REVIEW

Neonatal coagulation problems

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Bleeding problems often occur during the neonatal period. Although thrombocytopenia is the most common cause, coagulation problems often occur, and the two problems may co-exist. The causes, diagnosis, and management of coagulation problems in newborn infants are reviewed.

Bleeding problems are often encountered during the neonatal period particularly in intensive care. Thrombocytopenia is probably the most common cause but coagulation defects are also observed, and the two problems often co-exist. Although most coagulation problems reflect acquired disorders, a number of inherited conditions can also present at this time. Appropriate diagnosis and management of these conditions is highly dependent on prompt recognition of clinically abnormal bleeding and the initiation of appropriate investigations. Although acquired disorders most often present in sick term or preterm infants, many inherited disorders manifest in otherwise healthy infants. Recognition of the clinical setting in which bleeding occurs is therefore an important clue to the underlying diagnosis. Investigation requires careful observation of age dependent features, which are especially important during the early weeks of life.

NEONATAL HAEMOSTATIC SYSTEM

Normal haemostasis reflects a highly complex process, which is dependent on a series of interactions occurring between endothelial cells, platelets, and haemostatic proteins. Our understanding of this process has improved considerably in recent years, and it is now accepted that traditional models of haemostasis do not adequately reflect events in vivo and are an oversimplification of the processes involved. It is now recognised that the traditional extrinsic pathway, involving tissue factor and factor VIIa, is the major pathway whereby coagulation is initiated, and that thrombin plays a crucial role in both the activation and inhibition of coagulation and also in platelet activation.[1]

An understanding of the haemostatic system and features unique to the early weeks of life is important when it comes to the investigation of a neonate with a haemorrhagic problem. The haemostatic system is profoundly influenced by age, and the concentrations of many haemostatic proteins are dependent on both the gestational and postnatal age of the infant. At birth, concentrations of the vitamin K dependent (FII, FVII, FIX, FX) and contact factors (FXI, FXII) are reduced to about 50% of normal adult values and are further reduced in preterm infants.[2 3] Similarly, concentrations of the naturally occurring anticoagulants, antithrombin, protein C, and protein S, are low at birth, and, as a consequence, both thrombin generation and thrombin inhibition are reduced in the newborn period.[2 3] Plasminogen is the major protein involved in fibrinolysis, and again this is reduced during the neonatal period, resulting in a relatively hypofibrinolytic state.[4]

Despite this apparent functional immaturity, the neonatal haemostatic system seems to result in relatively few clinical bleeding problems for the healthy term infant. The haemostatic system matures during the early weeks and months of life, and the concentrations of most haemostatic proteins, both in term and preterm infants, are very close to adult values by 6 months of age.

Platelets are also influenced by age, although qualitatively rather than quantitatively. Thus the platelet count is within the normal adult range in both term and preterm infants. Although neonatal platelet numbers are normal, studies of platelet function suggest that neonatal platelets are hyporeactive compared with adult platelets. Despite this, the bleeding time, which can be viewed as an in vivo assessment of the platelet-vessel wall interaction, is shortened in normal healthy neonates.[5] This probably reflects multiple factors including increased concentrations of von Willebrand factor (vWF), the presence of large vWF multimers, and the high neonatal packed cell volume.[6]

INVESTIGATION OF THE NEONATE WITH ABNORMAL BLEEDING

Clinical considerations

A number of clinical considerations are important in the investigation of a neonate with a haemorrhagic problem and a possible underlying coagulopathy. Most important of these is probably the clinical setting in which the bleeding occurs. Bleeding in an otherwise well neonate is much more suggestive of an inherited coagulation or an immune mediated thrombocytopenia, whereas a sick preterm neonate is more likely to have a consumptive coagulopathy with disseminated intravascular coagulation (DIC). The presence of a family history of a bleeding disorder or of a previously affected infant can also be an important diagnostic pointer. Obstetric complications and problems at delivery can also affect the haemostatic system resulting in coagulation activation and DIC. Finally both maternal and

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Abbreviations: APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FII, FVII, FIX, FX, FXI, and FXII, factor II, VII, IX, X, XI, and XII; VKDB, vitamin K deficiency bleeding; vWD, von Willebrand disease; vWF, von Willebrand factor

Table 1 Laboratory investigation of neonatal coagulation disorders

Condition	PT	APTT	Fibrinogen	Platelets	Diagnostic tests/other useful tests
Inherited disorders					
Haemophilia A	N	↑	N	N	FVIII assay
Haemophilia B	N	↑	N	N	FIX assay
vWD (type III)	N	↑	N	N/↓	FVIII/vWF assays
FVII	↑	N	N	N	FVII assay
FX	↑	↑	N	N	FX assay
Fibrinogen	N/↑	N/↑	↓	N	Fibrinogen assay
FXIII	N	N	N	N	FXIII screen/assay
Acquired disorders					
DIC	↑	↑	↓	↓	D-Dimers
Vitamin K deficiency	↑	N/↑	N	N	FII, VII, IX, X
Liver disease	↑	↑	N/↓	N/↓	Factor assays

PT, Prothrombin time; APTT, activated partial thromboplastin time; N, normal; DIC, disseminated intravascular coagulation; FII, FVII, FIX, FX, FXI, and FXII, factor II, VII, IX, X, XI, and XII; vWD, von Willebrand disease; vWF, von Willebrand factor.

neonatal drugs, particularly with regard to vitamin K metabolism, may be highly relevant at this time.

Laboratory investigations

Initial screening investigations usually comprise a full blood count and a baseline coagulation screen. The results of these initial screening tests can then be used to guide the direction of further investigations. Sampling problems are common in the newborn period, and it is particularly important that samples for coagulation testing avoid contamination or activation before analysis. Reduced procoagulant concentrations result in prolongation of baseline coagulation variables, particularly the activated partial thromboplastin time (APTT), and it is therefore very important that results are interpreted in conjunction with age adjusted normal ranges. Ideally, laboratories processing large numbers of neonatal samples should derive their own in-house reference ranges, as these are both machine and reagent specific, but in practice this is often difficult to do, and the use of published ranges may be required.[2 3] As many of these ranges were derived some time ago and do not reflect current technology they must be used with care. The high neonatal packed cell volume also results in a minor degree of spurious prolongation of coagulation times, and this is particularly relevant in polycythaemic infants.

Where further investigation is required, this may include factor assays, which again must be interpreted using appropriate age adjusted ranges. In certain circumstances, more specialised techniques may be required to investigate for less common defects including abnormalities of platelet function.[7]

INHERITED COAGULATION DISORDERS

Haemophilia

Haemophilia A and B are the most common inherited bleeding disorders to present in the newborn period. These disorders result from deficiencies of FVIII and FIX respectively and are of variable severity reflecting the heterogeneous nature of the underlying molecular abnormalities. Both conditions are inherited as X linked recessive disorders, and clinical manifestations early in life are almost always confined to boys.

At least a third of all haemophilia cases occur in the absence of a positive family history and are therefore unsuspected at birth. Recent cohort studies suggest that 15–33% of cases may present with bleeding manifestations during the first month of life.[8–10] The pattern of bleeding observed during the neonatal period differs from that seen in older children, and a significant proportion of bleeds are iatrogenic in origin. Oozing or haematoma formation following venepuncture or vitamin K administration are relatively common manifestations. Major bleeding, both intracranial and extracranial, is also recognised, and, in a recent literature review, 41% of all reported cases of bleeding during the first month of life involved cranial bleeding.[11] This type of bleeding is often related to trauma at delivery and is associated with a poor outcome.[9]

On baseline coagulation screening, both haemophilia A and B typically result in isolated prolongation of the APTT, which in an otherwise healthy male infant is highly suggestive of the diagnosis (table 1). Confirmation of the diagnosis requires measurement of FVIII and FIX concentrations. As FVIII concentrations are within the normal adult range or mildly increased at birth, it is usually possible to confirm a diagnosis of haemophilia A regardless of the severity of the condition or the gestational age of the infant. The only exception to this is mild haemophilia A, where an initial result at the lower end of normal may warrant repeat screening when the infant is older. FIX concentrations, on the other hand, are significantly reduced at birth, which precludes the diagnosis of mildly affected cases until 3–6 months because of overlap with the normal range at this age.

It is important that infants presenting with abnormal bleeding are appropriately investigated for haemophilia and other inherited bleeding disorders. Unfortunately, the literature suggests that delays in reaching a diagnosis are quite common in these conditions.[12 13] This may reflect failure to recognise bleeding as abnormal or problems in initiating or interpreting appropriate investigations. In particular, physiological prolongation of the APTT must be interpreted with care, and it should also be noted that a mildly reduced FVIII concentration is not incompatible with a normal APTT. Factor assays should therefore always be performed if bleeding appears excessive.

Once the diagnosis has been reached, management is usually undertaken in consultation with a paediatric haematologist with experience in managing haemophilia. Management of bleeding problems requires appropriate factor replacement therapy, and, in the developed world, recombinant products are now the treatment of choice.[14]

von Willebrand disease

von Willebrand disease (vWD) is a relatively common inherited bleeding disorder which results from either quantitative or qualitative abnormalities in the vWF protein. The condition can be divided into three broad subtypes, of which type I disease is the most common and usually results in a relatively mild clinical phenotype.[15] Owing to the physiological increase in vWF concentrations at birth, type I disease does not usually manifest until later in life, and, even where there is a family history, it is not usually possible to make a diagnosis of this condition during the newborn period. Some

subtypes of type II disease are associated with thrombocytopenia, which may be apparent during the neonatal period and may result in bleeding.

Type III vWD is a rare autosomal recessive condition, which is more common in populations where consanguineous marriages are common. Typically both parents will be asymptomatic. In this condition, vWF concentrations are almost totally absent, and this results in a severe bleeding tendency that may present during the neonatal period. Manifestations are variable, although bleeding from mucous membranes is more common than in haemophilia.

In type III vWD, as with haemophilia, coagulation screening usually results in an isolated prolongation of the APTT, and the diagnosis is confirmed by measuring FVIII and vWF antigen and activity levels (table 1).

Management of bleeding in type III vWD is usually with factor replacement using an intermediate purity FVIII concentrate containing the high molecular weight multimers of vWF.[14]

Rare coagulation disorders

The so called rare coagulation disorders comprise a group of autosomal recessive deficiencies which in either a homozygous or compound heterozygous state may give rise to a major clinical bleeding diathesis. Owing to their mode of inheritance, these abnormalities occur more often in countries or populations where consanguineous marriage is common (table 2). Published information on clinical manifestations and management is relatively limited, but it is clear that a number of these disorders are associated with a severe bleeding tendency, which may manifest in the first few days of life.[16]

Severe deficiencies of fibrinogen, FVII, FX, and FXIII are the most likely conditions to present neonatally. Soft tissue bleeding and umbilical stump bleeding are typical manifestations, with umbilical bleeding reported in 80% of cases of severe FXIII deficiency. It is also clear, however, that intracranial bleeding is a relatively common feature of these disorders. This highlights the need to exclude an inherited bleeding disorder in any neonate presenting with an unexplained intracranial bleed.

Except for FXIII deficiency, all of these abnormalities are likely to result in some perturbation of the baseline coagulation screen, although, as with haemophilia, problems with the interpretation of abnormal screen results can result in a delayed diagnosis. Table 1 shows typical coagulation patterns observed in each disorder. Specific factor assays are then required to confirm the diagnosis. FXIII deficiency, even in its most severe form, is associated with a normal coagulation screen and has to be assessed specifically using either a screening test or a FXIII assay. The FXIII screening test is only sensitive to the most severe forms of the deficiency, and there is currently debate about optimal testing strategies. These tests are not widely available, and a local reference centre is usually used.

Table 2 Rare coagulation disorders

Deficiency	% of UK inherited bleeding disorders
Fibrinogen	0.2
Prothrombin	0.02
Factor V	0.6
Factor VII	1.3
Factor V+VIII	0.3
Factor X	0.5
Factor XI	3.3
Factor XIII	0.5

Management of bleeding episodes in this group of conditions should be with a specific factor concentrate where this is available. Because of the high risk of intracranial haemorrhage, regular prophylaxis should be started as soon as a diagnosis of FXIII deficiency has been made and should also be considered for both severe FVII and FX deficiency.

ACQUIRED COAGULATION DISORDERS

DIC

DIC is a relatively common problem, especially in the unwell neonate. The neonatal age group appears to be particularly susceptible. DIC always occurs as a secondary event, and a number of perinatal and neonatal problems are associated with this complication: birth asphyxia, acidosis, respiratory distress syndrome, infection, necrotising enterocolitis, meconium aspiration, aspiration of amniotic fluid, brain injury, hypothermia, giant haemangioma, homozygous protein C/S deficiency, thrombosis, malignancy. As in older children and adults, once established, DIC is often associated with increased mortality. Although DIC is often regarded as a haemostatic problem, it is in fact a complex systemic process involving activation and dysregulation of both coagulation and inflammatory processes. Clinically both bleeding and thrombotic problems may occur, and microvascular thrombosis in particular contributes to multiorgan damage. Failure to regulate the coagulation process results in massive uncontrolled thrombin generation, with widespread fibrin deposition and consumption of coagulation proteins and platelets.

DIC, particularly in the early stages, can be difficult to diagnose, and the clinical setting can be an important initial pointer. The condition is much more commonly observed in the sick neonate, who may have obvious sepsis or other complications such as necrotising enterocolitis. The laboratory diagnosis of DIC in older children and adults is usually based on a typical pattern of reduced platelets, prolonged coagulation variables (prothrombin time, APTT with or without thrombin clotting time), reduced fibrinogen, and increased D-dimers (or other markers of fibrin or fibrinogen degradation). Although this pattern is likely to be present in a neonate with fulminating DIC, findings can vary, and a number of factors complicate the diagnosis during the neonatal period.

Thrombocytopenia can be an early manifestation of DIC, but is an extremely common haematological complication during the neonatal period, particularly in the neonatal intensive care population. Published studies suggest that thrombocytopenia develops in up to 22–35% of neonates admitted to the neonatal intensive care unit and is severe in 20%.[17] Up until recently, thrombocytopenia was often attributed to the presence of a consumptive process, but it now seems more likely that many of these episodes of apparently self limiting thrombocytopenia relate to underproduction of platelets secondary to placental insufficiency.[18] This contrasts with the development of profound, persistent thrombocytopenia a few days after delivery which is more likely to represent underlying DIC.

Coagulation variables, at least initially, may be minimally deranged, and there may be difficulties distinguishing what represents an abnormal result particularly in preterm infants. Similarly, there are no reliable normal ranges for D-dimers, and there is limited evidence to suggest that baseline concentrations may be higher during the neonatal period.[19] In addition, fibrinogen concentrations normally increase slightly during the first few days of life and may initially be preserved. Early diagnosis of this condition is likely to be increasingly important in order to target management, and, with this in mind, scoring systems have been developed for use in adults, which may help to predict early non-overt DIC.[20]

As DIC is a secondary process, it follows that an important aspect of the management of this complication is prompt and

effective treatment of the underlying cause. Although this is logical, once DIC is well established, it may be difficult to switch off the processes involved. Evidence based guidelines for other specific treatment modalities are lacking, which reflects the absence of recent randomised controlled trials in this age group. There is considerable interest in the use of activated protein C, which has been shown to be of benefit in sepsis associated DIC in adults, but there is only limited information on the use of this agent in the neonatal period.[21 22]

Much of the management of DIC thus continues to centre around the use of supportive treatment with fresh frozen plasma, cryoprecipitate, and platelets to try to maintain adequate haemostasis. Although the use of blood products and the thresholds set for transfusion are largely empirical, it would appear reasonable to institute replacement therapy, particularly where there is an increased risk of bleeding. Guidelines for the transfusion of platelets suggest that the platelet count should be maintained above 50×10^9/l by the transfusion of platelet concentrates (10–15 ml/kg).[23] Fresh frozen plasma (10–15 ml/kg) can be used to replace haemostatic proteins, although cryoprecipitate (5–10 ml/kg) is a better source of fibrinogen, which should be kept above 1 g/l.[24]

Vitamin K deficiency bleeding

Vitamin K deficiency bleeding (VKDB) refers to bleeding that occurs as a consequence of vitamin K deficiency during the first six months of life. Previously known as haemorrhagic disease of the newborn, it was renamed to emphasise that bleeding problems during the neonatal period are not confined to those arising from vitamin K deficiency and that bleeding secondary to vitamin K deficiency may occur beyond the first month of life.[25]

Concentrations of the vitamin K dependent factors (FII, FVII, FIX, and FX) are reduced in the newborn period and are functionally inactive in the absence of vitamin K. VKDB has traditionally been classified as early, classical, and late depending on the timing of the presentation. This classification reflects the differing risk factors associated with this condition. Early VKDB is typically associated with antenatal ingestion of drugs which interfere with vitamin K metabolism, whereas classical and late forms are associated with breast feeding and malabsorption. Bleeding manifestations are variable, but there is a relatively high incidence of intracranial haemorrhage, particularly in late VKDB, which is associated with considerable morbidity and mortality.

The diagnosis of vitamin K deficiency may be suspected from the results of coagulation screening where initially there is isolated prolongation of the prothrombin time, followed by prolongation of the APTT, in association with a normal fibrinogen concentration and a normal platelet count. Confirmation of the diagnosis requires measurement of the specific vitamin K dependent factors (II, VII, IX, X) which are corrected by the administration of vitamin K.

Once the diagnosis is confirmed, intravenous vitamin K should be administered to correct the existing deficiency. In suspected cases, vitamin K can be given while factor concentrations are pending. In the presence of major bleeding, factor replacement therapy may also be required with fresh frozen plasma, prothrombin complex concentrate (FII, FIX, FX), or a four factor concentrate containing all the vitamin K dependent factors.[24]

Optimal methods for the prevention of VKDB have been the subject of considerable debate in recent years and remain to be fully resolved. It is generally accepted that, although a single intramuscular dose of vitamin K administered after birth will prevent both classical and late VKDB, a single oral dose will not protect all infants against late VKDB. The safety of intramuscular vitamin K was questioned some years ago, and, although the results of this study have not been confirmed, many centres have preferred to use an oral dosing schedule for prophylaxis. The optimal formulation and dosing regimen for oral vitamin K prophylaxis remains to be defined, but it is clear that regimens consisting of multiple doses are more effective, particularly for breast fed infants.[26 27] Recent data have also shown that oral administration of mixed micellar vitamin K is not superior to older vitamin K preparations.[28]

CONCLUSION

A number of different coagulation disorders may manifest with bleeding problems during the neonatal period. Early recognition of abnormal bleeding together with careful use of appropriate diagnostic investigations and recognition of those features unique to the neonatal haemostatic system should facilitate prompt diagnosis and appropriate management for these infants.

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Notes