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Lupus anticoagulants in two children - bleeding due to non-phospholipid dependent antiprothrombin antibodies

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Running title: Non-phospholipid dependent prothrombin antibodies in conjunction with lupus anticoagulants

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Abstract

We describe two children with significant bleeding; one with multiple ecchymoses and the other with scrotal bleeding. In both patients, the activated partial thromboplastin time (APTT) was prolonged with positivity for lupus anticoagulants (LA). However, the Owren prothrombin time (PT), usually insensitive for LA, was also prolonged. Presence of LA is associated with diverse clinical manifestations, most patients being asymptomatic while others present venous or arterial thrombosis. Bleeding in conjunction with lupus anticoagulants is rare and it is unusual to see prolongation of the Owren PT assay due to LA. An extended laboratory investigation of one of the patient's plasma revealed not only LA but also a specific non-phospholipid dependent anti-prothrombin antibody causing an acquired hypoprothrombinaemia. *Conclusion:* It is likely that the low prothrombin activity and not the LA caused the bleeding. The bleeding signs and symptoms in both patients subsided when the PT was normalised although the prolonged APTT and the LA remained.

Introduction

Antiphospholipid antibodies, of which lupus anticoagulants (LA) is the most well known, comprise a heterogeneous group of antibodies directed against phospholipids and negatively charged phospholipid-protein complexes [4,18,13,14]. In children, LA diagnosis is often incidental, frequently after investigation of prolonged activated partial thromboplastin time (APTT) prior to surgery or in conjunction with viral infections. Usually, these antibodies are transient and clinically irrelevant and most importantly do not cause bleeding. It is reported that 3% of healthy children undergoing routine pre-surgical screening have isolated prolonged APTT due to transient circulating antibodies [13,14]. However, it has been demonstrated that LA represents a higher risk of thrombosis than other antiphospholipid antibodies [3] and LA has also been related with stroke and cerebral venous thrombosis in children [1,2,23]. Viral infections might be responsible for transient LA and for thrombotic events [20].

Prothrombin has been proposed as an important phospholipid-bound antigenic target of LA but the existence of and clinical relevance of specific antiprothrombin antibodies is controversial [7,15,17,29,24]. Phospholipid-independent anti-prothrombin antibodies, in absence of LA, has also been associated with paediatric thrombosis [27]. Thus, antibodies against the procoagulant prothrombin, with or without LA, may increase the thrombosis risk but the mechanism is unclear.

In addition there have been cases with acquired hypoprothrombinaemia and bleeding, most often in combination with LA [5,6,19,21,31,8-12,26,32]. Haemorrhagic LA syndrome is rare, less than 30 patients are described in the medical literature, and it has been attributed to increased clearance of prothrombin caused by non-neutralizing antiprothrombin antibodies. Their signs and symptoms have varied from mild bleeding such as bruising and haematoma to severe gum bleeding, epistaxis and in two cases haemarthrosis [5,6,19,21,31,8-12,26,32].

Autoimmune disease, e.g. systemic lupus erythematosus (SLE), appears to be associated with LA and antiprothrombin antibodies but only few children had concomitant SLE [6,9,19]. Most patients had no underlying autoimmune disorder and in half of these patients the bleeding was preceded by a viral infection either respiratory or gastrointestinal, and in half of the patients adenovirus was found. All of these patients were below 11 years of age and none of them developed an autoimmune or vasculitis disorder in conjunction with or in the observation period after the episode. All recovered within approximately 3 months with or without treatment.

We describe two patients with haemorrhagic signs and symptoms in conjunction with LA in both preceded by adenoviral infections. The bleeding in both patients subsided when the prothrombin time (PT) was normalised

although the prolonged APTT and the LA persisted. In one of the patients plasma was available for additional testing and we could show that the PT prolongation was due to non-phospholipid dependent prothrombin antibodies. It is likely that the low prothrombin activity and not the LA caused the bleeding signs and symptoms.

Materials and methods

Venous blood for coagulation analysis was collected in 5-mL vacuum tubes containing 0.5 mL of sodium citrate (0.129 M). The blood was centrifuged at $3600 \times g$ for 10 min within 30 min of collection, and the plasma was frozen in aliquots at $-70 \text{ }^{\circ}\text{C}$ until use. The investigation was performed using standard methods to determine the following: Quick and Owren PT assays, APTT, free PS, antithrombin, protein C, factor (F)VIII, FIX, FXI and VWF both activity and antigen. The Quick PT was determined with a plain PT reagent, Thromborel S (Siemens, Marburg, Germany), and reported in seconds whereas the Owren PT was determined with a combined PT reagent SPA+ (Stago, Asnières sur Seine, France) and the results were given in international normalized ratio (INR). In general, the Owren PT assay is less affected by interfering substances in plasma, such as LA, as the final dilution of plasma is 1:21 compared to 1:3 for the Quick PT assay. LA was detected by an integrated test system based on the dilute Russell's viper venom time (dRVVT) using LA1 screening and LA2 confirmation test (Siemens). A dRVVT ratio (LA1 screen/LA2 confirmation) above 1.5 was established locally as a LA positive result. A quantitative enzyme-linked immunosorbent assay (ELISA) kits were used for detecting anti cardiolipin antibodies (ACA) IgG (Orgentec Diagnostika, Mainz, Germany) according to the manufacturers' instructions. In addition, an in-house quantitative ELISA was employed to determine anti-prothrombin auto antibodies in stored samples as previously described [27]. All samples were run in duplicate, and mean optical density (OD) values were calculated for blank (no sample), patient samples, and positive and negative controls. The mean OD and standard deviation (SD) for 10 healthy controls was calculated on each plate. The obtained ODs for samples were then expressed as the number of SD above the mean of the healthy controls. The cut-off for a positive result was set at +3 SD.

Case reports and results

Patient 1. An 11-year-old boy that presented with a scrotal haematoma after light trauma and where bleeding become more extensive after surgical exploration and continued post surgery. This was not preceded by an obvious infection but there had been short fever and loose stools a couple of weeks earlier. He had no family history of bleeding disorder and no prior history of spontaneous bleeding except a large haematoma, 3 cm in

diameter, in his forehead after light trauma one week earlier. His medical history included a post infectious glomerulonephritis and he had attention deficit hyperactivity disorder, treated with methylphenidate and atomoxetine. On admission he was well, afebrile and without lymphadenopathy or hepatosplenomegaly. He had no bruising but large bilateral haematomas and extensive swelling of the scrotum. Laboratory studies showed a normal complete blood count with normal liver and renal function. Coagulation screening revealed prolonged PT, both the Owren type PT assay expressed as INR and the Quick PT given in seconds, and APTT (Table 1). Investigations were also positive for LA but no ACA, which could explain the prolonged APTT but the Owren PT of INR 3 is rarely associated with LA. Factor assays showed a low prothrombin level and factor FIX and FXI were not measurable due to assay interference with LA. All other coagulations test including FVIII (chromogenic assay), VWF and thrombocyte function was normal. Furthermore, he tested negative for autoimmune markers (i.e. antinuclear antibodies). He received vitamin K and fresh frozen plasma as empirical therapy the day after surgery. It seemed to partially correct his coagulopathy. However, once the diagnosis had been established no further plasma replacement was administered.

Over the following week his scrotal haematoma cleared but did not completely stop heal or stop oozing.

Therefore one week after diagnosis he received one dose of IvIG (1g/kg) due to prolonged bleeding or lack of wound healing. His Owren PT had already by then returned to normal but his APTT was still prolonged and a strong positivity for LA remained. Thereafter the signs and symptoms resolved completely and he has had no other bleeding signs or symptoms during six months observation period. He tested positive for IgM and IgG for adenovirus indicating a recent infection, Repeat coagulation studies 3 months after the initial presentation (day 107) showed no evidence of the LA and the APTT and PT, both Owren and Quick assays, remained normal (Table 1). The presence of LA made what has been called haemorrhagic lupus a plausible diagnosis. The cause of the haemorrhagic signs and symptoms was not likely to be the LA in itself since the the bleeding stopped long before LA titers were normalized and the PT prolongation correlated well to the bleeding signs and symptoms. To further support the cause of bleeding we could show non-phospholipid dependent prothrombin antibodies that disappeared when the bleeding ceased and the prothrombin level increased.

Patient 2. A 4-year-old girl that presented with a history of lethargy and bruising over several months, bruising becoming more extensive over this time. She had neither a prior history of spontaneous bleeding, nor any significant heredity for bleeding disorders. The girl had asthma but was otherwise previously healthy.

On examination she was well, afebrile and had no lymphadenopathy or hepatosplenomegaly. She had extensive bruising over the bony prominences of her limbs and shoulders. She had no evidence of ongoing infection. The initial clinical impression was of malignancy or possibly a battered child. Laboratory studies showed a normal full blood count and platelets with normal liver and renal function. Coagulation screening revealed prolonged PT and APTT. Investigations revealed a positive LA and but no ACA. Factor assay showed a low prothrombin level and FIX and FXI were not measurable due to interference with LA. Factor VIII, VWF and bleeding time were normal. Her antinuclear antibody was negative. She tested positive for adenovirus in stool and blood. She received high dose steroids starting with 10 mg three times daily, tapered out and discontinued after a month. During that time her coagulopathy was corrected. Over the following weeks her bruising cleared and first her PT and later also the APTT returned to normal. Repeat coagulation studies 3 months after initial presentation showed no evidence of the lupus anticoagulant and the prothrombin deficiency had completely resolved already after two weeks. This, in addition to absence of antinuclear antibody and the transient presence of high titer LA, made it likely a virally caused haemorrhagic syndrome rather than a more generalized autoimmune disorder. Although this patient was not tested for non-phospholipid prothrombin antibodies also in her case the bleeding signs and PT were normalized but she remained positive for LA for approximately two additional months.

Discussion

Acquired antibodies of coagulation were first recognized in adults with autoimmune diseases, drug sensitivity, allergic disorders, and malignancy or in women postpartum. Antiphospholipid antibodies are recognized as the most common cause of acquired thrombophilia in adults and children [28]. In children, they tend to appear transiently after viral infections and, in contrast to what is seen in adults, they are usually not associated with other underlying disorders but can occur in conjunction with SLE or malignancy [13,14]. Although rare, there are reports on children who present with bleeding related to circulating antibodies [5,6,19,21,31,8-12,26,32]. The presentations described vary from all forms of mucosal and non-mucosal bleeding – bloody diarrhea, epistaxis, menorrhagia, purpura, macroscopic haematuria, bruising or spontaneous haematoma formation. Sporadic case reports suggest that viral illness may be an etiological factor [30,31]. Adenovirus has been implicated in most of the reported cases [19], but other viruses such as varicella, cytomegalovirus and epstein–barr virus have been associated. Both our patients tested positive for adenovirus. Both patients were treated with immune modulating therapy (IVIG and steroids respectively) which may have shortened the period of bleeding.

It is known that hypoprothrombinaemia may occur in patients with LA and Bajaj *et al.* have suggested that it is due to that LA forms complexes with circulating prothrombin [6]. Specific antibodies towards prothrombin have strangely enough been associated with both thrombosis and bleeding. It is not fully understood how auto antibodies against a procoagulant protein can result in a thrombosis phenotype. It has been suggested that these auto antibodies can enhance the binding of prothrombin to damaged endothelial cells which leads to an enhanced thrombin formation [25,33]. In vitro experiments have shown that anti-prothrombin IgG can interfere with the inactivation of activated FV by activated protein C, which might result in a hypercoagulable state [16]. It is also possible that anti-prothrombin antibodies has a prothrombotic effect due to their capacity to bind to thrombin and thereby protect it from down-regulation by its natural regulator antithrombin [22].

It is also not currently understood why some children with LA present with clinically significant bleeding while most do not. It has been postulated and is logical that the presence of antiprothrombin antibodies may be the determinant, but not all patients with a positive lupus anticoagulant screen and antiprothrombin antibodies will develop hypoprothrombinaemia and bleeding. Thus, the same type of antiprothrombin ELISA will detect both pro- and anticoagulant auto antibodies in a non-phospholipid manner and the ELISA by itself cannot discriminate between the two clinical phenotypes. It is unusual that the PT-assay is affected even if these antibodies can be detected. In the two cases with bleeding described here, it was the effect on the LA-insensitive PT assays that draw our attention to that there might be a more significant hypoprothrombinaemia, probably caused by a specific autoantibody, which caused the bleeding problems and not the LA. The hypoprothrombinaemia of both cases were clearly seen when the PT-derived 1-stage prothrombin assay (FII:C) was applied. The specificity for prothrombin was also shown when the other two PT-derived 1-stage assays, based on the same PT-reagent, resulted in normal levels of FVII:C and FX:C, respectively. The laboratory picture shown in case 1 is however complicated by the strong LA and its effect on the APTT-based 1-stage assays and it may be easy to generalize that all observed coagulation assay abnormalities are caused by interfering LA.

However, LA associated with thrombosis is rarely affecting the PT assays. In a retrospective survey of 917 consecutive positive LA patients (mainly adults) in our laboratory registry, only one case with a moderately high Owren PT/INR result (1.7) not caused by warfarin therapy, could be detected. All patients were referred to our centre for a venous thrombosis investigation indicating that the type of antiprothrombin antibodies that results in a hypoprothrombinaemia generating a high PT/INR is not associated with thrombosis, at least not in an adult

population. However, there is an apparent association between haemorrhagic LA and hypoprothrombinaemia with a prolonged PT, at least in children.

The case reports and the laboratory testing shed light on that an acquired haemorrhagic disorder is a difficult diagnosis both clinically and laboratory wise. A correct diagnosis and cause of bleeding is important guiding continued care and treatment of the patients especially since LA may remain several months after the cause of bleeding has disappeared. The finding of LA in children is not rare and the treating physician should be aware of the possible haemorrhagic complications in children with LA, especially if the PT assay is affected.

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Conflicts of interest

No conflicts of interest are declared

Table 1. Laboratory investigation of case 1.

Analysis	Day 1	Day 5	Day 13/18	Day 107	Ref. interval
APTT (sec)	59*	56*	77*	34	24-38
APTT mix (sec)	93*	61*	63*		<40
Owren PT (INR)	3.0*	1.1	0.9	0.9	<1.2
Quick PT (sec)	20*	14*	12		10-13
dRVVT (sec)	130*	83*	68*	32	<40
dRVVT ratio	3.3*	2.3*	2.3*	<1.5	<1.5
<i>PT-derived 1-st. assays</i>					
FII:C (kIU/L)	0.06*	0.39*	0.74	1.00	0.70-1.50
FVII:C (kIU/L)	1.03		1.29		0.60-1.60
FX:C (kIU/L)	0.72		0.94		0.70-1.52
<i>APTT-derived 1-st assays</i>					
FIX:C (kIU/L)	<0.01*	0.01*	0.06*	0.72	0.70-1.30
FXI:C (kIU/L)	<0.01*	<0.01*	0.07*	1.04	0.60-1.30
FXII:C (kIU/L)		0.06*	0.10*	0.33*	0.70-1.50
<i>Immunoassays</i>					
Anticardiolipin (ACA)	7	<5		<5	<9
Anti-FII ELISA (SD)	+73*	+61*	+30*	<3	<3

Results with an asterisk (*) denote results outside of the established reference interval or cut-off for the assay.

dRVVT denotes dilute Russell's viper venom time and is a specific test for lupus anticoagulants

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