

Bruising and bleeding in infants and children – a practical approach

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Summary

Bruising and bleeding are commonly seen in children and are usually associated with minor injury and trauma. However, in two groups of children the bruising may be more significant than expected: those with an underlying haemostatic abnormality, such as an inherited bleeding disorder, or those who have been subjected to non-accidental injury (NAI). Diagnosing inherited bleeding disorders in children is fraught with difficulty, from venous access to interpretation of results; the possibility of NAI should be borne in mind, even in those children with proven significant bleeding disorders when the severity of the injury and the history are non-compatible. We describe the investigation of the haemostatic system in children with bruising and/or bleeding with emphasis on the key haemostatic disorders that need to be excluded.

Keywords: bruising, bleeding, children, investigation, non-accidental injury.

The presentation of an infant or child with symptoms of bruising and/or bleeding commonly causes considerable anxiety to both paediatricians and haematologists. These symptoms may be due to a haemostatic disorder or due to non-accidental injury (NAI) or both and making an accurate assessment and diagnosis is vital to ensure that the further management of that child is appropriate and that the correct treatment is given if necessary.

It is important firstly to try and determine whether the bruising/bleeding is 'normal' or 'abnormal'; sadly the evidence base as to which bruising/bleeding patterns are suggestive of NAI and which are more likely to be due to a haemostatic disorder is scanty. Therefore, the judgements many clinicians make on whether NAI is likely are based more on personal experience than on published 'guidelines' or evidence. Having made the decision that there is abnormal bruising or bleeding that needs investigating, the next decision is 'how much needs to be done'? As this review outlines, a full haemostatic work-up

in small infants is complex and difficult but may need to be done in some cases. Certainly the legal system has evolved to such a degree that in many child protection cases, all disorders of haemostasis must be convincingly excluded before the Court will reach a final decision. The other salient reason why a comprehensive work-up may be necessary is that infants presenting with significant disorders of haemostasis have not uncommonly already been referred for possible NAI prior to the correct diagnosis being made and occasionally the delay may have actually caused harm to the infant.

This review aims to discuss the difficulties of the investigation of haemostatic disorders, particularly in the younger age group, and gives a brief review of the disorders that need to be excluded, highlighting the relevance of these conditions in children.

'Normal' bruising or bleeding

Bruising is caused by the escape of blood from damaged blood vessels into subcutaneous tissues. Published studies looking at patterns of bruising in 'normal' children have found that small bruises on bony prominences on the front of the body are commonplace in mobile preschool and school age children (Labbe & Caouette, 2001). Some bruising can be expected in all children from the time they begin to crawl, when bruises may also be found on the forehead as well as the knees and shins (Carpenter, 1999; Maguire *et al*, 2005a). In non-mobile infants – usually before the age of 9 months – significant bruising is unusual and often outwith the spectrum of 'normal' bruising. Uncommon sites for bruising at all ages include the back, buttocks, arm and abdomen (Sugar *et al*, 1999). Bruising is statistically more obvious ($P < 0.007$) in white children when compared to African-American children due to skin tone (Sugar *et al*, 1999), it increases with increasing family size (Carpenter, 1999) and is more commonly reported in the summer months when children play outside in lightweight clothing (Labbe & Caouette, 2001).

To guide clinicians on the boundaries of what is and what is not 'normal' bruising, there have been many attempts to score bruises by severity and age but, to date, there is still no universally accepted validated tool in clinical practice. Maguire *et al* (2005b) recently systematically reviewed all studies

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assessing the age of bruises and concluded that a bruise cannot be accurately aged from clinical assessment *in vivo* or on a photograph and the practice of estimating the age of a bruise from its colour should be avoided. Therefore, at present, there is no way to accurately age a subcutaneous injury or multiple injuries in those who may have been physically abused. This lack of clarity is further complicated by a wide interindividual variation in tendency to bruise and in the sequence of bruise progression (Nosek-Cenkowska *et al*, 1991). Generally, bruising is worse in areas, such as the skin around the eye or the genitalia, where the skin is lax or when the skin is more fragile, such as some collagen vascular disorders (Yeowell & Pinell, 1993; De Paep & Malfait, 2004). Skin pigmentation and some medications (e.g. steroid, anti-epileptic therapy, anti-platelet agents or non-steroidal anti-inflammatory drugs) can also impact on bruising tendency (Stephenson, 1997; Dunstan, 2002; Baraciak *et al*, 2003).

'Abnormal' bruising or bleeding

Children who present with what is judged to be 'abnormal' bruising and/or bleeding may have a bleeding disorder or NAI. It must be remembered that NAI and bleeding disorders are not mutually exclusive and that children with bleeding disorders can also be non-accidentally injured (O'Hare & Eden, 1984; Johnson & Coury, 1988; Wheeler & Hobbs, 1988; Harley, 1997; Thomas, 2004). In all cases, all options should be considered, although if a child presents with bruising or bleeding that is abnormal in site and severity relative to the history, suspicions of NAI increase. A second recent systematic review by Maguire *et al* (2005a) looked at 23 studies of bruising in children to assess which patterns of bruising were diagnostic or suggestive of child abuse. The authors concluded that bruising over soft tissue areas in non-mobile infants that carry the imprint of an implement or are multiple bruises with uniform shape are more suggestive of abuse than other forms of bruising but it is essential to consider the proposed cause and pattern of bruising in conjunction with the medical, social and developmental history of the infant or child.

Frenulum bleeding has historically been said to be a 'sign' of NAI (Teece & Crawford, 2005). In reality, any child can injure itself enough to bleed profusely from the frenulum but the bleeding will always be worse if there is a haemostatic disorder. On the other hand, bone fractures are not associated with haemostatic disorders, therefore any child presenting with bruising and a positive skeletal survey is likely to have been subjected to a NAI. The bleeding manifestations may be more severe, intracranial (Hymel *et al*, 1997) or retinal haemorrhage (Taylor, 1999; Mei-Zahen *et al*, 2002). Retinal haemorrhages are uncommon in children with known haemostatic disorders (Gayle *et al*, 1995) although they have been seen at diagnosis in children with leukaemia (Shaw & Eden, 1989). Conversely, intracranial haemorrhage is occasionally seen in children with bleeding disorders (Vorstman *et al*, 2003) and may be associated with birth trauma (Anwar & Miloszeski, 1999;

Chalmers *et al*, 2005) or other head trauma. As well as the bleeding or bruising episode of concern, any other associated symptoms or signs should be noted, as should the presence of petechiae, purpura or significant mucosal bleeding. A detailed personal and family history should be sought as there are often important clues to be gained. For example, specific questions about the neonatal period should be asked: was there any umbilical cord bleeding or delayed cord separation? Was there prolonged bleeding from the heelprick used to collect blood for the 'Guthrie' test? Was there significant haematoma formation following infant vaccinations or intramuscular vitamin K given after birth? The parents should be questioned on haemostatic challenges, such as circumcision, dental extraction or surgery and whether there was any associated bleeding, bruising or haematoma formation.

A complete family history should be taken, asking about consanguinity (Hathaway, 1977; Sham & Francis, 1994), neonatal death in the preceding generations, bleeding post-surgery, including religious circumcision or dental extraction, menorrhagia and postpartum haemorrhage, as many of these increase suspicion of a possible underlying bleeding disorder.

Investigation of the haemostatic system in children with bruising or bleeding – basic principles

Once a full clinical assessment of each case has been undertaken it is standard practice to perform baseline investigations. A full blood count (FBC) and blood film should exclude haematological causes of bleeding or bruising, such as thrombocytopenia or bone marrow failure syndromes, and will also allow morphological examination of platelets in particular. If there is prolongation of either the activated partial thromboplastin time (APTT) or prothrombin time (PT), the test should be repeated using a mix with equal volumes of test and normal plasma to differentiate between a factor deficiency and a circulating inhibitor. Lupus-like inhibitors are a relatively common cause of a prolonged APTT in children and are usually a transient postviral phenomenon of no consequence. A prolonged thrombin time (TT) may indicate hereditary or acquired fibrinogen abnormalities (dysfibrinogenemia or hypofibrinogenemia) (Triplett, 2000) or elevated fibrin/fibrinogen degradation products as seen in disseminated intravascular coagulation (DIC). A Clauss fibrinogen assay should be performed rather than relying on a fibrinogen value derived from the PT on the coagulation analyser (Mackie *et al*, 2003). Finally, biochemical screens should be undertaken, with particular emphasis on hepatic and renal functions as both liver and renal impairment can lead to platelet dysfunction, dysfibrinogenemia and other defects (Lane *et al*, 1977; Weigert & Schafer, 1998; Kozek-Langenecker *et al*, 1999).

If these baseline investigations are normal they exclude the severe forms of some disorders, such as haemophilia, but do not exclude severe forms of more rare disorders, such as factor XIII (FXIII) deficiency or Glanzmann Thrombasthenia (GT).

Table I. Haemostatic disorders which may present with normal coagulation screen and full blood count.

Mild von Willebrand disease
Mild haemophilia A or B
Mild factor XI or other single factor deficiency
Factor XIII deficiency
α -2 antiplasmin deficiency
Plasminogen activation inhibitor-1 deficiency
Glanzmann thrombasthenia
Platelet storage pool disease
Platelet release defect
Collagen disorders
Vitamin C deficiency

Nor do they exclude more common mild disorders, such as type 1 von Willebrand disease (VWD), mild FXI deficiency or mild platelet function disorders (Table I), all of which can cause easy bruising and/or bleeding. In these disorders, the FBC and coagulation screen may be normal or abnormal depending on the sensitivity of the assay system and reagents within the local laboratory. Each laboratory should be aware of the levels of the individual factors they expect to detect with their assay system, though it must be remembered that high levels of other factors – such as FVIII, which is common in sick children, may well mask mild deficiencies of the other factors. Therefore, in cases in which a haemostatic disorder is part of the differential diagnosis it is necessary to perform all factor assays even when the screen is normal, as equating normal screening tests to normal haemostasis could be interpreted as negligent. A simplified scheme for guiding further investigation is suggested in Fig 1, though many of these ‘second-line’ investigations are unlikely to be available in all Trusts and may only be available in specialist centres, such as those Trusts with Haemophilia Comprehensive Care Centres. At any rate, it is not uncommon for these cases to be complex and all such

children should, at the very least, be discussed with a paediatric haematology department.

When assessing the results of haemostatic investigations it is important to be aware that there are physiological differences between the coagulation systems of infants and children and those of adults and these differences are most significant in young infants. For instance, the levels of several clotting factors are considerably lower in healthy full-term infants at birth when compared to adults, with premature infants showing even more pronounced reductions. In general, the postnatal maturation of the coagulation system towards adult status is accelerated in premature infants when compared with full-term babies, and by 6 months of age most components of the coagulation system in premature infants begin to approach adult values (Andrew *et al*, 1987, 1988, 1992). This is reflected in alterations in thrombin regulation in children compared to adults, which are thought to be one of the reasons that children are protected from thromboembolism compared to adults (Andrew *et al*, 1994; Chan *et al*, 2002). There is also apparent platelet hypofunction in newborn babies (Ucar *et al*, 2005). It is therefore essential that gestational and/or postnatal age is taken into consideration when interpreting coagulation results. Ideally, all laboratories processing such samples should establish their own ‘in-house’ normal ranges but it is unethical and impractical to venesect ‘normal’ infants to establish these. In practice, the ranges published by Andrew (1987, 1988, 1992) are the most comprehensively available and are often used as a ‘guideline’ but must be used with caution as they were performed using different reagents and assay systems to those available now. More recently, Monagle *et al* (2003) has re-examined the reference ranges for haemostatic parameters in children between the age of 1 month and 16 years; this study confirmed developmental differences between different age groups and also showed disparity between those published by Andrew 11–15 years previously but has, to date, only been presented in abstract form (Monagle *et al*, 2003).

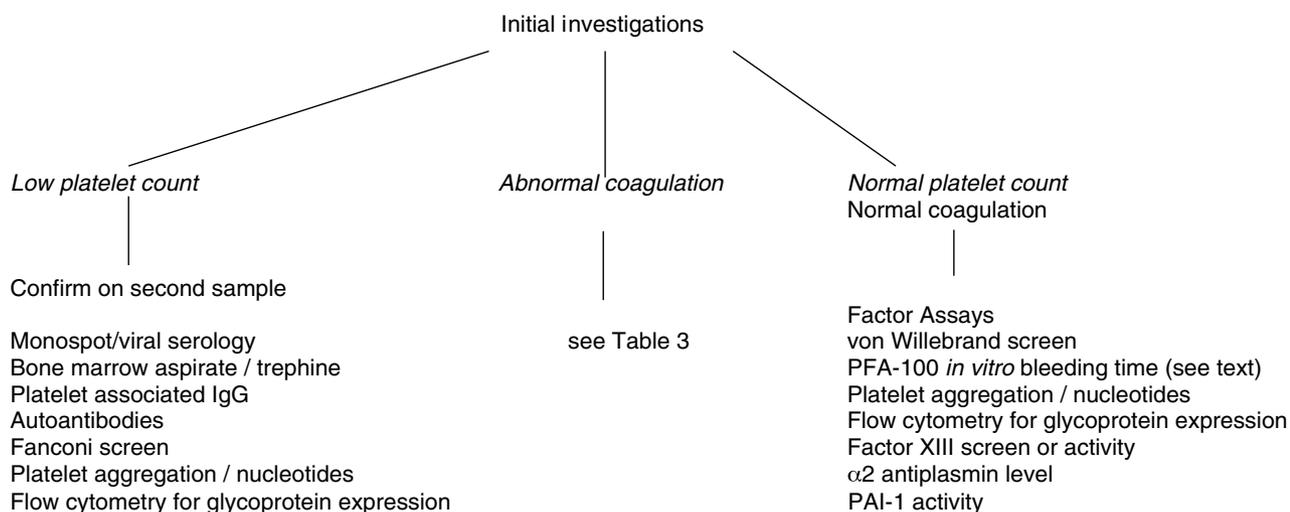


Fig 1. Investigation of abnormal bruising or bleeding (note not all investigations will be required for all patients).

Table II. Classification of coagulation disorders in children.

Inherited
Haemophilia A
Haemophilia B
von Willebrand disease
Deficiency of Factors II, V, VII, X, XI, XII or XIII
Dys-, hypo- or afibrinogenaemia
α -2 antiplasmin deficiency
Plasminogen activation inhibitor-1 deficiency
Acquired
Vitamin K deficiency
Liver disease
Disseminated intravascular coagulation
Massive transfusion syndrome
Dys- or hypo-fibrinogenaemia
Disorders associated with malignancy
Coagulation inhibitors

Haemostatic disorders that can present with bruising or bleeding in infants and children

Inherited coagulation disorders

Inherited coagulation disorders are relatively rare, but many children with persistently abnormal coagulation screens will have an underlying bleeding disorder and should be discussed promptly with, and referred to, a centre with expertise in paediatric haemostasis for further investigation (Liesner, 2002). Table II shows the classification of the most important coagulation disorders in children; Table III shows how the abnormal coagulation screens could be interpreted and suggests further investigations.

Haemophilia is the commonest severe bleeding disorder and it is not uncommon for affected boys to present with abnormal bruising and/or bleeding that leads to a suspicion of NAI prior to the true diagnosis being confirmed. Haemophilia affects about one in 5000 males; approximately 80% have haemophilia

PT	APTT	TT	Possible abnormality/further investigation required
↑	N	N	<ul style="list-style-type: none"> Factor VII deficiency Liver disease Vitamin K deficiency <i>Measurement of PT-based factors</i>
N	↑	N	<ul style="list-style-type: none"> Deficiency of factor VIII (due to haemophilia A or VWD) factors IX, XI, XII or contact factors (intrinsic pathway) <i>Measurement of APTT-based factors and VW 'screen' (FVIII:C, VWF:Ag, VWF:RCo, VWF:CB, PFA-100)</i> <ul style="list-style-type: none"> Lupus anticoagulant or other coagulation factor inhibitor <i>DRVVT, Exner, ACL, anti-β2GP1 antibodies</i>
N	N	↑	<ul style="list-style-type: none"> Hypofibrinogenaemia Dysfibrinogenaemia <i>Reptilase time + other thrombin time corrections</i>
↑	↑	N	<ul style="list-style-type: none"> Deficiency of factor II, V, X (common pathway) Vitamin K deficiency Liver disease Massive transfusion Oral anticoagulants PT- and APTT-based factors, INR
N	↑	↑	<ul style="list-style-type: none"> Heparin <i>Reptilase time and other thrombin time corrections</i>
↑	↑	↑	<ul style="list-style-type: none"> Disseminated intravascular coagulation Large amount of heparin Severe hypo- or afibrinogenaemia <i>D-dimers, Reptilase time and other thrombin time corrections</i>
N	N	N	All tests normal but history of bleeding – consider diagnoses in table 1

Table III. Interpretation of abnormal coagulation screens and suggested pathway of further investigation.

PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; N, within normal range; ↑, prolonged; VWD, von Willebrand disease; FVIII:C, factor VIII coagulant activity; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity; VWF:CBA, von Willebrand factor collagen binding activity; DRVVT, dilute Russell Viper Venom time; ACL, anticardiolipin antibodies; INR, international normalised ratio; PFA-100, platelet function analyser *in-vitro* bleeding time; anti- β 2GP1 antibodies, anti- β -2 glycoprotein-1 antibodies.

A (FVIII deficiency) and 20% haemophilia B (FIX deficiency). The current International Society of Thrombosis and Haemostasis classification denotes a factor level of <0.01 IU/ml as 'severe' haemophilia, 0.01–0.05 IU/ml 'moderate' and >0.05 IU/ml 'mild' haemophilia. The bruising/bleeding tendency correlates well with the plasma level of FVIII/FIX and usually the clinical phenotype is similar in all cases within the same family. Approximately one-third of all boys diagnosed with haemophilia have no previous family history and have a *de novo* mutation either in their FVIII or FIX gene or somewhere in the female lineage in the family. They may present at any stage in infancy, childhood or even adulthood but severe cases usually present within the first 2 years of life most commonly with severe bruising and joint bleeds. Studies looking at when severe haemophilia presents have found that 38–54% of severe haemophiliacs present in the first month of life, the majority with bleeding events (Conway & Hilgartner, 1994; Pollmann *et al*, 1999). A small percentage of severe cases present in the neonatal period often with severe birth trauma-induced bleeding – this is estimated to be in the order of 1–4% of infants though the precise risk remains unknown due to under-reporting or misdiagnosis (Kulkarni & Lusher, 2001). Ventouse extraction is commonly used to deliver babies who have a prolonged second stage of labour but the trauma resulting from the suction forces involved can cause profound extra and intracranial bleeding in infants with any severe bleeding disorder. Therefore instrumental delivery is ill-advised in such infants but, even if infants with severe haemophilia are born by Caesarean section or by normal vaginal delivery, there remains a small risk (<5%) of intracranial haemorrhage and it is therefore important to exclude haemophilia, as well as other severe bleeding disorders, in any case of neonatal intracranial haemorrhage (Kulkarni & Lusher, 2001; Chalmers *et al*, 2005). In pregnancies where there is a family history and the mother is known to be a carrier for haemophilia the diagnosis can easily be made on cord blood or a carefully taken venous sample. FVIII levels are normal or slightly elevated at birth in a normal infant and therefore any form of haemophilia A is reasonably reliably diagnosed on a neonatal sample. FIX, however, is a vitamin K-dependent factor and all infants have physiologically lower levels at birth. Nevertheless if the mother is a carrier for severe haemophilia B and the level of FIX is <0.01 IU/ml on cord blood then it is highly likely that the baby is affected. Circumstances when confusion arises are in the diagnosis of moderate or mild cases of haemophilia B on cord or newborn blood samples, as a degree of vitamin K deficiency in addition to the physiologically lower levels can result in the diagnosis being made erroneously. All babies with 'presumed' moderate or mild haemophilia B should have the diagnostic samples repeated at 6 months of age.

Boys with mild or moderate haemophilia typically have 'abnormal' trauma-related bruising or bleeding or excessive bleeding following surgery or dental extraction but rarely have spontaneous joint bleeds. Girls who carry haemophilia may also suffer from mild bruising or bleeding as they often have

factor levels below the lower limit of normal or they may present with heavy periods following the menarche.

The genetic defect responsible for haemophilia can now be determined in specialist laboratories in >90% of cases of haemophilia A and B and this allows reliable diagnosis of carriers of haemophilia and also facilitates antenatal diagnosis (Hedner *et al*, 2000). *von Willebrand disease* (VWD) is thought to be the most common inherited bleeding disorder with an incidence that is estimated to be between 1:100 and 1:1000 (Castaman *et al*, 2003). Theoretically, it should affect males and females equally but in practice, more females are diagnosed with VWD as it frequently causes menorrhagia. Significant menorrhagia from the menarche onwards should prompt investigation for VWD. Other typical symptoms are easy bruising and mucosal bleeding caused by quantitative or qualitative defects in von Willebrand factor (VWF), important for platelet adhesion in primary haemostasis. Type 1 VWD, the mildest and commonest form, is inherited as an autosomal dominant trait but with variable penetrance. The diagnosis can be notoriously complicated mainly because the levels of VWF can be borderline, around the lower end of the normal range, and it may require blood samples taken on at least three occasions to confirm or refute the diagnosis (Laffan *et al*, 2004). FVIII and VWF are 'acute phase proteins'; the levels can be raised by stress, infections or other systemic illness and difficult venepunctures to get the appropriate samples in small children can raise the levels and mask the diagnosis. The situation is further complicated as children who are blood group O have physiologically lower levels of FVIII and VWF than those of other blood groups, with a lower limit of normal 0.37 IU/ml rather than 0.50 IU/ml in non-blood group O individuals. There is also undoubtedly an overlap in that some children with blood group O and levels between 0.37 and 0.50 IU/ml are 'normal' whilst some have mild type 1 VWD. Current recommendations are that as many tests as possible should be performed in the assessment of whether VWD is present or not so that there is a maximal amount of information from which to come to a consensus (Laffan *et al*, 2004). In practice this means determining FVIII, von Willebrand antigen, von Willebrand ristocetin cofactor activity, von Willebrand collagen binding assay, ristocetin-induced platelet agglutination and a bleeding time using an *in vitro* bleeding time device, such as the platelet function analyser (PFA-100; Dade Behring, Marburg, Germany). It has been shown that the PFA-100 shows good sensitivity to the defect in primary haemostasis that occurs in VWD (Harrison *et al*, 2002a; Quiroga *et al*, 2004; Harrison, 2005). Results then have to be interpreted along with any family history of possible or confirmed VWD and the personal bleeding history of the child. Due to the complexity of establishing this diagnosis UK recommendations are that the care of these children is overseen by haemophilia comprehensive care centres, which will also facilitate the correct treatment approach if/when treatment is required. (Mannucci, 2001; Federici & Mannucci, 2002; Pasi *et al*, 2004).

The diagnosis of the type 2 subtypes and type 3 VWD is relatively straightforward compared to type 1 (Laffan *et al*, 2004). Type 3 usually presents in early infancy and is symptomatic through childhood, often with severe mucosal bleeding, particularly epistaxes, bruising and ecchymoses. The defect is severe as there is a total absence of FVIII and VWF and hence there is a profound defect in primary haemostasis. The parents may have type 1 VWD or be heterozygous for a null allele and the defect occurs when inherited as a homozygote or compound heterozygote. In adolescence, girls have protracted severe menorrhagia that may require regular treatment with VW replacement therapy and/or hormone suppression of the menstrual cycle. In type 2 VWD, the VWF is dysfunctional and the bleeding phenotype is usually more severe than type 1 but less than type 3. It is usually autosomal dominantly inherited and so, in practice, many children with this disorder will have a positive family history and may be diagnosed as part of family testing. In type 2B VWD there is an associated thrombocytopenia with enhanced sensitivity to ristocetin on platelet agglutination and therefore this form of VWD must be considered in the differential diagnosis of a congenital thrombocytopenia (see below).

Factor XI deficiency is the third most common disorder though this depends largely on the population mix in an area. It is most commonly seen in Ashkenazi Jewish races and population studies in Israel have found that up to 8% of the population are heterozygous for FXI deficiency (Asakai *et al*, 1991). The bleeding tendency tends to be relatively mild in both homozygotes and heterozygotes and the plasma level of circulating FXI does not correlate well with bleeding tendency (Bolton-Maggs *et al*, 1995). Although this disorder can cause easy bruising or abnormal bleeding, in practice, children with this disorder are often diagnosed incidentally following coagulation screening presurgery or even following surgical challenge if no pre-operative screening was done. Boys may be diagnosed if they have postcircumcision bleeding in the first 2 weeks of life but this is not invariably the case and in girls, menorrhagia is common.

The rare and very rare coagulation disorders

The other factor deficiencies are all diagnosed very infrequently even in large haemophilia comprehensive care centres (Bolton-Maggs *et al*, 2004; Mannucci *et al*, 2004). However, they are very important, as severe homozygous forms of these can result in a profound, life-threatening bleeding diathesis and making the correct diagnosis early is paramount to avoid significant morbidity or death. The majority of cases of infants and children with severe forms of fibrinogen and factors II, V, VII, X and XIII deficiencies have consanguineous parents and they present early in infancy (Girolami *et al*, 1998; Ingerslev & Kristensen, 1998; Anwar & Miloszeski, 1999; Peyvandi & Mannucci, 1999). They may present with umbilical stump bleeding and/or delayed cord separation, intracranial or gastro-intestinal haemorrhage, muscle haematomas, easy

bruising or prolonged bleeding following trauma, including heelpricks done for the Guthrie test. They are easily detected on appropriate factor assays following abnormal coagulation screening except for FXIII deficiency, which is not detectable on a routine coagulation screen and has to be assayed for by requesting a FXIII clot solubility screen or a FXIII activity assay (Jennings *et al*, 2003). As well as characteristic problems with umbilical cord bleeding and intracranial haemorrhage (Almeida *et al*, 2002), bleeding is characteristically delayed for hours or days after the traumatic insult and there is a healing defect with prominent scarring (Anwar & Miloszeski, 1999).

Heterozygotes (or 'carriers') for factors V, VII and X deficiencies can occasionally also have a mild bleeding/bruising tendency but they are often asymptomatic and so rarely are diagnosed in childhood. Depending on the sensitivity of the assay system and reagents used, the standard coagulation screen may not be prolonged in patients with heterozygous deficiencies and therefore measuring these factor levels should be part of a comprehensive haemostatic work-up. Disorders of fibrinogen can be quantitative (hypo/afibrinogenaemia) and/or qualitative (dysfibrinogenaemia). Hypofibrinogenaemia is probably the heterozygote form of homozygous afibrinogenaemia and can be a cause of an increased bruising/bleeding tendency, hence the need to accurately measure the fibrinogen level when assessing a child for a possible haemostatic disorder (Mackie *et al*, 2003). Dysfibrinogenaemia may cause bleeding or thrombosis (Lak *et al*, 1999; Roberts *et al*, 2001).

α 2-Antiplasmin deficiency is an extremely rare abnormality of coagulation (13 cases reported in the literature) that does not affect clotting times *in vitro*, thus a level should be performed in children with a real bleeding diathesis and negative coagulation screens (Favier *et al*, 2001). Another very rare defect with only a handful of reported cases is plasminogen activator inhibitor-1 deficiency; it causes hyperfibrinolysis and lifelong bleeding (Minowa *et al*, 1999).

Inherited platelet disorders

Low platelet count. The FBC in the initial screen will indicate a quantitative platelet abnormality that can be either an isolated finding or part of a generalised bone marrow failure; qualitative platelet function disorders are much more complicated to diagnose. If the platelet count is low it should be repeated to ensure that the first count is not artefactually lowered by platelet clumping. The mean platelet volume should be noted and platelet size and morphology examined on a blood film. Congenital thrombocytopenias are rare but usually manifest within the first few years of life with petechiae, bruising or mucosal bleeding. They often require comprehensive investigation in specialist centres and have recently been reviewed extensively (Balduini *et al*, 2003; Cattaneo, 2003; Drachman, 2004).

There are a number of congenital platelet disorders in which thrombocytopenia and platelet dysfunction coexist and in

these disorders the degree of bleeding diathesis appears more severe than would be expected from the thrombocytopenia alone. The most notable of these is Bernard–Soulier syndrome (BSS); the absence of the glycoprotein-1b/IX receptor complex on the platelet surface results in defective binding of platelets to VWF and results in a moderate or severe bruising/bleeding tendency from infancy (Cattaneo, 2003; Nurden, 2005). BSS is autosomal recessive and therefore most commonly seen in consanguineous families. There is usually moderate macrothrombocytopenia ($30\text{--}80 \times 10^9/l$) a very prolonged *in vitro* bleeding time, failure of the platelets to agglutinate with ristocetin and flow cytometry can be used to confirm the absence of expression of the glycoprotein on the platelet surface. The small volumes of blood required for flow cytometry means that the diagnosis can be made with a reasonable degree of certainty in small infants in whom the condition is a possibility.

Another disorder in which there is both a low platelet count and a degree of dysfunction is Wiskott–Aldrich Syndrome (WAS); an X-linked immune deficiency disorder associated with eczema (Mullen *et al*, 1993; Imai *et al*, 2004). The platelets are usually extremely small and often appear like specks of dust on light microscopy of the blood film, although in occasional cases, the platelet size may be normal or near normal. The degree of thrombocytopenia and dysfunction is variable but WAS should be considered when there is also eczema and/or recurrent infections. The more severe forms may present with bruising within the first 6 months of life and may precede the onset of recurrent infections.

Gray platelet syndrome is due to platelet alpha-granule deficiency and results in severe bruising and bleeding from an early age. There is mild thrombocytopenia and examination of the blood film by light or electron microscopy usually makes the diagnosis, as agranular platelets are seen (Hardisty, 2000).

Normal platelet count. If the platelet number and morphology are normal there are still a number of platelet dysfunction disorders that could be present in a child with bleeding and bruising and unfortunately there is no reliable ‘screening’ test to exclude all forms of platelet dysfunction. Historically, the template bleeding time (BT) (Sutor, 1998) was used but there is now wide belief that it is insensitive and non-reproducible and it is difficult to perform, standardise and interpret when used in children (Rodgers & Levin, 1990; Cariappa *et al*, 2003). To a certain extent it has now been replaced by the *in vitro* bleeding time devices – the most widely used is the platelet function analyser (PFA-100). However, results from this device must be interpreted with caution and expertise; the device is extremely sensitive and therefore useful in screening for severe platelet function disorders, such as BSS or GT (see below) and also most forms of VWD, but is not sensitive to all the milder disorders, such as platelet storage pool disease (SPD) or secretion defects (Harrison *et al*, 2002b; Liesner *et al*, 2004; Quiroga *et al*, 2004; Harrison, 2005). The use of the PFA-100 as a screening device can also cause problems when the results

suggest a defect of primary haemostasis but no defect can be demonstrated on full investigation – so called ‘false-positive’ results. The device is sensitive to poorly taken and poorly mixed blood and it is likely that many false-positive results are due to this.

The ‘gold-standard’ investigation to prove or disprove a platelet function disorder is therefore still platelet aggregation following preparation of platelet-rich plasma (PRP) and assessment of platelet nucleotides. Difficulties arise because these specialised tests are generally only performed in large well-equipped coagulation laboratories, are time consuming, technically challenging and require a minimum of 15–20 ml of whole blood from which the PRP is obtained and this volume of blood can be difficult to obtain in small infants. There are possibilities that PRP aggregation could be replaced by whole blood methods that require lower volumes of blood in the next few years, but at present these methods require further validation (Calatzis *et al*, 2004; Dyszkiewicz-Korpanty *et al*, 2005). The other disadvantage in small children is again the issue of ‘normal’ ranges, particularly platelet nucleotide ranges in the <1 year age group which are poorly standardised. ‘Abnormal’ results in the first year of life can be difficult to interpret with certainty – they may suggest an extremely mild platelet disorder, such as one akin to taking an aspirin daily. This can cause considerable confusion and debate in cases where bruising could be due to NAI and the legal system is requesting that all possible haemostatic disorders are excluded prior to attributing the symptoms to NAI. Often in reality, the best approach is to repeat the tests at a later date when the child is older and when the results are easier to interpret though further difficulties arise as legal cases cannot usually be kept ‘open’ for a matter of years pending further results.

Platelet function disorders. The most severe of the dysfunction disorders in which the platelet number and morphology is normal is GT and it is very important that this condition is diagnosed promptly and treated appropriately. It is also autosomal recessively inherited and is more common if the parents are related to each other. The defect is in the platelet membrane glycoprotein IIb/IIIa, the main fibrinogen receptor on the platelet surface. If fibrinogen cannot be bound then effective platelet aggregation and *in vivo* clot propagation cannot occur (Cattaneo, 2003; Nurden, 2005). The glycoprotein expression is absent in type 1 GT and an abnormal dysfunctional glycoprotein receptor is expressed in type 2 GT. Typically, GT presents in infancy, with severe, often spontaneous bleeding usually from the mucous membranes, which can be life threatening if there is a delay in treatment. Petechiae are common, especially following restriction for venesection and bruising is usually extensive following even trivial injury. The diagnosis is confirmed using the *in vitro* bleeding time, flow cytometry and platelet aggregation; there is absent aggregation to all agonists except ristocetin. In practice, it can be difficult to complete platelet aggregation tests in these small infants and in this circumstance the prolonged

in vitro bleeding time and the absence of glycoprotein IIb/IIIa expression on the platelet surface can make the diagnosis of GT highly likely. Also parental samples often demonstrate 50% expression on flow cytometry.

Platelet storage pool disorders (SPD), with a deficiency in the nucleotide content of the dense granules of the platelet, can be idiopathic or part of a more complex disorder. Generally, SPD causes a mild to moderate bruising tendency but in some children there is brisk bleeding following trauma or surgery. The inheritance is poorly understood, though it is known that WAS, which can be associated with a SPD, is X-linked whilst Hermansky Pudlak syndrome (HPS) is autosomal recessive (Harrison *et al*, 2002a). HPS is a disorder characterised by oculocutaneous albinism and SPD. The bleeding tendency is usually mild but there are case reports in the literature that demonstrate how, on rare occasions, spontaneous bleeding may occur (Russell-Eggitt *et al*, 2000). Albinism is also a feature of Chediak Higashi syndrome in which there are characteristic giant organelles in leucocytes, susceptibility to infection, mental retardation and SPD.

Platelet release or aspirin-like defects may also cause a mild bruising/bleeding tendency; commonly they only present after surgical challenges. They are a heterogeneous group of disorders of signal transduction or thromboxane generation resulting in poor granule release on platelet activation (Sham & Francis, 1994).

Acquired disorders of coagulation and platelet function

The development of an acquired disorder of coagulation or platelet function in a child who is unwell from systemic or organ disease is generally much more common than congenital disorders and any bruising or bleeding that ensues as a result is easy to explain; suspicions of NAI are unusual. Vitamin K deficiency is probably the most common acquired bleeding disorder of childhood and it can result in any degree of bleeding from minor bruising through to severe life-threatening haemorrhage (Sutor, 1995). It is most commonly caused by conditions that cause liver dysfunction, gastro-intestinal disorders and drug therapy, particularly antibiotics and oral anticoagulants. Neonatal vitamin K deficiency can cause haemorrhagic disease of the newborn (HDNB) where bleeding can vary from bruising or petechiae in the first few days of life through to severe and life-threatening intracranial haemorrhage and/or gastrointestinal bleeding. HDNB can be prevented by administration of a single intramuscular injection vitamin K soon after birth (Sutor *et al*, 1999; Zipursky, 1999).

Children with severe liver disease commonly have a coagulation disorder, caused by impaired synthesis of coagulation factors and clearance of activated clotting factors, enhanced fibrinolysis and there can also be an acquired platelet function defect. However, the liver has large reserves so often only 10–15% of children have significant bleeding (Chalmers & Gibson, 2000). Acquired dys- or hypo-fibrinogenaemia can occur in

some systemic diseases in childhood, including renal or liver disease, and following drug therapy, for example L-asparaginase and sodium valproate (Roberts *et al*, 2001).

Disseminated intravascular coagulation (DIC) occurs in children who are critically ill and is best managed in an intensive care setting. The full list of causes of DIC can be found in any full paediatric or haematology text but can be broadly categorised into severe infections, tissue or vascular injury or intravascular haemolysis (ABO incompatible transfusion, liver disease and malignancy). DIC can cause profuse bleeding into the skin, gastro-intestinal tract and central nervous system. The laboratory findings include abnormalities in the coagulation screen (Table III), micro-angiopathic haemolysis as well as thrombocytopenia, low fibrinogen and elevated D-dimers.

Coagulation inhibitors are rare in children who do not have an underlying inherited coagulation disorder (Scott-Timperley & Haire, 1997). They can occur in association with malignancy (Leung *et al*, 2004) or occasionally postsurgery. Inhibitors to phospholipid are more common but are rarely associated with an excess bleeding risk except when the anti-phospholipid antibody is directed against prothrombin (FII) and results in consumption of FII. These usually follow viral infections in otherwise well children and are generally transient (Anderson *et al*, 2003). A FII level should therefore be requested in any child with bruising and a poor correction of a prolonged APTT with 50:50 mix with normal plasma especially if there is also a prolonged PT. It is unusual for this transient bleeding diathesis to require treatment.

Transient abnormalities in platelet function causing temporary bruising are common following ingestion of non-steroidal anti-inflammatory drugs or aspirin, which is sometimes used therapeutically as an anti-platelet agent in paediatric practice. Acquired platelet dysfunction is also a common complication of uraemia or liver disease and can also follow cardiopulmonary bypass procedures (Hardisty, 2000).

The <6 month old infant – what to do

The text above has highlighted the difficulties in accurately investigating the haemostatic system of small infants, particularly when there is a question as to whether the baby has been the subject of NAI and there is a drive (often by the parents) to demonstrate an abnormality, however mild, to explain the bruising that has occurred. The situation is relatively simple if there are no child protection concerns – in these cases it is important to rule out severe and mild coagulation disorders with factor assays and VW screen and severe platelet disorders can be excluded reliably using the *in vitro* bleeding time device when a closure time of >300 s with both cartridges is suggestive of a severe defect of primary haemostasis. Flow cytometry should be used to confirm absence of either glycoprotein complex Ib/IX or IIb/IIIa. If the clinical situation requires it – the baby requires an operation or may require appropriate treatment for ongoing symptoms – then attempts should be made to accurately and fully assess platelet function

using methods outlined above, although this may require venesection on more than one occasion due to the volumes of blood required. If full assessment can wait until after the age of 1 year then this will allow a better chance of getting the required volumes of blood and the normal ranges, particularly for platelet nucleotides, are more reliable.

In cases where there are child protection concerns it may be necessary to attempt to do everything even in the young infant to satisfy the court that the child has no demonstrable haemostatic abnormalities, although in practice this does mean that the child may require more than one visit to obtain all the blood and/or repeat tests that may give borderline results – this inevitably delays the court process and resolution of the case.

Conclusions

The investigation of bruising and bleeding in children can be extremely difficult. The first reason for this is that somebody, usually a senior healthcare professional, has to decide whether a child with bruising or bleeding has 'normal' or 'abnormal' bruising/bleeding. Then the decision has to be made as to how many tests to do and how far to investigate each child, as there is no doubt that to do 'all the tests' on every child is unnecessary and, in fact, would constitute a form of 'child abuse' in itself. However, many infants with severe bleeding disorders do go undiagnosed for a matter of days or even weeks or months because the basic tests are delayed and, even though these disorders remain rare, with prompt diagnosis and appropriate treatment these children can grow up with minimal health-related complications.

Once the 'tests' are requested difficulties arise with interpretation because many laboratories employ adult normal ranges and methodologies only and there is poor recognition of the differences between the haemostatic systems of children and adults that are essential for accurate diagnosis.

To try and ensure prompt and appropriate management of infants and children who present with any form of 'abnormal' bruising or bleeding, all Trusts that treat children should have protocols for investigation and management in place and these protocols should be agreed between local paediatricians and haematologists. Complex cases may well require more specialised expertise; discussion or referral to paediatric haematologists or paediatric haemophilia comprehensive care centres for further investigation and management.

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