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Citation	Journal of Obstetrics and Gynaecology Research. 2024, 50(7), p. 1258-1262
Version Type	VoR
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Received: 25 December 2023 | Accepted: 1 April 2024

DOI: 10.1111/jog.15949

CASE REPORT

Severe hemolysis, elevated liver enzymes, and low platelet syndrome requiring differentiation of thrombotic microangiopathy: Four cases from a nationwide survey in Japan

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Funding information
Perinatal Research Network Group in Japan; MEXT KAKENHI, Grant/Award Numbers: JP21K09447, JP20K09618

Abstract

Severe cases of hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome requiring plasma exchange or dialysis should be differentiated from other thrombotic microangiopathy (TMA) and treated appropriately. To evaluate the prevalence and clinical characteristics of such cases in Japan, a questionnaire-based survey was conducted among obstetricians who are members of the Perinatal Research Network Group in Japan. There were a total of 335 cases of HELLP syndrome over a 3-year period in the 48 facilities that responded to the survey. Four patients required plasma exchange or dialysis, of which two were diagnosed with atypical hemolytic uremic syndrome and two with TMA secondary to systemic lupus erythematosus. Although such severe HELLP syndrome is rare, identifying the clinical features and making accurate differential diagnosis are critical for optimal clinical outcomes for mothers and neonates.

KEYWORDS
atypical hemolytic uremic syndrome, HELLP syndrome, pre-eclampsia, pregnancy, thrombotic microangiopathy

INTRODUCTION

Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is associated with 10%–20% of pre-eclampsia cases, and high maternal and infant mortality rates have been reported.[1] Preeclampsia and HELLP syndrome are rarely associated with severe organ damage that requires plasma exchange or dialysis. Such cases necessitate a differential diagnosis of thrombotic microangiopathy (TMA).[2] TMA is a group of diseases characterized by hemolytic anemia, thrombocytopenia, and thrombotic organ damage, in which thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) can be triggered by pregnancy.[3,4] HELLP syndrome may be classified as TMA secondary to pregnancy.[3] Recently, HELLP syndrome has been suggested to share a common pathology with aHUS, and the effectiveness of treatment based on complement regulation, as typified by anti-C5 inhibitors, has attracted attention.[3–6] However, the pathogenesis of HELLP syndrome remains unclear, and it is unknown in which patients and in how many cases anti-C5 inhibitors are beneficial. Therefore, we conducted a nationwide survey in Japan to determine the number of cases of HELLP syndrome. We also present the detailed clinical course of four of the total identified cases that required plasma exchange and dialysis.

METHODS

Study design and nationwide survey.

Questionnaires were collected by mail from obstetricians who are members of the Perinatal Research Network

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Group in Japan. The primary survey included the type of facility, presence of an intensive care unit (ICU) or emergency medical care center (EMCC), presence of full-time specialists, the number of deliveries per year, HELLP syndrome over the 3-year period (2017–2019), and the number of cases requiring plasma exchange or dialysis. Diagnostic criteria for HELLP syndrome was not defined and relied on obstetricians discretion at each hospital, with suspected cases of HELLP syndrome also being included in the registry. Cases undergoing plasma exchange or dialysis were selected for a secondary survey to investigate the details of pregnancy and postpartum.

All the patients included in this study provided written informed consent for the publication of their clinical data, and the study design was approved by the appropriate ethics review board (19313-3) and conforms to the provisions of the Declaration of Helsinki.

RESULTS

Background of responding facilities

We invited 169 members for the survey, of whom 48 responded (response rate, 28.4%). All responding facilities were advanced medical facilities capable of treating severe obstetric cases, with about 80% having ICU or EMCC. All facilities had full-time pediatricians and anesthesiologists, with nephrologists present in 85.4% of them. The total number of deliveries per year was 35 994 in 48 facilities (Table 1).

Cases of severe HELLP syndrome over 3-year response period

In total, 335 cases of HELLP syndrome were identified during the 3-year study period, of which four were treated with plasma exchange or dialysis (Table 1). The clinical characteristics, the main laboratory parameters (not the values at a specific point in time but the highest or lowest values), and the final diagnosis and outcomes of these four severe cases are summarized at Table 2. The next section summarizes the clinical course of these cases.

TABLE 1 Summary of the primary survey results.

Survey items	Number
Background of respondent facilities	N = 48 (% of total)
Perinatal medical center	25 (52.1)
University hospital	21 (43.8)
General hospital	2 (4.2)
Availability of ICU	40 (83.3)
Availability of EMCC	34 (70.8)
Presence of pediatricians	48 (100)
Presence of anesthesiologists	48 (100)
Presence of nephrologists	41 (85.4)
Total annual deliveries	35 994
Number of HELLP syndrome cases during 3 years	335
Plasma exchange performed	3
Plasma exchange and dialysis performed	1

Abbreviations: EMCC, emergency medical care center; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet syndrome; ICU, intensive care unit.

Case 1

A 36-year-old woman (gravida 1, para 0) without any underlying disease was diagnosed with fetal growth restriction (FGR) at 21 weeks of gestation. At 30 weeks and 2 days of gestation (hereafter denoted as 30w2d), her blood pressure was 152/86 mmHg, proteinuria was detected, and pre-eclampsia was diagnosed. At 32w1d, the blood pressure increased to 190/117 mmHg, and an abnormal fetal heart rate was observed; consequently, emergency cesarean section was performed and diagnosis of placental abruption was made. The neonate weighed 1092 g (−2.7 standard deviation [SD]), with Apgar scores of 5 and 7 at 1 and 5 min, respectively. Postoperative day (POD)1 blood tests revealed platelet (Plt) count, 17 000/μL; lactate dehydrogenase (LDH), 2835 U/L; aspartate aminotransferase (AST), 668 U/L; and alanine transaminase (ALT), 347 U/L. Thus, she was diagnosed with HELLP syndrome. She also had abnormal coagulation findings with fibrinogen of 72 mg/dL and fibrinogen/fibrin degradation products (FDP) of 15.91 μg/mL. Additionally, her serum creatinine was 1.64 mg/dL, indicating abnormal renal function. TMA, such as TTP and aHUS, was suspected, and plasma exchange was initiated. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was 78% and Shiga toxin was negative, ruling out TTP and Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome. With various autoantibodies testing negative and no underlying disease, secondary TMA was ruled out. Genetic testing did not identify aHUS-causing gene; however, exclusionary aHUS was diagnosed (Figure 1a).

Case 2

A 28-year-old woman (gravida 2, para 1) with a history of IgA nephropathy, presented with abdominal pain at 36w1d and was diagnosed with placental abruption and intrauterine fetal death. Her Plt was 250 000/μL, fibrinogen was 189 mg/dL, and FDP was 1222 μg/mL. The delivery proceeded spontaneously, and the fetus was delivered the next day. During delivery, 6 g of fibrinogen and 2 units of red blood cell transfusion were administered. Immediately after delivery, her blood pressure increased to 180/100 mmHg, renal dysfunction was observed, and she was diagnosed with pre-eclampsia. Postpartum day 1 blood tests revealed Plt, 40 000/μL; LDH, 3827 U/L; AST, 244 U/L; and ALT, 67 U/L, and

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TABLE 2 Clinical characteristics, main laboratory parameters, differential diagnosis of TMA, and outcomes.

Case	1	2	3	4
Age (years)	36	28	28	25
Gravidity and parity	G1P0	G2P1	G3P0	G1P0
Underlying disease	None	History of IgA nephropathy	SLE, Sjögren syndrome	None[a]
Mode of delivery	CS	VD	CS	CS
Onset (weeks of gestation or postpartum date)	PD 1	PD 1	W25	W31
Complications				
PE	+	+	+	−
FGR	+	−	−	+
PA	+	+	−	−
Laboratory data				
Hemoglobin (g/L)	9.0	8.7	5.7	6.6
Platelet count (/μL)	17 000	40 000	7000	41 000
LDH (U/L)	2835	3827	1080	274
AST (U/L)	1008	244	49	19
ALT (U/L)	402	67	41	12
Creatinine (mg/dL)	2.35	6.9	1.02	1.10
Fibrinogen (mg/dL)	72	189	n/a	692
FDP (μg/mL)	15.91	1222	n/a	10.0
ADAMTS13 activity (%)	78	74	56	76
Diagnosis of TMA	aHUS	aHUS	Secondary TMA (SLE)	Secondary TMA (SLE)
Outcome				
Mother	Survived	Survived, persistent renal failure	Survived	Survived, repetition of TMA
Infant	Survived	Died (IUFD)	Survived	Survived

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; ALT, alanine transaminase; AST, aspartate aminotransferase; CS, cesarean section; FDP, fibrin/fibrinogen degradation product; FGR, fetal growth restriction; IUFD, intrauterine fetal death; LDH, lactate dehydrogenase; n/a, not available; PA, placental abruption; PD, postpartum day; PE, preeclampsia; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; VD, vaginal delivery; W, gestation week.
[a]The case was diagnosed with SLE after the onset of TMA.

she was diagnosed with HELLP syndrome. Additionally, her creatinine level was abnormal (4.05 mg/dL). TMA was suspected, and plasma exchange and dialysis were initiated. ADAMTS13 activity was 74% and there were no underlying diseases. Genetic testing did not identify the aHUS-causing gene; however, exclusionary aHUS was diagnosed. The patient continued to be treated by a nephrologist for prolonged renal function abnormalities (Figure 1b).

Case 3

A 28-year-old woman (gravida 3, para 0) presented with systemic lupus erythematosus (SLE) and Sjögren's syndrome. She was diagnosed with autoimmune thrombocytopenia (Plt, 26 000/μL) at 25w6d, and steroid pulse therapy was initiated at 26w0d. At 26w5d, her blood pressure was 140/90 mmHg, and proteinuria was noted, leading to pre-eclampsia diagnosis. TMA, including HELLP syndrome, was also suspected because LDH increased to 1080 U/L, and crushed red blood cells were detected at 27w1d. Plasma exchange was performed for 3 days starting at 27w2d; however, her Plt remained below 10 000/μL, and hypertension and urinary protein also worsened. Therefore, after a 20 units of platelet transfusion at 27w5d, a cesarean section was performed. The neonate weighed 868 g (−1.5 SD), with Apgar scores of 6 (1 min) and 8 (5 min). The patient's condition gradually improved after delivery. ADAMTS13 activity was 56%; thus, TTP was ruled out, and she was diagnosed with TMA secondary to SLE (Figure 1c).

Case 4

A 25-year-old woman (gravida 1, para 0) with no known underlying diseases was diagnosed with FGR at 24 weeks of gestation. At 31w4d, blood tests revealed Plt, 46 000/μL; creatinine, 1.10 mg/dL; and crushed red blood cells.

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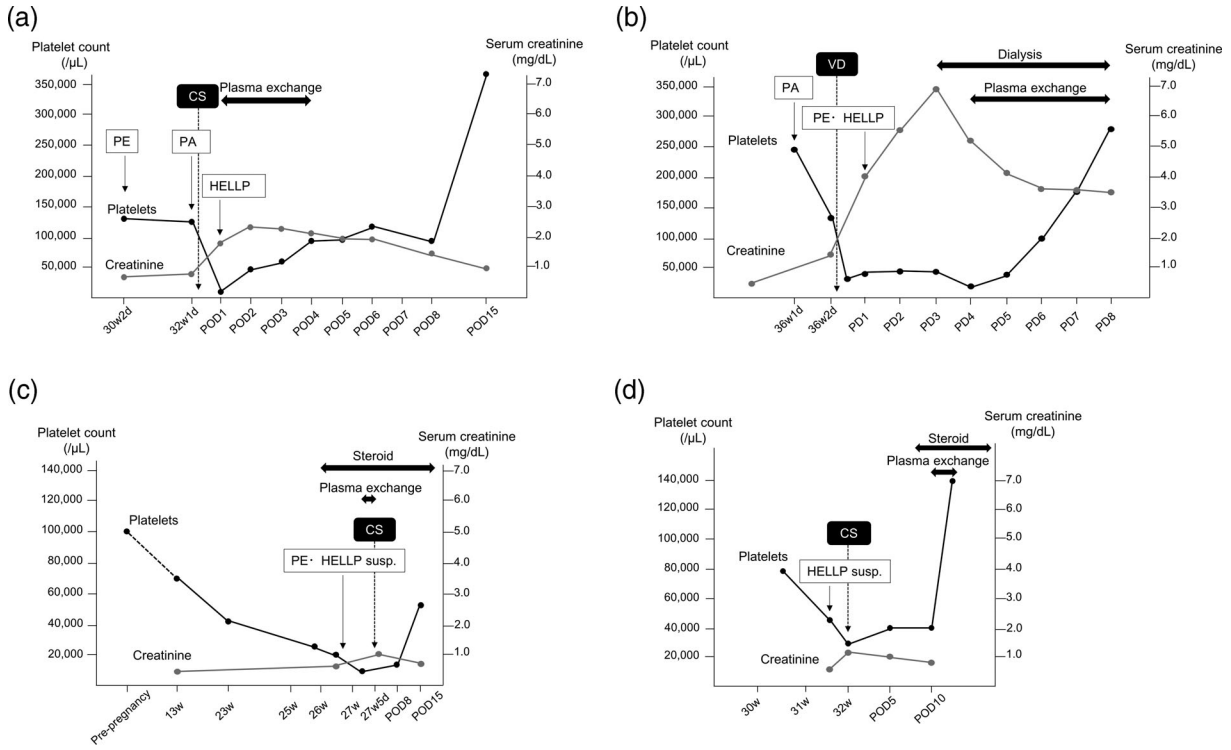

FIGURE 1 Creatinine and platelet counts during pregnancy and postpartum in four patients with HELLP syndrome. Changes in platelet count and serum creatinine levels were observed in each case. The timing of the onset of preeclampsia, HELLP syndrome, placental abruption, delivery (vaginal delivery or cesarean section), as well as the duration of plasma exchange, dialysis, and steroid therapy are also included in the figure. (a) Case 1, (b) Case 2, (c) Case 3, (d) Case 4. CS, cesarean section; HELLP, hemolysis, elevated liver enzymes, and low platelet syndrome; PA, placental abruption; PD, postpartum day; PE, preeclampsia; POD, postoperative day; susp, suspected; VD, vaginal delivery.

Thus, TMA, including HELLP syndrome, was suspected. At 32w0d, thrombocytopenia and abnormal renal function worsened; hence, after 30 units of platelet transfusion, a cesarean section was performed. The neonate weighed 1202 g (−2.3 SD), with Apgar scores of 6 (1 min) and 7 (5 min). After delivery, her renal dysfunction improved spontaneously, whereas the thrombocytopenia persisted. ADAMTS13 activity was 76%, so TTP was ruled out. After delivery, she developed symptoms of palmar erythema, tested positive for antinuclear antibodies and lupus anticoagulant, and a biopsy of the palmar erythematous area showed findings of TMA, leading to a diagnosis of TMA secondary to SLE. Although steroid pulse therapy was initiated on POD5, the thrombocytopenia did not improve; therefore, plasma exchange was initiated on POD10. Her condition gradually improved, but TMA flared 1 month after delivery, and she was treated again (Figure 1d).

DISCUSSION

This study investigated a number of severe HELLP syndrome cases in a group of medical facilities in Japan that required differentiation from other TMA and clarified their clinical characteristics. In this 3-year survey, 4 of 335 patients identified with HELLP syndrome required plasma exchange or dialysis; 2 were classified as aHUS and the other 2 as secondary TMA.

The frequency of HELLP syndrome and aHUS was 3.1/1000 deliveries and 1.9 cases/100 000 deliveries, respectively. The results were approximately consistent with previous literature, which reported a frequency of 1 case/1000 pregnancies for HELLP syndrome and approximately 4 cases/100 000 pregnancies for aHUS.[4] However, this study may not reflect the actual frequency in Japan because the definition of HELLP syndrome is ambiguous and the facilities surveyed were limited.

Pregnancy-associated aHUS occurs in approximately 80% of cases during the postpartum period and is characterized by renal dysfunction.[4] The pathogenesis of aHUS is complement dysregulation, and identification of complement-related genetic abnormalities is the basis for diagnosis. However, genetic abnormalities are identified only about 50% of aHUS cases, and most cases are diagnosed by exclusion of other TMAs.[3] Cases 1 and 2 were diagnosed by exclusion, but the patients also presented with disseminated intravascular coagulation (DIC) due to placental abruption, which made differentiation difficult. TMA and DIC share common clinical symptoms and can be distinguished by hemolytic findings in TMA and marked coagulation factors abnormalities in DIC.[7] However, in both these cases, findings suggested the coexistence of TMA and DIC.

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Cases 3 and 4 involved secondary TMA caused by SLE. The major autoimmune diseases that cause pregnancy-associated TMA are SLE and anti-phospholipid antibody syndrome, which can lead to thrombocytopenia with pregnancy.[8] In these two cases, patients had low basal platelet counts during pregnancy, and after the onset of TMA, they had more pronounced and prolonged thrombocytopenia than the other patients. In contrast, liver and kidney damage was mild.

This study had some limitations. First, it was a retrospective questionnaire survey, which limited the facilities surveyed to advanced medical facilities. Second, the response rate was low. Therefore, it was impossible to identify all the cases of HELLP syndrome in Japan.

In conclusion, even cases initially considered HELLP syndrome, those with severe prolonged organ damage may be classified as other TMA. Although these conditions are rare, accurate differentiation and early appropriate treatment can improve the prognosis for mothers and neonates.

ACKNOWLEDGMENTS

This study was supported by Perinatal Research Network Group in Japan and MEXT KAKENHI Grant Numbers JP21K09447, JP20K09618. The authors would like to thank Editage (www.editage.com) for English language editing. This study was presented at the 42nd Annual Congress of the Japan Society for the Study of Hypertension in Pregnancy, October 30, 2022, Tokyo, Japan.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The raw data of this study cannot be fully shared because it contains personally identifiable information. We will share the data set of the primary survey (Table S1, Supporting Information). The data that support the findings of the secondary survey in this study are fully provided in the text. Further data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Komatsu R, Mimura K, Matsuyama T, Kawanishi Y, Nakamura H, Tomimatsu T, et al. Severe hemolysis, elevated liver enzymes, and low platelet syndrome requiring differentiation of thrombotic microangiopathy: Four cases from a nationwide survey in Japan. J Obstet Gynaecol Res. 2024. https://doi.org/10.1111/jog.15949

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