Antiphospholipid syndrome may induce non-thrombus internal jugular vein stenosis - Two cases report and literature review

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Case report

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Abstract

Background: Antiphospholipid syndrome (APS) is associated with artery or venous thrombosis. However, non-thrombus venous stenosis is rarely reported.

Case presentation: This study described two young women with APS-related internal jugular vein stenosis (IJVS) and reviewed current literatures on this issue, including clinical features, diagnosis and treatment.

Conclusions: IJVS is a rather rare complication of APS. This is first report of non-thrombus venous stenosis resulted from aPL mediated vessel wall damage. High titer of aPL could induce stenosis without thrombosis formation due to long-term standardized anticoagulation. Follow-up of autoantibodies are necessary to be done dynamically. Treatment for patients with IJVS of autoimmune etiology should be concomitant use of anticoagulants and steroids.

Background

Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis in young adults with persistent laboratory evidence of high titer of antiphospholipid antibodies (aPL)[1–3]. However, APS induced cerebral venous damage may present various entities, such as thrombosis and non-thrombus venous stenosis. Herein, we reported two cases of APS with non-thrombus internal jugular vein stenosis (IJVS) inducing intracranial hyper-pressure. We presumed that APS might trigger autoimmune inflammatory damage, leading to edema and thickening of the venous wall, and eventually resulting in non-thrombus IJVS. However, there was no thrombus formation in IJV during long term standardized anticoagulation of these two patients. To our knowledge, this is the first report about this issue up to now. We believed this report can provide an important reference for physicians.

Case Presentation

Case 1

A 33-year-old woman complained of a history of five-year worsening blurry vision, intermittent headache on temporal regions and nocturnal bilateral tinnitus. She also reported progressive memory loss for six months on the day of presentation. There was no history of nausea and vomiting, no weakness or sensory symptoms in the face and limbs, no sphincter incontinence and loss of consciousness or seizures. Comorbid medical issues included a 5-year history of APS (confirmed primary APS at Beijing Union Hospital) and deep vein thrombosis (DVT) in the left leg. From then on, she underwent corticosteroid for one year combined with continuously standardized anticoagulation till this admission. She denied the family history of thrombotic diseases. On physical examination, her body temperature was 37.0°C, blood pressure was 128/78mmHg, heart rate was 79 beats/minute and respiratory rate was 20 breath/minute. Her Body mass index (BMI) was 31.1. No focal neurological signs were found.

Both the platelet count ($373 \times 10^9/L$) and plateletcrit (0.36%) were above the normal-cutoff levels in her baseline peripheral blood test. Protein C exceeded the normal upper limit (155%) a little. Other items related to coagulation showed no positive significance. All the results of serological tests including aPL, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and complements C3 and C4 were negative. The lumbar puncture opening pressure was 250 mmH₂O with a normal cerebrospinal fluid profile. Funduscopy examination revealed bilateral optic disc edema (Frisén score = 2).

Color Doppler ultrasound revealed venous valve insufficiency involving bilateral common femoral veins, right deep femoral vein and left superficial femoral vein. Transcranial Doppler (TCD) and Carotid ultrasound showed no abnormalities. However, jugular vein ultrasound revealed a small diameter in the upper segment (J3) of the right IJV with decreased flow volume (Table 1). Contrast-enhanced magnetic resonance venography (CE-MRV) of brain and neck identified the stenosis located at left transverse sigmoid sinus junction (Figure 1: a, b) and the upper segment (J3) of the left IJV (Figure 1: c, d). No thrombus was found in either cerebral venous sinus or IJV in the Black-blood thrombus image (BBTI) (Figure 2). Digital subtraction angiography (DSA) further confirmed severe non-thrombus stenosis in left IJV. All the aforementioned symptoms and signs attenuated after her undergoing 14 days of corticosteroid (25mg/day of oral prednisone) treatment. Her standardized anticoagulation (20 mg of oral rivaroxaban daily) was continued.

Case 2

A 32-year-old woman presented with two-week progressively aggravated pains in her head and neck accompanied by nausea and vomiting, and three-days of visual disorder (double vision) after she was recovered from pneumonitis. She once had similar symptoms two years ago. Her lumbar puncture opening pressure (LPOP) was 330 mmH₂O at that time measured in a local hospital, and she was diagnosed as idiopathic intracranial hypertension (ICH) and underwent mannitol and corticosteroid. Her intracranial pressure (ICP) was decreased to 150 mmH₂O at lumbar puncture follow-up before discharge. However, two weeks prior to this admission, her symptoms reappeared. Her LPOP was over 400 mmH₂O at local hospital. Mannitol could not attenuate her symptoms.

On this admission, she presented with severe headache in a spasmodic manner, especially on the left, accompanied by persistent nausea, sometimes, vomiting undigested food. She also described the impaired vision, such as objects being blurry and doubled horizontally. Ophthalmologic examination revealed papilledema (Frisén score = 4) with small local bleeding spots. Her vital signs were as follows: body temperature, 36.5°C; blood pressure, 115/68mmHg; heart rate, 78 beats/minute; and respiratory rate, 20 breath/minute. Her BMI was 20.1. Neurological examination revealed partially left abduces palsy.

Peripheral blood and cerebral spinal fluid examination results were summarized in Supplementary Table 1. Dynamic changes of abnormal laboratory results were shown in Figure 3. Platelet count decreased dramatically to $39 \times 10^9/L$ on the first day and was gradually back to normal level in one week. The

activated partial thromboplastin time (APTT) was 80.3 seconds (normal range: 25–43.5 sec). Protein S was lower than the normal lower limit (35%). The level of serum IgG increased (16.7 g/L), while the levels of serum complements C3 and C4 were below normal ranges (C3: 0.79–1.52; C4: 0.16–0.38). Anti- β 2-glycoprotein 1 (anti- β 2GPI) antibody (50.0 RU/mL) was positive significance (normal range: 0.0–20.0 RU/mL). ANA and ANCA were negative. In terms of neuroimaging, we confirmed the left IJV stenosis and excluded both arterial and venous thrombosis via computed tomography venography (Figure 4) and BBTI (Figure 5: a, b). She underwent oral rivaroxaban 10mg/day after admission. A lumbar puncture followed up after the platelet count turned to normal showed that ICP was more than 330 mmH₂O (three weeks after onset). Finally, local stenosis at J3-segment of left IJV was confirmed by DSA and corrected by stenting (Figure 5: c, d). The headache and visual disorder mitigated immediately after stenting, whereas, LPOP was still more than 330 mmH₂O. She then underwent rivaroxaban 10 mg/day combined with prednisone 30mg/day. The dose of prednisone was gradually reduced to 5mg/day afterward.

About one month after admission (two months after onset), the patient presented with diarrhea for four days. She reported headaches and double vision were not as severe as before. Follow-up BBTI could not find thrombus (Figure 5: e, f). ICP detected by lumbar puncture was 210 mmH₂O. Immunological tests revealed constantly positive anti- β 2GPI antibodies (47 RU/mL) and low titers of serum complements C3 and C4. As every onset of high ICP is associated with infection and high titers of immunological items, we presumed that the stenosis may result from autoimmune-mediated inflammation. In a repeated serological test, anti- β 2GPI antibodies were still positive while ANA turned positive for the first time (1:320). A confirmatory diagnosis was made as primary APS. She then underwent immunomodulatory therapy with prednisone at 5mg/day and hydroxychloroquine at 5mg bid as well as rivaroxaban at 10 mg/day and aspirin 100mg/day to prevent thrombi formation.

Six months of outpatient neuroimaging follow-up including CT, BBTI, CE-MRV, DWI, TCD, and carotid ultrasound) showed no abnormalities in both cerebral arteries and veins (Figure 5: g, h). No CVST and/ or IJV thrombus was found. Former symptoms of headache and diplopia were no longer reported. The APTT decreased to 48.5 seconds. Levels of serum complements C3 and C4 remained lower than the normal range. The clinical course was summarized in Figure 3.

Discussion

Our previous work demonstrated that the etiologies of IJVS included non-thrombus and non-osseous compressive entities, such as venous wall lesion[4]. It is well known that venous thrombosis is the most common complication of APS[4]. To our knowledge, this study reported non-thrombus IJVS as a complication of APS for the first time. Whereby, this report is of great significance to understand the relationship between IJVS and APS.

With regard to the pathogenesis of APS, recent studies indicated that most aPL was directly targeted at phospholipid-binding proteins[2]. Although aPL is a heterogeneous group of antibodies, anti- β 2GPI antibodies play a central role in the development of APS. They recognize β 2GPI on the surface of

endothelial cells and immobilized platelets, then leading to cellular activation and expression of procoagulant activity[5]. Furthermore, the effect of lupus anticoagulants (LA) is also realized through β 2GPI or anti- β 2GPI antibodies[6, 7]. Anti- β 2GPI antibodies are associated with a higher risk of thrombosis than anticardiolipin (aCL) or anti-prothrombin antibodies[6, 7]. Other mechanisms implicate that aPL is also related to interfering with the function of coagulation factors[8–10] and complement-mediated neutrophil activation[11, 12]. In sum, the interaction between aPL and endothelial cells, coagulation cascade (primary and secondary), and inflammatory cells could result in vessel wall lesions, contributing to thrombosis and/or stenosis.

The evaluation of thrombotic risk in patients with APS was usually based on the level of plasma aPL[13], however, some patients with previously positive aPL profile would turn negative, which then became a challenge for the physicians to evaluate the thrombotic risk. Besides, Bazzan et al found that despite appropriate anticoagulant treatment, the thrombotic recurrence rate in APS has been reported as high as 7.5/100 patient-years in the first 5 years after the first thrombotic event[14]. Nevertheless, sometimes there are exceptions, such as the case–2 in this study, whose aPL levels were in a persistently moderate titer (>40 RU/mL) but without thrombotic event recurrence. Based on the clinical processes of the two cases, we speculated that this exception might be due to their long-term preventive anticoagulation. Although standardized anticoagulation successfully prevented thrombosis formation, the risk of non-thrombosis IJVS, which might result from irreversible immune damages of vascular endothelium caused by aPL, was still existed. Then, IJVS might lead to ICH.

Compared with case–1, case–2 did not receive corticosteroid for APS intervention before referred to our department. And her persistent moderate level of anti- β 2GPI antibodies could cause more severe damage to the vessel wall, which might explain her symptoms recurrence and refractory high ICP.

A combination of anti-Xa inhibitor (rivaroxaban) and corticosteroid (prednisolone) was prescribed to the two patients. A previous study indicated that stenting was a promising therapeutic option for focal stenosis of IJV[4]. However, we did not perform stenting/balloon angioplasty in case 1, as her stenosis of IJV was moderate, and the risk of stenosis aggravation was lower under her stable low titer of aPL.

There is still controversy on the choice of anticoagulation. The vitamin K antagonist (VKA), most commonly warfarin, is widely used for APS–mediated thrombus [2]. Whereas, VKA has many limitations in practical use, such as its interaction with food and drug, bleeding complications and need for frequent monitoring. Moreover, aPL may affect thromboplastin reagents, tending to affect the international normalized ratio measurement. Rivaroxaban is an effective and safe alternative to warfarin in patients with atrial fibrillation and venous thromboembolism. However, a prospective randomized trial evaluated the efficacy of rivaroxaban (20mg/day) in high-risk APS patients (with triple aPL-positive level), which showed that rivaroxaban was associated with an increased arterial thrombotic risk of events compared with warfarin (www.clinicaltrials.gov; NCT02157272)[15]. A suboptimal drug concentration may account for the thromboembolic complications during this trial. Therefore, we prescribed rivaroxaban at its relatively low dose (20mg/day) to test the optimal dose for the patient with negative aPL. Although her

symptoms improved, long-term outcome still need to be followed up. Moreover, several studies have shown the benefit of immunosuppressive drugs, especially steroids. Rodriguez et al discovered that the materno-fetal prognosis could be improved by the addition of low-dose prednisolone during the first trimester of pregnancy in women with APS [16]. Cervera et al summarized the clinical approach to treat catastrophic APS as a combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulins[17]. Sugie et al reported one case of CVST in APS was treated successfully by the combined use of rivaroxaban and prednisolone [18]. However, to avoid deterioration of IJVS and the occurrence of new-onset venous thrombosis due to steroid-induced hypercoagulability, we administered low-dose prednisone (equivalent to 0.35mg/kg and 0.55 mg/kg in case 1 and case 2, respectively).

To sum up, these two cases reminded us that firstly, except for thrombotic events, there was non-thrombus venous stenosis resulted from aPL mediated vessel wall damage. IVJS may be a rare complication of APS, with clinical features similar to high intracranial pressure syndrome. Secondly, high titer of aPL could induce vessel wall damage despite long-term standardized anticoagulation for thrombosis prevention. Thus, follow-up of autoantibodies should be done dynamically. Thirdly, concomitant use of anticoagulants and steroids is suggested as the mainstay therapy. Long-term preventive anticoagulation might only inhibit thrombotic event and corticosteroid might attenuate aPL-mediated venous wall damage. The last but not least, the BBTI was a very useful imaging tool on confirming intravenous thrombus as well as non-thrombus stenosis induced by immune mediated inflammation. A combination of CE-MRV and BBTI may be the first option to identify non-thrombus IJVS precisely and non-invasively, although DSA is still as the golden standard to make a confirmatory diagnosis. We highly suggest future studies could shed more attention on early diagnose and treatment in patients with IJVS of autoimmune etiology.

Conclusion

IJVS is a rather rare complication of APS. This is first report of non-thrombus venous stenosis resulted from aPL mediated vessel wall damage. High titer of aPL could induce stenosis without thrombosis formation due to long-term standardized anticoagulation. Follow-up of autoantibodies are necessary to be done dynamically. Treatment for patients with IJVS of autoimmune etiology should be concomitant use of anticoagulants and steroids.

Declarations

Availability of Data and Materials

The data and materials related to these two cases are available on request to the corresponding author.

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Authors' contributions

MR: manuscript drafting and revision, and study concept and design. S-SY: manuscript drafting and revision, study concept and design, collection, assembly, and interpretation of the data. MR, S-SY, D-YC, RG: manuscript writing and final approval of manuscript. RG and D-YC deeply edited the revised version and contributed critical revision.

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Ethics approval and content to participate

Not applicable

Consent for publication

Not applicable

Competing interests

All authors report no conflicts of interest.

Abbreviations

APS: Antiphospholipid syndrome; IJVS: internal jugular vein stenosis; aPL: antiphospholipid antibodies; BMI: Body mass index; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; TCD: Transcranial Doppler; MRV: magnetic resonance venography; BBTI: Black-blood thrombus image; DSA: Digital subtraction angiography; ICP: intracranial pressure; APTT: activated partial thromboplastin time; LPOP: lumbar puncture opening pressure; aCL: anticardiolipin; VKA: vitamin K antagonist; anti-β2GPI: Anti-β2-glycoprotein-1; IIH: idiopathic intracranial hypertension; ICP: intracranial pressure

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Figures

Figure 1

Magnetic resonance venography images of the head (a, b) and neck (c, d) in Case 1. The red arrow indicates the focal stenosis of internal jugular vein and cerebral vein sinus.

Figure 2

. Non-contrast enhanced (a, c) and contrast enhanced (b, d) black-blood thrombus images of head in Case 1. The red asterisk represents internal jugular vein and the red arrow indicates the focal stenosis.

Figure 3

Dynamic changes of laboratory results and clinical process of the Case 2.

Figure 4

3D-computed tomography venography images (CTV) (a-c) and 3D-CTV (d-f) with bone remodeling of the head and neck in Case 2. 3D-CTV with bone remodeling excluded possibility of IJVS related to bone compression.

Figure 5

. Non-contrast enhanced (a, c, e, g, h) and contrast enhanced (b, d, f) black-blood thrombus images of head in Case 2. Figure 5a and b: on admission; Figure 5c and d: post-stenting at one week; Figure 5e and f: post-stenting at one month; Figure 5g and h: post-stenting at six-month. The stenosis attenuated gradually (the red asterisk represents internal jugular vein and the red arrow indicates the focal stenosis).

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