CASE REPORT

Transient lupus anticoagulant: an unusual cause of bruising in children

A-K Anderson, U Mohan, R Liesner

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A child presented with excessive bruising and prolonged activated partial thromboplastin time. Mixing studies in plasma were positive for phospholipid dependence of the anticoagulant, confirming a diagnosis of lupus anticoagulant. Factor II level was reduced. Laboratory findings normalised after three months, with spontaneous resolution of bruising. This case demonstrates a transient antiphospholipid antibody syndrome as a rare presentation of bleeding diathesis in a previously healthy child, and should be considered in children with new onset bruising and prolonged activated partial thromboplastin time.

Antiphospholipid antibodies (APA) are a diverse group of autoantibodies directed against phospholipids antigens. This group includes lupus anticoagulants (LAs) and antiphospholipid antibodies. Antiphospholipid antibodies may be associated with systemic lupus erythematosus, other autoimmune disorders, connective tissue disorders, malignancies, drug use, and infections or with no underlying disease. In adults they are usually associated with thrombotic complications, including thrombocytopenia syndrome, spontaneous abortion, livedo reticularis and placental infarction, or remain symptom free. Haemorrhage is much less common and is usually attributable to either associated thrombocytopenia or prothrombin deficiency. In children APA are usually transient and have no sequelae. However, children may rarely develop complications such as stroke. We describe the association of transient LA with a prolonged aPTT and reduced factor II levels in a previously healthy 3 year old girl, who presented with bruising.

CASE REPORT

A previously well 3 year old white girl was referred by her general practitioner with a history of spontaneous bruising over the previous few days. Coagulation studies had revealed a prolonged activated partial thromboplastin time (aPTT).

Four months previously, the patient had, over a four week period, developed recurrent nosebleeds during a viral illness that settled without treatment. Two weeks before presentation, our patient and her younger sibling had a diarrhoeal illness with fever, which preceded the development of bruising on her upper and lower limbs. There was no previous history of abnormal bruising or bleeding and no family history of coagulation disorders.

On examination, she was a well child with multiple small bruises on her legs, back, and sides of thighs, forearms, and upper arms. There was no gum hypertrophy, lymphadenopathy, or hepatosplenomegaly.

Full blood count and blood film were normal. Repeat coagulation tests showed normal prothrombin time and thrombin time but a markedly prolonged aPTT (table 1). Mixing studies with 1:1 dilution of patient and pooled normal plasma performed did not fully correct the aPTT from 67.4 s to 53 s on mixing. This implied the presence of a circulating anticoagulant acting as an inhibitor in the intrinsic pathway. A modified Russell viper venom time (mRVVT) was prolonged at 118 s. There was significant shortening of the mRVVT after the addition of platelets, confirming the presence of LA. Anticardiolipin antibodies were not detected. Factor II activity was reduced to 40%. Factors V, VII, VIII, IX, X, XI, XII, and Von Willebrand factor were normal. Serological tests to detect underlying autoimmune disease were negative, including antinuclear antibodies, antibody to double stranded DNA, and rheumatoid factor.

She received no treatment, and her bruising resolved spontaneously over four weeks. Coagulation studies normalised in parallel with clinical recovery, with disappearance of the LA and factor II level increased to normal by the time she was tested three weeks later. She remains well, three months later, with normal physical activity.

DISCUSSION

This case demonstrates the presence of antiphospholipid antibodies as a rare cause of transient haemorrhagic manifestations in children and emphasises the usefulness of coagulation studies in elucidating the diagnosis. LAs may be associated with connective tissue disorders, malignancies, drug use, and infections, or with no underlying disease. Although patients may remain free of symptoms, LAs are commonly associated with deep vein thrombosis, placental infarction, and stroke in adults. Rarely, haemorrhagic symptoms have been reported, mainly in children. Estimated in 10%–20% of patients with LAs, levels of prothrombin will be decreased. It is now recognised that many APA are targeted to the prothrombin protein but it remains unusual for there to be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Laboratory findings in patient with lupus anticoagulant</th>
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<tbody>
<tr>
<td>Patient (seconds)</td>
<td>Normal range (seconds)</td>
</tr>
<tr>
<td>aPTT</td>
<td>67.4</td>
</tr>
<tr>
<td>aPTT after mixing</td>
<td>53</td>
</tr>
<tr>
<td>PT</td>
<td>12</td>
</tr>
<tr>
<td>Factor II</td>
<td>40</td>
</tr>
<tr>
<td>mRVVT</td>
<td>118.1</td>
</tr>
<tr>
<td>mRVTT and platelets</td>
<td>30.5</td>
</tr>
<tr>
<td>β2 glycoprotein I</td>
<td>negative</td>
</tr>
<tr>
<td>Anticardiolipin antibodies (IgG and IgM)</td>
<td>negative</td>
</tr>
<tr>
<td>Adenovirus serology</td>
<td>negative</td>
</tr>
</tbody>
</table>

APTT, activated partial thromboplastin time; PT, prothrombin time; mRVVT, modified Russell viper venom time.

Abbreviations: aPTT, activated partial thromboplastin time; LA, lupus anticoagulant; APA, antiphospholipid antibody
evidence of prothrombin consumption and reduced levels of prothrombin (factor II) in plasma with apparent reduction in its half life.

The evaluation of unusual bleeding or bruising in previously healthy children should begin with a full blood count, film, platelet count, PT, and aPTT and fibrinogen as screening tests. As in this case, any abnormalities should then guide further evaluation. The presence of a prolonged aPTT with normal PT and TT indicate the need for mixing studies. Mixing of the patient’s plasma with normal plasma followed by repeating the aPTT will differentiate between a child with a factor deficiency or an inhibitor, for example, antifactor antibody or LA. Failure to correct the aPTT with the addition of normal plasma indicates the presence of an inhibitor in contrast with a factor deficiency. In this patient the aPTT failed to correct with normal plasma, indicating the presence of circulating anticoagulant. With symptoms of bruising or bleeding, you would suspect an inhibitor against VIII, IX, and XI resulting in a factor deficiency. However, these inhibitors are rare and usually occur spontaneously only in elderly people. However, in this case the finding was that of an antiphospholipid antibody, which is much more common than acquired factor inhibitors in individuals without a congenital factor deficiency.

There are three recognised components of the laboratory confirmation of LAs: (a) the use of sensitive screening reagents; (b) mixing studies to confirm the presence of a circulating anticoagulant; and (c) proof that the anticoagulant is phospholipid dependent. All were present in this case.

The addition of platelets as a rich source of phospholipids will neutralise the antiphospholipid antibody. Significant shortening of a prolonged mRVTT after the addition of platelets as seen in this child (table 1) supports the diagnosis of LA. The use of a platelet neutralisation procedure adds specificity to the diagnosis. Factor II activity was also low despite a normal prothrombin time in both the local and tertiary hospital laboratories.

LA is a laboratory phenomenon that results from autoantibodies, inhibiting a variety of in vitro phospholipid dependent coagulation tests. The autoantibodies are against negatively charged phospholipids or phospholipid binding proteins, including the phospholipid dependent clotting proteins such as PT and aPTT. At least two phospholipid bound plasma proteins are associated with LA, namely, prothrombin and β₂ glycoprotein I. The assay of antibodies to these proteins are generally performed in research laboratories rather than being widely available. In our case, β₂ glycoprotein I and antiphospholipid IgG and IgM antibodies were both negative. A prothrombin antibody was not performed.

The first description of lupus anticoagulant causing bleeding was by Rapaport et al., in 1960, describing an 11 year old girl with severe bleeding and systemic lupus erythematosus. However, the LA persists in autoimmune disorders and is not transient, as seen in our case. Because of the increasing frequency of occurrence of LAs with autoimmune disease, a high level of suspicion for the manifestations of systemic lupus erythematosus and other autoimmune diseases should be maintained, particularly if LA is persistent.

Becton et al reported six cases of previously healthy children with clinical signs of bleeding and prolonged aPTT resulting from positive mixing studies and evidence of phospholipid dependence of the antibodies. Five of the six patients demonstrated anticardiolipin antibodies and the four test had reduced factor II activity levels. In all of his patients, the prothrombin time was prolonged at presentation. In our case, anticardiolipin IgG and IgM antibodies were negative; the prothrombin time was normal and therefore not sensitive to the reduction in factor II. In all of Becton’s cases, the bleeding symptoms resolved spontaneously within three months and laboratory findings returned to normal within six months. Association of antiphospholipid antibodies with infections have been observed previously including Mycoplasma pneumonia, viruses particularly adenovirus, Rocky Mountain spotted fever, Lyme disease, measles, mumps, chicken pox, and acquired immunodeficiency. We speculate that this patient has acquired the LA secondary to a transient viral illness, although this could not be confirmed with positive viral titres as she presented later in the course of her illness. Adenovirus serology was negative.

LAs related to infections or drug use tend to be transient rather than persistent and usually require no treatment other than treating the underlying infection or withdrawing the suspected drug. For the unusual cases where treatment is required for significant bleeding, corticosteroids can be tried or for serious bleeds replacement with either fresh frozen plasma or a factor II containing plasma derived product could be used (prothrombin complex concentrate). The response to such infusions should be monitored clinically and laboratory if ongoing antibody activity is suspected. Corticosteroids have been used in some patients.

Establishing an aetiology of bruising in children presents a challenge to the physician. It is important to think of unusual causes like transient LA in the differential diagnosis of these children, along side other causes including non-accidental injury.

Therefore, in a previously well child presenting with bruising or bleeding and a prolonged aPTT, a possible cause is transient LA syndrome. The failure to correct the aPTT on mixing studies, the presence of LA without other clinical manifestations of autoimmune disease and the resolution of the symptoms and laboratory findings within three months confirm the diagnosis. The entity represents the most common confirmed diagnosis in patients with prolonged aPTT other than a factor deficiency, and probably represents a condition distinct from thrombotic LA syndromes.

We therefore recommend that any child presenting with haemorrhagic manifestations should have a coagulation study in addition to a full blood count, film, and further studies to elucidate the diagnosis.

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