Evaluation of Regional Cerebral Blood Flow with ^{99m}Tc-HMPAO in Primary Antiphospholipid Antibody Syndrome

Chia-Hung Kao, Jung-Liang Lan, Jih-Fang Hsieh, Yung-Jen Ho, Sheng-Ping ChangLai, Jong-Kang Lee and Hueisch-Jy Ding

Department of Nuclear Medicine and Division of Rheumatology, Taichung Veterans General Hospital, Taichung; Department of Nuclear Medicine, Chi-Mei Foundation Hospital, Tainan; Department of Radiology, Jen-Ai Hospital, Taichung; Department of Nuclear Medicine, Chung-Shan Medical and Dental College and Hospital, Taichung; Department of Nuclear Medicine and School of Technology for Medical Sciences, Kaohsiung Medical College, Kaohsiung, Taiwan

In this study, ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT was used to evaluate the regional cerebral blood flow (rCBF) of the brain in patients with primary antiphospholipid antibody syndrome (PAPS). **Methods:** Twenty-two women who were PAPS patients, aged 28–60 y, with mild neuropsychiatric manifestations and normal brain MRI findings were enrolled in this study. Brain HMPAO SPECT was performed to detect brain abnormalities. Meanwhile, serum anticardiolipin antibodies (ACA) and lupus anticoagulant (LA) were measured. **Results:** HMPAO SPECT revealed hypoperfusion lesions in 16 of 22 (73%) PAPS patients. Cerebral cortex and cerebellum were the most and the least commonly involved areas, respectively. Eighteen of 22 (82%) and 14 of 22 (64%) patients had positive ACA and positive LA, respectively. ACA and LA results were related to HMPAO SPECT findings. **Conclusion:** HMPAO SPECT is a sensitive tool for detecting brain abnormalities in PAPS patients with only mild neuropsychiatric manifestations and normal brain MRI findings.

Key Words: regional cerebral blood flow; ^{99m}Tc-hexamethyl propyleneamine oxime; antiphospholipid antibody syndrome

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Antiphospholipid antibody syndrome (APS) is a disorder of recurrent vascular thrombosis, pregnancy losses and thrombocytopenia associated with persistently elevated levels of antiphospholipid antibodies (APLs) (*1*). APLs are a heterogeneous group of autoantibodies that recognize various phospholipid and protein complexes and includes anticardiolipin antibodies (ACAs) and lupus anticoagulants (LAs) (*2–5*). Many patients with APS have clinical and laboratory features that are found in other autoimmune diseases, particularly systemic lupus erythematosus (SLE). Some authorities have suggested that such patients be defined as having "secondary" APS to distinguish them from patients with features of APS alone ("primary" APS [PAPS]). APS is a hypercoagulable disorder that can cause arterial thromboses that have a predilection for the brain. Strokes and transient ischemic attacks are the most common thrombotic brain manifestations (*2–5*). However, brain infarction may be silent and mild. Subtle signs of brain disease include headache, cognitive function deficits, personality disorders, depression, memory loss and lowered intelligence testing scores (*2–5*).

Brain MRI has been performed to identify focal lesions in APS patients with severe neuropsychiatric manifestations such as stroke and epilepsy (*6–10*). However, brain SPECT with ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) that is used to assess regional cerebral blood flow (rCBF) has been considered to be more sensitive than MRI for detecting brain abnormalities in patients with different connective tissue diseases and only mild neuropsychiatric manifestations (*11–14*).

No complete reports have been published concerning the application of brain HMPAO SPECT to evaluate rCBF in PAPS patients. Therefore, we used this sensitive brain-imaging technique for detecting brain abnormalities in PAPS patients with only mild neuropsychiatric manifestations and normal brain MRI findings.

MATERIALS AND METHODS

Patients

Criteria for APS include clinical features, such as venous thrombosis, arterial thrombosis, unexplained pregnancy loss or thrombocytopenia, and laboratory features, such as LA, IgG ACA (1 > 20 IgG phospholipid units) or IgM ACA (> 20 IgM phospholipid units). Our patients had to have at least one clinical and one laboratory feature to be diagnosed with APS (*2*). As a prerequisite for enrollment in this study, patients had to have APS as a primary disorder without other autoimmune diseases. In addition, patients had to present with only neuropsychiatric manifestations, including headaches, cognitive function deficits, personality disorders, depression, memory loss and lowered intelligence testing scores, that could not be attributed to any other cause (such

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For correspondence or reprints contact: Chia-Hung Kao, MD, Department of Nuclear Medicine, Taichung Veterans General Hospital, 160 Taichung Harbor Rd., Section 3, Taichung 40705, Taiwan.

as uremia, hypertension or infection). Patients with abnormal brain MRI (Vista MR2055 HP scanner; Picker Intl., Cleveland, OH) findings, including focal and diffuse hyperintensity lesions, infarcts, hemorrhage and significant atrophy, were excluded from this study. A total of 22 women (aged 28–60 y) who fulfilled the aforementioned criteria were enrolled in this study. Brain HMPAO SPECT was performed on all 22 patients. Meanwhile, serum levels of ACA were measured by enzyme-linked immunoassay kits (Quanta Lite ACA IgG/IgM; INOVA Diagnostics, Inc., San Diego, CA). Serum LA was detected by Russell's viper venom test (IL Test LAC Screen/LAC Confirm; Instrumentation Laboratory Co., Lexington, MA).

Brain HMPAO SPECT

^{99m}Tc-HMPAO was prepared from a commercial kit (Ceretec; Amersham International, Little Chalfont, UK) by adding 1110 MBq (30 mCi) freshly eluted ^{99m}Tc-pertechnetate to 5 mL saline solution. The solution was administered no more than 30 min after preparation. SPECT was performed at least 1 h after intravenous injection of ^{99m}Tc-HMPAO. We fixed the position of the head during SPECT imaging using a hemicylindrical plastic headholder with a radiolucent plastic neck-contoured head rest. The scanning equipment consisted of a rotating, large-field-of-view, dual-head gamma camera (Helix HR; Elscint Ltd., Haifa, Israel) fitted with a fanbeam collimator. Data were acquired in a 64 × 64 matrix with 1.3 zooming, through a 360° (180° for each head) rotation at three intervals, for 25 s per arc interval. After data acquisition, the data were normalized for the correction of the rotating camera head speed in different directions (upward and downward) and decay of ^{99m}Tc from the first to last frame; the number of counts within each frame of SPECT were the same. Reconstruction of the image was performed using attenuation correction, with Hanning filters, to produce transaxial sections. The spatial resolution of the camera with fanbeam collimator was 6.3-mm full width at half maximum. The prominent brain structures ("landmarks" included the caudate, putamen, thalamus, corpus callosum, ventricles, cingulate gyrus and the cortical surface outline, particularly at the anterior point of the frontal lobe and the vertex of the occipital lobe) that were visible on brain SPECT were compared with the corresponding slices of brain MRI. For SPECT images, the transaxial sections were reoriented parallel to the base of the brain to obtain coronal and sagittal reconstructions to determine the proper anatomic regions of brains. After image reconstruction, all slices of the SPECT images were normalized to produce the final images with

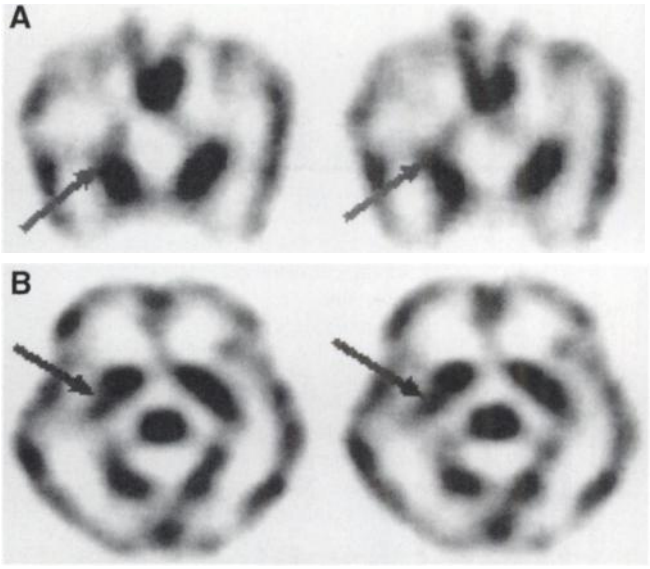

FIGURE 2. Coronal (A) and transaxial (B) sections of patient 7, a 34-y-old woman. Brain HMPAO SPECT revealed areas of hypoperfusion in right basal ganglion (arrows).

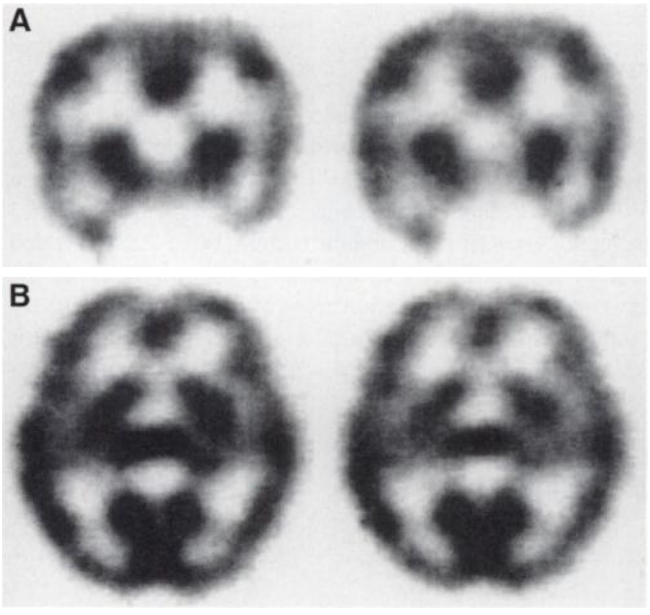

FIGURE 1. Coronal (A) and transaxial (B) sections of healthy 35-y-old woman. Normal brain HMPAO SPECT findings consisted of homogeneous rCBF in gray matter of cerebral cortex, basal ganglia and cerebellum without focal hypoperfusion or visible asymmetry.

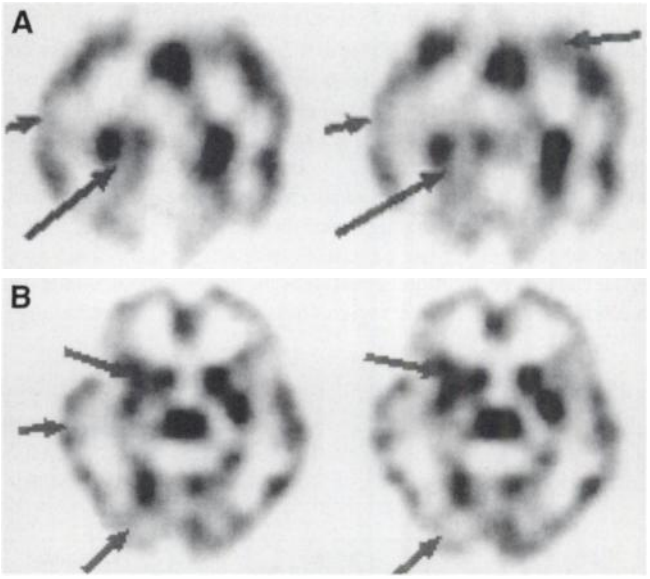

FIGURE 3. Coronal (A) and transaxial (B) sections of patient 8, a 36-y-old woman. Brain HMPAO SPECT revealed hypoperfusion areas in bilateral parietal lobes, right occipital lobe and right basal ganglion (arrows).

TABLE 1
Detailed Data of PAPS Patients

Patient no.	Age (y)	Neuropsychiatric manifestations	Lesion	Hypoperfusion areas on HMPAO SPECT	Serologic measurements	
					LA	ACA
1	28	Headache, depression		Neg	Pos	Pos
2	28	Headache	Diffuse	Lt P-T, Lt C	Pos	Pos
3	29	Memory loss, lowered intelligence testing scores	Diffuse	Bil P-B	Neg	Pos
4	31	Headache, lowered intelligence testing scores	Diffuse	Bil F-P-B	Neg	Pos
5	33	Memory loss	Diffuse	Bil B	Pos	Pos
6	33	Headache, memory loss		Neg	Pos	Neg
7	34	Personality disorder, cognitive function deficits	Focal	Rt B	Pos	Pos
8	36	Memory loss, cognitive function deficits	Diffuse	Bil P, Rt O, Rt B	Pos	Pos
9	37	Headache	Diffuse	Lt P-T	Pos	Pos
10	39	Headache, lowered intelligence testing scores	Diffuse	Bil F-P-B	Neg	Pos
11	41	Memory loss	Diffuse	Bil P	Neg	Pos
12	42	Headache		Neg	Pos	Pos
13	43	Headache, memory loss		Neg	Pos	Neg
14	45	Headache, memory loss		Neg	Neg	Pos
15	48	Memory loss	Focal	Rt C	Pos	Neg
16	48	Memory loss	Diffuse	Bil P	Neg	Pos
17	50	Memory loss, lowered intelligence testing scores	Diffuse	Bil P-B	Neg	Pos
18	52	Depression, memory loss	Diffuse	Bil B	Pos	Pos
19	55	Memory loss	Diffuse	Bil F-P	Pos	Neg
20	57	Cognitive function deficits	Focal	Lt P	Pos	Pos
21	59	Cognitive function deficits	Focal	Rt P	Pos	Pos
22	60	Memory loss		Neg	Neg	Pos

PAPS = primary antiphospholipid antibody syndrome; HMPAO = hexamethyl propyleneamine oxime; LA = lupus anticoagulant; ACA = anticardiolipin antibody; Neg = negative; Pos = positive; Lt = left; P-T = parietal and temporal lobes; C = cerebellum; Bil = bilateral; P-B = parietal lobe and basal ganglion; F-P-B = frontal lobe, parietal lobe and basal ganglion; B = basal ganglion; P = parietal lobe; O = occipital lobe; F-P = frontal and parietal lobes.

contrast set within the same range of 0–255 gray scales based on the computer screen. To find areas of abnormal perfusion, three independent experienced observers who were unaware of the clinical information visually interpreted the SPECT images from each patient twice in random order. Normal ^{99m}Tc-HMPAO brain imaging findings consisted of homogeneous rCBF in the gray matter of cerebral cortex and basal ganglion without focal hypoperfusion or visible asymmetry (Fig. 1). Abnormal findings included heterogeneous rCBF with focal hypoperfusion or visible asymmetry on at least two consecutive slices noted twice by at least two observers. Abnormal findings were categorized according to the observed focal or diffuse pattern. Focal pattern was defined as a single lesion or multiple small lesions limited to one lobe of cerebral cortex or to one region (basal ganglion or cerebellum) (Fig. 2). Diffuse pattern was defined as lesions involving two or more lobes or regions (Fig. 3).

RESULTS

Detailed patient data are listed in Table 1. Brain HMPAO SPECT findings were abnormal (with hypoperfusion lesions) in 16 of 22 (73%) PAPS patients. Diffuse and focal lesions were found in 12 of 22 (55%) and 4 of 22 (18%) patients, respectively. Cerebral cortex (14 of 22, 63%) and cerebellum (2 of 22, 9%) were the most common and the least common hypoperfusion areas of the brain, respectively (Table 2). Positive serum ACA and LA were found in 18 of 22 (82%) and 14 of 22 (64%) cases, respectively. In

TABLE 2
Brain HMPAO SPECT Findings

Patient	Lesion location							Lesion pattern	
	Cerebral cortex					Basal ganglion	Cerebellum	Diffuse	Focal
	Frontal	Parietal	Temporal	Occipital	Total				
Number	3	12	2	1	14	8	2	12	4
Incidence	14%	55%	9%	5%	64%	36%	9%	55%	18%

HMPAO = hexamethyl propyleneamine oxime.

TABLE 3
Relationship Between Serum ACA Results and Brain HMPAO SPECT Findings

ACA	HMPAO SPECT	
	Positive	Negative
Positive	14	4
Negative	2	2

ACA = anticardiolipin antibody; HMPAO = hexamethyl propyleneamine oxime.

addition, both ACA and LA results were related to brain HMPAO SPECT findings (McNemar chi-square tests; P = 0.4142 for ACA and 0.5271 for LA, respectively) (Tables 3 and 4).

DISCUSSION

There have been only a few reports of APS patients with hypoperfusion lesions on brain SPECT and no obvious abnormalities on MRI (*15,16*). Our findings are consistent with the results of those previous reports. In this study, brain HMPAO SPECT was abnormal in 16 of 22 (73%) patients with normal brain MRI findings (Figs. 2 and 3). From these results, we suppose that changes in rCBF on brain HMPAO SPECT are more easily detected than changes in anatomic structure on brain MRI in PAPS patients. Microscopic examination of the brain of PAPS patients shows occlusion of small brain vessels caused by fibrin thrombi or endothelial proliferation in the vessel lumen (*17–19*). These findings could explain and support the hypoperfusion findings of APS patients on brain HMPAO SPECT (*15,16*).

The territory of the middle cerebral artery (MCA) is at a higher risk for cerebral vasculopathy than other territories in autoimmune diseases (*11–14,20*). The most common hypoperfusion area found on HMPAO SPECT in this study was the parietal lobe (12 of 22 patients, 55%), which is under the territory of MCA (Table 2). In addition, high-resolution instrumentation has improved SPECT image quality and has made the detection of deficits in deeper cerebral structures (such as basal ganglion) more accurate (*11–14*). In this study, basal ganglia involvement had the second highest incidence (8 of 22 patients, 36%) (Table 2).

TABLE 4
Relationship Between Serum LA Results and Brain HMPAO SPECT Findings

LA	HMPAO SPECT	
	Positive	Negative
Positive	10	4
Negative	6	2

LA = lupus anticoagulant; HMPAO = hexamethyl propyleneamine oxime.

We did not think that a semiquantitative method of brain HMPAO SPECT interpretation was valid for these patients, because brain involvement diffusely (12 of 22 patients, 55%) and bilaterally (10 of 22 patients, 45%) affected the brain structures. The visual analysis of brain HMPAO SPECT images performed by independent and experienced observers, and dependent on normal databases obtained in our own laboratory (*11–14*), was sufficient to identify lesions. In addition, according to previous studies (*21–23*), the reader reproducibilities of visual interpretation of brain HMPAO SPECT are good. Therefore, in this study, we selected visual interpretation instead of a quantitative method.

Cervera et al. (*7*) reported that ACAs and LAs were found in 91% and 92% of 50 APS patients, respectively. In our patients with only mild neuropsychiatric manifestations, the positive incidences of ACA (82%) and LA (64%) were lower. However, ACA and LA are not specific for APS. The occurrence of ACAs and LAs in the general population is 14% and 4%, respectively. In SLE patients, the frequencies of ACA and LA are 61% and 65%, respectively (*3,5*). APLs, including ACA and LA, are strongly associated with thrombosis. In contrast to LA, arterial brain vessel thromboses are commonly associated with ACA (*24*). In this study, participants with positive ACA results have a higher incidence of positive HMPAO SPECT findings (14 of 22 patients, 64%) (Table 3) than participants who have positive LA results (10 of 22 patients, 45%) (Table 4). However, the relationships between ACA or LA results and HMPAO SPECT findings were significant ($P > 0.05$).

CONCLUSION

Early detection of cerebral abnormalities allows steps to be taken to protect against irreversible brain injuries. Therefore, brain HMPAO SPECT should be performed in PAPS patients with only mild neuropsychiatric manifestations and normal brain MRI findings.

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