

PERSONAL PRACTICE

An approach to investigation of easy bruising

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Easy bruising presents several investigative dilemmas in primary and secondary practice, not least because it raises the spectre of physical abuse. When, and to what extent, should general paediatricians investigate before referral to a specialist? When can it be safely concluded that an underlying bleeding disorder has been excluded, so that further investigations can focus on ruling out suspected non-accidental injury? When, despite an abnormal clotting test, should the latter investigations still be pursued?

The intention of this review is to attempt to answer these questions from the perspective of routine practice without recourse to a comprehensive review of bleeding disorders or non-accidental injury. We intend to address only the patient seen electively in the outpatient clinic for investigation of easy bruising, not an acutely ill child presenting to accident and emergency with purpura, whose differential diagnosis varies from, most often, no cause found, to, less commonly, meningococcal sepsis or Henoch–Schönlein purpura.

Distinguishing “normal” from “abnormal” bruising

Bruising caused by accidental injury is common around the age of 1, when most infants have started “cruising”.¹ To distinguish “abnormal” from “normal” bruising requires attention to the pattern of bruising, associated symptoms, and drug and family history.² As a rule, normal bruising is restricted to the lower limbs,¹ not associated with petechiae, purpura, or mucosal bleeding, and the family history is negative. The latter should be interpreted cautiously as it is often negative in disorders of haemostasis, and not infrequently positive in families with unexplained easy bruising or epistaxis, who may carry the nebulous entity of “increased skin fragility” which is usually associated with “hyperextensible” joints, but without the classic features of Ehlers–Danlos syndrome (see below).³ It is also important to obtain a comprehensive family history, which includes grandparents and the extended family, and taking special care to note, where this may be the case, the different parentage of all the siblings.

Documenting a history of the response to haemostatic stress is useful in determining the likelihood of a significant bleeding disorder. Excessive bleeding after tooth extractions or minor surgery (for example, tonsillectomy) is a characteristic of disorders of haemostasis, and

its absence excludes significant abnormality. Steroid inhaler or non-steroidal anti-inflammatory drug (NSAID) use, current or previous, should be excluded in those cases where an abnormal pattern of bruising is the sole cause for concern. Long term use of high dose inhaled steroids, and even a single dose of NSAIDs, can predispose to easy bruising that persists for weeks to months after cessation. Other drugs, such as anticonvulsants, may also be a cause of easy bruising and a comprehensive drug history should be an important part of the initial assessment.

The target of further investigation should therefore be patients with bruising over the trunk, neck, or face, irrespective of limb or mucosal bleeding, those with excessive blood loss after minor surgery, or a positive family history.

Causes of abnormal bruising

Abnormal bruising is not exclusively a result of haemostatic disorders.⁴ In addition to non-accidental injury, collagen disorders, though rare, should be considered in the differential diagnoses.⁵

THROMBOCYTOPENIA

Immune thrombocytopenic purpura (ITP) is the commonest haemostatic disorder of childhood to present with easy bruising, usually associated with petechiae, purpura, and mucosal bleeding. The diagnosis is of exclusion, and made on the basis of an otherwise well patient, without lymphadenopathy or organomegaly, with isolated thrombocytopenia and a normal blood film and clotting screen. The latter two in a well child excludes leukaemia, meningococcal septicaemia, and haemolytic uraemic syndrome. Persistence of thrombocytopenia beyond a few months from presentation should trigger referral to a specialist for further investigations. These should be directed towards exclusion of rare congenital causes of isolated thrombocytopenia (such as May–Hegglin syndrome and other giant platelet familial thrombocytopenia syndromes, Fanconi’s anaemia, and amegakaryocytic thrombocytopenia), before concluding that the patient has chronic ITP. Although investigations at this stage may include examination of the bone marrow, if this has not already been performed, careful reexamination of the blood film and parental blood counts may be the simplest way to exclude some of these rare conditions.

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PLATELET FUNCTION DISORDERS

Poor platelet aggregability is caused by a variety of acquired and inherited disorders, the commonest being NSAID use.⁶ Inherited disorders of platelet function are rare, but should be suspected in a patient with symptoms of thrombocytopenia but a normal platelet count, or mild thrombocytopenia relative to the severity of haemorrhagic symptoms. The best known, and easiest to diagnose, are Glanzmann's thrombasthenia and Bernard Soulier syndrome, which result from a measurable (by flow cytometry) lack of expression of platelet membrane receptors essential for activation and aggregation. Storage pool deficiency is harder to diagnose, as few patients have the classical clinical and laboratory features, and the laboratory tests required to exclude it are difficult to perform and interpret. Inheritance of most platelet function disorders is autosomal recessive, so it may not be apparent without testing the extended family. Given the difficulties in diagnosis, it is probably best to refer patients suspected of a platelet function defect to a specialist.

DISORDERS OF COAGULATION FACTORS

Inherited

Autosomal dominantly inherited Von Willebrand's disease (VWD) is the commonest congenital disorder of haemostasis, affecting up to 1% of the population; it often presents with easy bruising as the sole symptom, although mucosal bleeding is also common. Purpura and petechiae are not common despite the abnormal platelet aggregation, which is a feature of this condition along with a variable reduction in concentrations of von Willebrand factor (VWF) and factor VIII. Post-pubertal females may have menorrhagia. Family history is frequently positive, but may be silent and only uncovered on parental testing. The majority of cases are mild with concentrations just below the normal range. This may cause diagnostic difficulty, as the venepuncture ordeal can stimulate release of factor VIII and VWF from endothelial stores, often pushing marginally sub-normal concentrations to within the normal range. Where suspicion is strong, and concentrations borderline normal, repeat tests may be justified, but should be postponed until a management decision rests on the diagnosis (for example, impending surgery), or venepuncture is being undertaken for another purpose.

Mild haemophilia A (factor VIII deficiency) or B (factor IX deficiency) are much less common, but can present with symptoms similar to those of VWD. X linked recessively inherited, female carriers can be affected as a result of skewed lyonisation. Moderate and severe haemophilia A or B presents in infancy with atypical bruising, and haemarthroses later on when it should be easy to diagnose, although the latter is not infrequently misdiagnosed as pyogenic arthritis. Family history is absent in the 30% of sporadic haemophilia cases arising from a new mutation in maternal or grandparental germ line.

Congenital deficiencies of other coagulation factors are much rarer and variably associated with a risk of bleeding, except for factor XII deficiency, which is always asymptomatic.

Acquired

Sick neonates bruise easily, usually as a result of a low platelet count. Bruising in infants younger than 9 months is rare, and should always prompt a search for a cause.¹ Physical abuse should be suspected at this age, more than any other, if another explanation for bruising is not found.

An uncommon cause of bruising at this age is haemorrhagic disease of the newborn (HDN), which occurs when prophylactic vitamin K has not been administered at birth, or has been given orally to subsequently breast fed infants without the one and three month boosters. Unrecognised, it can result in catastrophic intracranial haemorrhage. Once recognised it is easily treated with intravenous vitamin K.

Outside infancy, vitamin K deficiency is usually caused by malabsorption, liver disease, or a combination of the two. Coeliac disease may present with easy bruising as the sole symptom, although most patients will have other signs of malabsorption. Similarly, inflammatory bowel disease and chronic liver disease may have easy bruising as a dominant presenting symptom. These diagnoses should be clinically obvious, but are worth excluding as a cause of isolated prolongation of the prothrombin time.

COLLAGEN DISORDERS

Vascular integrity is essential for primary haemostasis to be effective. Defective collagen compromises capillary and skin elasticity, thereby manifesting symptoms similar to those of thrombocytopenia or platelet function defect.⁸ Not all patients have the classic features of Ehler-Danlos syndrome,³ Marfan's syndrome, or acquired autoimmune disorders. A simple test of thumb hyperflexibility is claimed to identify patients with a mild inherited bleeding diathesis without abnormalities of haemostasis or other features of a collagen disorder.⁹

NON-ACCIDENTAL INJURY

Suspicion of this comes from a variety of medical and social indicators that have been comprehensively described elsewhere. An atypical pattern of bruising in the absence of other haemorrhagic symptoms and a normal count and clotting screen should prompt a review of other indicators to exclude non-accidental injury.¹ It is important to remember that non-accidental injury and a bleeding disorder are not mutually exclusive.¹⁰

Investigation approach

Figure 1 shows a simple approach to investigation of easy bruising. Having established the need for blood tests, a blood count and clotting "screen" (see table 1) are essential baseline

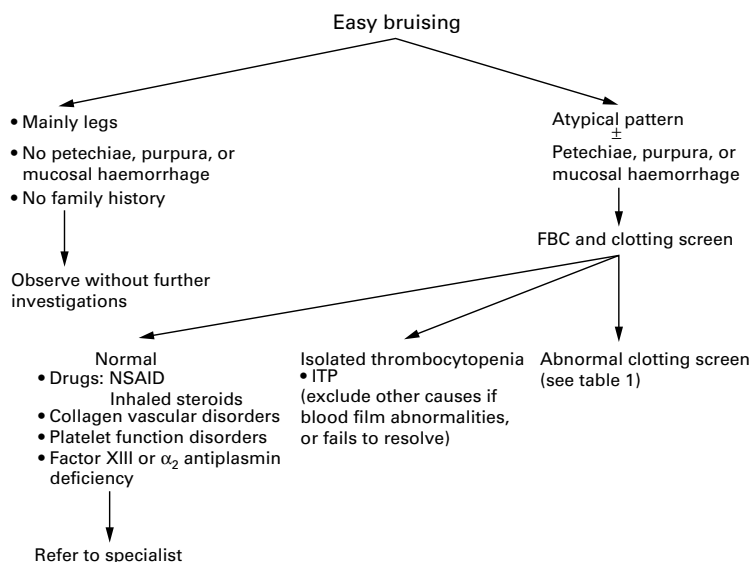


Figure 1 A simple approach to investigation of easy bruising.

investigations. The latter consists of a prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen concentration; some laboratories also perform a thrombin time (TT). It is now known that the model of discrete pathways of coagulation described by these tests is an artificial construct of test tube conditions that do not always prevail in vivo. However, they are the best available tools to screen for abnormalities of the coagulation cascade, and narrow the focus of further investigations. To avoid repeated needle puncture in the patient who may need further tests, it is worth at this stage taking a 5 ml clotting screen (citrated) sample and requesting the laboratory to save the residual plasma in several aliquots for investigation of abnormalities revealed by the screening tests.

It is extremely important to interpret clotting screen results in relation to age related normal ranges. If the blood count and clotting screen are normal, a significant disorder of haemostasis is unlikely. However, these can be normal in mild subtypes of VWD (for reasons given above), platelet function disorders, rare congenital coagulation factor deficiencies such as of factor XIII and α_2 antiplasmin, and collagen vascular disorders. If these are suspected because of a significant bleeding history, we would advocate referral to a specialist for

further investigations. Most importantly, investigations for these disorders should not be undertaken merely to establish a diagnosis of non-accidental injury by exclusion.

Further investigations of screening test abnormalities are dictated by the specific abnormality. Thrombocytopenia raises suspicion of ITP, although, if the bruising history is of insidious onset and the thrombocytopenia is associated with a raised mean cell volume, Fanconi's anaemia should be excluded.

An isolated prolongation of the PT is most likely to be a result of vitamin K deficiency or liver disease, and should be investigated further by performing a factor VII assay. Isolated prolongation of the APTT may be caused by a deficiency of any of the intrinsic pathway coagulation factors, or heparin if the sample has been taken from a heparinised catheter or cannula. If the latter is suspected, a TT and reptilase time (RT) should be performed before undertaking coagulation factor assays. Prolongation of the TT with a normal RT is suggestive of heparin contamination. If both the RT and TT are prolonged, the most likely cause is a low fibrinogen concentration, or dysfibrinogenaemia if this is normal.

If heparin contamination is not suspected, or is excluded, an isolated prolongation of APTT requires factor assays to exclude VWD or coagulation factor deficiency. It is sensible to start with factor VIII "complex" studies, including VWF antigen and function (ristocetin co-factor assay), and a factor IX assay, as these are clinically significant abnormalities that are important to exclude. If these are normal, factor XI and XII concentrations should be checked. If these too are normal, a lupus anticoagulant should be suspected. Usually this results in a prolonged APTT uncorrected by addition of normal plasma to the test, but this is not always the case. A dilute Russell viper venom time (DRVVT) is the diagnostic test for lupus anticoagulant. If positive, it usually has no clinical significance in children, as it is most often a result of transient antiphospholipid antibodies after a viral infection that can persist for months to years causing no clinical problems. In adults it is associated with an increased risk of arterial and venous thrombosis. The APTT is often prolonged without an apparent cause on detailed investigations and is most often a result of clinically insignificant factor XII deficiency.

Combined abnormalities of the PT and APTT are often a result of moderate to severe vitamin K deficiency or liver failure. Although unlikely in children, warfarin overdose can produce the same abnormality, and should be suspected in cases of Munchausen syndrome by proxy or accidental poisoning caused by certain types of rat poisons, which contain coumarin analogues. The most common cause of combined PT and APTT abnormalities is disseminated intravascular coagulopathy, but this is usually not a differential diagnosis for a child investigated in the clinic for easy bruising. Inherited deficiencies of factors V or X also produce similar laboratory abnormalities but are very rare.

Table 1 Abnormalities of clotting screen

Abnormality	Cause
Isolated prolongation of PT	1. Vitamin K deficiency (HDN, malabsorption) 2. Liver failure 3. (Warfarin)
Isolated prolongation of APTT	1. VWD 2. Coagulation factor deficiencies: • Factors VIII, IX and XI—clinically significant • Factor XII—not significant 3. Lupus anticoagulant—DRVVT 4. (Heparin)
Combined abnormalities	1. Liver failure 2. Vitamin K deficiency 3. (DIC) 4. Rare—afibrinogenaemia or dysfibrinogenaemia

() Suspect in certain circumstances as described in text.

Platelet function defects cannot be excluded on the basis of a normal count and clotting screen, but require specific tests for diagnosis, including bleeding time, platelet aggregometry, and nucleotide release assays.¹ Bleeding times are operator dependent and are difficult to perform in very young children. Although yet to be fully validated, new methods of in vitro bleeding time assay such as the PFA-100 may in time supersede these, and provide an easy method to exclude platelet function disorders. The PFA-100 instrument measures the time it takes flowing blood to block an aperture coated with collagen and adrenaline or ADP. Initial experience suggests that it is useful in detecting platelet defects as well as most cases of von Willebrand's disease.¹¹ We would strongly recommend that patients suspected of platelet function disorders be referred to a specialist for further investigations.

Summary and conclusion

A relatively simple approach to the investigation of easy bruising is summarised in fig 1. It indicates when investigations are warranted, and at which point specialist advice should be sought. Although we do not guarantee it will solve the mystery of easy bruising in every case,

we hope it will provide general paediatricians with a pragmatic approach to investigation of this often perplexing problem.

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