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# Blood coagulation in healthy and severely ill newborn infants

By

G. Gyódi, E. Vágvölgyi, L. Fekete, A. Jakó

Department of Paediatrics and Blood Transfusion Service, County Hospital, Kaposvár

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Normal values of blood coagulation factors were investigated in 30 healthy newborn infants. On the basis of these normal standards 8 infants with DIC were evaluated. All of them had serious underlying disease. By appropriate treatment of the primary disorder and replacement of depleted procoagulants, the bleeding disorder disappeared in six of eight patients without heparinization. Diagnostic criteria and management of neonatal disseminated intravascular coagulation are discussed.

During the past two decades, knowledge about fetal and neonatal physiology and pathology has greatly increased. Application of the new discoveries has dramatically improved the neonatal mortality rate in recent years. By maintenance of fluid and electrolyte balance, correction of acidosis, parenteral nutrition and modern respiratory therapy a great number of newborns and prematures can be treated successfully.

Among the life-threatening acute events of the newborn period blood coagulation disorders have a special importance because of their severity and multiple aetiology [2, 4, 5, 6, 19, 21, 23].

The bleeding disorders and blood coagulation standards of adults are well-known but less is known concerning their values in the newborn period [3, 14]. The normal values for blood coagulation factors in newborns are not only different from those of adult life but there is also a considerable variation between laboratories.

In this paper we present coagulation standards of healthy newborn infants, and on the basis of these normal values we have investigated some infants suffering of disseminated intravascular coagulation (DIC) caused by various diseases.

## Material and Methods

Thirty healthy newborn infants were investigated from July, 1977, to July, 1979. All were full-term babies, their mean gestational age was $39.6 \pm 0.39$ weeks, their mean birth-weight was $3380 \pm 960$ g. The pregnancies and deliveries were uneventful. Apgar score values at one and five minutes were eight or more. The babies did not receive vitamin K prophylactically. All were brestfed. Their blood gas values and other relevant data are shown in Table I.

Blood was sampled for coagulation studies at 12 hours of life and on the 3rd and

TABLE I

Clinical data of the healthy newborn infants

| Gestational age, week | Birth weight, g | Apgar | $pO_2$ mmHg | pH |
|---|---|---|---|---|
| 39.6 ± 0.99 | 3380 ± 960 | ≥8 | 58.66 ± 9.9 | 7.33 ± 0.17 |

| BE mEq/l | Temperature, °C | SeCa, mEq/l | Blood sugar, mg/dl | Htc per cent |
|---|---|---|---|---|
| −6.3-± 1.18 | 35.6 ± 0.1 | 4.77 ± 0.37 | 53.9 ± 16 | 57.7 ± 6.9 |

| Hgb g/dl | Sebi mg/dl | GOT IU | GPT IU |
|---|---|---|---|
| 19.6 ± 2.29 | 5.17 ± 2.8 | 25.7 ± 14.5 | 10.3 ± 6.7 |

TABLE II

Blood coagulation factors of healthy newborn infants

| Day | | $\overline{X}^{1}$ SD | $\overline{X}^{3}$ SD | $\overline{X}^{7}$ SD | Adult values |
|---|---|---|---|---|---|
| Fibrinogen | mg/dl | 172.7 ± 32.3 | 254.8 ± 40.2 | 257.1 ± 73.8 | 200—400 |
| Platelets | $\times 10^3$ mm$^3$ | 226 ± 57 | 215 ± 43.5 | 261 ± 48 | 150—400 |
| PA | per cent | 72.3 ± 20.9 | 33.2 ± 12 | 70.77 ± 18 | 80—110 |
| PTT | sec | 71.26 ± 9.9 | 76.07 ± 21.61 | 56.6 ± 7.25 | 40 |
| TT | sec | 30.13 ± 2.86 | 29.68 ± 3.11 | 30.7 ± 3.0 | 20 |
| Platelet factor 4 | sec | 93.25 ± 38.2 | 93.11 ± 38.2 | 71.75 ± 29.5 | 55 |
| AT III | | 1.53 ± 0.52 | 1.41 ± 0.49 | 1.18 ± 0.36 | 0.9—1.3 |

7th day. The blood was taken from a peripheral vein. Coagulation was inhibited by 3.8% sodium citrate or 1.4% potassium oxalate 9 : 1.

The following coagulation factors were studied: platelet count [13], fibrinogen concentration, prothrombin activity (PA) [30], partial thromboplastin time (PTT) [29], thrombin time (TT) [24], platelet factor 4 [28] and antithrombin III (AT III) [31]. For detecting the presence of fibrin monomer, the ethanol gelation test was used [15].

In addition to the healthy babies 8 newborn infants with disseminated intravascular coagulation (DIC) were studied. In 7 out of the 8, the bleeding disorder started within 15 hours after birth. All had had serious prolonged intrauterine asphyxia. One infant with DIC had sepsis and the bleeding symptoms appeared on the 11th day of life. Two of the 8 newborns died within 6 hours after birth. Relevant clinical data of the patients are shown in Table II.

Adequate treatment of the underlying disease was applied and 5 patients were given fresh blood transfusion or fresh blood plasma.

Student's $t$ test was used to evaluate the results.

## Results

Normal values for blood coagulation factors obtained in the 30 healthy newborn infants are shown in Table III, where the right column shows the normal adult values of the haematology laboratory of our hospital.

As can be seen, platelet count and fibrinogen concentration were within the normal adult range except on the first day of life. Prothrombin activity was significantly lower ($p < 0.01$) than in adults, especially on the third day of life. Partial thromboplastin time was significantly prolonged ($p < 0.001$) compared to the normal adult value. During the neonatal period these values gradually decreased but the difference was still significant on the seventh day ($p < 0.01$). Thrombin time was significantly lower than the average adult value and it did not change during the first seven days ($p < 0.001$). Platelet factor 4 activity was lower than in adults ($p < 0.001$). It increased by the seventh day, but even then it was significantly lower than the adult value. Antithrombin III activity was low as seen from the high plasma antithrombin index, then it gradually decreased by the seventh day.

As can be seen from these results, the coagulation factors are low in the neonatal period. This fact must be taken into account when evaluating the laboratory data [22].

During the past two years we have observed eight infants suffering from DIC. All but one had severe intrauterine asphyxia, marked acidosis after birth and bleeding symptoms starting within 15 hours of life. One infant exhibited symptoms of DIC after the eleventh day of life; the underlying disease was septic shock.

Two infants died within six hours. One infant had a hypoplastic left ventricular syndrome with coarctation of the aorta. The other infant had a grave gastrointestinal haemorrhage shortly after birth; it involved the gastrointestinal, pulmonary and central nervous systems.

The most characteristic features of our patients were petechiae, suffusions, bleeding from sites of puncture. The laboratory findings showed decreased prothrombin activity, prolonged partial thromboplastin time and thrombin as compared to our normal values. The most pronounced changes were thrombocytopenia and a marked decrease of blood fibrinogen. Table IV shows the relevant blood coagulation findings of the patients.

Antithrombin III activity was examined in few patients; low values were found. It is interesting that heparin added to plasma caused a further decrease in antithrombin III activity.

The ethanol gelation test was not positive in every case. The most important feature of the treatment was the elimination of the causative factor and replacement of the decreased or missing coagulation factors. For this reason the underlying disease was promptly and vigorously treated in all newborns, acidosis and hypoxia were corrected and the blood volume

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TABLE III

Clinical data of eight infants with DIC

| | Gest. age, week | Birth weight, g | Underlying disease | Onset of symptoms | Presentation of bleeding | Treatment | Improvement of values | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1. P. L. | 36 | 2750 | Breech delivery i.u. asphyxia | 2 hours | petechiae suffusion venipuncture gastrointestinal | plasma transfusion | | death at 6 hours |
| 2. Sz. G. | 36 | 2800 | Maternal diabetes i.u. asphyxia vacuum extraction | 8 hours | venipuncture gastrointestinal | | 20 hours | survival |
| 3. Cs. K. | 37 | 2600 | Toxaemia i.u. asphyxia | 4 hours | venipuncture gastorintestinal | transfusion | 7 days | survival |
| 4. O. K. | 42 | 3500 | I.u. asphyxia vacuum extraction | 6 hours | petechiae intracranial gastrointestinal | | 9 days | survival |
| 5. V. J. | 37 | 2500 | Hypoplastic left ventricle | 2 hours | petechiae suffusion venipuncture gastro-intestinal pulmonary | plasma | | death at 6 hours |
| 6. B. Cs. | 34 | 2600 | Premature rupture of membranes, sepsis | 11 days | venipuncture gastrointestinal | transfusion | 1 month | survival |
| 7. N. G. | 42 | 3000 | I.u. asphyxia Caesarean section | 15 hours | suffusion venipuncture | transfusion | 10 days | survival |
| 8. N. T. | 42 | 2500 | I.u. asphyxia i.u. retard. M. Down | 1 hour | suffusion venipuncture | | 10 days | survival |

TABLE IV

Values of blood coagulation factors of eight infants with DIC

| | Time of investigation, hour | Fibrinogen, mg/dl | Platelet count | PA per cent | PTT sec | TT sec | AT III | Ethanol gel test | Platelet factor 4 sec | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. P.L. | 4 | | 66,000 | no coagulation | | | | | | death |
| 2. Sz.G. | 8 | 130 | 45,000 | 50 | 95 | 34 | | + | | survival |
| | 20 | 170 | 60,000 | 55 | 72 | 26 | | — | | |
| 3. Cs.K. | 6 | 160 | 100,000 | 66 | 140 | 37 | | + | | survival |
| | 54 | 160 | 37,000 | 50 | 65 | 29 | | + | | |
| | 7. day | 250 | 130,000 | 100 | 61 | 32 | | — | | |
| 4. O.K. | 8 | 140 | 67,000 | 25 | 95 | 43 | 1.5 | + | | survival |
| | 80 | 105 | 30,000 | 35 | 85 | 43 | 3.08 | — | | |
| | 9. day | 190 | 140,000 | 100 | 45 | 37 | 1.87 | — | | |
| 5. V.J. | 4 | | 170,000 | 20 | >240 | | | + | | death |
| 6. B.Cs. | 11. day | 80 | 12,000 | 23 | 175 | 50 | 4.07 | — | 90 | survival |
| | 12. day | 110 | 16,000 | 57 | 72 | 32 | | + | 87 | |
| | 6. week | 175 | 600,000 | 68 | 48 | 22 | 1.15 | — | 75 | |
| 7. N.G. | 16 | 130 | 90,000 | 23 | 170 | 40 | 3.0 | — | 130 | survival |
| | 40 | 120 | 64,000 | 35 | 120 | 50 | 3.05 | — | >600 | |
| | 10. day | 265 | 36,000 | 54 | 73 | 31 | 1.04 | — | 480 | |
| 8. N.T. | 1.5 | 110 | 40,000 | 40 | 90 | 45 | 2.2 | + | 95 | survival |
| | 22 | 100 | 40,000 | 42 | 93 | 45 | 1.07 | — | 220 | |

was replaced. Since the blood coagulation factors of the newborn are physiologically weak, they were replaced by transfusion of fresh whole blood or blood plasma. Heparin was not applied.

Three patients improved dramatically without blood or plasma transfusion. The bleeding tendency of the surviving patients was abolished within 24—48 hours but the laboratory findings showed low values even after one week. The platelet count was the last to normalize among the blood coagulation factors examined. It became normal by about the end of the third week

## DISCUSSION

Normal haemostasis is a complicated process involving vascular integrity and coagulation factors. Changes in any of these parameters can cause bleeding disorders in the neonatal period [18, 19, 20]. Antiepileptic treatment of the mother, birth asphyxia, hypoxia, acidosis, hypothermia, infection together with the physiological depletion of clotting factors can all trigger DIC in the neonate.

The laboratory diagnosis of neonatal haemorrhage is often difficult, due to differences between normal

neonatal and adult coagulation values and to the fact that the neonates have low levels of certain clotting factors, especially of those dependent on vitamin K. In addition, slight variations in blood sampling and assay methods occur between laboratories. For this reason it is necessary that each hospital should establish its own normal values. Any abnormal value of a coagulation factor must be compared to own normal neonatal standards.

The primary aim of our work was to establish these neonatal coagulation standards. The results found in our healthy newborn infants agreed well with those of the literature [9].

DIC must be suspected whenever diffuse bleeding occurs and if there is an underlying disease known to be associated with DIC [10, 25, 27, 34, 36].

The condition is characterized by petechiae, suffusions, bleeding from puncture sites and sometimes gastrointestinal haemorrhage [1]. Coagulopathy is suspected when the patient has thrombocytopenia, prolonged clotting time, prolonged PT and PTT, and low fibrinogen concentration [9]. Complete analysis of all coagulation factors is not available everywhere. For this reason the minimum criteria for diagnosis are, thrombocytopenia, hypofibrinogenaemia, prolonged TT, and a positive ethanol gelation test.

Since DIC is a secondary condition, appropriate treatment of the underlying process alone will abolish the coagulopathy. In some cases other steps have to be taken, first of all replacement of the deficient procoagulants by fresh blood or plasma transfusion [9, 17, 25, 32]. In infants, interruption of the process by anticoagulants is rarely indicated [16, 26, 31, 35). A number of reports strongly suggests that replacement therapy alone is effective in DIC particularly in newborns afflicted by septic shock or respiratory distress syndrome.

Once the coagulopathy has improved due to early correct diagnosis and vigorous treatment of the primary disorder, heparin therapy which may be life-saving in fulminant purpura, giant haemangioma and some cases of malignancy [7, 8, 11, 12, 33], is needed only exceptionally. In the neonatal period management of the underlying disease and replacement therapy will make the DIC disappear without the use of anticoagulants.

## References

1. Abildgaard, C. F.: Recognition and treatment of intravascular coagulation. J. Pediat. **74**, 163 (1969).
2. Abstatt, L. B., Dennis, L. H. Sundell, H., Malan, A., Harrison, V., Hedvell, G., Eichelberger, J., Fogel, B., Stahlman, M.: Disseminated intravascular coagulation and hyaline membrane disease. Biol. Neonate. **19**, 227 (1971).
3. Bleyer, W. A., Hakami, N., Shepard, T. H.: The development of hemostasis in the human fetus and newborn infant. J. Pediat. **79**, 838 (1971).
4. Chadd, M. A., Elwood, P. C., Gray, O. P., Muxworthy, S. M.: Coagulation defects in hypoxic full-term newborn infants. Brit. med. J. **4**, 516 (1971).
5. Chessells, J. M., Wigglesworth, J. S.: Coagulation studies in severe birth asphyxia. Arch. Dis. Childh. **46**, 253 (1971).
6. Chessells, J. M., Wigglesworth, J. S.: Coagulation studies in preterm infants with respiratory distress and intra-

cranial haemorrhage. Arch. Dis. Childh. **47**, 564 (1972).
7. Corrigan, J. J., Jordan, C. M.: Heparin therapy in septicemia with disseminated intravascular coagulation. New Engl. J. Med. **283**, 778 (1970).
8. Corrigan, J. J., Jordan, C. M., Bennett, B. B.: Disseminated intravascular coagulation in septic shock. Amer. J. Dis. Child. **126**, 629 (1973).
9. Corrigan, J. J.: Disseminated intravascular coagulopathy. Pediatrics **64**, 37 (1979).
10. Ease, D.: Coagulation abnormalities associated with localized hemorrhage in the neonate. J. Pediat. **92**, 989 (1978).
11. Edson, J. R., Krivit, W., White, J. G., Sharp, H. L.: Intravascular coagulation in acute stem leukemia successfully treated with heparin. J. Pediat. **71**, 342 (1967).
12. Ellman, L.: Meningococcemia and consumption coagulopathy treated with heparin and Dextran. Arch. intern. Med. **127**, 134 (1971).
13. Feissly, R., Lüdin, H.: Microscopie par contrastes de phases; applications á l'hématologie. Rev. Hémat. **4**, 481 (1949).
14. Fetten, A., Straub, P. W.: Coagulation studies of cord blood, with special reference to "Fetal Fibrinogen". Thrombos. Diathes. haemorrh. (Stuttg.) **22**, 273 (1969).
15. Godal, H. C., Abidgaard, U.: Gelation of soluble fibrin in plasma by ethanol. Scand. J. Haemat. **3**, 342 (1966).
16. Göbel, U., Voss, H., Jürgens, H., Petrich, C., Pothmann, R., Sproch, I., Lemburg, P.: Efficiency of heparin in the treatment of newborn infants with respiratory distress syndrome and disseminated intravascular coagulation. Eur. J. Pediat. **133**, 47 (1980).
17. Gross, S. Melhorn, D. K.: Exchange transfusion with citrated whole blood for disseminated intravascular coagulation. J. Pediat. **78**, 415 (1971).
18. Hathaway, W. E., Mull, M. M., Pechet, G. S.: Disseminated intravascular coagulation in the newborn. Pediatrics **43**, 233 (1969).
19. Hathaway, W. E.: Coagulation problems in the newborn infant. Pediat. Clin. N. Amer. **17**, 929 (1970).
20. Hathaway, W. E.: The bleeding newborn. Semin. Hemat. **12**, 175 (1975).
21. Hollán, S. R., Révész, T.: Disseminated intravascular coagulation. In: Perinatal Medicine. Eds: Kerpel-Fronius, E., Véghelyi, P. V. and Rosta, J. Akadémiai Kiadó, Budapest 1978. p. 1127.
22. Honig, R. G.: Intravascular coagulation disorders. In: Neonatology. Diseases of the Fetus and Infant. Ed: Behrman, R. E. C. V. Mosby Co., St Louis 1973. p. 209.
23. Karpatkin, M.: Diagnosis and management of disseminated intravascular coagulation. Pediat. Clin. N. Amer. **18**, 23 (1971).
24. Kaulla, K. N., Kaulla, E.: Estimation of trombin tine of plasma. In: Blood Coagulation Haemorrhage and Thrombosis: Method of Study. Eds: Tocantins, L. M., Kazal, L. A. Grune and Stratton, New York 1964.
25. Lascari, A. D., Wallace, P. D.: Disseminated intravascular coagulation in newborns. Survey and appraisal as exemplified in two case histories. Clin. Pediat. **10**, 11 (1971).
26. Loo, S. S., Hitzig, W. H., Frich, P. G.: Clinical experience with anticoagulant therapy in the management of disseminated intravascular coagulation in children. Acta haemat. (Basel) **45**, 1 (1971).
27. Margolis, C. Z., Orzalesi, M. M., Schwartz, A. D.: Disseminated intravascular coagulation in the respiratory distress syndrome. Amer. J. Dis. Child. **125**, 324 (1973).
28. O'Brien, J. R., Etherington, M., Jamieson, S., Lawford, P.: Heparin thrombin clotting-time and platelet factor 4. Lancet **2**, 656 (1974).
29. Proctor, R. R., Rapaport, S. I.: The partial thromboplastin time with kaolin. A simple screening test for first stage plasma clotting factor deficiencies. Amer. J. clin. Path. **36**, 212 (1961).
30. Quick, A. J.: Hemorrhagic Diseases. Lea and Febiger, Philadelphia 1957. p. 379.
31. Seeler, R. A.: Recovery from disseminated intravascular coagulation without heparin therapy. J. Amer. med. Ass. **215**, 1827 (1971).
32. Skyberg, D., Jacobsen, C. D.: Defibrination syndrome in a newborn and its treatment with exchange transfusion. Acta paediat. scand. **58**, 83 (1969).
33. Wachsman, J. S., Flessa, H. C., Glueck, H. I., Will, J. J.: Coagulation defects and giant cavernous hemangioma. Amer. J. Dis. Child. **111**, 71 (1966).
34. Watkins, M. N., Swan, S., Caprini, J. A., Gardner, T. H., Zuckerman, L., Vagher, J. P.: Coagulation changes in the newborn with respiratory failure. Thrombosis Res. **17**, 153 (1980).
35. Whaun, J. M., Oski, F. A.: Experience with disseminated intravascular coag-

ulation in a children's hospital. Canad. med. Ass. J. **107**, 963 (1972).
36. Woods, W. G., Luban, N. L. C., Hilgartner, M. W., Miller, D. R.: Disseminated intravascular coagulation in the newborn. Amer. J. Dis. Child. **133**, 44 (1979).

G. Gyódi, M. D.
Megyei Kórház
Kaposvár, Hungary