

Lupus Anticoagulant Hypoprothrombinemia Syndrome Associated with Bilateral Adrenal Hemorrhage in a Child: Early Diagnosis and Intervention

Atsushi Sakamoto (✉ sakamoto-a@ncchd.go.jp)

National Center for Child Health and Development Research Center Department of Molecular Endocrinology: Kokuritsu Kenkyu Kaihatsu Hojin Kokuritsu Seiiku Iryo Kenkyu Center Bunshi Naibunpi Kenkyubu <https://orcid.org/0000-0002-2222-5425>

Masao Ogura

National Center for Child Health and Development

Atsushi Hattori

National Center for Child Health and Development

Kinji Tada

National Center for Child Health and Development

Reiko Horikawa

National Center for Child Health and Development

Hisaya Nakadate

National Center for Child Health and Development

Kimikazu Matsumoto

National Center for Child Health and Development

Keiji Nogami

Nara Medical University

Masahiro Ieko

Health Sciences University of Hokkaido

Akira Ishiguro

National Center for Child Health and Development

Case report

Keywords: Lupus anticoagulant, Hypoprothrombinemia, Adrenal hemorrhage, Adrenal insufficiency, Lupus anticoagulant hypoprothrombinemia syndrome

Posted Date: September 3rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-70842/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on March 17th, 2021. See the published version at <https://doi.org/10.1186/s12959-021-00271-0>.

Abstract

Background: Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) is characterized by bleeding and thrombosis in patients, usually associated with autoimmunity or infections. Pediatric LAHPS exhibits various degrees of bleeding, ranging from mild to severe; however, adrenal hemorrhage due to LAHPS and its long-term clinical course have not been sufficiently described.

Case presentation: A 9-year-old boy presented with prolonged abdominal pain and abnormal coagulation screening tests. The laboratory tests showed prolonged activated partial thromboplastin time and subsequently revealed the presence of lupus anticoagulant, anti-nuclear antibodies, and hypoprothrombinemia, leading to diagnosis of LAHPS. An enhanced computed tomogram demonstrated nodular lesions in the adrenal glands bilaterally, suggestive of adrenal hemorrhage. Laboratory and clinical manifestations exhibited life-threatening adrenal insufficiency that required hydrocortisone administration. The patient developed systemic lupus erythematosus, diagnosed 12 months later.

Conclusions: The patient with LAHPS developed rare adrenal failure due to adrenal hemorrhage, a life-threatening event that should be recognized and treated early. In our case, renal dysfunction was also observed when systemic lupus erythematosus was diagnosed one year after LAHPS. Our case emphasizes that early recognition of adrenal failure and careful observation for patients with autoantibodies are required.

Background

Lupus anticoagulant (LA) is an antiphospholipid antibody that inhibits phospholipid-dependent clotting without inhibiting the activity of individual coagulation factors, and often leads to severe blood clotting disorders [1]. Patients with concomitant acquired hypoprothrombinemia and LA, termed lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS), sometimes show decreased coagulation factor activity [2]. The patients occasionally develop LAHPS after viral infections, and present with bleeding symptoms in the pediatric age group [3]. Patients with LAHPS exhibit various degrees of bleeding, ranging from mild mucocutaneous bleeding to life-threatening intracranial hemorrhage; however, rare adrenal hemorrhage resulting from LAHPS and its long-term clinical observations have not been sufficiently described [4–6].

Adrenal insufficiency is occasionally a life-threatening event, resulting from adrenal hemorrhage [7]. Despite its risk for severe morbidity or mortality, signs and symptoms are subtle and the diagnosis is often delayed [2, 7]. Early recognition of adrenal hemorrhage enables early intervention, and the patient can be managed successfully without endocrine shock after adrenal insufficiency.

We report a rare case of progression of LAHPS into systemic lupus erythematosus (SLE) in a Japanese boy who had severe acute adrenal failure due to bilateral adrenal hemorrhage.

Case Presentation

A 9-year-old boy had generally normal perinatal history, growth, and development. He presented with a fever, abdominal pain, and vomiting, all starting five days before admission. Diarrhea and hematochezia were not noted. On admission, his vital signs were body temperature 38.0 °C, blood pressure 98/44 mmHg, heart rate 82/min, and respiratory rate 16/min with an O₂ saturation of 99%. Upper abdominal tenderness was found without abdominal swelling or hepatosplenomegaly. Complete blood count showed white blood cells 9540/μL, Hb 13.9 g/dL, and platelets 140 × 10³/μL. Biochemical parameters showed total bilirubin 0.56 mg/dL, aspartate transaminase 58 IU/L, alanine transaminase 47 IU/L, urea nitrogen 6.3 mg/dL, creatinine 0.23 mg/dL, sodium 134 mEq/L, potassium 4.1 mEq/L, and C-reactive protein (CRP) 3.7 mg/dL. Routine analyses revealed mild thrombocytopenia, liver dysfunction, and elevated CRP. Coagulation studies revealed prolonged activated partial thromboplastin time (aPTT) of 92.4 sec, elevated D-dimer 3.7 μg/mL, LA positivity, and slightly low prothrombin activity 58% (reference range [RR] 75% – 135%) due to immunoglobulin M (IgM) class anti-prothrombin antibody of 32.1 AU/mL (RR < 24.0 AU/mL). Immunoglobulin G (IgG) class anti-phosphatidylserine/prothrombin antibody was also positive (> 50.0 units, RR < 2.0 units), which is associated with strong LA activity. The patient's LA-positive plasma was examined using the thrombin generation test and clot waveform analyses (Fig. 1A, 1B, and 1C) as previously described [8]. The clotting times in LA-positive plasma were significantly prolonged, compared to a healthy control.

A diagnosis of LAHPS was made. The patient tested positive for anti-nuclear antibody (ANA) titer 1:160, anti-double-stranded DNA (dsDNA) antibody of IgG 22 IU/mL, anticardiolipin antibody of IgG 16 U/mL, and anti-β₂-glycoprotein I antibody of IgG > 50 units, but the patient did not fit the Systemic Lupus International Collaborating Clinics (SLICC) 2012 Classification Criteria [9]. A contrast-enhanced computed tomogram revealed nodular lesions in the adrenal glands bilaterally (Fig. 1D and 1E). The diagnosis of acute adrenal failure due to adrenal hemorrhage was made on the basis of the clinical manifestations, mild hyponatremia (134 mEq/L), high plasma ACTH 1586 pg/mL (RR 7.2–63.3), low plasma cortisol 3.24 μg/dL (RR 6.2–18.0), blood glucose 37 mg/dL, low serum aldosterone 43.1 pg/mL, and relatively elevated plasma renin activity 9.1 ng/mL/hr. Hence, he received glucose (0.6 g/kg/dose), hydration (1700 mL/m²), and hydrocortisone (50 mg/m²/day). Hydrocortisone and fludrocortisone were continued for the adrenal replacement treatment at physiological doses. Repeated coagulation studies still showed positive LA and prolonged aPTT for 12 months (Fig. 2A).

At 10 years of age, he visited our hospital because of gait disturbances and weakness in all extremities after acute viral infection. He had butterfly rash, discoid rash, optic disc swelling, deranged renal function, and showed higher levels of ANA and anti-dsDNA antibody. Renal biopsy was performed, resulting in a diagnosis of lupus nephritis (Fig. 2B and 2C). His condition was diagnosed as SLE on the basis of the SLICC 2012 Classification Criteria [9]. Intravenous pulsed treatments with methylprednisolone (30 mg/kg/day) and cyclophosphamide (500 mg/m²) were immediately initiated, followed by mycophenolate mofetil 400 mg/m²/day. The clinical signs were improved.

Discussion And Conclusions

Adrenal hemorrhage based on LAHPS is a rare complication; its subsequent adrenal failure potentially leads to poor outcomes [5, 7]. However, the early diagnosis of adrenal hemorrhage based on LAHPS is challenging due to the lack of specific clinical symptoms. From the viewpoint of LAHPS in a child, the present case provides two clinical messages: 1) early diagnosis and treatment are crucial for a favorable outcome after adrenal failure following adrenal hemorrhage, and 2) we emphasize the importance of careful observation of the patient with autoantibodies, LA and ANA, because autoantibodies precede clinical manifestations of autoimmune diseases, such as SLE [10].

LAHPS is mainly found in children with LA and is accompanied by a decrease in plasma prothrombin activity due to IgM class anti-prothrombin antibody [4, 5]. LAHPS was reported by Bajaj in 1983, and the pathophysiology of LAHPS is thought to be an immune complex with prothrombin antibody, which is rapidly excreted from the blood, resulting in low prothrombin activity [11]. In our case, a decrease in prothrombin activity supports a similar pathophysiology. LAHPS-associated adrenal hemorrhage is rare; however, pediatricians should pay attention to this complication for unexplained or prolonged abdominal pain.

Adrenal failure due to adrenal hemorrhage is rare, but potentially fatal [7]. In childhood, it generally presents with nonspecific signs and symptoms, such as fatigue, malaise, abdominal pain, nausea, and vomiting, without hyperpigmentation. Therefore, diagnosis and treatment may often be delayed. Our case showed prolonged abdominal pain and deranged coagulation, and early recognition of adrenal insufficiency due to adrenal hemorrhage enabled early intervention. The pathophysiology of adrenal gland bleeding remains unclear. The adrenal gland comprises a rich arterial supply with a single vein limiting blood drainage; a thrombosed vein can result in progressive increase in arterial blood pressure [12].

Previous reports have shown that patients with SLE developed LAHPS; however, it remains uncertain whether patients with LAHPS develop SLE [13]. Although our patient might have had an underlying disease, such as antiphospholipid syndrome, he developed SLE by the one-year observation [10, 13]. Moreover, the patient did not fit the SLICC diagnostic criteria for SLE, but autoantibodies, including LA and ANA, persisted. The previous report showed that development of autoantibodies precedes clinical manifestations of autoimmune diseases, such as SLE [10]. Renal dysfunction was also observed when SLE was diagnosed in our case. Therefore, we emphasize the careful observation of the patient with LA and ANA.

In conclusion, the development of acute adrenal failure due to bilateral adrenal hemorrhage in the context of LAHPS is a rare, but life-threatening event that should be recognized and treated early. Our case stresses the importance of careful observation of the patient with LA and ANA.

Abbreviations

LAHPS

Lupus anticoagulant-hypoprothrombinemia syndrome; LA:Lupus anticoagulant; SLE:Systemic lupus erythematosus; CRP:C-reactive protein; aPTT:Activated partial thromboplastin time; IgM:Immunoglobulin M; IgG:Immunoglobulin G; ANA:Anti-nuclear antibody; dsDNA:Double-stranded DNA; SLICC:Systemic lupus international collaborating clinics

Declarations

Acknowledgements

The authors wish to thank the medical editor from the Division of Education for Clinical Research at the NCCHD for editing this manuscript.

Funding

This study was supported in part by a grant from the National Center for Child Health and Development, grant numbers 29-8 and 2020C-5.

Availability of data and materials

All relevant data were included in this case study.

Authors' contributions

AS and AI conceived the study and wrote the manuscript. MO, AH, KT, and AI treated the patient. AS, AI, YI, and KN were responsible for clinical input and data collection. All authors have read and approved the final manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

In Japan, a case report does not require ethics approval. Our study adhered to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Japanese government.

Consent for publication

The patient and the parents provided consent to publish.

Competing interests

The authors declare that they have no competing interests.

References

1. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. *J Thromb Haemost.* 2009;7(10):1737–40.
2. Rapaport SI, Ames SB, Duvall BJ. A plasma coagulation defect in systemic lupus erythematosus arising from hypoprothrombinemia combined with antiprothrombinase activity. *Blood.* 1960;15:212–27.
3. Mulliez SM, De Keyser F, Verbist C, Vantilborgh A, Wijns W, Beukinga I, et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of two cases and review of the literature. *Lupus.* 2015;24(7):736 – 45.
4. Ieko M, Yoshida M, Naito S, Ohmura K, Takahashi N. Lupus anticoagulant-hypoprothrombinemia syndrome and similar diseases: experiences at a single center in Japan. *Int J Hematol.* 2019;110(2):197–204.
5. Mazodier K, Arnaud L, Mathian A, Costedoat-Chalumeau N, Haroche J, Frances C. et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of 8 cases and review of the literature. *Medicine.* 2012;91(5):251 – 60.
6. Pilia RK, Suri D, Jindal AK, Kumar N, Sharma A, Sharma P, et al. Lupus anticoagulant hypoprothrombinemia syndrome associated with systemic lupus erythematosus in children: report of two cases and systematic review of the literature. *Rheumatol Int.* 2018;38(10):1933–40.
7. Ramon I, Mathian A, Bachelot A, Hervier B, Haroche J, Boutin-Le Thi Huong D, et al. Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in the antiphospholipid syndrome: long-term outcome of 16 patients. *J Clin Endocrinol Metab.* 2013;98(8):3179–89.
8. Matsumoto T, Nogami K, Shima M. A combined approach using global coagulation assays quickly differentiates coagulation disorders with prolonged aPTT and low levels of FVIII activity. *Int J Hematol.* 2017;105(2):174–83.
9. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012;64(8):2677–86.
10. Ma WT, Chang C, Gershwin ME, Lian ZX. Development of autoantibodies precedes clinical manifestations of autoimmune diseases: a comprehensive review. *J Autoimmun.* 2017;83:95–112.
11. Bajaj SP, Rapaport SI, Fierer DS, Herbst KD, Schwartz DB. A mechanism for the hypoprothrombinemia of the acquired hypoprothrombinemia-lupus anticoagulant syndrome. *Blood.* 1983;61(4):684–92.
12. Aldajani H, Albahrani S, Saleh K, Alghanim K. Bilateral adrenal hemorrhage in antiphospholipid syndrome. Anticoagulation for the treatment of hemorrhage. *Saudi Med J.* 2018;39(8):829–33.
13. Veres K, Szodoray P, Szekanecz Z, Lakos G, Kiss E, Laczik R, et al. Clinical and immunoserological characteristics of the transition from primary to overlap antiphospholipid syndrome. *Lupus.* 2010;19(13):1520–6.

Figures

Figure 1

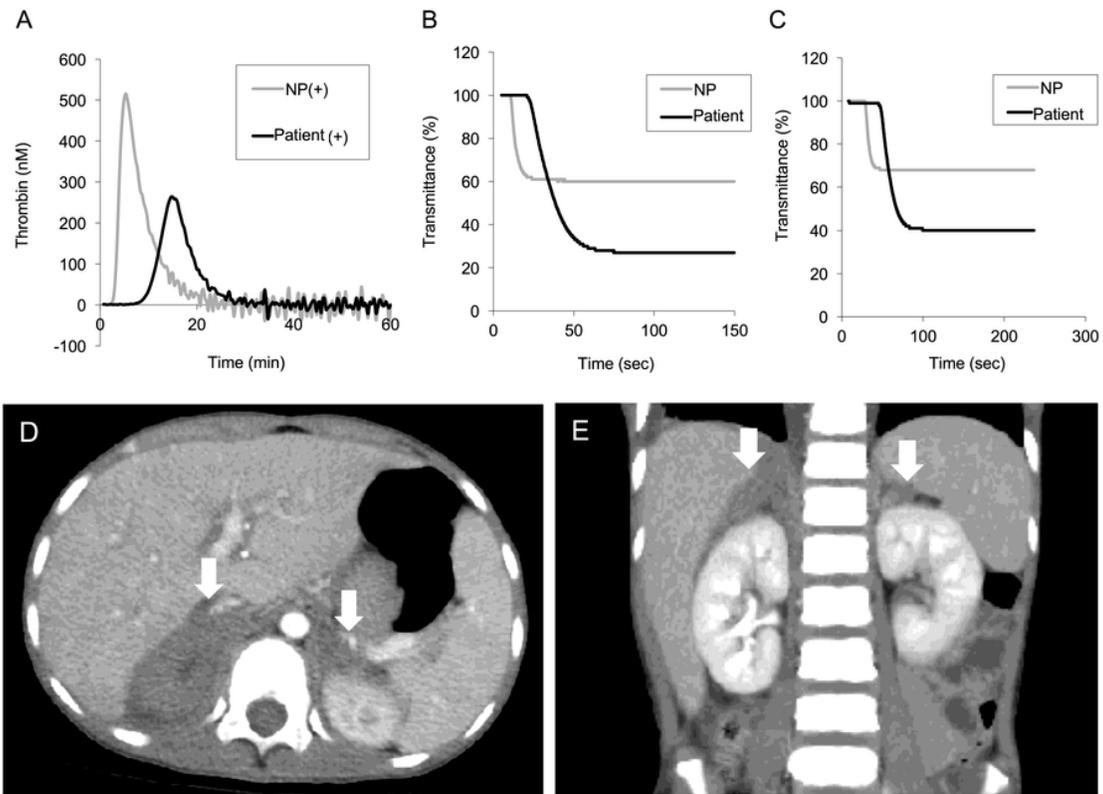


Figure 1

A: Thrombin generation assay which monitors one-step before fibrin formation. In contrast to a healthy control, the lag time in lupus anticoagulant (LA)-positive serum was delayed. The peak thrombin level in the patient was lower than in the control. B and C: Clot waveform analyses were evaluated by fibrin formation. The clot times in LA-positive serum were significantly prolonged compared to a healthy control. B, prothrombin time; C, activated partial thromboplastin time. D and E: Contrast abdominal computed tomograms show nodular lesions in the enlarged adrenal glands bilaterally, indicating adrenal hemorrhage (arrows). D, Axial; E, Coronal.

Figure 2

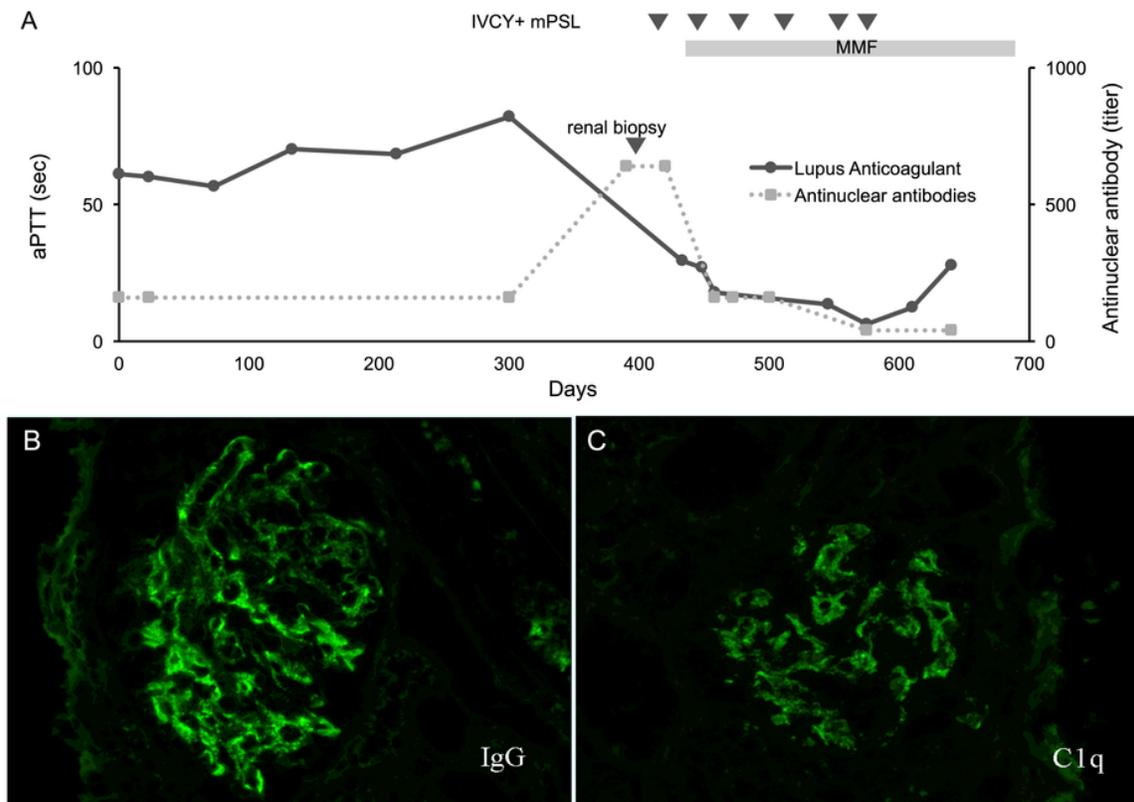


Figure 2

A: The clinical course of the patient. Lupus anticoagulant remained high, even with hydrocortisone administration. At diagnosis of SLE, high levels of antinuclear antibody are shown. After intravenous pulse treatments with methylprednisolone (30 mg/kg/day) and cyclophosphamide (500 mg/m²), a decrease in lupus anticoagulant and antinuclear antibody levels are shown. Abbreviations: IVCY, intravenous cyclophosphamide; mPSL, methylprednisolone; MMF, mycophenolate mofetil; aPTT, activated partial thromboplastin time. B and C: Immunofluorescence micrographs of renal biopsy specimens. B, granular IgG deposits in the glomerular capillary walls, in a diffuse and global distribution. C, granular deposits of C1q on the glomerular basement membrane.