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CASES WITH A MESSAGE

Lupus anticoagulant-hypoprothrombinemia syndrome and immunoglobulin-A vasculitis: a report of Japanese sibling cases and review of the literature

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Abstract

Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) is a rare bleeding disorder caused by antiprothrombin antibodies. LAHPS is associated with systemic lupus erythematosus (SLE) or infections. We describe two Japanese brothers with immunoglobulin-A vasculitis (IgAV) who met the diagnostic criteria of LAHPS. They presented with palpable purpura and abdominal pain, and had a prolonged activated partial thromboplastin time (APTT) and prothrombin deficiency with the presence of lupus anticoagulant. Pediatric LAHPS was reviewed in abstracts from the Japan Medical Abstracts Society that were written in Japanese and PubMed or Web of Science-listed articles in English between 1996 and 2019. Including our cases, pediatric LAHPS has been reported in 40 Japanese and 46 non-Japanese patients. We summarized the clinical and laboratory characteristics of all 86 cases, and found only one Japanese LAHPS case with IgAV, except for our cases. Of the 86 cases, most were associated with infections followed by SLE. The presence of SLE, older age, lower prothrombin levels, severe bleeding symptoms, and positivity of immunoglobulin G anticardiolipin antibodies and anticardiolipin/β_2-glycoprotein I antibodies and/or β_2-glycoprotein I-dependent anticardiolipin antibodies had higher odds of requiring treatment. Measuring the APTT and prothrombin time (PT) might be required in patients with IgAV when they do not have a typical clinical course or distinctive symptoms. LAHPS should be considered with prolongation of the APTT and/or PT. Additionally, it is important to maintain a balance between the risk of thrombosis and hemorrhage when normalization of the PT and FII levels occurs in LAHPS cases under treatment.

Keywords Immunoglobulin-A vasculitis · Henoch–Schönlein purpura · Lupus anticoagulant-hypoprothrombinemia syndrome · Hypoprothrombinemia · Japanese · Pediatric

Introduction

Development of lupus anticoagulant (LA) is associated with conditions, such as autoimmune diseases, infections, malignancies, or drugs. LA is also found in healthy individuals [1]. The presence of LA is related to venous and arterial thrombosis and pregnancy complications in antiphospholipid syndrome (APS) [2]. However, LA can cause bleeding

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complications that may be severe. Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) develops because of acquired hypoprothrombinemia with LA and the presence of antibodies against factor II (FII) (prothrombin). The mechanism of LAHPS was documented by Bajaj et al. as follows [3]. Antibodies that are directed against prothrombin without neutralizing its coagulant activity result in deficiency of prothrombin antigen secondary to rapid clearance of the antigen–antibody complexes by the reticuloendothelial system. Mazodier et al. reported that LAHPS mostly occurred in young women associated with autoimmune diseases, such as systemic lupus erythematosus (SLE) [4]. In 1960, Rapaport et al. reported the first pediatric LAHPS case associated with SLE [5]. In Japan, Morishita et al. described the first pediatric LAHPS case associated with upper respiratory tract infection in 1996.

Immunoglobulin-A vasculitis (IgAV) is the most common systemic vasculitic disease in children, with an annual incidence of 13.5 per 100,000 children, which is approximately 100 times that in adults. Approximately, 75% of IgAV cases occur in children younger than 10 years [6]. Many triggers that cause IgAV have been reported, such as infections, drug use, and vaccinations. Most IgAV cases are associated with infections. The pathological feature of IgAV is characterized by the deposition of IgA1-dominant immune complexes in small blood vessel walls [6]. The diagnosis of IgAV is based on European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria and classification definitions [7]. Most cases with IgAV improve without treatment, but some cases with severe abdominal pain and/or renal involvement require immunosuppressive treatment, such as steroids, cyclophosphamide, and cyclosporine A [6].

We describe two Japanese brothers with IgAV who met the diagnostic criteria of LAHPS. The characteristics of 40 Japanese and 46 non-Japanese pediatric LAHPS cases reported between 1996 and 2019 are summarized and compared. The relationship between IgAV and LAHPS is also discussed.

Materials and methods

Search strategy

A literature search was conducted using PubMed and Web of Science between 1996 and 2019, using the following terms: "lupus anticoagulant-hypoprothrombinemia syndrome", "acquired hypoprothrombinemia", "bleeding and lupus anticoagulant", "lupus anticoagulant-hypoprothrombinemia syndrome and immunoglobulin-A vasculitis", "acquired hypoprothrombinemia and immunoglobulin-A vasculitis", "lupus anticoagulant-hypoprothrombinemia syndrome and Henoch–Schönlein purpura", "acquired hypoprothrombinemia and Henoch–Schönlein purpura", "children", or "pediatric". Articles that were published in English were retrieved. During the same period, the search was also performed using a Japanese database, the Japan Medical Abstracts Society (JAMAS), using the same terms in Japanese. These data were combined with our two cases. In this study, pediatric cases were defined as patients who were diagnosed at the age of 15 years or younger.

Statistical analysis

Statistical analysis was performed using Welch's t test or the χ^2 test. A p value of < 0.05 was considered statistically significant in all cases. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Case report

Case 1

A 7-year-old boy presented with a 2-week history of diffuse abdominal pain. He also had a 5-day history of multiple palpable purpura and several ecchymoses, and petechiae of his lower limbs and several red welts (urticaria) on his forearms. There was no history of trauma and no symptoms suggestive of infectious diseases. He had atopic dermatitis and a food allergy, but was not taking medicine. His family history did not suggest any bleeding disorders. His physical examination was unremarkable, except for the presence of mild diffuse abdominal pain and rashes over his extremities. At presentation, a complete blood count (CBC) showed a white blood cell count (WBC) of 4.53×10^9/L (reference range $3.30–8.60 \times 10^9$/L), hemoglobin (Hb) of 131 g/L (reference range 137–168 g/L), and platelet count of 24.1×10^9/L (reference range $15.8–34.8 \times 10^9$/L) with a differential count and peripheral smear. Hepatic and renal function was normal. He was diagnosed with IgAV on the basis of EULAR/PRINTO/PRES criteria and classification definitions [7]. Initial coagulation studies were performed to exclude acquired hemophilia or any other coagulation disorder because his skin rashes were not uniform and were not found on the buttocks. These studies showed a prolonged prothrombin time (PT) of 69% (reference range 70–120%) and a prolonged activated partial thromboplastin time (APTT) of 118.1 s (reference range 26.9–38.1 s), with normal fibrinogen and D-dimer levels and antithrombin III activity (Table 1). On further work-up, factor assays showed that the FII level was low at 46% (reference range 75–130%), with decreased factors VII, VIII, IX, and XII

Table 1 Laboratory characteristics of our cases with lupus anticoagulant-hypoprothrombinemia syndrome

	Case 1	Case 2	Reference range
WBC count ($\times 10^9$/L)	4.53	8.97	3.30–8.60
Hb (g/L)	131	124	137–168
PLT count ($\times 10^9$/μL)	24.1	30.4	15.8–34.8
PT (%)	69	78	73–118
APTT (s)	118.1	76.2	26.9–38.1
Mix 1:1 (s)	116.0	60	
Mix 1:1 (after 2 h of incubation)	135.3	68.4	
Fibrinogen (mg/dL)	245	343	200–400
FII (%)	46	69	75–130
FVII (%)	55	85	75–140
FVIII (%)	17	73	60–150
FIX (%)	3	39	70–130
FX (%)	91	ND	70–130
FXII (%)	9	45	50–150
FXIII (%)	80	49	70–140
vWF (%)	137	ND	60–170
FVIII inhibitor (BU/mL)	2	0	0
FIX inhibitor (BU/mL)	3	0	0
C50 (U/mL)	< 14	52	30–50
C3 (mg/dL)	66.9	108.1	73–138
C4 (mg/dL)	4.1	23	11–31
LA/dRVVT	2.8	2	0–1.2
IgG aβ_2GPI (U/mL)	< 1.2	< 1.2	0–3.5

WBC white blood cell, *Hb* hemoglobin, *PLT* platelet, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *F* factor, *vWF* von Willebrand factor, *LA* lupus anticoagulant, *dRVVT* dilute Russell viper venom time, *IgG* immunoglobulin G, *aβ_2GPI* anti-β_2-glycoprotein I antibodies, *ND* not detected

levels. Factors X and XIII were normal. Inhibitors of factors VIII and IX were positive. The APTT-based mixing test did not show a correction of the APTT and LA was detected by the dilute Russell's viper venom time test. Therefore, acquired hemophilia was excluded and the presence of LA was confirmed. Immunoglobulin G (IgG) anti-β_2-glycoprotein I anticardiolipin antibodies (aβ_2GPI) were negative and components of complement (C3, C4) were low. Antinuclear antibodies and anti-double-stranded DNA were negative (Table 1). He was also diagnosed with LAHPS because of the presence of LA and FII deficiency. Immunosuppressive agents, such as steroids, were not administered because his rashes and abdominal pain improved only with bed rest. The rashes disappeared approximately 1 week after diagnosis. LA was undetectable and the APTT was normalized 3 months later. Hypocomplementemia at presentation was not checked later because the clinical symptoms had improved. We did not conduct a work-up for underlying infections because he had no symptoms suggestive of infections. He had no bleeding symptoms after more than 2 years.

Case 2

A 4-year-old boy presented with a 5-day history of diffuse abdominal and left knee pain, and a 2-day history of several palpable purpura and petechiae over his knees. He presented approximately 2 weeks after his brother was diagnosed. There was no trauma and no symptoms suggestive of infections, but there had been a 1-day fever 1 week earlier. He had chronic urticaria, but was not taking medicine. His family history did not suggest any bleeding disorders. His physical examination was unremarkable, except for the presence of the rashes over his knees. At presentation, a CBC showed a WBC of 8.97×10^9/L, Hb of 124 g/L, and platelet count of 30.4×10^9/L with a differential count and peripheral smear. His hepatic and renal function was normal. He was diagnosed with IgAV on the basis of EULAR/PRINTO/PRES criteria and classification definitions [8]. Initial coagulation studies showed a normal PT of 78% and a prolonged APTT of 76.2 s, with normal fibrinogen and D-dimer levels and antithrombin III activity. On further work-up, factor assays showed that factors II and XIII levels were low at 69% and 49%, respectively. Factors IX and XII levels were also low and factors VII, VIII, and X were normal. Inhibitors of factors VIII and IX were negative. The APTT-based mixing test did not show a correction of the APTT and LA was detected by the dilute Russell's viper venom time test. The presence of LA was confirmed. IgG aβ_2GPI were negative. Components of complement (C3, C4) were normal and antinuclear antibodies and anti-double-stranded DNA were negative (Table 1). He was also diagnosed with LAHPS owing to the presence of LA and FII deficiency. Similar to Case 1, he did not require any treatment. The rashes disappeared approximately 1 week after diagnosis. LA was undetectable 1 month later and the APTT was normalized 6 weeks later. He had no bleeding symptoms after more than 2 years.

The patients' parents approved publication of the presence of their symptoms and clinical findings.

Literature review

A total of 31 relevant articles with 40 Japanese pediatric LAHPS cases were identified, including our two cases, in PubMed and JAMAS between 1996 and 2019 (Table 2; Supplemental Table 1) [8–10]. The mean age at diagnosis was 4.7 years (range 0.8–15 years) with a female–male sex ratio of 1.4:1. Thirty-two (80.0%) cases were associated with infections followed by SLE in four (10.0%) cases. Only three (7.5%) cases, including our two cases, had IgAV. There were no underlying diseases in two cases. One case

Table 2 Clinical and laboratory characteristics of pediatric lupus anticoagulant-hypoprothrombinemia syndrome in 40 Japanese cases and 46 non-Japanese cases

	All cases	Japanese cases	Non-Japanese cases	*p* values
Number of cases	86	40	46	
Mean age (years) (range)	6.3	4.7 (0.8–15)	7.8 (1.8–15)	< 0.001
Sex				
Female, *n* (%)	50 (58.1)	23 (57.5)	27 (58.7)	1.000
Diagnosis				
SLE, *n* (%)	21 (24.4)	4 (10.0)	17 (37.0)	0.005
Infection, *n* (%)	53 (61.6)	32 (80.0)	21 (45.7)	0.002
IgAV, *n* (%)	3 (3.5)	3 (7.5)	0 (0)	0.100
Others, *n* (%)	6 (7.0)	0 (0)	6 (13.0)	0.027
None, *n* (%)	4 (4.7)	2 (5.0)	2 (4.3)	1.000
Symptoms				
Bleeding diathesis, *n** (%)	84 (84/86, 97.7)	38 (38/40, 95.0)	46 (46/46, 100)	0.213
Minor bleeding, *n** (%)	65 (65/84, 77.4)	36 (36/38, 94.7)	29 (29/46, 63.0)	
Severe bleeding, *n** (%)	19 (19/84, 22.6)	2 (2/38, 5.3)	17 (17/46, 37.0)	< 0.001
Thrombotic event	3 (3/86 3.5%)	1 (1/40, 2.5)	2 (2/46, 4.3)	
Coagulopathy				
Prolonged APTT, positivity, *n** (%)	81 (81/81, 100)	40 (40/40, 100)	41 (41/41, 100)	1.000
Prolonged PT, positivity, *n** (%)	77 (77/81, 95.1)	37 (37/40, 92.5)	40 (40/41, 97.6)	0.353
Factor II level, *n** (%)	68 (68/68, 100)	23 (23/23, 100)	45 (45/45, 100)	
Median (%) (range)	17.0 (0–69%)	26.0 (< 3–69%)	11.8 (0–40%)	0.004
Other decreased coagulation factors, positivity, *n** (%)	44 (44/61, 72.1)	23 (23/28, 82.1)	21 (21/33, 63.6)	0.154
Antiphospholipid antibodies				
Lupus anticoagulant, positivity, *n** (%)	86 (100)	40 (40/40, 100)	46 (46/46, 100)	1.000
IgG aCL, positivity, *n** (%)	23 (23/54, 42.6)	7 (7/21, 33.3)	16 (16/33, 48.5)	0.398
IgG aβ_2GPI or aCL/β_2GPI, positivity, *n** (%)	7 (7/36, 19.4)	2 (2/18, 11.1)	5 (5/18, 27.8)	0.402
IgG aPT, positivity, *n** (%)	17 (17/18, 94.4)	6 (6/7, 85.7)	9 (9/9, 100)	0.438
IgG aPS/PT, positivity, *n** (%)	15 (15/16, 93.8)	19 (19/19,100)	3 (3/4, 75.0)	0.174
Treatment				
Supportive treatment, *n** (%)	18 (18/80, 22.5)	2 (2/34, 5.9)	16 (16/46, 34.8)	0.002
Supportive treatment only, *n** (%)	8 (8/80, 10.0)	2 (2/34, 5.9)	6 (6/46, 13.0)	
Immunosuppressive agents	29 (29/80, 36.3)	4 (4/34, 11.8)	25 (25/46, 54.3)	< 0.001
Steroid only, *n** (%)	16 (16/80, 20.0)	2 (2/34, 5.9)	14 (14/46, 30.4)	
Steroid with other immunosuppressive agents, *n** (%)	10 (10/80, 12.5)	2 (2/34, 5.9)	8 (8/46, 17.4)	
Other immunosuppressive agents without steroid, *n** (%)	3 (3/80, 3.8)	0 (0/34, 0)	3 (3/46, 6.5)	
None, *n** (%)	43 (43/80,53.8)	28 (28/34, 82.4)	15 (15/46, 32.6)	< 0.001

SLE systemic lupus erythematosus, *IgAV* immunoglobulin-A vasculitis, *APTT* activated partial thromboplastin time, *PT* prothrombin time, *IgG* immunoglobulin G, *aCL* anticardiolipin antibodies, *aCL/β_2GPI* β_2-glycoprotein I-dependent anticardiolipin antibodies, *aPS/PT* antiphosphatidylserine-dependent antiprothrombin antibodies, *n** number of cases with data available

was identified during pre-operation (Supplemental Table 1, Case 15) and the other was identified because of gingival bleeding after dental extraction (Supplemental Table 1, Case 23). Of all 32 cases associated with infections, most cases were associated with gastroenteritis (23/32, 71.8%), followed by upper respiratory tract infection (7/32, 21.9%). Pathogens were detected in 13 cases as follows: adenovirus ($n = 8$), *Streptococcus pyogenes* ($n = 2$), cytomegalovirus ($n = 2$), rotavirus ($n = 1$), and mycoplasma ($n = 1$). All 40 patients, except for two, presented with a bleeding diathesis. One patient had elevated liver enzymes and the other had no symptoms (Supplemental Table 1, Cases 10 and 15). Minor bleeding occurred in 36 (94.7%) patients, such as purpura, ecchymoses, epistaxis, and gingival bleeding. Severe bleeding occurred in two (5.3%) patients, such as macroscopic hematuria (Supplemental Table 1, Cases 18 and 28). In all four patients with SLE, one had thrombocytopenia at presentation (Supplemental Table 1, Case 17). There was only one thrombotic event among all 40 patients (Supplemental Table 1, Case 24). In an 8-year-old girl with SLE, thrombotic

thrombocytopenic purpura occurred 36 h after labial salivary gland biopsy for the purpose of diagnosing Sjögren's syndrome. All 40 patients showed prolongation of the APTT, positive LA, and FII deficiency at presentation. The median FII level at presentation was 26.0% (< 3–69%). Prolongation of the PT was found in 37 (37/40, 92.5%) patients at presentation. IgG anticardiolipin antibodies (aCL) were reported in 21 cases of LAHPS with data available and were positive in seven (7/21, 33.3%). IgG aβ_2GPI and/or β_2-glycoprotein I-dependent anticardiolipin antibodies (aCL/β_2GPI) were positive in two (2/18, 11.1%) patients. IgG antiprothrombin (aPT) or phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) were reported in 25 cases of LAHPS with data available. aPT were positive in six (6/7, 85.7%) and aPS/PT were positive in 19 (19/19, 100%) patients. Treatment was reported in 34 cases of LAHPS with data available. No treatment was administered in 28 (28/34, 82.4%) patients. Four patients were treated with steroids and/or other immunosuppressive agents, such as mycophenolate mofetil, cyclophosphamide, and plasmapheresis (Supplemental Table 1, Cases 24, 28, 30, and 36). Three patients with SLE required immunosuppressive agents beyond the SLE disease activity (Supplemental Table 1, Cases 24, 28, and 30). Two patients received supportive treatment, including fresh frozen plasma and antibiotics (Table 2; Supplemental Table 1, Cases 1 and 7).

We compared 40 Japanese pediatric LAHPS cases with 46 non-Japanese pediatric LAHPS cases (Table 2; Supplemental Tables 1, 2). The mean age at diagnosis was significantly younger (4.7 vs. 7.8 years, $p < 0.001$) and the median FII level at diagnosis was significantly higher (26.0% vs. 11.8%, $p = 0.004$) in Japanese patients compared with non-Japanese patients. Significantly more Japanese cases were associated with infections compared with non-Japanese cases (80.0% vs. 45.7%, $p = 0.002$). Additionally, Japanese fewer patients did not require any treatment compared with non-Japanese patients (82.4% vs. 32.6%, $p < 0.001$). There were significantly more non-Japanese patients with severe bleeding symptoms (37.0% vs. 5.3%, $p < 0.001$) and those who required immunosuppressive agents (54.3% vs. 11.8%, $p < 0.001$) compared with Japanese patients [1, 4, 11–39]. Among all 46 non-Japanese patients, severe bleeding, such as macroscopic hematuria, menorrhagia, hematemesis, hemorrhagic diarrhea, melena, intramuscular hematoma, intracranial hemorrhage, and intraarticular hemorrhage, occurred in 17 patients. One patient with SLE died because of pulmonary hemorrhage (Supplemental Table 2, Case 24) [23] and there was one thrombotic event (Supplemental Table 2, Case 36) [32]. Of all four patients with thrombocytopenia at presentation, three were associated with SLE (Supplemental Table 2, Cases 37, 39, and 41) [33, 35, 36].

We also compared 29 patients who required immunosuppressive agents with 51 patients who required no treatment or only supportive care (Table 3; Supplemental Tables 1, 2). In the treatment group, the mean age at diagnosis was significantly older (10.3 vs. 4.1 years, $p < 0.001$) and the median FII level at diagnosis was significantly lower compared with the non-treatment group (12.4% vs. 20.0%, $p = 0.044$). All 20 patients with SLE were included in the treatment group, whereas the majority of patients with infections were included in the non-treatment group (69.0% vs. 0%, 13.8% vs. 90.2%, respectively, both $p < 0.001$). Among all three patients with IgAV, our patients were included in the non-treatment group and one patient was included in the treatment group (Supplemental Table 1, Cases 36, 39, and 40). Except for patients with SLE, infections, or IgAV, other patients with LAHPS had lupus-like features, autoimmune-mediated disease, and primary APS in the treatment group, and celiac diseases were found in the non-treatment group. Two patients had no underlying diseases. Interestingly, the positive ratios of IgG aCL and IgG aβ_2GPI and/or aCL/β_2GPI were significantly higher in the treatment group than in the non-treatment group (59.1% vs. 30.0%, $p = 0.049$ and 50% vs. 0%, $p < 0.001$, respectively).

Discussion

Both of our patients had palpable purpura with lower limb and diffuse abdominal pain, and Case 2 also had left knee pain. Our patients did not have any other symptoms suggestive of infections, autoantibodies associated with autoimmune diseases, or a history of drug use and vaccinations, but they had allergic diseases. Abdominal involvement can be caused by allergic diseases (e.g., food allergies and angioedema). Food allergies and allergic (histaminergic) angioedema are often associated with urticaria and with swelling episodes that typically resolve within 24–48 h. However, non-histaminergic-mediated angioedema is rare and not associated with urticaria. Non-histaminergic-mediated angioedema tends to be more severe, longer lasting, and much more likely to involve concurrent abdominal symptoms than allergic angioedema [40]. The feature of abdominal pain in our patients was not associated with these diseases because it was mild and long-lasting. The cutaneous features of IgAV are most commonly palpable purpura, petechiae, and ecchymoses mainly over the lower extremities. Each of the skin lesions, such as palpable purpura, ecchymoses, and petechiae, over the lower limbs in both of our patients, and several urticarial lesions of the forearms in Case 1 fulfilled the features of IgAV [7]. Therefore, both patients were diagnosed with IgAV on the basis of EULAR/PRINTO/PRES criteria and classification definitions [8]. However, purpuric lesions are usually found not only on the lower extremities, but also on the buttocks, in young children,

Table 3 Clinical and laboratory characteristics of 29 cases with treatment and 51 cases with no treatment or supportive care only in pediatric lupus anticoagulant-hypoprothrombinemia syndrome

	All cases	Treatment	No treatment or supportive care only	*p* values
Number of cases	80	29	51	
Mean age (years) (range)	6.4	10.3 (2–15)	4.1 (0.8–10)	< 0.001
Sex				
Female, *n* (%)	46 (57.5)	17 (58.6)	29 (56.9)	1.000
Diagnosis				
SLE, *n* (%)	20 (25.0)	20 (69.0)	0 (0)	< 0.001
Infection, *n* (%)	50 (62.5)	4 (13.8)	46 (90.2)	< 0.001
IgAV, *n* (%)	3 (3.8)	1 (3.4)	2 (3.9)	1.000
Others, *n* (%)	6 (7.5)	4 (13.8)	2 (3.9)	0.187
None, *n* (%)	2 (2.5)	1 (3.4)	1 (2.0)	1.000
Symptoms				
Bleeding diathesis, *n** (%)	79 (79/80, 98.8)	29 (29/29, 100)	50 (50/51, 98.0)	1.000
Minor bleeding, *n** (%)	60 (60/79, 75.9)	16 (16/29, 55.2)	44 (44/50, 88.0)	
Severe bleeding, *n** (%)	19 (19/79, 24.1)	13 (13/29, 44.8)	6 (6/50, 12.0)	0.001
Thrombotic event	1 (1/79, 1.3)	1 (1/29, 3.4)	0 (0)	
Coagulopathy				
Prolonged APTT, positivity, *n** (%)	75 (100)	29 (100)	46 (100)	1.000
Prolonged PT, positivity, *n** (%)	72 (72/75, 96.0)	29 (100)	43 (43/46, 93.5)	0.279
Factor II level, *n** (%)	67 (100)	27 (100)	40 (100)	
Median (%) (range)	16.9 (0–69%)	12.4 (0–57%)	20.0 (< 1–69%)	0.044
Other decreased coagulation factors, positivity, *n** (%)	41 (41/58, 70.7)	12 (12/18, 66.7)	29 (29/40, 72.5)	0.758
Antiphospholipid antibodies				
Lupus anticoagulant, positivity, *n** (%)	80 (100)	29 (100)	51 (100)	1.000
IgG aCL, positivity, *n** (%)	22 (22/52, 42.3)	13 (13/22, 59.1)	9 (9/30, 30.0)	0.049
IgG aβ_2GPI or aCL/β_2GPI, positivity, *n** (%)	7 (7/35, 20.0)	7 (7/14, 50.0)	0 (0)	< 0.001
IgG aPT, positivity, *n** (%)	13 (13/14, 92.9)	5 (5/5, 100)	8 (8/9, 88.9)	1.000
IgG aPS/PT, positivity, *n** (%)	21 (21/22, 95.5)	3 (3/3, 100)	18 (18/19, 94.7)	1.000

SLE systemic lupus erythematosus, *IgAV* immunoglobulin-A vasculitis, *APTT* activated partial thromboplastin time, *PT* prothrombin time, *IgG* immunoglobulin G, *aCL* anticardiolipin antibodies, *aCL/β_2GPI* β_2-glycoprotein I-dependent anticardiolipin antibodies, *aPS/PT* antiphosphatidylserine-dependent antiprothrombin antibodies, *n** number of cases with data available

and infectious diseases occur before the onset in approximately two-thirds of IgAV cases [41]. Initial coagulation studies were performed in our patients to exclude acquired hemophilia or any other coagulation disorder. Coagulopathy generally does not occur in IgAV, but our patients had prolongation of the APTT and further studies were performed. They showed the presence of LA with acquired hypoprothrombinemia. Both cases also met the criteria for LAHPS. Cutaneous manifestations of pediatric IgAV are characterized by several types of skin lesions, but in adults, these manifestations are often uniform [42]. Our patients had common skin lesions and did not have uncommon skin lesions, such as necrotic purpura and hemorrhagic vesicles. Additionally, our patients' lesions were not localized on the face, trunk, palms, and soles. These locations are not common in most pediatric IgAV cases [7]. For these reasons, a skin biopsy was not performed.

The activities of other coagulation factors, except for FII, were low in both of our cases. Inhibitors of factors VIII and IX and hypocomplementemia were also detected in Case 1. Deficiencies of other coagulation factors, except for factors II and XIII, and inhibitors were thought to be due to interference of LA. This is because the pattern of deficiencies of coagulation factors, except for factor XIII, and inhibitors was typical as in previously reported LAHPS cases [9]. Factor XIII deficiency was detected in more than 70% of cases of IgAV [43] and factor XIII deficiency was not common in LAHPS cases. Therefore, factor XIII deficiency in Case 2 was suggested to be related to IgAV. Hypocomplementemia has been detected in IgAV cases [44]. With regard to the mechanism of LAHPS, hypocomplementemia could also be caused by consumption of complement, which results from the antigen–antibody complexes that activate complement systems.

We summarized the characteristics of 40 Japanese and 46 non-Japanese pediatric LAHPS cases between 1996 and 2019 [1, 4, 9–39]. (Table 2; Supplemental Tables 1, 2). Of all 40 Japanese patients, three patients, including Case 2, had a normal PT. The FII level in Case 2 was 69%, which was the highest among Japanese LAHPS cases (median FII level 26.0%, < 3–69%). The mild bleeding symptoms in both cases might have been affected by the FII level. Japanese patients had more infections, a younger age, and higher FII levels compared with non-Japanese patients. The majority of Japanese patients did not have severe bleeding symptoms and did not require any treatment. There was no significant difference in the positive ratio of antiphospholipid antibodies (aPL) between Japanese and non-Japanese cases. The significant differences in age, FII levels, and severity of bleeding symptoms might have been affected by the number of cases with infections and SLE. Of all 86 pediatric LAHPS cases, only one case was associated with IgAV, except for our two cases. Possible explanations for this finding are as follows. First, LAHPS associated with IgAV might be underdiagnosed because of not checking coagulation parameters in uncomplicated IgAV cases in routine practice. Second, the incidence of LAHPS associated with IgAV might depend on race because Asians have a relatively higher incidence of IgAV than do Caucasians [45]. Finally, the immunoglobulin subtype of aPL might have an effect on the pathogenesis of IgAV and LAHPS.

Chen et al. reported that one of the etiological factors of IgAV was food allergies [41] and Chiu et al. also reported that chronic urticaria was associated with IgAV [46]. The genetic background underlying IgAV has been investigated recently, but there have been no reports on Japanese genetic data regarding the pathogenesis. Therefore, we cannot deny the possibility of asymptomatic viral infections and the genetic predisposition remains unknown. However, the pathogenesis of IgAV in our cases might have been related to allergic diseases. Additionally, Hočevar et al. reported that 31 (24.8%) patients had LA in 125 adult IgAV cases [47]. Yang et al. reported that 21 (81%) of 26 Chinese children who were affected by IgAV had a higher prevalence of aCL IgA than did healthy controls and juvenile rheumatoid arthritis cases [48]. Additionally, Kawakami et al. showed that 22 (73%) of 30 Japanese adult patients with IgAV were positive for IgA aCL, while 19 (63%) had IgA aPS/PT. In contrast, 20 (67%) patients were positive for IgM aPS/PT and six (20%) were positive for IgG aPS/PT in cases of IgAV [49]. These reports suggest that IgA plays an important role in aPL associated with IgAV.

We also compared 29 patients who required immunosuppressive agents with 51 who required no treatment or only supportive care (Table 3; Supplemental Tables 1, 2). Most patients with SLE were in the treatment group, whereas most patients with infections were in the non-treatment group. The median FII level at diagnosis was significantly lower and the mean age was significantly older in the treatment group than in the non-treatment group. In the treatment group, two-thirds (19/29, 65.5%) of patients were 10 years or older at diagnosis. Most patients with severe bleeding symptoms were included in the treatment group. Severe bleeding complications were likely to occur when FII levels were lower than 10% of normal [9]. The median FII level in the treatment group almost correlated with the result in the previous report. Additionally, a positive ratio of IgG aCL and IgG aβ_2GPI and/or aCL/β_2GPI was significantly higher in the treatment group than in the non-treatment group.

LA was reported to be positive in 0.7–2.4% of asymptomatic pediatric patients at preoperative coagulation screening, whereas 80 (84%) of 95 children with positive LA were asymptomatic [1]. Nine (10%) of 95 children had bleeding symptoms and five of nine patients were diagnosed with LAHPS. A total of 84 of the 86 patients had bleeding symptoms. All 21 patients with SLE had bleeding symptoms, although only four patients had thrombocytopenia. The percentage of patients who have SLE with LAHPS remains unclear. However, when patients, especially those with autoimmune diseases such as SLE, have bleeding symptoms without thrombocytopenia, LAHPS should be considered. Additionally, LAHPS is fully defined by the presence of a typical laboratory pattern with or without bleeding symptoms. Therefore, LAHPS might be underdiagnosed because most cases without bleeding symptoms do not have coagulation parameters checked.

There are several limitations in this study. In the absence of diagnostic criteria for IgAV, our cases were diagnosed on the basis of the existing classification criteria, such as EULAR/PRINTO/PRES criteria and classification definitions. Our cases met these criteria, but a skin biopsy might be required to confirm a definitive diagnosis of IgAV. Additionally, the number of pediatric LAHPS cases is too small to determine whether LAHPS is strongly associated with IgAV in Japan. Therefore, further larger studies on these issues will be required. However, the findings in our cases suggest that the APTT and PT should be recorded in patients with IgAV when they do not have a typical clinical course or a distinctive symptom, or when other coagulation disorders need to be excluded. LAHPS should be considered with prolongation of the APTT and/or PT in IgAV cases. When patients with IgAV and a significant deficiency of factor XIII have LAHPS, bleeding symptoms might be more severe. Furthermore, thrombotic events occur in LAHPS cases receiving steroids with the resolution of bleeding complications [50]. Therefore, if patients with IgAV require intensive therapies, such as steroids, measurement of the APTT and PT should be performed before treatment for screening of LAHPS. Because normalization of the PT and FII levels occurs in IgAV cases with LAHPS under treatment, paying close attention is important to maintain a balance between

the risk of thrombosis and hemorrhage. Additionally, our findings suggest that there are factors that could be used to predict a requirement for treatment. Intensive therapy could be considered in the following cases: (1) LAHPS is associated with SLE; (2) the age at diagnosis is older, especially 10 years or older; (3) cases with severe bleeding symptoms; (4) FII levels are lower than 10% of normal; and (5) IgG aCL and/or IgG β_2GPI and/or aCL/β_2GPI are positive.

Conclusion

Of the 86 reported pediatric LAHPS cases, approximately 60% were associated with infections followed by SLE. There were only three cases with IgAV. The reason why all patients with LAHPS and IgAV were Japanese remains unknown and whether these patients require treatment needs to be determined. Therefore, further study is required to confirm our conclusions. However, our findings suggest that the presence of SLE, older age, lower prothrombin levels, severe bleeding symptoms, and the positivity of IgG aCL and IgG aβ_2GPI and/or aCL/β_2GPI at diagnosis have higher odds of requiring treatment in pediatric LAHPS. Measuring the APTT and PT might be required in patients with IgAV when they do not have a typical clinical course or distinctive symptoms. LAHPS should be considered with prolongation of the APTT and/or PT. Additionally, when patients with LAHPS are treated with steroids and normalization of the PT and FII levels occurs, close attention should be paid to maintain a balance between the risk of thrombosis and hemorrhage.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (include name of committee + reference number) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from parents of the patients for publication.

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