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Three Cases of Child Lupus-Anticoagulant Hypoprothrombinemia Syndrome

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Abstract

The Lupus Anticoagulant-Hypoprothrombinemia Syndrome (LAHS)—the association of acquired factor II deficiency and lupus anticoagulant—is a rare disease drastically different from antiphospholipid syndrome in that it may cause predisposition not only thrombosis but also to severe bleeding. We performed a retrospective study of 3 patients with LAHS in etiology, clinical manifestations, diagnosis and treatment. Associated conditions mostly include autoimmune diseases such as systemic lupus erythematosus and infectious diseases, while the present case of LAHS secondary to Acute Lymphoblastic Leukemia (ALL) is the first report. Hormonal therapy was usually effective in the former, with a few requiring additional immunosuppression or Intravenous Immunoglobulin (IVIG); the later occurred mainly in children and usually resolved spontaneously within 3 months, with individual patients requiring hormonal therapy.

Keywords: Lupus-anticoagulant hypoprothrombinemia syndrome; Child; Acute lymphoblastic leukemia; thrombosis

Case Presentation

Case One

Female, 8 years and 4 months old. Complaint: recurrent epistaxis for 1 week, skin petechiae were found for 3 days. Clinical manifestations: epistaxis on the right side with no obvious trigger, average amount, hemostasis after about 5 minutes of compression, scattered petechiae visible on both wrists and lower limbs, size about 2*2 cm, no fever, black stool, hematuria, no abdominal pain, joint pain, no progressive pallor, no dizziness, palpitation and chest tightness, no shortness of breath, weakness. Denied family history of hemophilia, denied family history of SLE and autoimmune diseases. Clinical diagnoses: (1) Epistaxis, (2) Coagulation disorders. Clinical treatment: no specific treatment was given. On reexamination three months later, the LA turned negative, the level of coagulation factor II returned to normal, and the four coagulation indexes returned to normal.

Case Two

Female, 4 years and 6 months old. Complaint: Recurrent intermittent arthralgia for more than six months. Clinical manifestations: She was admitted to the hospital with "intermittent arthralgia for more than half a year", with arthralgia as the main manifestation, mainly pain in both ankle joints and both wrist joints, no obvious redness, swelling and limitation of activities, no fever, rash, no oral ulcer, no decrease in activity, no weight loss, no fatigue, abdominal pain and diarrhea. MR scan enhancement of the right ankle joint: multiple abnormal signals in the right distal tibial epiphysis and the bones of the right ankle joint, bone marrow edema was considered. Clinical diagnosis: (1) juvenile idiopathic arthritis; (2) coagulation dysfunction; the APTT was significantly prolonged on admission, positive for LA, and the activity of the complete set of coagulation factors was basically normal after dilution; coagulation dysfunction was considered to be caused by LA, no special treatment was given,

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and surgery was avoided. Clinical treatment: methotrexate 7.5 mg/dose once a week; folic acid tablets 5 mg/dose once a week (orally after 24 hours of methotrexate) and adalimumab 20 mg subcutaneous injection therapy (once every two weeks). After three months of review, the LA turned negative, the level of coagulation factor II returned to normal, and the four indicators of coagulation returned to normal.

Case Three

Female, 3 years and 1 month old, was diagnosed with Acute Lymphoblastic Leukemia (ALL) for more than 3 months, and was admitted to the hospital according to the appointment. The fusion gene was positive for TCF3/PBX1, and chemotherapy was started on December 14, 2020 according to the CCCG-ALL2020 regimen (intermediate risk group), and the induction remission phase (hormone, vincristine, erythromycin, pemantase) and consolidation therapy (3 HDMTX) have been completed. She was admitted to the hospital for the 4th HDMTX. Recently, he was able to sleep, eat and drink with normal bowel movements. Physical examination: scattered bleeding spots were seen in both lower limbs. The admission diagnosis was: (1) acute lymphoblastic leukemia, lineage B, intermediate risk; (2) bone marrow suppression after chemotherapy. After admission, the child was found to have difficulty in stopping the bleeding at the site of blood sampling, and blood still flowed out after removing the gauze the next day. Clinical treatment: The chemotherapy regimen for the primary disease was continued. Three months later, the LA turned negative, the level of coagulation factor II returned to normal, and the four coagulation indexes returned to normal.

No abnormalities were observed in routine blood test and liver function test of these three cases.

Specific laboratory test results in coagulation are detailed in Tables 1 as below:

(Table 1)

Discussion

Lupus Anticoagulant (LA) is a member of Anti-Phospholipid Antibody (APA). In vitro tests LA interferes with phospholipid-dependent coagulation monitoring and prolongs Activated Partial Thromboplastin (aPTT), among others, but in vivo, LA is more likely to cause thrombosis and rarely causes bleeding [1]. LA prolongation of Activated Partial Thromboplastin Time (aPTT), but there is generally no bleeding manifestation. If a positive LA is accompanied by low prothrombin (FII), bleeding may occur and is referred to as LAHS.

The diagnostic criteria for LAHS are as follows: (a) the child presents with bleeding manifestations of varying severity; (b) the coagulation function test reveals a prolonged APTT; (c) the APTT correction test reveals that it cannot be corrected; (d) a positive LA test and a negative factor VIII inhibitor, along with a coagulation factor test reveals reduced coagulation factor activity; (e) the coagulation factor dilution test reveals only reduced factor II activity, and excludes hemophilia, acquired hemophilia, etc [2].

The clinical presentation was varied, Pirania et al. 2018 conducted a retrospective analysis of 32 cases diagnosed with LAHS with a median age of 12 years and the majority were female [3]. Skin bleeding (50%), nasal bleeding (37.5%) were the most common clinical manifestations and severe menstrual bleeding was seen in 15.6% of cases, as well as a small percentage of gingival bleeding, hematomas, hematuria and subarachnoid hemorrhage. However, the symptom of bleeding is not considered necessary for diagnosis. FII is defined as lupus anticoagulant-hypoplasminogen syndrome as long as it is below 60 IU/dL, and some patients have both low FV and FX. With reference to the diagnostic criteria for hypoprothrombin, it should be more appropriate to have FII below 40 IU/dL, while below 10 IU/dL is a

Table 1: Results of laboratory tests of coagulation items in three children.

Test Items	Unit	Reference Range	Case One			Case Two			Case Three		
			Results of initial consultation	Result after dilution	Review in 3 months	Results of initial consultation	Result after dilution	Review in 3 months	Results of initial consultation	Result after dilution	Review in 3 months
APTT	S	32.2-49.1	98	-	41	81.2	-	34.6	71.3	-	38.9
PT	S	10.5-14.5	19.6	-	12.8	15.3	-	12.9	13.6	-	12
PT-INR	-	0.72-1.15	1.69	-	0.98	1.24	-	0.99	1.06	-	0.91
TT	S	13.2-20.1	18.7	-	16.5	19.1	-	17.4	14.8	-	17.4
FIB	g/L	2.0-4.0	2.81	-	2.55	2.42	-	2.27	3.13	-	1.28
FDP	μg/ml	0-5	-	-	0.93	1.32	-	-	1.3	-	1.32
DD	μg/ml	0-0.5	-	-	1.06	0.22	-	-	0.28	-	0.23
AT-III	%	80-120	-	-	0.99	105	-	-	129	-	96
VWF	%	50-160	67	-	-	-	-	-	74	-	63
FII:C	%	70-120	16	-	-	26	-	85	44	-	73
FV:C	%	70-120	101	-	-	100	-	94	115	-	99
FVII:C	%	60-150	98	-	-	62	-	96	93	-	148
FVIII:C	%	55-170	8	80	-	8	80	74	48	-	81
FIX:C	%	60-150	1	80	-	1	80	51	30	-	38
FX:C	%	70-120	73	-	-	79		91	86	-	93
FXI:C	%	60-150	23	120	-	32	160	118	59	-	39
FXII:C	%	60-150	4	120	-	14	120	67	37	-	29
LAC Standard Ratio	-	1.2	1.43	-	0.93	2.4	-	1.04	1.87	-	1.02
LAC Confirm Ratio	-	1.2	1.45	-	1.06	1.69	-	0.98	2.05	-	1.1
LAC Screen Ratio	-	1.2	2.08	-	0.99	4.06	-	1.02	3.83	-	1.12

*Coagulation factors were measured by one-stage clotting assays, aPTT/PT based. LA was by dRVVT.

heavy or intermediate type with a higher likelihood of bleeding, and above 10 IU/dL is a light type with milder bleeding manifestations [4]. The patient's diluted FII factor did not raise up, indicating that the patient did have FII deficiency. The patient's FII is reduced because an antibody is produced against prothrombin and forms a complex of prothrombin antigen and antibody, which is then rapidly cleared. However, the antibody does not inactivate prothrombinogen in vitro, so the patient's prolonged PT can be corrected by normal plasma. Lupus anticoagulants also interfere with the quantitative detection of coagulation factor inhibitors, and false-positive results can occur if the corresponding inhibitor test is performed because the patient has low FVIII, FIX, FXI, and FXII [4].

Treatment progress of LASH: There are no standardized and uniform management guidelines. In patients with secondary SLE, vasculitis and lymphoma, treatment of the primary disease is the main focus. Bleeding symptoms are likely to occur when FII activity is less than 10%. In 74 cases reported by Mazodier et al, the median plasma FII was 11% (<1.0-49%) and bleeding symptoms were seen in 89% of cases. It is generally accepted that if bleeding symptoms are mild or basically absent (mostly skin bleeding spots, purpura, etc.), no special treatment is recommended; when bleeding is mild, fresh frozen plasma, IVIG, vitamin K, etc [5]; when bleeding is not easily controlled or anemia is present requiring transfusion therapy, glucocorticoid therapy can be considered, and prophylactic application can also be used for preoperative patients or patients with very low prothrombinogen. For severe fatal hemorrhage or multisystem hemorrhage, a combination of hormone and immunosuppressive therapy, such as high-dose hormone shock, cyclophosphamide and rituximab, and plasma exchange therapy, if necessary, can be used [6].

The incidence of LAHS is low and there is too little knowledge about this condition to be easily misdiagnosed. Patients with prolonged APTT may have a positive LA test and patients with bleeding should be considered for LAHS [7]. Once diagnosed, patients with severe bleeding manifestations must be treated promptly, but do not over treat patients with minimal bleeding that does not require specific treatment; review after 12 weeks to see if it resolves spontaneously.

Author Statements

Ethical Approval Statement

This study was approved by the ethics committee of Shenzhen Children's Hospital, informed consent for publication was obtained from her parents of the individual participant in the study

Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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