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Coagulation Studies in Preterm Infants with Respiratory Distress and Intracranial Haemorrhage*

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Chessells, J. M., and Wigglesworth, J. S. (1972). *Archives of Disease in Childhood*, **47**, 564. **Coagulation studies in preterm infants with respiratory distress and intracranial haemorrhage.** Coagulation studies were performed on 48 preterm infants with respiratory distress or recurrent apnoea who were considered to be at risk from intracranial haemorrhage. One or more coagulation abnormalities were detected in 16 cases though only one infant had a bleeding diathesis in life. Coagulation abnormalities were more frequent in infants subsequently found to have intracranial haemorrhage (intraventricular or subarachnoid haemorrhage) than in those with hyaline membrane disease only.

Of 26 infants who died, 6 had hyaline membrane disease only, 17 had intracranial haemorrhage (usually intraventricular haemorrhage) with or without hyaline membrane disease, and 3 had other conditions. Fibrin thrombi were seen at necropsy in the tissues of 11 of the 12 infants with laboratory abnormalities who died and in 6 additional cases.

Since half the infants who died and two-thirds of the total cases had no evidence of haemostatic failure, it is concluded that abnormal haemostasis is not a constant feature of either hyaline membrane disease or intraventricular haemorrhage.

Respiratory distress and intracranial (in particular, intraventricular) haemorrhage remain among the most important causes of death in the premature infant. The possible role of deficiencies of platelets or coagulation factors in initiating or exacerbating intraventricular haemorrhage is uncertain. Grön-toft (1953) felt that because bleeding into the ventricles rarely occurred in association with bleeding at any extracranial site, intraventricular haemorrhage (IVH) was not a symptom of a haemorrhagic diathesis. This view has also been unquestioningly adopted by more recent authors (Harrison, Heese, and Klein, 1968). In the past few years there has been further speculation about haemostasis in infants with the respiratory distress syndrome (RDS) (Markarian *et al.*, 1967) and in infants with intracranial haemorrhage (Gray, Ackerman, and Fraser, 1968).

The present study was undertaken to try and elucidate, first if there is any recognizable defect of haemostasis in infants who have intraventricular haemorrhage at necropsy, and secondly if there is any evidence of a systemic haemostatic abnormality in infants with the respiratory distress syndrome.

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Patients and Methods

The 48 infants in the study were admitted to the Neonatal Ward at Hammersmith Hospital during the period 1969–70. All were 36 weeks of gestation or less as judged by external characteristics, neurological assessment, and mothers' dates; all were therefore potentially at risk from intraventricular haemorrhage. Umbilical arterial catheterization had been performed on all the infants because apnoeic attacks or respiratory distress (the presence of at least two of the following at 4 hours of age: respiratory rate over 60 per minute, sternal recession, or expiratory grunt) necessitated monitoring of the blood gases and *p*H. 46 infants fulfilled these criteria for the presence of respiratory distress; in 2 infants both of whom weighed less than 1500 g and were of 28 weeks' and 30 weeks' gestation, the indication for catheterization was the presence of recurrent apnoeic attacks which started before the age of 6 hours. Infants born at Hammersmith Hospital were not given vitamin K_1: those admitted from other units had usually been given 1 mg K_1 i.m. at birth. All the infants were fed with full strength milk feeds (breast milk where possible).

Blood for coagulation studies and platelet counts was taken at the time of insertion of the catheters. Catheters were inserted during the first 24 hours of life, except in

2 infants where they were inserted during the second 24 hours. Before any follow-up samples were taken, the catheters were flushed with normal saline. Samples were taken into a 1 in 10 dilution of 3·2% Na citrate with the addition of 1/10th volume of 10% ϵ-amino caproic acid to those samples intended for estimation of plasma fibrinogen and fibrin degradation products.

Methods have been described in detail elsewhere (Chessells, 1971). The following estimations were performed where possible: platelet count, plasma fibrinogen, Thrombotest, thromboplastin generation screening test (TGST), thrombin time. The Thrombotest was used as a screening test for deficiency of the vitamin K dependent coagulation factors, and the TGST as a screening test for deficiencies of the intrinsic coagulation system. Results of the thrombin time were expressed as a ratio patient/adult normal; the ratio in the normal newborn infant ranges from 1 to 2. Fibrin degradation products (FDP) were measured on thrombin-treated plasma by the method of Merskey, Lalezari, and Johnson (1969).

Permission for a full necropsy was obtained on all the infants in the study who died. The brain in each case was examined after fixation in formalin for at least one week. In addition to routine material stained with haematoxylin and eosin, sections of the tissues were stained with phosphotungstic acid haematoxylin and reviewed for the presence of fibrin thrombi.

Illustrative Case Histories

The two infants from the series whose case histories are here reported both died within the first 24 hours of life with intraventricular haemorrhage at necropsy.

Case 13. This infant was born suddenly in a doctor's surgery at 34½ weeks' gestation, birthweight 2850 g. He was not asphyxiated at birth but developed respiratory distress and became hypothermic; on admission to hospital at 7½ hours his temperature was only 32·8 °C. Within a few minutes of admission he became apnoeic and had a cardiac arrest. After resuscitation an umbilical arterial catheter was passed and coagulation studies showed platelets 240 × 10^3/mm^3, plasma fibrinogen 75 mg/100 ml, TGST 48 seconds, Thrombotest 14%, thrombin ratio 2·8, and FDP were detected in a titre of 16. No bleeding tendency was observed in life and he died at 9 hours. At necropsy the findings were of IVH with a separate subarachnoid haemorrhage, and there were disseminated fibrin thrombi in the kidneys, liver, and adrenals.

Comment. This infant with IVH had laboratory and histological evidence of disseminated intravascular coagulation. He had been profoundly asphyxiated and hypothermic at the time when coagulation studies were performed.

Case 24. This infant, born by spontaneous vertex delivery at 28 weeks' gestation, weighing 960 g, was asphyxiated at birth and required intubation and intermittent positive pressure ventilation for 10 minutes. He developed respiratory distress; his temperature on admission to the ward was 35·6 °C and never fell below this reading. A sample of blood taken at 3½ hours showed platelets 252 × 10^3/mm^3, plasma fibrinogen 445 mg/100 ml, TGST 11 seconds, Thrombotest 22%, thrombin ratio 2, and no FDP were detected. He died at 11 hours of age after recurrent apnoeic attacks and was found at necropsy to have IVH with subarachnoid extension. There was no evidence of fibrin deposition in the tissues.

Comment. This infant, who had typical IVH at necropsy, showed no evidence of any haemostatic abnormality in life and no fibrin deposition at necropsy.

Results

Laboratory. Results of the initial laboratory investigations on the 48 infants are detailed in Table I. The infants are divided into three groups:

Group I—infants with a clinical diagnosis of respiratory distress who survived (22 infants).

Group II—infants with respiratory distress who died with no evidence of intracranial haemorrhage at necropsy (9 infants).

Group III—infants who died and were found at necropsy to have intracranial haemorrhage (17 infants). Of these 17 infants, 12 had IVH and 4 had primary subarachnoid haemorrhage. One infant had both IVH and a separate primary subarachnoid haemorrhage.

The results are expressed in terms of ranges of values obtained for each test in each group.

Some infants from each group had laboratory evidence of marked haemostatic abnormality as shown by one or more of the following: platelet count less than 100 × 10^3/mm^3, plasma fibrinogen less than 100 mg/100 ml, TGST 30 seconds or more, Thrombotest less than 10%, or FDP in diluted serum. The number of infants in each group in whom such abnormalities were found is shown in Table II, and detailed results of laboratory studies in all the 16 infants with abnormal laboratory findings are shown in Table III.

Infants from Groups I and II were found to have isolated abnormalities including prolonged TGST (Cases 1 and 2) and circulating FDP (Cases 3 and 4); in one infant (Case 5) these abnormalities were combined. One infant had a low platelet count (Case 6) but neither he nor any other infant from Groups I and II had a bleeding tendency.

Significantly more frequent, and in some cases multiple, abnormalities were found in infants with intracranial haemorrhage (Group III) (see Table II). There was no obvious difference between the infants with IVH and those with subarachnoid haemorrhage apart from one infant, Case 14, who had thrombcytopenia and a bleeding tendency in life and massive subarachnoid haemorrhage at

TABLE I

Range of Results of Laboratory Investigations on All Infants

Gestation (wk)	Platelets (10^3/mm^3)	Fibrinogen (mg/100 ml)	Thrombotest (%)	TGST (sec)	Thrombin Ratio	Cases with FDP Present
Group I—Infants with respiratory distress who survived						
Less than 31 (5)	150–304	132–299	22–31	14–24	2·6	3
31–33 (11)	174–366	101–275	12–25	13–30	1·0–2·5	0
34–36 (6)	178–396	126–174	14–42	11–42	1·1–2·1	1
Overall range	150–396	101–299	12–42	11–42	1·0–2·6	4
(No.)	(22)	(22)	(20)	(19)	(15)	(22)
Group II—Infants with fatal respiratory distress—no intracranial haemorrhage						
Less than 31 (5)	214–263	142–273	14–22	14–60	1·9–2·5	1
31–33 (4)	60–216	105–183	10–22	11–20	2·0	0
Overall range	60–263	105–273	10–22	11–60	1·9–2·5	1
(No.)	(9)	(9)	(8)	(5)	(4)	(9)
Group III—Infants with intracranial haemorrhage at necropsy						
Less than 31 (9)	130–395	112–445	7–22	11–50	1·8–2·6	4
31–33 (4)	30–215	66–190	8–51	16–26	2·0–2·5	0
34–36 (4)	194–240	75–148	9–16	11–48	1·8–2·8	3
Overall range	30–395	66–445	7–51	11–50	1·8–2·8	7
(No.)	(17)	(17)	(17)	(16)	(13)	(17)
Healthy premature infants 36 weeks gestation and less on day 1						
Range	168–330	127–305	22–32	13–25	1·2–1·8	—

TABLE II

Incidence of Abnormal Laboratory Findings in 48 Infants

	Number of Infants in Each Group with Abnormal Findings			
	Group I	Group II	Group III	
			IVH	SAH
No. of infants	22	9	12	5
No. with laboratory* abnormality	4	2	6	4
Platelets $<100 \times 10^3$/mm^3	0	1	0	1
Fibrinogen <100 mg/100 ml	0	0	0	2
Thrombotest <10%	0	0	3	2
TGST—30 seconds or more	2	1	3	1
FDP in diluted serum	2	1	3	2

IVH—intraventricular haemorrhage
SAH—subarachnoid haemorrhage.
*Number of infants with laboratory abnormalities in Group III (10 of 17) is significantly greater than the number in Group II (2 of 9) $\chi^2 = 7{\cdot}48$, $P < 0{\cdot}01$.

necropsy. The plasma fibrinogen level in this infant fell to 70 mg/100 ml at 18 hours of age but no FDP were detected. No other infant showed clinical evidence of haemostatic failure.

Necropsy. In most cases significant lesions on macroscopical and routine histological study were confined to lungs and brain. However, one infant (Case 17) died from necrotizing enterocolitis and another (Case 16) had thrombosis of one branch of the left coronary artery with early myocardial infarction.

Infants without intracranial haemorrhage (Group II, Table IV). It can be seen from Table IV that 6 of the 9 infants in this group had HMD, one of the other 3 infants had pulmonary fibroplasia probably secondary to HMD, and the remaining 2 (both under 1000 g birthweight) had pneumonia.

Infants with intracranial haemorrhage (Group III, Table V). These cases may be subdivided into those with IVH with or without spread to the subarachnoid space through the foramina of the fourth ventricle (13 infants) and those with primary subarachnoid haemorrhage not originating in an IVH (4 cases). One infant, Case 13, had IVH and a separate subarachnoid haemorrhage. 11 of the 17 infants had HMD at necropsy. Other pathology seen included pneumonia and pulmonary haemorrhage.

Incidence of fibrin thrombi at necropsy (Tables IV and V). Fibrin thrombi were seen in the sinusoids of liver and/or adrenals of 4 of the 9 infants without intracranial haemorrhage; all 4 were infants with HMD. Fibrin thrombi were seen also in the liver

TABLE III

Investigations in 16 Infants with Laboratory Abnormalities

Case No.	Birthweight (g)	Gestation (wk)	Platelets (10^3/mm^3)	Fibrinogen (mg/100 ml)	Thrombotest (%)	TGST (sec)	Thrombin Ratio	FDP Titre
Group I								
1	1580	32	366	260	14	30	1·1	0
2	2040	34	283	152	14	42	2·0	0
3	1700	30	150	299	31	14	2·6	4
4	3000	35	178	163	15	11	2·1	4
Group II								
5	1080	29	213	154	14	60	—	4
6	1460	33	60	105	—	—	—	0
Group III								
7	1070	27	163	117	9	50	2·0	0
8	1150	28	205	140	15	32	—	2
9	1080	30	168	244	14	50	1·9	0
10	1650	36	194	105	9	11	2·2	0
11	1020	28	264	149	7	18	2·6	2
12	1286	26	395	368	22	—	—	4
13	2850	34	240	75	14	48	2·8	16
14	920	31	30	112	8	21	2·4	0
15	1720	28	232	187	9	14	2·0	8
16	2290	33	215	66	10	19	2·5	0

and/or adrenals of 13 of the 17 infants with intracranial haemorrhage including all 5 of those with a primary subarachnoid haemorrhage. The 17 infants in whom fibrin thrombi were seen at necropsy included 11 of 12 with laboratory abnormalities in life, and 6 in whom no laboratory defect had been demonstrated. The incidence of fibrin thrombi was similar in those infants who had hyaline membranes only (4 out of 7) to that in the infants with intracranial haemorrhage only (5 out of 7). Thrombi were seen in 8 out of 10 infants with both conditions.

In general there was little evidence of fibrin within the lungs. Hyaline membranes usually stained poorly for fibrin except in relation to areas of haemorrhage where the membranes appeared to consist largely of fibrin. Masses of fibrin seen in the airways were also related to focal haemorrhage. Mixed antemortem thrombi in small arteries or veins were seen in 8 cases; 6 of them had additional fibrin thrombi in hepatic or adrenal sinusoids. Sites of mixed thrombi were: lung, myocardium, thyroid, placenta, and umbilical cord, twice each, and liver, tracheal submucosa. salivary gland, and thymus on one occasion each.

Discussion

Previous investigations. Previous investigations of haemostasis in infants with respiratory distress have pursued two main lines of inquiry; the search for local factors influencing fibrinolysis in the lungs of affected infants, and the study of

TABLE IV

Necropsy Findings in Infants from Group II

Case No.	Birthweight (g)	Gestation (wk)	Age at Death	Findings	Fibrin Thrombi		
					Liver	Adrenals	Other Sites
5	1080	29	2 days	HMD	+	+	
6	1460	33	16 days	Pulmonary fibroplasia			
17	940	28	7 days	Pneumonia: necrotizing enterocolitis			
18	910	30	5 days	Pneumonia; early pulmonary fibroplasia			
19	1100	29	3 days	HMD and pneumonia		+	
20	1300	30	11 hours	HMD	+		
21	2260	32	5 days	HMD and early pulmonary fibroplasia			
22	1630	32	40 hours	HMD	+	+	
23	2510	33	21 hours	HMD and pneumonia			

HMD = hyaline membrane disease.

TABLE V

Necropsy Findings in Infants from Group III

Case No.	Birthweight (g)	Gestation (wk)	Age at Death (hr)	Type of Intracranial Haemorrhage	Other Pathology	Fibrin Thrombi		
						Liver	Adrenals	Other Sites
7	1070	27	30	IVH	I.U. malnutrition, HMD	+	+	
8	1150	28	28	IVH	HMD	+		
9	1080	30	48	IVH	Pneumonia, pulmonary haemorrhage	+		
10	1650	36	3 dy	IVH	HMD, pneumonia	+		
11	1020	28	2 dy	IVH		+	+	
12	1286	26	3 dy	IVH	Pneumonia	+	+	
24	960	28	11	IVH				
25	1200	28	6 dy	IVH				
26	1260	30	40	IVH	Pulmonary haemorrhage, HMD	+		
27	1580	31	42	IVH	HMD			
28	1680	34	37	IVH	HMD	+	+	
29	2310	36	30	IVH	HMD			
13	2850	34	9	IVH and SAH	HMD	+	+	+
14	920	31	24	SAH	HMD	+		
15	1720	28	48	SAH	Aspiration pneumonia	+		
16	2290	33	15	SAH	HMD		+	
30	1240	32	40	SAH	HMD	+		

coagulation factors in the peripheral blood. The present investigation was not designed to examine local influences in the lungs; such investigations have been the subject of reports by Ambrus, Weintraub, and Ambrus (1966) and by Lieberman (1969).

In 1961 Wade-Evans reported finding a high incidence of hepatic thrombi in infants with fatal HMD; this report was followed by speculation that RDS may be regularly accompanied by consumption of coagulation factors and platelets (Stark, Abramson, and Erkan, 1968). Hathaway, Mull, and Pechet (1969) found evidence that disseminated intravascular coagulation (DIC) occurred in some infants with RDS but pointed out that this finding did not necessarily mean that the haemorrhages occurring in such infants were due to DIC. Since respiratory distress is frequently accompanied by IVH it is important to clarify the role of haemostatic failure in causing this form of bleeding.

There are two theoretical ways in which haemostatic defects might cause or exacerbate intraventricular haemorrhage. First, the combination of hepatic immaturity and anoxia in a sick premature infant could theoretically result in impaired synthesis of coagulation factors, manifesting itself as an abnormality of the Thrombotest or TGST. Secondly, haemostatic failure might occur as a consequence of DIC. If DIC had occurred the laboratory findings might include thrombocytopenia, abnormalities of the intrinsic coagulation system (reflected as a prolongation of the TGST), low plasma fibrinogen and circulating FDP.

Present laboratory findings. Our investigations of infants with respiratory distress revealed abnormal laboratory findings in one-third of infants; these abnormalities were more common in infants with intracranial haemorrhage at necropsy than in infants surviving or in those dying with no evidence of intracranial haemorrhage. No uniform pattern of laboratory abnormalities was detected but two main patterns emerge.

First, the complex abnormalities found in Cases 5, 8, 13, and 14 are suggestive of a diagnosis of DIC. A prolongation of the TGST was the main abnormal finding in another group of infants (Cases 1, 2, 7, and 9). As individual coagulation factors were not assayed it was not possible to say if this abnormality was due to defective hepatic synthesis of V, IX, and X or the result of utilization of factors V and VIII; the absence of marked depression of the Thrombotest in Cases 1, 2, and 9 and the demonstration of fibrin thrombi in those patients who died (Cases 7 and 9) might indicate that the abnormality was due to utilization of coagulation factors.

Secondly, in 3 infants (Cases 10, 11, and 15) the main abnormal finding was a marked reduction of the Thrombotest percentage though in 2 of the infants (Cases 11 and 15) FDP were also detected.

In two-thirds of the infants in the study, including half of those with IVH at necropsy, there were no clearly abnormal laboratory findings.

Discussion of necropsy findings. The finding of fibrin thrombi in the organs of many of the infants at necropsy is in keeping with the earlier

reports of Wade-Evans and requires further discussion. In the present study there was an apparently poor correlation between the laboratory evidence of DIC and the histological findings.

It may be that in some of these infants DIC was a preterminal event and was not suspected in life because no sample for coagulation studies was taken just before death. Alternatively the fibrin deposition may not have been sufficiently extensive to result in depletion of platelets and coagulation factors. We have pointed out previously both the technical difficulties of identifying thrombi in necropsy specimens and the discrepancies between the extent of fibrin shown histologically and the extent of abnormal laboratory findings (Chessells and Wigglesworth, 1971a).

Implications of present findings; significance of DIC. In the present study haemostatic abnormalities were common in premature infants with respiratory distress; the most common pattern of abnormalities was consistent with a diagnosis of disseminated intravascular coagulation. We feel, however, that this is no reason to assume that intraventricular haemorrhage, when it occurs in such infants, does so as a *result* of haemostatic failure. A number of infants in the study, Case 24 is a good example, showed neither laboratory nor histological evidence of haemostatic failure; if deficiency of coagulation factors plays a role in causing intraventricular haemorrhage, it is clearly not the only cause of bleeding. Moreover, all the infants with IVH had a normal platelet count; bleeding in the newborn infant with DIC is, in our experience, associated with thrombocytopenia. Case 14, the only infant in the study with a bleeding diathesis, had a platelet count of only 30×10^3/mm^3, and at necropsy, despite her size and immaturity, had not IVH but a massive subarachnoid haemorrhage. By contrast, Case 13, with a normal platelet count despite a low level of plasma fibrinogen and disturbance of the intrinsic coagulation system and FDP in high titre, showed no bleeding at any extracranial site at necropsy.

We think it probable that the apnoeic attacks and hypothermia from which all premature infants with respiratory distress are at risk and which are especially common in infants with IVH (Ross and Dimmette, 1965) may in themselves result in pathological activation of coagulation, thus causing abnormalities of haemostasis and leading to the finding of fibrin thrombi at necropsy. We have shown that such a train of events may occur in severe birth asphyxia (Chessells and Wigglesworth, 1971b). It seems likely that a similar pattern of events may follow apnoeic episodes and that DIC may be a result rather than a cause of intraventricular haemorrhage.

Relation of IVH to primary deficiency of coagulation factors. Since the incidence of IVH is not influenced by prophylactic administration of vitamin K (Gröntoft, 1953), any primary deficiency of coagulation factors in premature infants with IVH must be due to inability to use the vitamin or to make coagulation factors because of hepatic immaturity or anoxia. Gray *et al.* (1968) found low Thrombotest percent levels in infants with intraventricular haemorrhage at necropsy, and suggested that deficiency of the vitamin K dependent factors as measured by the Thrombotest might play a part in causing or exacerbating IVH. We found very low Thrombotest levels in only 5 infants; 3 with IVH and 2 with other forms of bleeding. In 4 of the 5 infants other abnormalities of haemostasis were present, and in at least 2 of them (Cases 7 and 14) the cause of the abnormalities was considered to be DIC. The Thrombotest is not, of course, in itself a valuable index of consumption of factors (as witnessed by the levels in Cases 5, 8, and 13), since it measures chiefly those coagulation factors that are not utilized in the process of coagulation. If the Thrombotest was not reduced in our infants because of DIC, it may have been low because of poor utilization of vitamin K in a sick infant. The healthy premature infant is able to use vitamin K (Aballi, 1965); the sick infant who has respiratory distress and apnoea may be unable to do so. Thus it is possible that the low Thrombotest levels, like other abnormalities, may be the result rather than the cause of haemorrhage.

Until it is possible to time the actual onset of IVH and relate it to the alterations of levels of coagulation factors in premature infants, all such considerations must remain purely speculative.

Therapeutic implications. If haemostatic failure is the consequence rather than the cause of IVH in premature infants, is any measure to influence the abnormal laboratory findings likely to be of value? It is, perhaps, conceivable that correction of abnormal laboratory findings might prevent further extension of any haemorrhage present.

Effective correction of laboratory abnormalities depends on the cause of these abnormalities. If primary deficiency of coagulation factors, in particular vitamin K dependent factors, is present, vitamin K is unlikely to be effective for reasons already discussed. The alternative therapy would

be the use of fresh frozen plasma; since evidence of a primary deficiency is uncommon this form of therapy would rarely appear indicated. If deficiency of coagulation factors is secondary to DIC, neither vitamin K nor plasma are likely to be effective. One must bear in mind that many such episodes are not continuous and recovery may be spontaneous. Any form of treatment in such a situation may be drastic; the use of heparin in a sick infant with intracranial bleeding can hardly be advocated. The alternative of exchange transfusion with fresh heparinized blood could be indicated only if there was very strong evidence of continued bleeding (e.g. in Case 14).

We feel that since haemostatic failure is probably a secondary event in these infants, it is more important to avoid those factors that may initiate haemostatic failure by avoidance of hypothermia, prompt resuscitation of apnoeic attacks, and correction of acidosis. We would make a plea for further investigation into the problem of timing the onset of intracranial haemorrhage of all types.

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