

PERSONAL PRACTICE

The bleeding child; is it NAI?

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As a paediatric haematologist, the question of whether a child has been abused or whether they might have a bleeding diathesis is a question that I am regularly asked. When I first became a consultant, I would often find that not enough information was available; for example, incomplete histories had been taken or investigations were incomplete and difficult to interpret. This inevitably led to delays in confirming the cause of the bleeding and meant that if parents or carers contested a diagnosis of abuse, excluding a bleeding disorder was extremely difficult. I was also aware that carers of several of my patients with haemophilia or other bleeding disorders had initially been under suspicion of abuse, most usually at the time of the first few presentations. By highlighting important questions in history taking, having a specific haematological screen for children being investigated for bleeding in the context of non-accidental injury, and encouraging discussion of abnormal results with a haematologist, these difficulties can, for the most part, be avoided.

As doctors who care for children, we have a responsibility to be aware of signs and symptoms suggestive of child abuse, including non-accidental injury. Equally however, we must also recognise that medical and physical conditions may simulate abuse and that appropriate measures need to be taken to rule out these conditions. Haemostatic abnormalities are manifest usually as bruising or other bleeding into the skin or mucosal membranes, and similarly cutaneous lesions are by far the most common presenting features of child abuse.¹ An incorrect diagnosis of child abuse can be devastating for the family and if a serious underlying blood disorder is later identified, regaining the trust of that family may be very difficult. Delay in diagnosis of a condition such as haemophilia will mean that no treatment can be offered which may lead to increased morbidity and even mortality. It is important to remember, however, that diagnosis of a bleeding disorder does not rule out abuse² and that these children will be at greater risk of bleeding secondary to abuse.

CLINICAL HISTORY AND PRESENTATION

When a child presents with bruising or bleeding, the main differential diagnoses are physiological or accidental bleeding, non-accidental injury, or a bleeding diathesis.

Presenting complaint

The history of the presenting complaint will include questions as to how the injury occurred and an assessment made as to whether this explains the injuries or bleeding seen. Guidance is given that abuse should be suspected if there is significant bruising or bleeding with no history of trauma or a history inconsistent with the severity of the injury,³ but in a child with a bleeding diathesis, this may be precisely how the child presents. Where a child has bruising in a recognisable pattern such as a belt or hand, then suspected abuse must be reported regardless of the results of laboratory tests.⁴ However, fingertip bruising can be seen in children with a bleeding diathesis from normal physical interaction. A drug history should also be elicited, particularly one of anticoagulant use.

Past history

Past history of bleeding and haemostatic challenges add important information and specific questions should be asked about birth; for example, whether there was a cephalhaematoma, unexpected bleeding from the umbilical stump, or bruising after intramuscular injections. Active children usually have bruises on their shins, but not normally on unexposed areas. Persistent mucocutaneous bleeding such as gum bleeding or epistaxis (often bilateral) in addition to bruising might indicate thrombocytopenia, a platelet disorder, or von Willebrand disease.

Significant haemostatic challenges

Significant haemostatic challenges will include operations such as circumcision, tonsillectomy, or removal of teeth. Bleeding response to injury such as a bitten tongue or a wound that requires stitching can yield useful information. In girls, menstrual loss may be an indicator of a bleeding diathesis. Bleeding may be due to other disease states that affect haemostasis such as hepatocellular dysfunction, renal disease, or malabsorption.

Family history

A family history of bleeding may be apparent and is more often seen in dominantly inherited or X-linked conditions such as haemophilia A or B. However, haemophilia A, the commonest type of haemophilia, arises as a result of spontaneous mutation in about 30% of cases and therefore family history will be lacking.⁵ The sex of the patient and the age also help to distinguish between possible causes of bleeding. X-linked disorders such as haemophilia A and B usually occur in males. Such disorders may occur in girls but unless consanguinity or Turner's syndrome is present, the chances are very small. Extreme Lyonisation of the X chromosome can also result

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in girls being clinically affected; therefore, although such diagnoses are unlikely, they should be tested for as part of a full evaluation. The age at presentation influences the likelihood of a particular cause of a bleeding diathesis. A patient with a severe congenital bleeding diathesis is unlikely to present for the first time as an adolescent. It must also be remembered that the plasma concentration of many of the coagulation and fibrinolytic proteins are age dependent and therefore appropriate normal ranges must be used for interpretation. Ideally the laboratory should establish normal ranges for age using their reagents and methods for at least the more common parameters measured. Details of ethnic origin and consanguinity should be taken as certain disorders are more frequent in particular groups; for example, factor XI deficiency in those of Ashkenazy Jewish descent⁶ and recessive disorders are more common in consanguineous families.

Examination of the child

When examining the child, the general health and state of the child should be assessed.

Bruises

If the child is presenting with bruising, particular note should be made of the distribution and size of the bruises. The age of a bruise is very difficult to ascertain with certainty and depends on the integrity of the coagulation system and vessels and the force and location of the injury.⁷ Accompanying tissue swelling and abrasion may be present in more recent bruises. Bruises of different ages are seen both in abuse and in children with a bleeding diathesis. The pattern of bruising should be recorded, in particular if marks indicate use of an object such as a belt or flex. As has been noted above, fingertip bruising is not infrequently found in children with a bleeding diathesis. The distribution of bleeding may indicate a diagnosis of Henoch-Schönlein purpura, which presents as symmetrical bruising on extensor surfaces. It is due to a vasculitis rather than a coagulopathy, giving a normal coagulation screen and full blood count, and may be confused with non-accidental injury.^{3,8} Neuroblastoma may present with bilateral black eyes due to tumour infiltration of the bone. However, the child is usually unwell with signs and symptoms of systemic disease. In contrast, comparatively minor injury may cause the same sign in a child with haemophilia who will be otherwise well.

Petechial haemorrhages

Presence or absence of petechial haemorrhages will help differentiate disorders associated with thrombocytopenia. Such haemorrhages however can occur in the distribution of the superior vena cava in association with a severe bout of coughing or vomiting in children without a bleeding diathesis or in cases of strangulation.

Bleeding into joints

A swollen, tender joint may indicate a bleed into that joint as is seen in haemophilia, but tender joints may also be seen in Henoch-Schönlein purpura, acute leukaemia, or neuroblastoma.

Haematological investigation

Haematological investigation of a bruised child is mandatory in all cases where the bruising is unexplained or implausible, and in cases where some explanation is given or found but the bleeding that results is disproportionate to the injury sustained. In a child who may have been abused, it is essential that the investigations are as atraumatic as possible and yield the maximum information. Initial screening and investigation are primarily aimed at the diagnosis of the

commoner causes of bleeding and to exclude or confirm some of the rarer causes for the safety and management of the child. Further investigation might be needed if no explanation of the bleeding is found or no admission of non-accidental injury is made.

Venepuncture; reducing investigation artefact

A set of screening investigations should be performed on blood taken from a single venepuncture, and analysed without delay by laboratories experienced in handling small samples. Artefact can significantly distort results and lead to misdiagnosis. The utmost care must be exerted in the way the specimens are taken and handled prior to processing. Ideally, they should be taken by a person experienced in paediatric phlebotomy, with the minimum of venous stasis and during core working hours.

Pitfalls in specimen collection

Common pitfalls in specimen collection and processing include poor venepuncture technique, whereby there is contamination by tissue fluid or air bubbles leading to activation of the sample in vitro which can result in both prolongation or shortening of clotting times as well as thrombocytopenia. If blood is taken from a cannula which has been heparinised, heparin contamination can occur, resulting in prolongation of the activated partial thromboplastin time (aPTT). Over or under filling of the specimen tube will result in an altered ratio of the anticoagulant (citrate) to plasma, giving shortened or prolonged clotting times respectively. Prolonged clotting times may also be seen in severe polycythaemia where there is a reduced plasma volume. Inappropriate storage or transport of the specimen may result in activation of the sample or loss of factor activity.

First line investigations

Initial tests should include a coagulation screen consisting of a prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and thrombin time (TT), plus a full blood count, platelet count, and blood film. A factor VIII, factor IX, and von Willebrand factor antigen and activity (Ristocetin cofactor) are also recommended in all cases of suspected non-accidental injury as a normal or marginally

Table 1 Patterns of coagulation results; possible diagnoses

Test results	Possible diagnosis
Prolonged aPTT PT/fibrinogen/platelets normal	von Willebrand disease* Factor VIII deficiency Factor IX deficiency Factor XI deficiency
Prolonged PT aPTT/fibrinogen/platelets normal	Warfarin ingestion Early vitamin K deficiency Early liver dysfunction Factor VII deficiency
Prolonged PT and aPTT Fibrinogen/platelets normal	Over warfarinisation Severe vitamin K deficiency Over heparinisation Factor X, factor V, or prothrombin deficiency Acquired inhibitors
Prolonged PT and aPTT Decreased fibrinogen Normal or low platelets	Severe liver dysfunction Dysfibrinogaemia/ afibrinogaemia Disseminated intravascular coagulation (including meningococcal sepsis)

*von Willebrand disease subtype 2B is associated with reduced platelets; aPTT is not always prolonged.

prolonged aPTT can be associated with a significant decrease in factor VIII or IX levels or with von Willebrand disease. If the blood is flowing well, a few millilitres extra can save a second venepuncture if an abnormality is found, for example a prolonged aPTT, and further testing is required. It is important that results are compared against age specific ranges as test results and coagulation factor levels vary with age.⁹ Platelet function is not tested in this screen, and although there are some screening tests none is completely satisfactory. A bleeding time is an invasive test requiring a small incision to be made in the forearm, and although it will show the integrity of the platelet–vessel wall interaction, is unnecessary in the early stages of investigation and is highly operator dependent. An automated system, the PFA-100, measures both aggregation and the release reaction of platelets using small volumes of whole blood. This method is sensitive in detecting classical defects resulting in major platelet dysfunction, such as Bernard-Soulier syndrome and Glanzmann's thrombasthenia, and also von Willebrand disease. Apart from Glanzmann's thrombasthenia, which has a history highly suggestive of a severe bleeding disorder and is very rare, the other disorders can be detected by or suspected from the screening tests outlined above. False negative results occur in milder platelet defects such as storage pool disorder, and release defects which are not detectable by the routine laboratory tests,¹⁰ and the test is not sensitive to vascular collagen disorders. Its use in identifying those who have a bleeding diathesis in cases of possible non-accidental injury has not been tested. It can be helpful to bleed parents, especially if results are equivocal or subsequent testing for clarification of any abnormality requires large volumes of blood. Identification of the child's natural parents, however, is not always certain, or they may not be available or locatable, and this approach may not be possible.

Patterns of abnormal results

The pattern of abnormalities obtained using first line tests along with the clinical presentation and history may well indicate or identify any underlying disorder (table 1). It is important to remember that some significant bleeding disorders give normal screen results (table 2) and that some abnormal results are not associated with bleeding. It is this latter category, if not properly investigated, that can cause confusion and misdiagnosis. The causes of bleeding in a well child can be subdivided into likely causes with or without normal results and unlikely causes with or without normal results (table 2).

Likely causes of bleeding with a normal full blood count and coagulation screen include Henoch-Schönlein purpura and von Willebrand disease.

Likely causes with an abnormal screen include idiopathic thrombocytopenic purpura where the platelet count is low but all other parameters are normal. Haemophilia A and B are the commonest, inherited causes of severe abnormal bleeding and both give an isolated, prolonged aPTT, and low levels of factor VIII or IX respectively (table 3). Vitamin K deficiency or warfarin prolongs the PT with or without a prolonged aPTT depending on the degree of deficiency or of warfarinisation (table 3). Heparin administration is suspected if both the aPTT and thrombin time are prolonged (table 3) and can be confirmed by demonstration of a normal Reptilase time. In this test, fibrinogen is converted directly to fibrin, a reaction which is not inhibited by heparin. The thrombin time relies on activation of fibrinogen to fibrin by thrombin which is inhibited by heparin.

Unlikely causes of bleeding in a child whose initial results are normal include both platelet disorders and factor deficiencies as well as vascular/collagen disorders (table 2). Factor XIII deficiency results in reduced clot stability and is associated with delayed haemorrhage and poor healing. There is delayed and repeated bleeding from superficial wounds and classically delayed separation by up to four weeks of the umbilical stump. Deficiency of α_2 antiplasmin gives a clinical picture similar to factor XIII deficiency, whereas deficiency of another of the anticoagulant proteins, plasminogen activator inhibitor-1, is associated with a less severe phenotype with bleeding usually after surgery or trauma. Vitamin C deficiency, resulting in perifollicular haemorrhages and bony changes, and Ehlers-Danlos syndrome are examples of collagen abnormalities that give rise to bleeding. However, all these causes are extremely rare, and apart from plasminogen activator inhibitor-1 deficiency, have a distinct clinical presentation.

Rare causes of bleeding with an abnormal screen include both platelet disorders and factor deficiencies (table 1). Congenital platelet abnormalities (excluding Glanzmann's thrombasthenia) such as Bernard-Soulier or Wiskott Aldrich syndromes are associated with abnormal platelet numbers and morphology. Deficiencies of factors II (prothrombin), V, and X result in prolongation of the aPTT or PT or both, depending on the reagents used, whereas factor VII deficiency gives an isolated, prolonged PT, and factor XI deficiency an isolated, prolonged aPTT. Abnormalities of the PT or aPTT should trigger appropriate factor assays (table 3). Dysfibrinogenemias, hypo- and afibrinogenemias are picked up by a prolonged thrombin time and low or absent fibrinogen levels (table 3).

Table 2 Causes of bleeding in a well child

	Coagulation screen* or platelets	
	Normal	Abnormal
Common	von Willebrand disease Henoch-Schönlein purpura	ITP Haemophilia A or B Vitamin K deficiency Warfarin or heparin
Uncommon	Glanzmann's thrombasthenia Platelet storage pool disorder Factor XIII deficiency PAI-1 deficiency α_2 antiplasmin deficiency Ehlers-Danlos Vitamin C deficiency	Congenital platelet abnormality (excluding Glanzmann's) Deficiencies of factors II, V, VII, X, XI Dysfibrinogenemia Afibrinogenemia

ITP, idiopathic thrombocytopenic purpura; PAI-1, plasminogen activator inhibitor-1.
*Excluding von Willebrand factor.

Table 3 Initial and further investigations

Initial Investigation	Further investigation	Consider
PT	Isolated prolongation	Early warfarin therapy; early vitamin K deficiency, early liver disease. Possible factor VII deficiency
aPTT	Isolated prolongation: 50:50 plasma mix Correction—factor deficiency, measure levels No correction—inhibitor	Factor VIII or factor IX deficiency von Willebrand disease Factor XI deficiency (rare) Factor XII deficiency (not associated with bleeding) Lupus anticoagulant; heparin contamination
PT and APTT	Both prolonged (fibrinogen normal)	Warfarin, vitamin K deficiency, heparin Liver disease Rare factor deficiencies, e.g. II, V, X
Fibrinogen	Decreased Prolonged PT and aPTT, decreased platelets If <0.8 g/l, PT and aPTT will be prolonged Platelets normal	Disseminated intravascular coagulation Severe liver disease Dys/fibrinogenaemia
Thrombin time	Prolonged—reptilase time Normal Prolonged	Heparin as for low fibrinogen
Factor VIII	Low levels <40%	Haemophilia A
Factor IX	Low levels <40%	Haemophilia B
von Willebrand factor	Low antigen and/or activity (ristocetin co-factor) levels	von Willebrand disease

Abnormal screening tests with no bleeding diathesis

An abnormal screen does not necessarily indicate a bleeding diathesis; the two most common abnormalities giving rise to this are factor XII deficiency and the lupus anticoagulant, which is an inhibitor of *in vitro* coagulation. Both these conditions give rise to a prolonged aPTT but do not result in a bleeding state (table 3). A factor deficiency can be differentiated from an inhibitor using mixing techniques. A 50:50 mix of patient plasma and normal plasma are incubated and the abnormal test repeated. Correction of the aPTT by >50% indicates a deficiency, whereas lack of correction indicates an inhibitor. If the pattern of correction is one of a deficiency, factors VIII, IX, XI, and XII should be checked. Factors VIII and IX should have already been assayed as part of the screen, and once factor XI and XII are measured, if the only deficient factor is XII, then this is not associated with a bleeding state. Factor XII is only necessary for coagulation *in vitro* but does not have a role *in vivo*. If the pattern is one of an inhibitor, once heparin has been excluded (by a normal Reptilase time), further investigations to confirm a lupus anticoagulant can be performed. This should be possible without delay if enough blood is taken at the initial venepuncture. A lupus anticoagulant will prolong a dilute Russel viper venom time (DRVVT) but show correction with platelet neutralisation. Prolongation of the aPTT in children secondary to a lupus anticoagulant is not an uncommon finding. The lupus anticoagulant only exerts its anticoagulant effect *in vitro* where it interferes with the exogenous phospholipids added to the test tube. *In vivo*, the phospholipid is provided by the platelet and is protected from the antiphospholipid effect of the lupus anticoagulant. It is usually a transient phenomenon and occurs secondary to infection resolving within about three months. Unless confirmed however, it may mislead clinicians into thinking a bleeding disorder is present.

SPECIFIC DISORDERS

Inherited disorders

Von Willebrand disease

Von Willebrand disease (vWD) is the commonest of the inherited bleeding disorders with a prevalence of 1–2%,¹¹

whose typical presentation is one of mucocutaneous bleeding. It is inherited as an autosomal dominant but with marked variability of both phenotypic penetrance and expressivity, and thus a clear family history is not always elicited. Haemorrhagic tendency is variable and depends on the type and severity of the disease. Many in whom vWD is diagnosed have modestly reduced von Willebrand factor (vWF) levels that are associated with mild bleeding in some family members but not others.¹² Some cases are easy to diagnose, with the patient suffering from repeated and significant bleeding with exceptionally low vWF levels. However, many cases are not clear cut, despite repeated investigation and testing of family members. It is therefore important to include measurement of this protein and its activity routinely as recommended above, but to be cautious when attributing bruising in a child with suspected non-accidental injury to low von Willebrand factor levels if identified.²

Haemophilia

Haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency), although rare, are the commonest inherited factor deficiencies associated with a bleeding diathesis. They are both X-linked conditions and the severe forms occur almost exclusively in males. The two types are indistinguishable from each other in their clinical presentation. Although an inherited disorder, approximately one third of cases arise as a result of a new mutation, and a positive history is only elicited in around 50% of cases. They are the commonest inherited bleeding disorders to present in the neonatal period,¹³ and 90% of those with severe disease will have presented by the age of 1 year. After the immediate neonatal period, the infant is unlikely to bleed unless accidental injury, although generally trivial, occurs. Once the child begins to crawl and walk, soft tissue bleeding and haemarthroses occur more readily. Several reports describe children who have been misdiagnosed as victims of non-accidental injury before full evaluation of the possible causes of bleeding has been undertaken.^{4 14 15} A coagulation screen in haemophilia A or B will show an isolated prolongation of the aPTT which will correct on 50:50 mixing with normal

plasma. Specific factor assays will identify the deficient factor. Moderate and mild haemophilia will present later, and in the case of mild haemophilia usually only after trauma. The aPTT is not very sensitive to mildly reduced levels of factors VIII and IX, and therefore measurement of these factors is recommended in the routine screen as above.

Haemophilia C

Factor XI deficiency, haemophilia C, is a rare inherited bleeding disorder and is found mostly but not exclusively among the Ashkenazi Jewish population. It is inherited in an autosomal recessive manner and bleeding is usually mucocutaneous in nature. A coagulation screen shows an isolated, prolonged aPTT.

Rare coagulation deficiencies

The rare coagulation deficiencies occur with a frequency of 1 in 500 000 to 1 in 2 million, and include fibrinogen and prothrombin and factors V, VII, X, and XIII. Apart from factor XIII deficiency, all result in abnormalities of the coagulation screen (tables 1 and 2).

Congenital platelet disorders

The majority of the inherited platelet disorders that are associated with bleeding result in a degree of thrombocytopenia, for example, Bernard Soulier syndrome, Wiskott Aldrich syndrome, May Hegglin anomaly. Glanzmann's thrombasthenia is a severe condition where the patient's platelets lack the IIb-IIIa receptor essential for binding of fibrinogen and platelet aggregation. There is a positive history of bleeding from birth, with mucocutaneous bleeding, spontaneous bruising, and significant bleeding with minor trauma. It is inherited as an autosomal recessive condition and thus there is usually no family history. Diagnosis is made from platelet function tests. Platelet storage pool disorders are often associated with a mild bleeding phenotype and require platelet function tests for diagnosis. Again, the diagnosis of a platelet storage pool disorder does not rule out non-accidental injury, and the history and clinical findings are very important.

Acquired disorders

Reduced vitamin K dependent factors

Vitamin K deficiency can occur in the neonatal period or early infancy. Early presentation may be secondary to maternal ingestion of vitamin K antagonists such as warfarin or anticonvulsants, or to lack of vitamin K prophylaxis at birth. Later presentation is commonly associated with exclusive breast feeding and either lack of vitamin K at birth or a single oral dose only. About 50% of babies who present late do so with intracranial haemorrhage, with high morbidity and mortality. Misdiagnosis of haemorrhagic disease of the newborn as child abuse has been reported.¹⁴ The coagulation screen shows a prolonged PT, with a variably prolonged aPTT dependent on the severity of the deficiency.

Warfarin exerts its action by preventing carboxylation and thus activation of the vitamin K dependent factors. Again the PT is prolonged with variable prolongation of the aPTT, dependent on how much warfarin has been taken. Warfarin can be administered therapeutically, accidentally, or non-accidentally and can be tested for specifically.

Heparin prolongs the aPTT and thrombin time and is a common contaminant of blood taken from heparinised cannulae, even if a large discard sample has been taken. Occasionally children are given heparin therapeutically. The presence of heparin can be confirmed with this pattern of results and a normal Reptilase time.

Thrombocytopenia

This is easily identified from the full blood count. In a well child the most likely cause is idiopathic thrombocytopenic purpura (ITP), and under these circumstances the haemoglobin and white cell count is usually normal as is the coagulation screen. Other causes of acquired thrombocytopenia, such as bone marrow infiltration from malignant disease or leukaemia, or disseminated intravascular coagulation are associated with additional abnormalities of the blood count or coagulation screen, and are seen in an ill child.

SUMMARY

When trying to establish whether bleeding is due to a haematological disorder or to abuse, it is essential to take a pertinent personal and/or family history, investigate appropriately and without delay, and to limit the trauma to the child and the carers. Having a protocol for investigation of a possible bleeding diathesis allows laboratory investigation to proceed, including institution of some second line tests dependent on initial results, without unduly delaying the processes of investigation and reporting of suspected non-accidental injury. Importantly, it also establishes involvement of a haematologist in interpretation of tests in the light of history and clinical findings. Initial screening tests should include a PT, aPTT, thrombin time, and fibrinogen, a factor VIII and factor IX level, and von Willebrand factor antigen and activity. This set of tests is not comprehensive but will identify the majority of bleeding disorders or indicate which further tests are necessary. If there is a significant discrepancy between history and findings and the initial tests are normal, either there is a bleeding disorder which has not yet been identified or abuse has taken place. Discussion with parents or carers should take place at this stage and if discrepancies still exist, further investigation might include platelet function testing or specific factor assays such as factor XIII. If the case is likely to receive a formal legal challenge, even the rarest of causes may require exclusion. It is important to remember that diagnosis of a bleeding diathesis, especially if associated with a mild phenotype, does not exclude non-accidental injury, and where these are found concurrently, the child will be at even greater risk.

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