Acquired antiprothrombin antibodies: an unusual cause of bleeding

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SUMMARY

Acquired inhibitors of coagulation causing bleeding manifestations are rare in children. They emerge, normally in the context of autoimmune diseases or drug ingestion, but transient and self-limiting cases can occur after viral infection. We describe, an otherwise healthy, 7-year-old girl who had gingival bleeding after a tooth extraction. The prothrombin time (PT) and the activated partial thromboplastin time (APTT) were both prolonged with evidence of an immediate acting inhibitor (lupic anticoagulant). Further coagulation studies demonstrated prothrombin (FII) deficiency and prothrombin directed (FII) antibodies. The serological tests to detect an underlying autoimmune disease were all negative. The coagulation studies normalised alongside the disappearance of the antibody. This article presents lupus anticoagulant hypoprothrombinaemia syndrome (LAHS) as a rare case of acquired bleeding diathesis in childhood.

BACKGROUND

The association of acquired factor II deficiency and lupus anticoagulant (LA) is a rare disease that can be related to sudden, severe or fatal haemorrhage. In children, most cases occur after viral infection, and are mostly transient and self-limiting. The paediatrician should be suspicious of this syndrome whenever a child shows recent bleeding symptoms. There is no consensus regarding the treatment of this condition.

CASE PRESENTATION

A previously healthy 7-year-old girl was admitted in our emergency ward, with active gingival bleeding after tooth extraction.

She had been seen by her family doctor 7 days earlier with fever and gastroenteritis. No medication was given besides antipyretics, and the condition was solved prior to this bleeding episode. She had her first tooth extraction a few months earlier with no complications.

Her medical history was unremarkable with no previous history of haemorrhage or easy bruising. The family history was negative for bleeding disorders. There was no exposure to drugs.

Upon physical examination, the patient appeared well, except for the bleeding.

INVESTIGATIONS

The initial laboratory evaluation revealed a normal complete blood count (haemoglobin=9 g/dl; haematocrit=30%, white blood cell count= $6.9 \times 10^3/\mu\text{l}$ with a normal differential count, platelet count= $433 \times 10^3/\mu\text{l}$). The blood smear and all the routine chemistry were normal. The prothrombin time (PT)

and the activated partial thromboplastin time (APTT) were both prolonged. The prolonged APTT was not corrected with a 1:1 mixture of the patient plus normal plasma. Further coagulation studies have demonstrated the presence of an immediate-acting inhibitor and prothrombin deficiency (factor II <1%), as shown in table 1.

The serological tests to detect an underlying autoimmune disease were all negative. These included antinuclear antibodies, neutrophil cytoplasmic antibodies, anticardiolipin IgG and IgM; Anti- $\beta 2$ glycoprotein I IgG and IgM and double-stranded DNA antibody.

Further studies excluded familial deficiency in factor II.

DIFFERENTIAL DIAGNOSIS

The isolated factor II deficiency can be observed in patients with lupus anticoagulant. This uncommon association appears to be mostly associated with systemic lupus erythematosus (SLE), but it has been reported in a few other conditions, including primary antiphospholipid syndrome, infections and occasionally drugs and lymphoma.

TREATMENT

At admission local haemostasis procedures were performed using haemostatic absorbable gelatin sponge (Spongostan). Active bleeding persisted despite those measures, so fresh frozen plasma (10 ml/kg q12h on the first day of admission) and aminocaproic acid (100 mg/kg q8h until the sixth day of admission) were infused as empirical therapy.

OUTCOME AND FOLLOW-UP

Intermittent active bleeding episodes occurred until the sixth day of admission. She was discharged 7 days after admission with no active bleeding.

On follow-up, no life-threatening bleeding occurred. Four weeks after admission, the factor II level was 95% and the prothrombin time (PT) was normalised. Eight weeks after hospitalisation, no lupus anticoagulant (LA) or antiprothrombin antibodies were detectable.

Eighteen months after discharge, the child is healthy, has normal coagulation parameters and shows no signs of systemic lupus erythematosus (SLE) or other autoimmune disease.

DISCUSSION

Lupus anticoagulant (LA) is an antiphospholipid antibody that causes prolonged in vitro coagulation times.¹ In children, it is reported that LA diagnosis is often incidental, frequently during investigation for a prolonged activated partial thromboplastin time (APTT), and about 3% of healthy children

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Table 1 Coagulation studies during admission and follow-up

	PT (ctrl) (s)	APTT (ctrl) (s)	Mix test (s)	LA ratio	F II (%)	F V (%)	F VII (%)	F X (%)	F VIII (%)	F IX (%)	F XI (%)	F XII (%)
Admission	27.9 (12)	111 (30)	+	+++	<1	70	78	64	85	32	32	44
4 weeks	12.5 (12)	63 (30)	+	+	95	153	120	91	120	93	101	123
8 weeks	12.2 (12)	41 (31)	–	–	125							
6 months	12 (12)	42 (32)	–	–	97							
12 months	11.8 (12)	43 (30)	–	–	110							
18 months	12.5 (12)	33 (30)	–	–	98							

APTT, activated partial thromboplastin time; (ctrl), control; LA, lupic anticoagulant; PT, prothrombin time; (s), seconds.

undergoing routine surgery have isolated prolonged APTT due to transient circulating antibodies.²

However, it has been demonstrated that LA leads to an increased risk of venous and arterial thrombosis, hypoprothrombinaemia associated with an LA presents as a haemorrhage instead of thrombosis.

Hypoprothrombinaemia associated with LAs is caused by antiprothrombin (FII) antibodies, which are heterogeneous and can be directed against prothrombin or phosphatidylserine/prothrombin complex. They usually act by a 'non-neutralising' mechanism, increasing the clearance of antibody-factor. These are diagnosed by a positive lupus anticoagulant, prolonged partial thromboplastin time (APTT) and prothrombin time (PT), low levels of FII; inhibitor screening positive (mix test) and identification of an antiprothrombin antibody.¹

The prothrombin-directed autoantibodies are associated with sudden, severe or fatal haemorrhage. They emerge, normally in the context of autoimmune diseases (mainly SLE), infections, drug ingestion or even in healthy individuals.^{1–4}

In a literature review of 74 cases of lupus anticoagulant hypoprothrombinaemia syndrome (LAHS)³ (ages 2–76 years at diagnosis, 58% under 15) 41 (55%) were associated with autoimmune disease mainly SLE (28), 25 (33%) were associated with infection (23 viral infection), 2 (3%) lymphoma, 2(3%) presumed drug induced and in 7 (9%) no other disease was associated. All cases of LAHS and viral infection were children. The clinical features were haemorrhagic diathesis in 66 (89%), 46 of them with minor bleeding and thrombosis in 10 (13%).

The prognosis of LAHS associated with infection was good, with spontaneous disappearance of LA and normalisation of PT, APTT and factor II levels in all cases, except for four which experienced major bleeding. No relapse occurred. Transfusions of packed red cells and corticosteroids were used in two children because of severe bleeding.³

Thrombotic and haemorrhagic complications occurred mostly in patients with LAHS and autoimmune diseases or lymphoma, but not in those with infections.³

Eight patients developed thrombotic manifestations under immunosuppressive treatment for LAHS, in these patients the LA titres were still detected despite the normalisation of factor II level and PT, suggesting that a subtle balance between bleeding and thrombosis is difficult to reach in LAHS patients who receive treatment.³

There are currently no standardised recommendations for treatment of acquired LAHS.

Prothrombin deficiency associated with transient LAs usually resolves spontaneously, so when patients are asymptomatic or present only minor bleeding, there is no need for special therapy.^{4–5} Treatments based on blood products or vitamin K may be required in minor bleeding.⁵

In cases where clinically significant bleeding is present or the antibodies persist, the required treatment consists mainly of immunosuppressive drugs, corticosteroids being the first line of therapy (prednisone 60 mg once a day or 1 mg/kg/day). When these are ineffective, a more aggressive immunosuppressive therapy can be started.^{4–5} Cyclophosphamide has been used as an adjunctive treatment in cases refractory to corticosteroids.⁴ Other treatments such as intravenous immune globulin, azathioprine, therapeutic plasma exchange and rituximab have been used in a few patients with positive results.^{3–4}

A correct diagnosis is important since LAs may remain in circulation several months after the cause of bleeding has disappeared.^{1–4} The findings of LA is not rare in children, and the physician should be aware of the possible haemorrhagic complications, especially if associated with prolonged PT and hypoprothrombinaemia. Further studies to detect an underlying disease should be performed and clinical and laboratory follow-up is recommended.

In our case, the girl was previously healthy and presented minor bleeding. No autoimmune disease was detected and the underlying probable cause was a previous viral infection. The treatment consisted of local haemostatic procedures, plasma and an antifibrinolytic agent. Four weeks after hospitalisation, TP and FII were normal despite the presence of LAs and 8 weeks after hospitalisation no LAs or antiprothrombin antibodies were detectable.

Learning points

- ▶ Lupus anticoagulant hypoprothrombinaemia syndrome (LAHS) is a rare case of acquired bleeding diathesis in childhood.
- ▶ Spontaneous disappearance is the rule in children who develop LAHS after a viral infection.
- ▶ In the event of mild bleeding, conservative treatment is required.
- ▶ Immunosuppressive therapies should be restricted to severe cases/autoimmunity associated because of the risk of thrombosis.
- ▶ Associated autoimmune diseases or malignancies should be investigated, and clinical follow-up for relapses/autoimmune disease is suggested.

Competing interests None.

Patient consent Obtained.

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