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Lesson of the Week

Severe bleeding disorders in children with normal coagulation screening tests

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Congenital bleeding disorders may present in many ways, usually doing so in infancy or early childhood. In any child presenting with unexplained bruising one must also consider the possibility of non-accidental injury. In many cases it may be impossible to exclude non-accidental injury because the history and signs may only be pointers, the true facts becoming apparent only by careful follow-up.

I report on two children in whom the diagnosis of possible non-accidental injury, along with "normal clotting studies," led to delayed diagnosis of congenital bleeding disorders.

Case 1

A 10-month-old West Indian child was admitted for observation at the mother's request because of irritability. He had reportedly been throwing himself about his cot. Initially on examination he had only occipital bruising, with no other abnormal signs. The mother was young, unmarried, and pregnant with a further unwanted child. She had two other normal, well children. She was a regular clinic attender and had also seen her general practitioner because of the baby's "horrendous bruises." Non-accidental injury had been suspected. There was no family history of bleeding or tendency to bruise. The next morning the bruising had become a large occipital and periorbital haematoma, with further ecchymoses over the upper arms, wrist, and shins. On further questioning the mother mentioned non-accidental injury herself. The results of investigations showed: haemoglobin concentration 5.3 g/dl (reticulocytes 8.3%); platelet concentration $247 \times 10^9/l$ ($247\,000/mm^3$); prothrombin time 13 s (control 12 s); partial thromboplastin time 59 s (control 55 s); bleeding time (Ivy) $6\frac{1}{2}$ min (normal 2-7); skeletal survey normal; serum iron concentration $8\,\mu mol/l$ (45

When non-accidental injury is suspected it is important to exclude a bleeding disorder by careful screening of haemostasis

$\mu g/100\,ml$) (normal 14-29 $\mu mol/l$; 78-162 $\mu g/100\,ml$). The child had a blood transfusion, and a case conference was arranged.

After two days the right pupil was smaller than the left, the left knee jerk had become brisk, there was neck retraction, and the level of consciousness varied. He was transferred to the regional neurosurgical unit because of presumed intracranial bleeding. Investigations, including computed tomography and lumbar puncture, were normal, however. After the infant returned the right thigh appeared swollen, though there was no bruising or tenderness. This settled spontaneously. At the case conference we decided that non-accidental injury was a possibility and follow-up by a social worker was arranged. Before he was discharged a repeat bleeding time was two minutes; further clotting studies were requested, but the specimen clotted and a second specimen was not sent. After he was discharged the mother complained that the child had a nosebleed and also bled from the tongue, and finally a further large haematoma appeared on the anterior chest wall. He was readmitted and investigation this time showed: haemoglobin concentration 7.9 g/dl; prothrombin time 13 s (12 s); partial thromboplastin time 80 s (48 s); platelet concentration $275 \times 10^9/l$ ($275\,000/mm^3$); bleeding time 6 min (but oozed later); factor VIII 1%. A boy was born to the mother, and he also had severe haemophilia.

Case 2

A girl was first admitted at age 9 months because of a possible head injury, after having apparently fallen from a bed. She was the only child of a young unmarried mother. Examination was unremarkable, and there was no relevant family history. Routine investigation at that time showed a haemoglobin concentration of 10.2 g/dl, with iron-deficient film and "sufficient" platelets. Epistaxes were suggested as a possible

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cause, and as non-accidental injury was thought unlikely she was discharged with no hospital follow-up on a course of oral iron treatment. She was readmitted at age 2 years because her mother had noted bruises over the abdomen and legs. She said that the child tended to bruise easily and had nosebleeds. Investigations showed: prothrombin time 13 s (control 12 s); partial thromboplastin time 45 s (control 39 s); haemoglobin concentration 8.2 g/dl; serum iron concentration 9 $\mu\text{mol/l}$ (50 $\mu\text{g}/100\text{ ml}$) (normal 13–32 $\mu\text{mol/l}$; 73–179 $\mu\text{g}/100\text{ ml}$); platelet concentration $188 \times 10^9/\text{l}$ (188 000/ mm^3); skeletal survey normal.

The mother was noted to be a little rough with the child during the admission and close follow-up by a social worker was arranged. In the outpatients department further epistaxes and bruising were noted; coagulation studies and platelet counts were again normal. Finally, a bleeding time was requested and found to be 25 minutes. Further investigation showed a platelet count of $351 \times 10^9/\text{l}$ (351 000/ mm^3), some with increased size. Aggregation studies showed no response with ADP, adrenaline, and thrombin. The diagnosis of Glanzmann's disease was then made.

Comment

"Unfortunately, haemostasis and blood coagulation are often regarded as synonymous."¹ To achieve haemostasis requires vascular constriction, platelets, and fibrin formation, with later adequate repair processes. The precise importance of any of these factors depends on the site, size, and type of injury. For instance, it is possible even with a severe coagulation disorder for bleeding to stop initially in the time expected, usually to restart later. Several tests are needed to screen the whole process of haemostasis adequately² (see table).

Tests needed to screen for haemostasis

Full blood count and film Platelet count, size, and morphology Prothrombin time (extrinsic system)* Activated partial thromboplastin time (intrinsic system)* Bleeding time (IVY method or a modification of it)* Thrombin clotting time† Clot solubility test†

*Exact choice of tests may depend on the laboratory's preference. Therefore any screening should be agreed with the local laboratory and suitable bottles for paediatric specimens provided.

†These tests of rare disorders are included for completeness, and are unlikely to present in a way that mimicks non-accidental injury.

The diagnosis of non-accidental injury should be suspected in cases of unexplained bruising, and once suspected it is often difficult to exclude entirely. Absolute diagnostic criteria, such as fractures or typical burns, are often lacking, so it is the social "risk" factors that may be the main evidence used in supporting the diagnosis at the case conference and in deciding on the best course to take. Too often the possibility of a disorder of haemostasis is dismissed by asking for a "clotting screen," with no details of the precise tests required and no attempt to screen for all the possible defects, since the diagnosis is not really contemplated. In these two children our failure to make the correct diagnoses initially was the result of several basic errors in the investigation of a bleeding disorder and was made worse by our suspicions of non-accidental injury. Firstly, both children were young, and it was thus difficult to obtain a clean venepuncture. It should be more widely known that difficulty in obtaining blood may lead not only to contamination with tissue fluid, with apparently normal coagulation tests,³ but also to partial clotting in the syringe with consumption of coagulation factors and platelets leading to falsely abnormal results.⁴ These problems may be overcome only by testing samples collected by direct venepuncture using, perhaps, a two-syringe technique⁵—the contents of the second syringe are tested. Unfortunately, it is often difficult to do a venepuncture on an infant or toddler, and doing a capillary sampling technique should be considered.⁶

Secondly, we failed to specify the precise tests required, thus missing the critical investigation of the bleeding time in the child in case 2. Only by carrying out all the tests listed in the table can a patient be screened adequately. Lastly, we accepted the normal results obtained from our screening tests, despite the abnormal history; this was the greatest omission, as even moderate bleeding disorders may have normal screening tests—for instance, a normal partial thromboplastin time with a factor VIII concentration only 10% of normal.⁷ If there is clinical evidence of a bleeding disorder—for instance severe bruising in response to minor trauma, recurrent epistaxes or prolonged bleeding after surgery—then further investigation, after consultation with the haematologist, is warranted. Depending on the type and site of the bleeding, this may include measurements of factor concentrations or measurement of platelet function.

We now investigate all possible bleeding disorders using the standard tests listed in the table. Blood specimens are obtained by direct venepuncture and any difficulty is noted. Above all, we would now investigate any child whose history has any suggestion of a bleeding disorder, even if initial screening is normal.

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What might be the cause of widely varying concentrations of serum lithium in a mentally subnormal man being treated with lithium carbonate, which he seems to be taking as instructed?

There are two things to remember about lithium treatment. The first is that the serum concentration of lithium is always varying, particularly in the first seven hours after each dose, so that the only way to use it as a guide to treatment is to standardise the time of taking the blood for the measurement. You must know the time the last dose was taken by the patient and take the blood at least eight and preferably 12 hours after that time. Are you sure the serum values you are using have all been obtained in this way? The second is that the serum concentration is determined only by a balance between two rates—the rate of excretion of lithium in the urine and the rate of absorption into the blood from the gut. Renal excretion depends on the blood flow through the kidneys (dependent on blood pressure, some other drugs) and on the intake of sodium chloride. Absorption from the gut depends not only on the dose swallowed but also on the type of preparation of the drug. Sustained-release or delayed-release capsules or tablets may be carried through the gut too rapidly (as in diarrhoea), but in any case there is evidence that they do not always release their contained lithium—so they can provide an irregular and somewhat unpredictable dose. The commonest cause of fluctuating serum lithium concentrations, however, is not taking the tablets regularly. Make sure they are being taken to a timetable, and not forgotten or bunched. Check the timing of the blood tests and the accuracy of the laboratory (divide a specimen of blood into two, put a second name on one specimen and see if both yield the same answer). Use plain lithium carbonate every 12 hours rather than a sustained-release preparation.—JOHN CRAMMER, reader in biological psychiatry, University of London.