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Letter to the Editor

Ischemic stroke in a young woman with anti-phosphatidylserine/prothrombin (aPS/PT) complex antibody: a case report

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1. Case report

The laboratory criteria for diagnosis of antiphospholipid syndrome (APS) comprises 3 tests for anti-cardiolipin (aCL), anti-beta2-glycoprotein I (b2GPI) antibodies, and lupus anticoagulant (LA) [1]. Several other antibodies, including anti-phosphatidylserine/prothrombin (aPS/PT) complex antibody, have been shown to correlate with APS [2] and thromboembolic diseases [3]. Oral contraceptive is also thought to be a risk factor for thromboembolic diseases [4]. We report an ischemic stroke patient using an oral contraceptive with aPS/PT complex antibody.

A 27-year-old, right-handed woman was emergently admitted to our hospital after suddenly developing conscious disturbance. She had started to use an oral contraceptive 4 days before. On admission, she had conscious disturbance with a Glasgow Coma Scale score of 9, right pupillary dilatation, left hemiplegia, weakness of her right lower limb, and a positive Babinski reflex in both lower limbs. Her blood pressure was 128/82 mmHg with a regular heart rate of 68 beats/min. Diffusion-weighted magnetic resonance imaging (DWI) showed high-signal intensity areas in both sides of the occipital lobe, thalamus, cerebellum, midbrain, and pons (Fig. 1A, B). Magnetic resonance angiography (MRA) showed left posterior cerebral artery (PCA) occlusion (Fig. 1C). We diagnosed her as acute ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score of 24. Chest radiography, 12-ch electrocardiogram (ECG), carotid ultrasonography, transthoracic echocardiography, transesophageal echocardiography, and Holter ECG recording did not show any embolic sources. Doppler study on carotid ultrasonography revealed normal waveforms of bilateral vertebral arteries [5,6]. On day 2, MRA revealed the recanalization of the left PCA. Laboratory findings did not reveal dyslipidemia or diabetes mellitus. Hematological, liver, renal, coagulation, and autoimmune diseases were not detected in physical or laboratory examination. The laboratory data are shown in Table 1. The patient did not have histories of livedo reticularis or migraine. However, serum hemolytic complement activity (CH50) was decreased (17.3 U/mL; cut-off range, 29.0–48.0) and serum IgG aCL antibody was slightly increased (11.0 U/mL; cut-off range, < 10.0). Although plasma D-dimer level was within normal range, mural thrombus of the right external iliac vein was detected with ultrasonography on Day 6. We thought these findings suggested a possibility of APS. We initiated anticoagulation with a vitamin K antagonist for secondary prevention of stroke. On day 45, she transferred to a rehabilitation hospital with an NIHSS score of 4 and a modified Rankin Scale score of 2. The second analysis for diagnosis of APS on day 131 showed normal serum aCL and b2GPI antibody levels, and a normal LA ratio. However, the activated partial thromboplastin time (APTT) was prolonged to 45.9 s and CH50 was decreased (25.3 U/mL). In this second analysis, we measured the serum IgG aPS/PT complex antibody level, and it was markedly increased at > 200 U/mL (cut-off range < 12.0).

2. Discussion

This is the first reported case of an ischemic stroke just after the beginning of oral contraceptive with aPS/PT complex antibody. In this case, prolonged APTT, decreased serum hemolytic complement activity, and deep vein thrombosis were thought to be associated with occult APS. Although the laboratory findings did not meet the criteria for APS, we believe that the beginning of oral contraceptive promoted the potential risk of aPS/PT antibody for ischemic stroke.

Other than aPS/PT antibody, “non-criteria” clinical features include heart valve disease, livedo reticularis, thrombocytopenia, and nephropathy [1]. This patient did not have histories of these diseases. Systemic lupus erythematosus (SLE) is well known to be associated with APS. Among the factors of criteria for SLE, decreased serum hemolytic complement activity was found in this patient, which might have reflected the activation of compliment system. Compliment system is thought to play a key role not only for SLE but also for APS [7].

We could not diagnose the current patient as APS according to the classification criteria for APS [1]. Thus, we finally diagnosed acute ischemic stroke with other cause, i.e., oral contraceptive use, according to SSS-TOAST classification criteria [8]. However, serum IgG aPS/PT complex antibody level was markedly elevated. Atsumi et al. reported that aPS/PT complex antibody, but not anti-prothrombin (aPT) antibody, was closely associated with LA [2]. A systematic review showed

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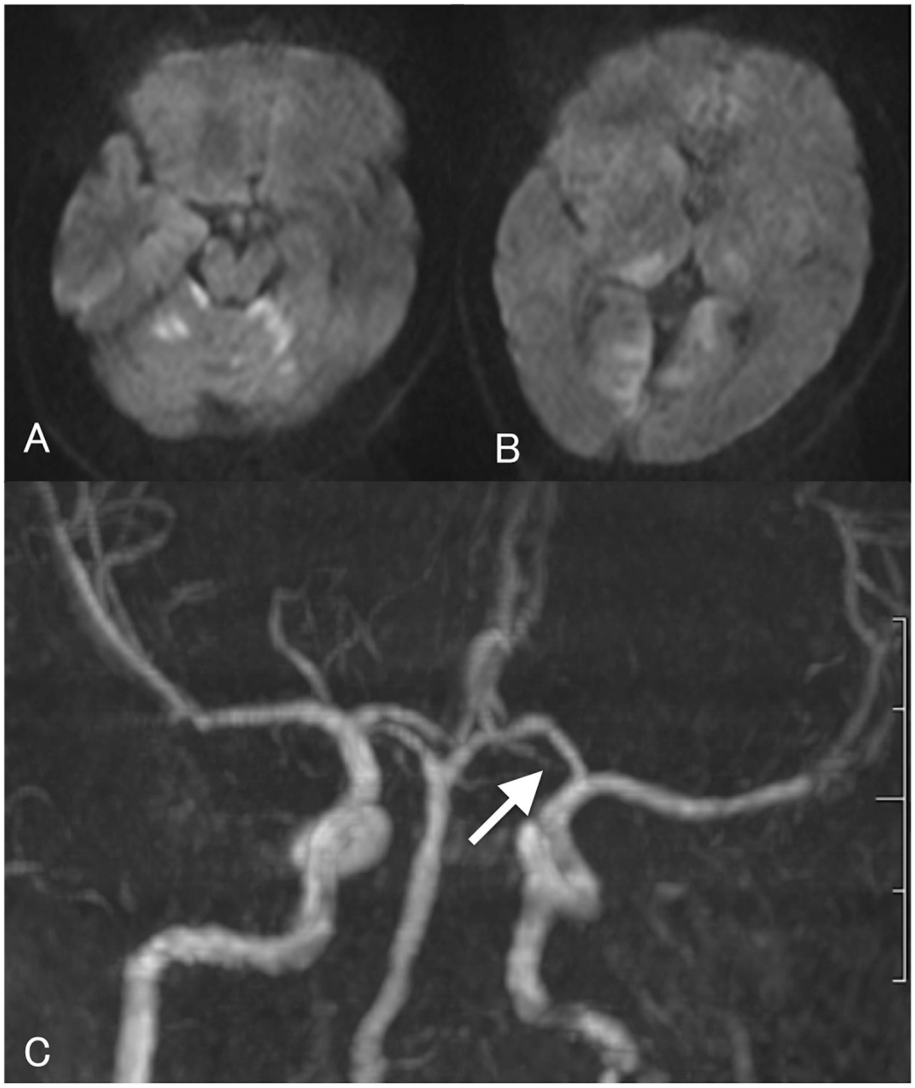

Fig. 1. Magnetic resonance imaging on admission. A, B: Initial magnetic resonance diffusion-weighed imaging shows a slightly high-intensity area in both sides of the occipital lobe, thalamus, cerebellum, midbrain, and pons. C: Magnetic resonance angiography shows left posterior cerebral artery occlusion (arrow).

Table 1
Laboratory test resutls on Day 1, 3, and 131

	Normal range	Day 1	Day 3	Day 131
Hemoglobin (g/dL)		14.1		14.1
Hematocrit		41.7%		40.9%
RBC (10^4/μL)		446		457
Platelet (10^4/μL)		23.6		21.0
PT-INR		0.87		1.97
APTT (sec)	24.3–38.9		25.3	45.9
D-dimer (μg/mL)		0.2		0.2
AT-III (mg/dL)	70%–130%		69.8%	30.0
Protein C activity	64%–135%		85%	
Protein S activity	60%–127%		78%	
aCL (GPL)	< 10.0		11.0	6.0
b2GPI (U/mL)	< 3.5		1.0	< 0.7
LA (dRVVT)	< 1.2		1.0	1.0
aPS/PT (U/mL)				> 200
Complement activity (CH50) (U/mL)	29.0–48.0		17.3	25.3
C3 (mg/dL)	65–135			62
C4 (mg/dL)	13–35			9

RBC indicates red blood cells; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; AT-III, antithrombin-III; aCL, anti-cardiolipin; b2GPI, anti-beta2-glycoprotein I; LA, lupus anticoagulant; dRVVT, dilute Russel's viper venom time; aPS/PT, anti-phosphatidylserine/prothrombin; and CH50, 50% hemolytic complement activity.

that aPS/PT complex antibody, but not aPT antibody, was a risk factor for both arterial and venous thrombosis with an odds ratio of 5.11 (95% confidence interval, 4.2 to 6.3) [3]. Although these studies include patients who meet the criteria for APS, these findings support our thought that aPS/PT antibody may be one of the causes of ischemic stroke in the current case.

Oral contraceptive is also known to be an independent risk factor for thromboembolic diseases including ischemic stroke. In a 15-year Danish historical cohort study, ethinyl estradiol with doses with 30 to 40 μg, which are approved doses in Japan, was reported to be associated with ischemic stroke with a relative risk of 1.75 (95% confidence interval [CI], 1.61 to 1.92) [4]. In a multicenter population-based case-control study, the odds ratio for ischemic stroke in patients with LA was 43.1 (95% CI, 12.2–152.0), which increased to 201.0 (95% CI: 22.1–1828.0) in women with LA who used oral contraceptives [9]. Currently, a “second-hit” is thought to be required for development of thromboembolic diseases in APS patients [10]. These findings support our thought that the beginning of oral contraceptive promoted the potential risk that aPS/PT antibody may cause ischemic stroke.

In this current case, we selected an anticoagulant therapy as an antithrombotic therapy for secondary prevention. The reasons are as follows. First, although the transesophageal echocardiography did not reveal right-to-left shunt, the patient had deep venous thrombosis in

right external iliac vein. Second, repeated MRA revealed the vessel recanalization, which suggested embolic stroke mechanism. Third, we suspected the current case as having APS. Because of these 3 reasons, we thought that antiplatelet therapy was insufficient to prevent recurrent ischemic stroke and pulmonary thromboembolism.

Apart from the above, several limitations should also be noted. First, prolonged APTT found on day 131 could be due to vitamin K antagonist. However, it could be also due to “occult” LA. Second, we only tested for LA with diluted Russell's viper venom time, but did not test with other methods including cross mixing test. Insufficient LA testing could be the reason for “occult” LA. Third, although serum IgG aPS/PT complex antibody level was markedly elevated, it was only determined once 131 days after the ischemic stroke.

We recommend analyzing laboratory tests for APS including aPS/PT complex antibody in a young stroke patient, especially if the patient has some other characteristics of APS including prolonged APTT, decreased serum hemolytic complement activity, decreased platelet count, and deep vein thrombosis, even if the patient has other known risk factors for stroke. We also recommend analyzing these tests for APS before beginning of oral contraceptives.

Disclosure statement

We report no disclosure associated with this report.

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