[haematologica reports]
2006;2(10):66-70

The bleeding neonate

S. ARONIS-VOURNAS

Director Haemophilia
Center, Haemostasis Unit,
Aghia Sophia Children's Hospital,
Athens, Greece

A B S T R A C T

The neonate is born with a combined deficiency in plasma coagulation factors, natural inhibitors of haemostasis and components of the fibrinolytic system. In the healthy neonate, there is a balance between haemostatic systems, therefore under normal circumstances, the healthy neonate does not present haemorrhage or thrombosis. However several coagulation disorders, congenital or acquired, may be expressed during the neonatal period in a healthy or diseased neonate. Haemophilia A, B (Haem-A, B) and von Willebrand disease (vWD) are the most common inherited coagulation disorders, whereas congenital deficiencies of FI, FII, FV, FVII, FX, FXI, FXII or FXIII occur rarely. Cephalematoma, intracranial haemorrhage (ICH), bleeding from the umbilicus cord may be the first signs of congenital FXIII, FVII or FVIII deficiency. Acquired coagulation plasma factors deficiency is usually associated with vitamin K deficiency (early, classic, late haemorrhagic disease, secondary haemorrhagic disease), liver insufficiency (hepatitis, metabolic diseases e.t.c) or disseminated intravascular coagulation, complicating severe sepsis. Platelets are produced from the 11th gestational week of the foetus. The healthy neonate, full-term or premature, is born with a normal platelet value (>150x10^9/L). Any value <100x10^9/L should be investigated. Thrombocytopenia is frequent in the neonatal period (0.7-0.9%), whereas it occurs in 20-40% of patients in a neonatal intensive care Unit. 20-40% of the cases are of unknown aetiology. Congenital quantitative (Tarr, Wiskott-Aldrich syndrome, amegakaryocytic thrombocytopenia, Alport syndrome, Fanconi's anaemia, vWD type II, Mediterranean megathrombocytopenia, Flechtner syndrome, Sebastian anomaly, Trousseau syndrome, Chediak-Higashi syndrome) or qualitative platelet disorders (Glanzman, Bernard-Soulier syndrome, May Hegglin anomaly), are rare. On the contrary, acquired thrombocytopenias or thrombasthenias occur more often. Thrombocytopenia due to increased platelet destruction is usually associated with several diseased states (bacterial/viral infections, fungal or protozoal infections) or an immune mechanism (autoimmune, isoimmune thrombocytopenia). The risk of ICH is higher in neonates with isoimmune thrombocytopenia. Finally, secondary thrombasthenias are most often associated with antibiotics anti-inflammatory drugs, anti-histamines, indomethacin e.t.c. Haemostasis screening includes thrombin time, prothrombin time, APTT, platelet count, clot retraction and bleeding time. Further investigation unmasks the defect and determines the necessity and type of therapeutic intervention, taking under consideration the bleeding manifestations and infant's clinical condition.

The healthy neonate is born with combined defects; coagulation factors II, VII, IX, X, XI, XII, XIII are decreased. Natural inhibitors of haemostasis (TFPI, AT, PC, PS) are also reduced; however, free PS is normal. C4BP (C4 Binding Protein), which binds PS, is deficient in the newborn. Of the anticoagulants a2MG is increased during infancy. Plasminogen (plg), and tissue plasminogen activator (tpA) are decreased, however plasminogen activator inhibitor (PAI) and a2-antiplasmin (a2AP) are increased. The latter abnormalities are expressed by a decreased fibrinolytic activity. Platelets are produced from the 11th week of foetal life and are normal at birth, regardless of the maturity of the newborn; nevertheless, platelets appear with a transient functional defect. The severity of the above haemostatic abnormalities depends on the maturity of the liver, the gestational age, and the birth weight of the neonate. However, in spite of the multiple haemostatic defects, a dynamic equilibrium is maintained amongst the coagulation systems, thus under normal circumstances, the healthy neonate does not bleed or thrombose. Congenital or acquired disorders of haemostasis associated with underlying diseases may tip off the equilibrium towards either direction. Bleeding in the neonate may be the result of congenital or acquired haemostasis disorders, which may be the result of platelet disorders, plasma factors deficiency or both.

Platelet disorders

Quantitative platelet disorders

Thrombocytopenia (TP) is considered any platelet value below $150x10^9$/L (normal values; 150-400 $x10^9$/L). Platelets count $<100x10^9$/L should be investigated. The incidence of TP in the neonatal population is 0.7-0.9%, and in ICU (intensive care units) 20-40%. 20-40% of the cases are of unknown aetiology. Of the thrombocytopenic neonates, 20% present platelet count $<50x10^9$/L. In this group of patients the mortality rate is high, as is the rate of neurological sequelae, following an intracranial haemorrhage (ICH).

Congenital thrombocytopenias

Patients with congenital TPs may have one or more of the following characteristics; macrothrombocytopenia/microthrombocytopenia, immunological defects, skeleton abnormalities, mental retardation, deafness / cataract/albinism, renal dysfunction, cardiac defect e.t.c. The mode of inheritance may be sex linked (rarely) or autosomal, recessive or dominant.

Tarr syndrome (TP + absent radii), Wiskott Aldrich syndrome (TP + low platelet volume + immunologic defect + eczema, x-linked transmission), amegakaryocytic thrombocytopenia (TP without limb abnormalities) are rare quantitative platelet disorders. Alport syndrome (macrothrombocytopenia + renal functional defect + congenital abnormalities), Fanconi's anaemia (pancytopenia + congenital abnormalities, autosomal recessive inheritance) are known congenital syndromes. von Willebrand disease type IIb (macrothrombocytopenia, abnormal platelet agglutination + low vWF, autosomal dominant transmission), Mediterranean macrothrombocytopenia (low grade TP + macrothrombocytes, autosomal dominant inheritance), Bernard-Soulier syndrome (glycoprotein Ib deficiency + macrothrombocytopenia + abnormal platelet agglutination, autosomal recessive inheritance), May - Hegglin anomaly, Sebastian anomaly (autosomal dominant inheritance) are all associated with macrothrombocytopenia. Fechtner syndrome (TP + renal functional defect + cataract + inclusions in the polymorfonuclear cells, autosomal dominant inheritance), Trousseau syndrome (PT + 11q23 deletion + normal platelet volume + abnormal inclusions, autosomal dominant inheritance), Chediak-Higashi syndrome (TP + thrombocytopathy + immunologic defect + albinism, autosomal recessive transmission) are rare disorders.

Acquired thrombocytopenias

The mechanism of acquired TPs may be the result of decreased platelet production, abnormal release of platelets from megakoryocytes, increased platelet destruction or a combination of them. Decreased platelet production may be caused by bone marrow infiltration, as in congenital neuroblastoma, congenital leukaemia or Letterer-Swive. TP due to increased platelet destruction may occur in the following disease states or conditions; bacterial or viral infections, fungal and protozoal infections, immune thrombocytopenias, DIC (disseminated intravascular coagulation), necrotizing enterocolitis, Kasabach-Merritt syndrome, HELLP syndrome, TORCH syndrome. TP may also occur in RDS, phototherapy, HUS/TTP (haemolytic uremic syndrome/thrombotic thrombocytopenic purpura), neonatal hyperviscosity syndrome (congenital cyanotic cardiac diseases), metabolic diseases, intrauterine growth retardation, after exchange transfusions e.t.c.

In neonatal sepsis, TP is an early laboratory evidence, both in septicaemia caused by Gram- or Gram+ bacteria. Progressive increase of platelet count (PC) is an indication of response to therapy, whereas persistence

Table 1. Congenital thrombocytopenias.

Tarr syndrome
Wiskott-Aldrich syndrome
Amegakaryocytic thrombocytopenia
Alport syndrome
Fanconi's anaemia
Von Willebrand disease type IIb
Mediterranean macrothrombocytopenia
Bernard- Soulier syndrome
May-Hegglin anomaly
Sebastian syndrome
Fechtner syndrome
Trousseaux syndrome
Chediak-Higashi syndrome

Table 2. Acquired thrombocytopenias.

Congenital neuroblastoma
Congenital leukaemia
Letterer Swive
Bacterial/viral infections
Fungal/protozoal infections
Immune thrombocytopenia
DIC (disseminated intravascular coagulation)
Necrotizing enterocolitis
Kasabach-Merritt syndrome
HELLP syndrome
Torch syndrome
RDS
Phototherapy
HUS/TTP
Neonatal hyperviscosity syndrome
TP after exchange transfusions
Metabolic diseases
Intrauterine growth retardation

of TP is an indication of non-response to therapy and necessitates change in antibiotics. TP may occur as isolated or at the setting of DIC.

Neonatal Immune TP may be the result of platelet destruction in the circulation due to an autoimmune or alloimmune mechanism. Neonatal autoimmune TP (NATP) may occur, if the mother suffers from ITP (immune TP), SLE (Systemic Lupus Erythimatosus), Evans syndrome or drug-induced TP. In a study of 284 pregnant women with ITP, TP was documented in 22.4% of the newborns, however only 6.3% of the infants presented a mild bleeding tendency. Mother is usually thrombocytopenic, although there are cases in which mother may have normal platelet count, as a result of medication or splenectomy or a past history of ITP. In these instances, TP in the neonate is the result of enough antibodies production in the maternal circulation which cross the placenta and destroy neonates' platelets.

The clinical presentation of NATP is milder than the NITP. The risk of ICH is 1%. Remission of TP occurs within 2-3 months. If mother suffers from ITP and her platelet count is < $10x10^9$/L, caesarean section should be considered. Cord blood sample should be examined for TP and U/S of brain should be performed for exclusion of a possible ICH. PC has to be repeated for the first 3-4 days of life. If prenatal diagnosis has been decided it could be done with blood sampling from the umbilical cord or the scalp vessels. In the latter case, false TP may be diagnosed. Possible complications are haemorrhage in the mother or the neonate and foetal loss (1-2%). If prenatal diagnosis has been decided, IVIG / steroids should be given to the mother. In case of neonatal haemorrhage, IVIG or and steroids should be infused to the neonate.

Neonatal isoimmune TP (NITP) is the result of platelet incompatibility between mother and father, in case the foetus inherits the father's genotype. The most potent (strong) responsible antigens are HPA1a, HPA5b, and HLA. If the mother is negative for the responsible antigen, she produces antiplatelet antibodies which cross the placenta and cause TP to the neonate. 2.5% of women lack the HPA1a antigen; however sensitization occurs in 1/20-50 women (1:1500 gestations). The risk for TP is 40-50% for the first pregnancy and 80-90% for every further pregnancy. ICH may occur in 10% of untreated cases (half of them occur in uterus) with 20% of them presenting neurological sequelae. The diagnosis of NAITP in an otherwise healthy neonate is made by exclusion of underlying diseases or conditions which are associated with TP. Genotyping of parents' antigens by IF / Fluocytometry confirms the diagnosis. Besides, mixing of maternal serum with paternal platelets gives abnormal platelets aggregation. In case of ICH, other life threatening haemorrhage or PC < $10x10^9$/L, therapeutic intervention with IVIG (1g/kg/d x 2d) is justified. Washed platelets from the mother or compatible platelets from typed donors could be infused. If the neonate does not bleed, U/S is performed for documentation of a possible ICH. The overall duration of NITP is approximately 3 weeks.

Antenatal treatment in case of a second pregnancy; if there is a history of previous affected sibling with ICH, a foetal blood sample is taken at the 24th week of gestation and a platelet count is performed. If the foetus proves to be thrombocytopenic, weekly transfusions of compatible platelets are recommended up to delivery (32nd-34th week), however the procedure is complicated by an 8.3% foetal loss. Maternal treatment with IVIG should be instituted and maintained during pregnancy. If the previously affected sibling has not suffered ICH, no foetal monitoring is recommended, but IVIG is still given to the mother.

Gestational benign TP: mild asymptomatic TP (PC: ~$100x10^9$/L) which is noted during the 3d trimester of pregnancy in healthy pregnant women. Antiplatelet antibodies are not detected; however the platelet survival is decreased due to activation of the coagulation system. This type of TP is not associated with TP in the neonate.

Qualitative platelet disorders

Congenital thrombasthenias are rare qualitative disorders of platelets, which are not usually expressed during the neonatal period. Glanzman thrombasthenia (ADP, epinephrine, collagen, thrombin aggregation: abnormal, ristocetin aggregation: normal), Bernard Soulier syndrome (TP, FVIIIC + vWF: normal; ristocetin aggregation: abnormal, giant platelets) and May Hegglin anomaly (large platelets) are well known entities, though rare. The mode of inheritance is autosomal recessive for the first two and autosomal dominant for the third one. Petecheae, ecchymoses and bleeding from the mucosal membranes are the main manifestations in infants and toddlers. The screening tests of haemostasis are normal, albeit bleeding time and clot retraction, nevertheless the diagnosis is confirmed by the typical pattern of aggregation tests for each disorder.

Acquired thrombasthenias are quite frequent and are usually associated with antibiotics, anti-inflammatory drugs, anti-histamines, and indomethacin. Aspirin is contraindicated in patients with bleeding disorders, since it interferes with platelets function and worsens the haemorrhagic diathesis.

Coagulation factors deficiency

Congenital coagulation disorders

Deficiency of all plasma factors (I, II, V, VII, X, XI, XII,

and XIII) except FVIII and FIX are extremely rare disorders transmitted with an autosomal recessive manner of inheritance with parents being usually relatives. FVII deficiency presents a variable clinical expression. FXI and FXII do not cause problems in the neonatal period. On the contrary, FXIII is usually manifested at birth with cephalaematoma, ICH and umbilical cord haemorrhage.

Afibrinogenaemia/hypofibrinogenaemia: the haemorrhagic diathesis is of variable severity: cephalaematoma, ICH, haematemesis/malaena, haematuria, haemorrhage from the umbilicus cord and post-traumatic or post-surgical haemorrhage. The screening tests are abnormal (except reptilase time), and I is not detectable or reduced.

Dysfibrinogenaemia: qualitative defect of fibrinogen, due to a point mutation. More than 100 different types of dysfibrinogenaemia have been described. The mode of inheritance is autosomal dominant. The severity of the clinical expression is variable. Some types of dysfibrinogenaemia predispose to thrombosis. Thrombin time, prothrombin time, APTT and reptilase time are all prolonged. Fibrinogen may be normal or reduced. The bleeding time is prolonged. The electrophoretic pattern of I on double-crossed electrophoresis is abnormal, as are the aggregation tests with ADP, collagen, epinephrine and thrombin.

Haemophilia A (or B): it is a sex-linked inherited disorder, transmitted by the X chromosome, thus females are carriers of the defect and males with the abnormal gene express the disease. The reported incidence is 1:5000 male births. Cephalaematoma, ICH, bleeding after circumcision or heel puncture may occur at birth. Neonates with either type of haemophilia are otherwise healthy, however, in case of excessive blood loss in the scalp or brain, the baby looks pale and restless. Later in life haemarthroses represent 90% of the haemorrhagic episodes of a severely affected haemophiliac (FVIII/IX <1%). Most often there is a known family history, but 1/3 of cases are sporadic. The APTT is prolonged and FVIII or IX are absent or reduced according to the severity of the disease. Prenatal diagnosis of the disease is feasible by DNA techniques in families in which the genetic defect has been identified in the propositus- intron 22 inversion is the most common genetic defect in severely affected patients. During the 10[th]-12[th] gestational week, in a sample obtained from the chorion villi, the gender of the foetus is determined and DNA analysis for haemophilia is performed, if the foetus is male. The haemophilia treater (physician) and the obstetrician provide all the information about the disease transmission and the current strategy in haemophilia care, however, the couple makes the final decision for terminating the pregnancy or not.

Von Willebrand disease (vWd) is the most common hereditary disorder occurring with an incidence of 1% in the general population. There are several types of the disease, nevertheless the severe form, vWd type III, is extremely rare. The disorder is transmitted with an autosomal mode of inheritance, recessive or dominant. The disease is not usually expressed clinically during the neonatal period. Bleeding from mucous membranes is the most common manifestation of the disease in toddlers. The diagnosis of the defect is made by measuring the activities of FVIII (↓FVIIIC, ↓vWFAg, ↓vWF, ↑bleeding time).

FVII deficiency is a rare congenital disease transmitted with an autosomal recessive trait. It has variable expression, regardless of the severity of the defect. ICH or life threatening haemorrhage from several organs may occur at birth, if the delivery is laborious. Later in life, haemarthroses/haematomata or haemorrhage from mucous membranes are the main clinical manifestations in severely affected patients. The prothrombin time is typically prolonged and the FVII levels are reduced.

Acquired coagulation disorders

Haemorrhagic disease of the newborn, secondary haemorrhagic disease, DIC and liver dysfunction are well known entities associated with haemorrhagic diathesis in the neonate.

Early haemorrhagic disease of the newborn is manifested in neonates born to mothers taking anticoagulants or anticonvulsants which antagonize vitamin K. If mother is not monitored properly, umbilicus haemorrhage, cephalaematoma, haemorrhage from various systems occur at birth. The mortality rate is high, ranging from 10-50%. Neurological sequelae, due to ICH are not infrequent.

Classic haemorrhagic disease of the newborn (CHDN) is manifested on the 3[rd] day of life, with bleeding from mucous membranes, umbilicus or ICH, in an otherwise healthy neonate. It usually appears in babies of mothers coming from relatively low socioeconomic conditions. Mothers are poorly fed, thus they do not provide a sufficient amount of vitamin K to the neonate. Normal supply of vitamin K and liver maturity are the prerequisites for vitamin-K dependent factors (FII, FVII, FIX, and FX) production. The defect is more profound if the baby is breast-fed, since maternal milk is poorer in vitamin K content than formula milk. The incidence of CHDN has been reported to be 5.4 cases/1,000,000 births. The prophylactic administration of vitamin K in every neonate, regardless of the body weight and the clinical condition, eliminated the disease.

Late haemorrhagic disease: it occurs in breast-fed neonates who have not received vitamin K at birth. It

is extremely rare in infants who have received prophylaxis at birth. It is expressed usually with ICH (50% of cases) or mucous membranes' haemorrhage after the 3rd week of life until the second month or even later. Haemostasis testing reveals prolonged PT, APTT, but normal TT. FII, FVII, FX, FIX are reduced, as are PC and PS (vitamin-K dependent anticoagulants).

Secondary haemorrhagic disease: several conditions are associated with vitamin K deficiency, such as prolonged diarrhoea, cystic fibrosis, α1-antithrypsin deficiency, α-β lipoproteinaemia, biliary atresia, surgical exertion of the small intestine, certain antibiotics intake (cyclosporines, β-lactames) and parenteral nutrition.

Liver disease: almost all plasma factors except FVIII are produced by the liver, therefore liver insufficiency of any aetiology is associated with reduction in several factors (FII, FVII, FIX, FX, I, FXI, FXII). FVIIIC is increased, as it is synthesized by the RES. Natural inhibitors of haemostasis (PC, PS, AT) are also decreased. Thrombocytopenia and increased D-dimers are indications of the co-existence of a low grade DIC.

DIC: it is a secondary condition usually complicating severe diseases or states. Sepsis, asphyxia, trauma, severe RDS, Kasabach-Merritt syndrome, cancer are the most common conditions associated with a variable degree of DIC. All systems of haemostasis are triggered; the generation of thrombin enhances thrombus formation in several organs. In the procedure of clot formation several coagulation factors (I, FVII, FV, FVIII, PC, PS, AT, platelets, D-dimers) are consumed and the patient may bleed from the site of venepunctures or mucous membranes.

Laboratory testing

Screening tests of haemostasis: Thrombin time (TT), Prothrombin time (PT), APTT, Platelet count (PC), Clot retraction, Bleeding time (BT), whole blood count, blood-smear. Further investigation is performed, according to the above results taking under consideration the history of the neonate, the family and the obstetrical history. Further investigation unmasks the defect and determines the necessity and type of therapeutic intervention.