Journal of the Neurological Sciences xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Neurological antiphospholipid syndrome: Clinical, neuroimaging, and pathological characteristics

De-Sheng Zhu [a], Jue Fu [b], Yue Zhang [c], Shi-Xu Li [c], Guang-Xian Zhang [d], Yang-Tai Guan [c,*], Qiang Dong [a,**]

[a] Department of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, China
[b] Department of Pathology, Fuzhou Medical College of Nanchang University, Fuzhou 344000, China
[c] Department of Neurology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China
[d] Department of Neurology, Thomas Jefferson University, PA 19107, USA

ARTICLE INFO

Article history:
Received 12 July 2014
Received in revised form 24 July 2014
Accepted 4 August 2014
Available online xxxx

Keywords:
Antiphospholipid syndrome
Antiphospholipid antibodies
Clinical features
Neuroimaging
Pathology
Central nervous system

ABSTRACT

Background: Neurological antiphospholipid syndrome (NAPS) is often misdiagnosed or missed. Only limited clinical and neuroimaging information about it is available, and the pathological characteristics was rarely reported before. This study aimed to explore the clinical, neuroimaging, and pathological characteristics of NAPS.
Methods: We performed a retrospective analysis of 51 patients with APS, categorized into NAPS ($n = 16$) and rheumatology antiphospholipid syndrome (RAPS) groups ($n = 35$). Demographics and clinical profile were compared between the two groups, and the neuroimaging and pathological information of NAPS was also analyzed.
Results: The mean age of the NAPS patients, 81.25% of whom were female, was 37.56 ± 12.36 years, and the average duration was 1.32 ± 0.96 years (range = 18 days to 3.5 years). No significant differences in age, sex, disease duration, classification, and comorbidities at baseline were observed between NAPS and RAPS patients ($p > 0.05$). Chief complaint of headache and thromboembolic events was higher in NAPS patients than in RAPS patients ($p < 0.05$). Neuroimaging detected multiple infarcts and demyelination lesions were distributed in subcortical and cortical area asymmetrically. Skin biopsy examination showed small vessel occlusion with inflammatory cells, while brain biopsy examination showed erythrocyte accumulation with some neuron degeneration and local demyelization. Antithrombotic and immunosuppressive therapy proved to be effective.
Conclusion: Headache and thromboembolic events are more common in NAPS than RAPS. Neuroimaging and biopsy examination demonstrated that NAPS is an ischemic cerebrovascular disease caused by vascular stenosis or occlusion. These characteristics might help to reduce the misdiagnosis of NAPS.

1. Introduction

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by the production of antiphospholipid antibodies (aPL), which promote recurrent vascular thrombosis (venous, arterial, and microvascular) and/or pregnancy complications and failure, frequently accompanied by moderate thrombocytopenia [1]. Presence of aPL in serum, including anticardiolipin antibody (aCL), lupus anticoagulant (LA), and anti-β_2 glycoprotein-I antibody (anti-β_2GPI), is a characteristic indicator of APS [2].

The preliminary classification criteria for APS were formulated during a post-conference workshop held on October 10, 1998, in Sapporo, Japan [3]. In 2006, revisions to the classification and diagnostic criteria for APS were proposed in Sydney [2]. The disease is classified into primary antiphospholipid syndrome (PAPS), secondary antiphospholipid syndrome (SAPS), and catastrophic antiphospholipid syndrome (CAPS), a relatively rare subtype [4].

APS, which was first reported by Hughes in 1983 [5], had been reported by doctors specializing in rheumatology, obstetrics and gynecology, and vascular surgery. Some estimates indicate that the incidence of the APS is around five new cases per 100,000 persons per year, and the prevalence is around 40–50 cases per 100,000 persons [1]. Thrombosis is one of the prominent clinical features of APS. According to an observational study of 1000 APS patients in 13 European countries, thrombotic events appeared in 166 (16.6%) patients during the first 5-year study period and in 115 (14.4%) during the second 5-year period [6]. APS patients with aCL who suffer from hypertension and hypertriglyceridaemia are at increased risk of arterial thrombosis [7].

Currently, however, literature describing the neuroimaging characteristics of APS is limited, and few studies, both domestically and internationally, have examined the brain biopsies of APS patients. Some studies on the pathological features of APS have been conducted but

* Correspondence to: Y.-T. Guan, Department of Neurology, Changhai Hospital, Second Military Medical University, No. 168, Changhai Road, Shanghai 200433, China. Tel.: +86 13386271865; fax: +86 21 64085875.
** Correspondence to: Q. Dong, Department of Neurology, Huashan Hospital, Fudan University, No. 12, Mid. Wulumuqi Road, Shanghai 200040, China. Tel.: +86 13701747065; fax: +86 21 64085875.
E-mail addresses: yangtaiguan@hotmail.com (Y.-T. Guan), qiangdong-fudan@hotmail.com (Q. Dong).

http://dx.doi.org/10.1016/j.jns.2014.08.010
0022-510X/

only in experimental animals. The main finding from examination of cortical tissue from APS mice was the thrombotic occlusion of capillaries in combination with mild inflammation [8]. One distinct pathological feature of APS appears to be intravascular thrombus formation in all vessels of all levels instead of vasculitis, but this finding cannot be considered a uniform pathological diagnostic criterion. Current treatment guidelines for APS emphasize the importance of early diagnosis and recommend aggressive therapies to alleviate damage to the CNS, especially to prevent recurrence of thrombosis [9–11]. However, the intensity and duration of anticoagulation therapy in APS syndrome have been debated for long [12–14]. Treatment for recurrent thrombosis in APS patients requires further clarification, since pathological studies on APS patients are scarce.

APS often affects the central nervous system (CNS) and causes cerebral infarction, epilepsy, and consciousness disorder or limb dysfunction [15]. Research on rheumatology antiphospholipid syndrome (RAPS) is common; few studies thus far have conducted a detailed investigation of neurological antiphospholipid syndrome (NAPS), and the available information, from clinical features to the imaging and pathological characteristics of NAPS, is limited. Sophisticated neuroimaging techniques, including CT, MRI, DSA, and Doppler ultrasound, would facilitate us a better understanding of NAPS.

The aim of the present study is to explore the clinical features and imaging and pathological characteristics of NAPS via a retrospective analysis of clinical data.

2. Patients and methods

2.1. Patients

We performed a retrospective analysis of all patients with APS from neurology wards and rheumatology wards of Huashan Hospital and Changhai Hospital between January 2008 and December 2013. In this study, 51 patients with APS were enrolled and followed up at least six months, including 16 patients who had symptoms of CNS impairment from neurology wards and 35 patients from rheumatology wards. All patients had been diagnosed with APS on the basis of the criteria proposed in 2006 in Sydney [2]. This study only included APS patients with LA, aCL and anti-β_2GPI antibody of IgG and/or IgM isotype in serum or plasma, on two or more occasions at least 12 weeks apart, measured by an inhibitor of phospholipid-dependent clotting or standardized ELISA according to the criteria.

2.2. Clinical information

Retrospective analyses were performed on the following information: (1) Demographic information (gender, age, disease duration before hospitalization, and medical and pregnancy history); (2) initial symptoms (headache, limbs weakness, cognition disorder, elapse and thrombosis); (3) biochemical indicators (aCL, LA, anti-β_2GPI, antinuclear antibody (ANA), and anti-double-stranded-DNA (dsDNA) and anti-ss-DNA (ssDNA) antibodies; rheumatoid arthritis (RA); complete blood count (CBC); international normalized ratio (INR); prothrombin time (PT); partial prothrombin time (APTT); erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); and findings of cerebrospinal fluid (CSF) examination); (4) neuroimaging (cranial computed tomography (CT); magnetic resonance imaging (MRI); digital subtraction angiography (DSA); echocardiography; and cervical vascular ultrasound); (5) pathological features (brain biopsy and skin biopsy); and (6) therapy (antiplatelet drugs, anticoagulants, glucocorticoids, and immunosuppressive agents).

2.3. Ethics

This study was approved by the institutional review board of Huashan Hospital, Fudan University (Shanghai, China).

2.4. Statistical analysis

Categorical variables were presented as counts and percentages and analyzed by Fisher's exact test or the Chi-square test. Continuous variable was reported as means and standard deviation (normal distribution) and analyzed by the independent-*t*-tests.

Statistical analyses were performed using Statistical Package of the Social Sciences Software version 16.0 (SPSS, Chicago, IL, USA), setting the level of significance at a two-tailed *p*-value of <0.05.

3. Results

3.1. Demographics

The demographic and clinical profiles of the patients are presented in Table 1. The mean age of the NAPS patients, 81.25% of whom were female, was 37.56 ± 12.36 years. The average disease duration of the NAPS patients was 1.32 ± 0.96 years (range = 18 days to 3.5 years). Six patients were accompanied by a history of autoimmune diseases and viral infections (37.5%).

No significant differences in age, sex, disease duration, classification, and comorbidities at baseline were observed between two groups. Chief complaint of headache was higher and limb weakness was lower in NAPS patients than in RAPS patients ($p < 0.05$). NAPS patients showed more thromboembolic events than RAPS patients ($p < 0.01$). Misdiagnosis before confirm was higher in NAPS patients than in RAPS patients ($p < 0.01$).

3.2. Clinical manifestations, thromboembolic events and laboratory analysis

Data of NAPS patients on the initial symptoms, thromboembolic events, and results of laboratory tests are presented in Table 2. The most common initial symptoms were headache, and limb weakness. Clinical manifestations of NAPS patients during the course were complex and varied. The incidence of headache and that of cerebral infarction were ranked in the first and second respectively in this study, which was different with foreign literature. A comparison of the incidence of clinical manifestations between our study and that reported in foreign literature is presented in Table 3 [6–10].

Laboratory analysis of NAPS patients showed that one patient was rheumatoid factor positive, two patients were dsDNA and ssDNA antibody positive, and one patient was anti-smooth muscle antibody positive. CRP and ESR were higher than normal in two patients. CBC showed that the platelet count was lower than normal in five patients (31.25%). CSF examination showed that the CSF pressure was higher in three patients (37.5%), and that the erythrocyte count was higher

Table 1
Demographics and clinical profile of the study objects.

Information	NAPS ($n = 16$)	RAPS ($n = 35$)	*P*-value
Age (years)	37.56 ± 12.36	40.57 ± 7.28	0.377
Sex (male/female)	3/13	7/28	1.000
Disease duration (years)	1.32 ± 0.96	2.04 ± 1.35	0.061
Classification (PAPS/SAPS)	12/4	23/12	0.746
Comorbidities at baseline			
SLE, RA, SS	4 (25%)	12 (34.28%)	0.746
Miscarriages, preeclampsia	3 (18.75%)	5 (14.28%)	0.694
Herpes zoster, viral influenza	2 (12.5%)	5 (14.28%)	1.000
Chief complaint			
Headache	8 (50%)	7 (20%)	0.029
Limb weakness	6 (33.33%)	25 (71.43%)	0.021
Thromboembolic events	12 (75%)	8 (22.86%)	0.001
Misdiagnosis before confirm	14 (87.50%)	6 (17.14%)	0.000

NAPS: neurological antiphospholipid syndrome, RAPS: rheumatology antiphospholipid syndrome.

Please cite this article as: Zhu D-S, et al, Neurological antiphospholipid syndrome: Clinical, neuroimaging, and pathological characteristics, J Neurol Sci (2014), http://dx.doi.org/10.1016/j.jns.2014.08.010