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Possible episodes that trigger thrombotic events in patients with antiphospholipid syndrome

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Abstract The presence of antiphospholipid antibodies and/or lupus anticoagulant (LA) increase the risk of thrombosis, while the onset of thrombosis is usually sudden. The objective of this study was to determine whether or not some episodes triggered thrombotic events in patients possessing antiphospholipid antibodies. Fifteen patients who presented with thrombosis (primary antiphospholipid syndrome (APS), six cases; secondary APS, nine cases) were retrospectively examined to discover whether or not any specific episodes occurred prior to a total of 21 thrombotic events. In five events occurring in five female patients, specific episodes were identified, including the wearing of tight underwear, dehydration due to fever and standing in hot and humid weather, fever following the extraction of a carious tooth, steroid pulse therapy, toxemia during pregnancy, and intrauterine fetal death. To prevent the occurrence of thrombosis in patients possessing antiphospholipid antibodies, it appears to be important to avoid such triggering episodes and also to reduce the risk factors for thrombosis.

Key words Antiphospholipid syndrome · Thrombosis · Risk factor

Introduction

Thrombosis is one of the characteristic symptoms of antiphospholipid syndrome (APS). The presence of antiphospholipid antibodies and/or lupus anticoagulant (LA) increases the risk of thrombosis, while the onset of thrombosis is usually sudden.

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Asherson reported that some factors tend to cause patients with "simple" APS to suddenly develop "catastrophic APS." These factors include surgical procedures, various medications (sulphur-containing diuretics, captoril, oral contraceptive therapy), anticoagulation withdrawal, and infections.[1] Regarding the thrombotic event(s) that were noted even in "simple" APS patients or those possessing antiphospholipid antibodies and/or LA, various episodes might trigger thrombotic events, while some factors other than antiphospholipid antibodies might also increase the risk of developing such events. Triplett et al. reported that APS patients often have multiple "hits" or triggering factors (e.g., pregnancy, oral contraception, infections, etc.) which increase the chances of developing thrombotic events.[2,3]

In this study, we retrospectively examined APS patients to determine whether or not certain episodes might have triggered the thrombotic events, or whether some factors other than antiphospholipid antibodies augmented the risk of such events in the patients. Such information should be helpful in reducing the frequency of thrombosis in patients possessing antiphospholipid antibodies.

Patients and methods

Fifteen patients who presented with thrombosis (primary APS, six cases; secondary APS, nine cases; M:F = 3:12; Table 1) were retrospectively examined in order to clarify whether or not any specific episodes had occurred prior to a total of 21 thrombotic events.

IgG-anti-CL antibodies and IgG anti-CLβ2GPI antibodies were detected using ELISA kits (the MESACUP cardiolipin test, MBL, and anti-CLβ2GPI kit, Yamasa Shoyu, respectively). The cut-off value for the MESACUP cardiolipin test was 10 U/ml, and that for the anti-CLβ2GPI kit was 3.5 U/ml. LA was screened by the prolongation of the activated partial thromboplastin time, and was confirmed by either the platelet neutralization procedure, the phospholipid neutralization method, or the cross-mixing test.

Table 1. Characteristics of the thromboses in 15 patients with APS and/or SLE

Patient No.	Sex	Diagnosis	Times of thrombosis	Age at the thrombosis	Thrombosis
1	F	Primary APS	3	27, 33, 39	Subclavian A/T, DVT (2)
2	F	Primary APS	1	32	MCA/T
3	F	Primary APS	1	64	ICA/T
4	F	Evans' synd. +SLE + APS	1	30	Frontoparietal CI
5	F	SLE + APS	1	28	Middle pons CI
6	F	SLE + APS	1	39	Midbrain CI
7	F	SLE + APS	1	38	Multiple small CI[a]
8	F	Primary APS	2	39, 43	Retinal V/T, small CI
9	M	SLE + APS	3	29, 31	Cerebellar I, DVT (2)
10	M	SLE + APS	1	27	DVT
11	F	SLE + APS	2	56	ACA/T, small Ce/I
12	M	SLE + APS	2	27, 32	Budd–Chiari synd.
13	F	Primary APS	1	49	Retinal V/T, multiple small CI
14	F	Primary APS	1	59	Spinal A/T
15	F	SLE + APS	1	56	Multiple small CI

A/T, arterial thrombosis; DVT, deep vein thrombosis; MCA, middle cerebral artery; ICA, internal carotid artery; CI, cerebral infarction; Ce/I, cerebellar infarction; synd., syndrome

[a] Multiple small infarctions that were noted by MRI and counted as one episode of thrombosis

Table 2. Possible triggering episode(s) of thrombosis and smoking habit in each patient

Patient No.	Stasis of the venous flow	Fever/dehydration	Extraction of a carious tooth	Steroid pulse therapy	Pregnancy toxemia and intrauterine fetal death	Smoking
1	Pos.	(−)	(−)	(−)	(−)	(−)
2	(−)	Pos.	(−)	(−)	(−)	20 cig. × 15 Y
3	(−)	(−)	Pos.	(−)	(−)	(−)
4	(−)	(−)	(−)	Pos.	(−)	(−)
5	(−)	(−)	(−)	(−)	Pos.	(−)
6	(−)	(−)	(−)	(−)	(−)	(−)
7	(−)	(−)	(−)	(−)	(−)	(−)
8	(−)	(−)	(−)	(−)	(−)	(−)
9	(−)	(−)	(−)	(−)	(−)	8 cig. × 10 Y
10	(−)	(−)	(−)	(−)	(−)	(−)
11	(−)	(−)	(−)	(−)	(−)	(−)
12	(−)	(−)	(−)	(−)	(−)	(−)
13	(−)	(−)	(−)	(−)	(−)	(−)
14	(−)	(−)	(−)	(−)	(−)	(−)
15	(−)	(−)	(−)	(−)	(−)	(−)

A specific episode in patient No. 1 was described before the onset of the third time of thrombosis
cig, cigarettes; Y, years; Pos., positive; (−), negative

Results

In five events occurring in five female patients (Patients Nos. 1–5 in Table 2), specific episodes were observed that might have provoked and/or could be closely associated with the onset of thrombosis. The possible episode(s) that might trigger thrombotic events in each patient are summarized below.

Case 1

A 39-year-old woman first experienced an itchy sensation, pain, and Raynaud's phenomenon in her left hand at 27 years of age. Thereafter, the left radial artery gradually became undetectable. Six years later, she suddenly developed swelling in the left leg and pain in the lower left abdomen and thereafter was admitted to our department. Left ascending phlebography showed an occlusion of the external iliac vein, and arteriography revealed an obstruction in the left subclavian artery. She was diagnosed as having primary antiphospholipid syndrome. She was successfully treated with heparin, platelet agglutination inhibitors, anticoagulants, and steroids. We have reported her clinical course in detail elsewhere.[4] After being discharged, she was followed up at our outpatient clinic. She was treated with 81 mg/day aspirin and 1800 mg/day ethyl icosapentate for the prevention of thrombosis.

About 6 years after first presenting, she wore a tight new girdle for about 10 h. She later noticed swelling with pain in her left leg that continued even after she took the girdle off. She had not discontinued her medication. She was readmitted to our ward because the symptoms lasted for 7 days. Her left leg was swollen and painful. Homans' sign and

Table 3. Laboratory data for the patients

Patient No.	ANA	Anti-CL (IU/ml)	Anti-CLβ2GPI (IU/ml)	Anti-DNA (IU/ml)	APTT (s (cont.))	LA	Plt ($\times 10^4/\mu l$)	TAT[a] (ng/ml)	T.Chol (mg/dl)	HDL-C (mg/dl)
1	1:640	<8	16	1	56.8 (34.4)	Pos.	13.4	ND	114	39.3
2	1:80	<8	29.7	6	83.3 (33.1)	Pos.	12.7	ND	160	55.4
3	1:640	<8	11.6	<1	117.5 (29.6)	Pos.	13.6	8.1	115	26.5
4	1:80	25	<3.5	4	41.2 (31.2)	Pos.	0.5	ND	251	49
5	1:80	25	<3.5	<1	34.0 (32.2)	Pos.	13.3	8.2	187	42

LA, lupus anticoagulant; TAT, thrombin antithrombin complex; ND, not done
[a]The cut-off value of TAT is 3.0 ng/ml

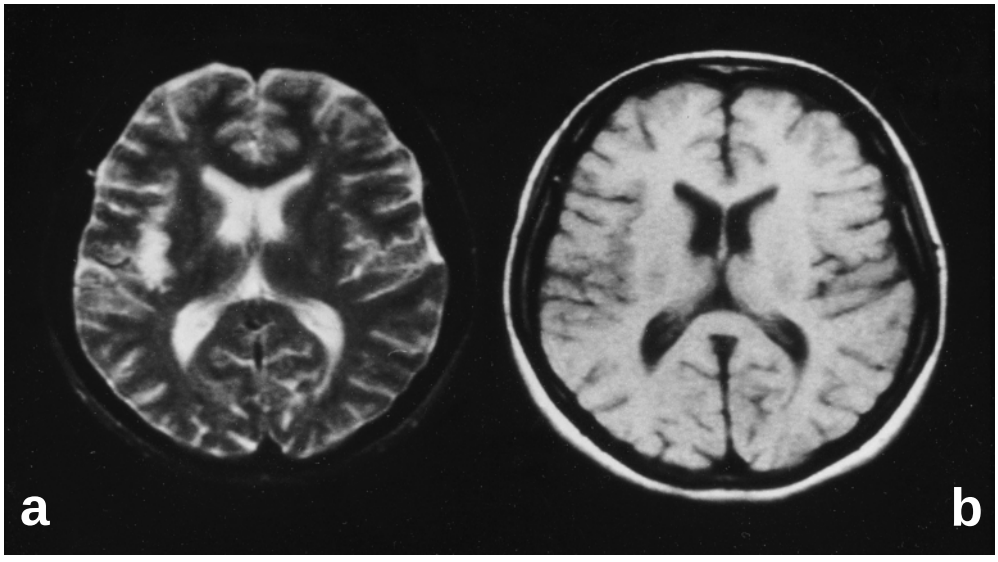

Fig. 1. Transaxial MR images in case 2, 7 days after the onset of cerebral infarction. **a** T2-weighted image shows a high intensity area at the left putamen. **b** T1-weighted image shows a low intensity area in the same place

Lowenburg's test on the leg were both positive. From these clinical symptoms, a diagnosis of reappearance of deep vein thrombosis was made. The laboratory data on admission are given in Table 3. Heparin at a dose of 15 000 U/day was administered continuously, and this successfully ameliorated the symptoms.

Case 2

A 32-year-old female patient was admitted to our hospital because of right hemiplegia and aphasia. Nine days before this presentation, she developed symptoms of a common cold, including a fever of up to 38.5°C. Seven days earlier, while standing and waiting for a train in hot and humid weather, she unconsciously dropped her bag several times and felt hypesthesia in her right hand. She had a 15-year history of smoking (see Table 1). Brain magnetic resonance (MR) images revealed an infarction involving the left putamen (Fig. 1).

Case 3

A 64-year-old female patient had been admitted to our hospital a total of four times because of Adam–Stokes syncope due to paroxysmal ventricular tachycardia at 48, 49, 50, and 51 years of age.

She was again admitted because of aphasia and right hemiparesis. Two weeks earlier, she had had a tooth extracted. Since then, symptoms of fever, headache, and muscle weakness in her right arm gradually developed. On day 0, a family member found the patient collapsed on the floor and an ambulance was immediately called to take her to hospital. She had been taking Bepridil-HCl (300 mg/day) for the prevention of paroxysmal ventricular tachycardia for 15 months before admission. She had never discontinued that medication. Her pulse was regular on admission (Table 4). Angiography showed the left internal carotid artery to be occluded at the bifurcation (data not shown).

Case 4

A 30-year-old female patient was admitted to our hospital because of bleeding from the gums, lips, and palpebra. Six months before admission, when she was six months pregnant, she began to suffer from nasal and gingival bleeding. She gave birth normally, but thereafter, the bleeding symptoms worsened and she was admitted 2 weeks after giving

Table 4. Vital signs and complications in patients 1–5 on admission

Patient No.	Blood pressure (mmHg)	Heart rate (/min)	Body temperature (°C)	Diabetes mellitus	Arrhythmia	Thrombus in cardiac chambers
1	108/70	78	35.7	(−)	(−)	(−)
2	150/98	90	36.8[a]	(−)	(−)	(−)
3	134/70	72	36.8	(−)	(−)	(−)
4	128/88	72	37	(−)	(−)	(−)
5[b]	150/100	82	36.7	(−)	(−)	(−)

[a] 38.5°C for 2 days before the onset of cerebral infarction
[b] Data obtained 13 days after admission when the patient was transferred from the obstetrics ward to the internal medicine ward

birth. On admission, her platelet count was only 5000/μl. She was diagnosed as having SLE and Evans' syndrome autoimmune (autoimmune thrombocytopenic purpura + autoimmune hemolytic anemia). Methylprednisolone pulse therapy (1 g/day for 3 consecutive days) was performed. Immediately after starting that therapy, she suffered left hemiparesis. Computed tomography (CT) scan findings demonstrated a low-density area extending from the right posterior part of the frontal lobe to the parietal lobe (data not shown). Additional laboratory examinations revealed that the patient also had APS (Table 3).

Case 5

Elsewhere,[5] we reported the details of a 28-year-old pregnant female patient with lupus anticoagulant positive systemic lupus erythematosus (SLE) complicated by intrauterine fetal death, eclampsia, and brain stem damage. Here, we briefly describe her triggering episodes.

She had suffered from SLE for 19 years and had a history of spontaneous abortion. At the age of 28 she again conceived a child. During the first and second trimesters, she showed no signs of organization gestosis nor any active symptoms of SLE. During the 28th week of pregnancy, she suddenly showed the symptoms of pregnancy toxemia and intrauterine fetal death. Labor induction with amniotomy and continuous administration of prostaglandin was attempted immediately. Ten hours after the beginning of the induction, she had several sets of convulsions. A dead male fetus was delivered. Further complications included consciousness disturbance, left-dominant bilateral paresis, and hypesthesia. Brain CT scan findings showed multiple middle pons infarctions.

Laboratory data, vital signs and complications for patients Nos. 1–5 are summarized in Tables 3 and 4, respectively.

Discussion

Many acquired risk factors for arterial thrombosis, such as ischemic heart disease, have been reported, including hyperlipidemia, diabetes mellitus, hypertension, and smoking. These factors tend to induce atherosclerotic changes, e.g., atheromatous plaque. Various episodes, including normal daily activities[7] and mental stress,[8] can trigger a thrombotic event. Muller et al.[7] described the mechanism by which daily activities trigger coronary thrombosis as follows: (1) physical or mental stress produces hemodynamic changes leading to plaque rupture; (2) these changes also cause increased coagulability; (3) various other stimuli can also lead to vasoconstriction.

With respect to venous thrombosis, various risk factors have been reported,[9] such as: (1) stasis of the venous blood flow as the result of a bedridden state, a post-surgical state, pregnancy, or iliac compression syndrome; (2) abnormalities in the venous vessel walls, including phlebitis, trauma, injection, and an indwelling venous catheter; (3) hypercoagulability, including infection, malignancy, oral contraceptives, pregnancy, dehydration, polycytemia, protein C deficiency, protein S deficiency, and the presence of antiphospholipid antibodies. One of these risk factors alone can trigger venous thrombosis, but if a patient has two or more such factors, the risk of thrombosis greatly increases.

It has yet to be proven that antiphospholipid antibodies play a causal role in the pathogenesis of APS, but some studies have revealed these antibodies to be closely associated with an increased risk of thrombosis. It has been suggested that various molecular mechanisms of these antibodies might directly provoke thrombosis, e.g., the inhibition of prostacyclin production and release by endothelial cells,[10] the inhibition of the heparan sulfate function,[11] and the enhancement of β2GPI binding to phospholipids.[12] In addition, some SLE and/or APS patients have other risk factors for thrombosis in addition to antiphospholipid antibodies, such as reduced concentrations of antithrombin III, plasminogen, and free protein S and protein C,[13] as well as elevated concentrations of fibrinopeptide 20A and thromboxane B2.[14]

In the present study, 24% of the thrombotic events observed in patients possessing antiphospholipid antibodies were preceded by some specific episode(s) (see Table 2). The wearing of a tight girdle in case 1 might have caused "artificial" iliac compression syndrome.[15] In case 2, there is the possibility that dehydration[16] due to fever and standing in hot and humid weather had increased blood coagulability. This patient also had another risk for thrombosis, namely a 15-year history of smoking (see Table 1). The blood coagulant pathway is activated in cigarette smokers.[17] In case 3, dehydration due to fever and/or transient bacteremia[18] following the extraction of a carious tooth might

have provoked hypercoagulability. The high-density lipoprotein-cholesterol (HDL-C) of this patient had also decreased considerably (see Table 3). Lahita et al.[19] described an association between antibody against cardiolipin and low levels of HDL-C. In case 4, steroid pulse therapy might have increased the blood coagulability. Wysenbeek et al.[20] reported an SLE patient who developed cerebral infarction during steroid pulse therapy. Case 4 was also in puerperium, which might also be related to the pathogenesis of her thrombosis.[21] In case 5, potent thrombogenic stimuli due to pregnancy toxemia and intrauterine fetal death might have provoked multiple middle pons infarctions. In ordinary disseminated intravascular coagulation (DIC), the deposition of small thrombi and emboli throughout the microvasculature have been noted.[22] Patient No. 5 also had antiphospholipid antibodies, which might have induced the multiple middle pons infarction.

To prevent the occurrence of thrombosis in patients possessing antiphospholipid antibodies, it appears to be important either to avoid these potentially triggering episodes or to reduce the risk factors for thrombosis, such as smoking.[23] When it is not possible to do so, special care should be taken to prevent the (re)appearance of thrombosis.

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