no clotting was found. The venous blood did not coagulate. On admission, on the fifteenth day of life, we found a greatly decreased prothrombin content (47 units), almost total absence of pro-accelerin and a low value for pro-convertin. The fibrinogen content of the plasma was 0.01 mg. per 100 ml. The plasma showed no fibrinolytic activity. The total protein content of plasma and serum was 3.7 g. per 100 ml. (lowest normal value 5.5 g.).

In this infant a very pronounced fibrinopenia was found (the normal value in newborns is 0.1 g. per 100 ml. and in older children 0.2 g. per 100 ml.), a pronounced hypoprothrombinaemia (the lowest value found by us, van Creveld, Paulssen, and Teng, 1952, was 66 units per ml. in a child on the third day of life) and a nearly total absence of pro-accelerin (in normal infants we never found a value lower than 13 units) combined with a marked hypoproconvertinaemia (see Table 1).

The clot-promoting influence on haemophilic blood of the plasma of our patient was examined on the fifteenth day of life. This appeared to be completely normal; the plasma contained a normal quantity of anti-haemophilic substance. We could assume further that the content of the factor which is lacking in Christmas disease was also normal, for the so-called thromboplastin-generation test (Biggs and Douglas, 1953; Biggs, Douglas, MacFarlane, Dacie, Pitney, Merskey and O'Brien, 1952) performed with the patient's serum, the patient's plasma treated with

BaSO₄ so that the factor F (the plasma thromboplastin component) is eliminated (van Creveld and Paulssen, 1953) and a suspension of normal platelets proved to be normal.

The results of the repeated examination of the clotting-factors are summarized in Table 1, which shows that the prothrombin content of the plasma gradually increased, as well as that of the other deficient clotting-factors.

Twelve days after admission the antithrombin content proved to be normal.

The marked fibrinopenia on admission as well as the

FIG. 1.—I is the paper electrophoretic protein spectrum of the plasma of a normal baby of the same age as our patient.

II is the same of our patient at the age of 20 days.

F is the line indicating fibrinogen fraction.

A is the line indicating albumin fraction.

normal fibrinogen content later in the course of the disease were examined by chromatography obtained by means of paper electrophoresis (Dr. Govers). Fig. 1 shows the chromatogram of our patient on the twentieth day of life compared with that of a normal baby of the same age.

Parallel with the improvement of the disturbance in the clotting mechanism the clotting time *in vitro* gradually became normal.

TABLE 1
CLOTTING FACTORS

Age in Days	Prothrombin (units)	Pro-accelerin (units)	Proconvertin (%)	Additional Data
16	47	1	1	Normal clotting-promoting effect of plasma on haemophilic blood (A.H.F.); clotting time indefinite; one-stage prothrombin time (Quick) indefinite; thromboplastin generation test normal
18	60	1	2	Plasma fibrinogen 0.01 g./100 ml.
20	96	—	10	Paper electrophoresis of plasma (repeated at the age of 44 days)
23	103	—	—	
27	—	—	52	
28	150	12	—	Antithrombin normal
34	126	10	38	
41	132	13	57	Plasma fibrinogen 0.18 g./100 ml.
48	138	14	60	A.H.F. normal. Thromboplastin generation test normal

Table 2 shows the lowest and highest values found by us in normal, full-term, newborn infants.

TABLE 2

Prothrombin	first day of life		84-202 u./ml.
"	second day of life		80-158 u./ml.
"	third day of life		66-148 u./ml.
"	fifth day of life		86-198 u./ml.
"	seventh day of life		114-210 u./ml.
Pro-accelerlin	during first week of life		13-17u./ml.
Pro-convertin	sixth day of life		15-56%
"	seventh day of life		17-58%

Comment

The factors which in this patient were temporarily deficient are all factors which, according to our hypothesis of the clotting mechanism, play a part in the second phase of clotting. This is evident from Fig. 2.

FIG. 2.

As to the cause of the combined disturbance in the clotting-factors, we cannot express a definite opinion. It is reasonable to assume a relationship with the heart failure at a very early age. Whether the administration of vitamin K, eventually also of digalen, favourably influenced the restoration of all clotting-deficient factors, cannot be ascertained.

But, apart from this, our case is a remarkable example of a combined disturbance in the clotting mechanism. Moreover it is an illustration of the fact that in such a combined disturbance the clinical manifestations of haemorrhage may be small.

Finally the observation of this patient has a special

theoretical value. Opinions here of late have differed with regard to the factors which are of importance in the formation of thromboplastin; no agreement exists about the question whether proconvertin (factor VII) is necessary for its formation (Biggs and Douglas, 1953). An argument in favour of the fact that convertin is not necessary for the formation of thromboplastin is that in our case at the time when proconvertin in the plasma was practically absent, we still found thromboplastin normally formed *in vitro* by adding the patient's plasma treated with BaSO₄ to his serum and a suspension of normal platelets. In a former investigation (van Creveld, Paulssen and Mochtar, 1953) we had already obtained some evidence for this fact.

It is also important that, at the first examination, the patient's blood plasma in which fibrinogen was virtually absent promoted normal coagulation in the blood of a haemophilic. This is somewhat contradictory to the current conception that the anti-haemophilic factor in plasma is always fixed to fibrinogen.

Summary

An infant is described with congenital heart disease and heart failure and slight symptoms of a haemorrhagic diathesis. All the clotting-factors taking part in the second phase of the clotting process were temporarily absent or considerably decreased.

Special stress is laid on the fact that at the beginning of life the plasma contained practically no fibrinogen but notwithstanding exerted a normal coagulation-promoting activity upon haemophilic blood. The so-called thromboplastin-generation test gave a normal result, although the plasma contained practically no proconvertin.

REFERENCES

- Biggs, R. and Douglas, A. S. (1953). *J. clin. Path.*, 6, 23.
- , MacFarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C. and O'Brien, J. K. (1952). *Brit. med. J.*, 2, 1378.
- Creveld, S. van and Paulssen, M. M. P. (1953). *Lancet*, 1, 823.
- and Mochtar, I. A. (1953). *Ned. T. Geneesk.*, 97, 2702.
- and Teng, S. K. (1952). *Et. néo-natales*, 1, 87.
- , Ens, J. C., Mey, C. A. M. v.d., Versteegh, E. T. B. and Versteeg, P. (1954). *Et. néo-natales*, 3, 1.