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Congenital and acquired bleeding disorders in infancy

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ABSTRACT

The diagnosis of congenital and acquired bleeding disorders in infants requires an understanding of developmental haemostasis and the effect on laboratory testing. A systematic approach to bleeding in neonates will aid clinicians in the diagnosis and treatment, which may be caused by a wide variety of diseases. The clinical setting will help to direct the diagnostic pathway. This review will focus on the presentation and diagnosis of congenital and acquired bleeding disorders, including platelet disorders. Current research in this field is ongoing, including investigation into neonatal platelets and their different functionalities, platelet transfusion thresholds and how changes in coagulation factors may be linked to other homeostatic mechanisms.

Contents

1. Introduction

Neonatal bleeding is stressful for physicians and parents alike. The diagnostic approach needs to take developmental haemostasis into account for interpretation of tests. The most common abnormality found is thrombocytopenia; however, coagulation derangements also occur and the two can co-exist together. Acquired coagulation defects are often present in sick neonates, and inherited coagulation defects can present in otherwise healthy neonates. Here, we review bleeding in the neonate, with attention paid to developmental haemostasis, acquired and inherited bleeding disorders and thrombocytopenia as well as interpretation of laboratory tests.

2. Developmental haemostasis

The haemostatic system of the neonate and infant is evolving, dynamic and very different from the adult. Normal neonatal coagulation factor levels would be interpreted as pathological in an adult [1,2]. However, the coagulation system of an infant is differently set, and protective against both haemorrhage and thrombosis. Haemostasis is classified into primary, secondary and tertiary, which is fibrinolysis. Primary haemostasis refers to the adhesion, activation and aggregation of platelets at a site of vessel wall injury. Secondary haemostasis results

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from the activation of coagulation factors, resulting in the formation of covalently cross-linked fibrin that stabilizes the platelet plug. Activation of the fibrinolytic pathway triggers clot breakdown to maintain or restore blood flow. These processes are intimately related to the activity and functions of the endothelial cells, particularly the dynamic expression of tissue factor and other key molecular activators and inhibitors (Fig. 1).

Platelets appear in the human fetus at 5 weeks post-conception, and increase during fetal life to reach a mean of 150 per nanoliter (nL) by the end of the first trimester [3]. A recent study of neonates reported that the lower limit of normal for platelet counts for neonates less than 32 weeks gestation is 104/nL, and 123/nL for neonates of more than 32 weeks [4]. Assessment of platelet function is difficult, regardless of age, since it requires large volumes of blood and specialized laboratory expertise, and is also a poor surrogate for *in vivo* primary haemostasis [5,6]. Studies examining neonatal platelet function have mostly been performed on cord blood rather than peripheral blood, and while cord blood permits larger volumes, it is not equivalent in function to peripheral blood [7]. Overall, these studies demonstrate that neonatal platelets are hyporeactive compared with adults in some tests, and hyperreactive in others [5,6]. *In vivo* tests of platelet function such as bleeding time and platelet function analyser (PFA-100) are similar to normal adults. The reduction in reactivity is likely balanced by an increase in large von Willebrand factor (VWF) multimers, enhanced VWF levels and increased packed cell volume [7,8].

Coagulation factors can be detected from 10 weeks gestation [9] and their concentration increases with age, and are consequently lower in preterm compared with term infants [5]. Reference ranges for coagulation assays in neonates and infants vary with laboratory analyser and reagent system and this needs to be taken into consideration when comparing results from different laboratories.

Neonates have lower levels of most coagulation factors compared with adults [10]. Levels of the vitamin K–dependent coagulation factors (F) II, VII, IX and X are half to a third of adult values (measured after vitamin K prophylaxis at birth). The contact factors are also reduced (FXI, FXII, prekallikrein and high molecular weight kininogen). These and the vitamin K–dependent factors gradually increase to approach adult levels by 6 months of age. FV and FVIII are similar to adult values at birth. The physiological causes for these developmental changes are not clear; however, one hypothesis is that the changes are driven by the function of coagulation proteins in other physiological systems such as angiogenesis, inflammation and wound repair [11].

Levels of the major anticoagulant protein levels, antithrombin, protein (P) C and S, are also reduced at birth compared with adults. The plasma concentration of antithrombin (AT) is physiologically low at birth (~0.50 U/mL), and does not increase to adult values until 3 months of age. Sick premature infants often have values of less than 0.30 U/mL. Whether the overall activity of the PC/PS system varies with age is unknown. However, at birth, the plasma concentration of PC is very low, and remains decreased during the first 6 months of life. Although the total PS is decreased at birth, available PS is completely free and active, because of the absence of C4-binding protein [12,13]. Plasminogen levels of the newborn are also lower than in adults, demonstrating reduced fibrinolytic activity [14].

This functional immaturity of neonatal pro and anticoagulant proteins demonstrates that the haemostatic system is set differently to adults and under normal circumstances the infant is not at increased risk of either haemorrhage or thrombosis. These differences from adults are summarized in Table 1.

3. Approach to the bleeding neonate

The clinical setting of the neonate presenting with bleeding is extremely important; often, indicating the likely cause. Investigations can thus be tailored to allow rapid diagnosis and treatment. Bleeding in an otherwise well neonate is suggestive of an inherited bleeding disorder, vitamin K deficiency or immune-mediated thrombocytopenia. The sick preterm infant is much more likely to have an acquired coagulopathy, such as disseminated intravascular coagulation (DIC). The family history can help direct the investigations, especially if a previous child has been affected. The medication history from the mother is also important, particularly of drugs that affect vitamin K metabolism.

Sites of bleeding which may suggest a coagulation disorder in neonates include

- Puncture sites (heel prick, newborn screen, or immunisations)
- Upper and lower gastrointestinal tract
- Bleeding from umbilical stump
- Extracranial (subgaleal hemorrhage, cephalohaematoma)
- Intraventricular haemorrhage (IVH)
- Pulmonary haemorrhage

Extensive purpura and/or bruising suggests a platelet disorder (of number and/or function). Purpura caused by platelet disorders must be distinguished from lesions caused by microvascular thrombosis (see below).

Initial screening should include a full blood count (FBC) with blood film examination (since examination of platelet size and morphology can prompt the diagnosis), and coagulation studies including fibrinogen. These results, in conjunction with clinical setting and family history, can then direct subsequent investigations.

The interpretation of laboratory tests in neonates and infants must be approached with caution (Table 2). Sampling problems are common in neonates. Difficult venipuncture often results in contamination and activation of the sample by tissue factor. In an infant with a suspected bleeding disorder, an experienced operator should obtain the samples in order to obtain adequate samples and reliable results. For example, tissue factor activation in a sample may be sufficient to mask severe FVIII deficiency (haemophilia A).

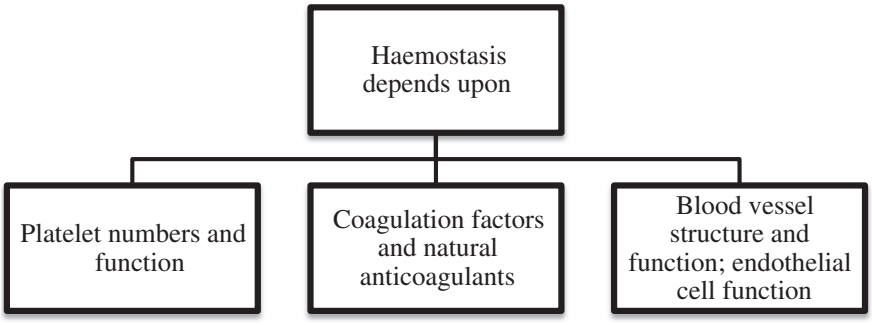

Fig. 1. The components of haemostasis. Primary haemostasis: Damage to vessel wall resulting in vasoconstriction and platelet aggregation and deposition. Secondary haemostasis: Activation of coagulation system leading to fibrin plug with platelets.

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