—Case Reports—

Percheron Artery-Plus Syndrome: A Syndrome Beyond Stroke Chameleon

Fu-Yi Yang[1], Jeng-Luen Hung[2] and Shinn-Kuang Lin[1,3]

[1]Stroke Center and Department of Neurology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[2]Department of Emergency, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[3]School of Medicine, Tzu Chi University, Hualien, Taiwan

The artery of Percheron (AOP) is an anatomical variant of the thalamoperforating arteries. AOP occlusion can cause bilateral paramedian thalamic infarctions and is referred to as a "stroke chameleon" because it lacks the classic signs of stroke. Coexistence of AOP occlusion and other neurologic disease is rare and can cause disturbance of consciousness. A 78-year-old woman had acute onset of left limb weakness and drowsy consciousness. Brain magnetic resonance angiography (MRA) revealed acute bilateral paramedian thalamic infarctions. However, serum and cerebrospinal fluid (CSF) cryptococcal antigen titers were 1:16 and 1:128, respectively. The CSF culture grew *Cryptococcus neoformans*. Although consciousness and muscle power improved after treatment, the patient later died of pneumonia. A 68-year-old woman developed acute disturbance of consciousness followed by delirium. Brain MRA revealed acute bilateral paramedian thalamic infarctions. Elevated free thyroxine, anti-thyroperoxidase, and anti-thyroglobulin antibodies were detected. She received 3 days of steroid pulse therapy followed by oral prednisolone. Her consciousness gradually improved after Hashimoto encephalopathy and stroke were controlled. AOP occlusion was diagnosed early in these two patients. However, other concomitant life-threatening diseases could have been overlooked because of the complicated diagnostic determination. Further serum cryptococcal antigen, anti-TPO Ab, and anti-TG Ab surveys might help to exclude cryptococcal meningitis and Hashimoto encephalopathy. CSF study is warranted when central nervous system infection is strongly suspected. This "Percheron artery-plus syndrome" comprises multifaceted disorders beyond the stroke chameleon and requires attention.

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Key words: artery of Percheron, bilateral paramedian thalamic infarcts, cryptococcal meningitis, Hashimoto's encephalopathy, stroke chameleon

Introduction

The artery of Percheron (AOP), an anatomical variant of the thalamoperforating arteries, originates from the posterior cerebral artery (PCA) and is estimated to be present in 4% to 11.7% of the general population[1]. AOP occlusion can cause bilateral paramedian thalamic infarction, with or without rostral midbrain involvement, and is responsible for only 0.1% to 2% of ischemic strokes[2]. The clinical presentation of AOP occlusion varies widely; the most common symptoms are altered consciousness, vertical gaze palsy, and cognitive impairment[3]. AOP occlusion is considered a "stroke chameleon" because it lacks the classic signs of stroke, although mild hemiparesis may be a part of the initial presentation. Confusion and coma have been observed in 53% and 42% of patients with AOP occlusion, respectively[3]. Hence, diagnosis and treatment of AOP occlusion tend to be delayed when patients present to the emergency department. Percheron artery-plus syndrome, a concept derived from Parkinson-plus syndrome, is a group of acute ischemic strokes that has the features of Percheron artery occlusion, plus additional features that distinguish such strokes from simple Percheron artery occlusion. Because AOP occlusion is an uncommon stroke subtype, the coexistence of bilateral

Correspondence to Shinn-Kuang Lin, Department of Neurology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No 289 Jian Guo Road, 231, Xindian district, New Taipei City, Taiwan
E-mail: stuartlin0428@gmail.com, sk2022@tzuchi.com.tw
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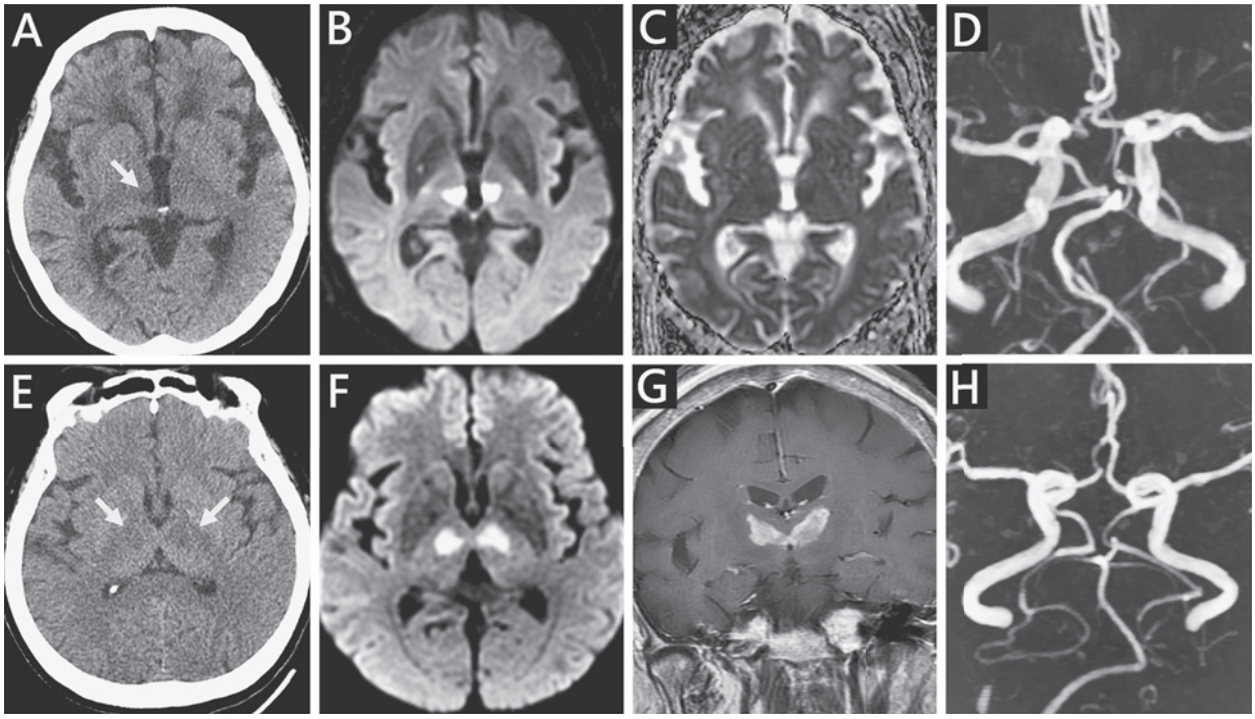

Fig. 1 Brain imaging studies of patients 1 (A-D) and 2 (E-H). (A) and (E) Axial brain computed tomography (CT) images revealing small hypodense lesions in the paramedian thalamus (arrows). (B) and (F) Axial magnetic resonance (MR) images revealing acute infarctions in the bilateral paramedian thalami as high-intensity lesions in diffusion-weighted images. (C) Axial MR images of patient 1 revealing acute infarctions in the bilateral paramedian thalami as low signals in apparent diffusion coefficient images. (G) Coronal T1-weighted images with contrast enhancement of patient 2 revealing a "V"-shaped enhanced lesion of bilateral paramedian thalamic infarcts. (D) and (H) MR angiography results revealing no vasospasm in both patients with the fetal-type left posterior cerebral artery (in patient 1) and dominant left posterior cerebral artery (in patient 2).

paramedian thalamic infarction and another neurologic disease, which also causes disturbance of consciousness, is even rarer. Emergent magnetic resonance angiography (MRA) could allow for early diagnosis of bilateral paramedian thalamic infarctions during acute stroke, while detection of a possible coexisting neurologic disease is challenging. Herein, we describe two cases of Percheron artery-plus syndrome. Both patients had AOP occlusion and initially presented with altered consciousness. The initial symptom of altered consciousness was accompanied by cryptococcal meningitis in one patient and by Hashimoto encephalopathy (HE) in the other patient.

Report of Cases

Patient 1

A 78-year-old woman with a history of hypertension had undergone lumbar spine surgery for spondylolisthesis, 6 months earlier, and laparoscopic cholecystectomy for acute cholecystitis 1.5 months after that. Cystic duct leakage and an intra-abdominal abscess with sepsis were noted 2 weeks after cholecystectomy and gradually resolved with appropriate treatment. However, she had reduced verbal output after discharge and developed acute left limb weakness and drowsy consciousness at 1 month after discharge. The Glasgow Coma Scale (GCS) was E2 V2M5 without eyeball movement limitation, and the muscle power of her left limbs was grade 3/5 (Medical Research Council of Great Britain). No fever or stiff neck was noted.

Emergent brain computed tomography (CT) revealed a small low-density area at the right medial thalamus (**Fig. 1A**). A hemogram and C-reactive protein test results were within normal limits. A brain MRA revealed acute bilateral paramedian thalamic infarctions (**Fig. 1B-D**) without venous sinus thrombosis. We prescribed clopidogrel for acute ischemic stroke. Owing to the unusual disturbance of consciousness, additional laboratory tests were performed. The results were normal for thyroid and cortisol levels and negative for anti-thyroperoxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-TG Ab). Electroencephalography revealed a moderate diffuse slow-wave abnormality without epileptiform discharge. However, her serum cryptococcal antigen titer was 1:16. Analysis of cerebrospinal fluid (CSF) revealed a white blood cell count of 81 cells/uL (2% neutrophils and 76% lymphocytes), glucose level of 24 mg/dL, and protein

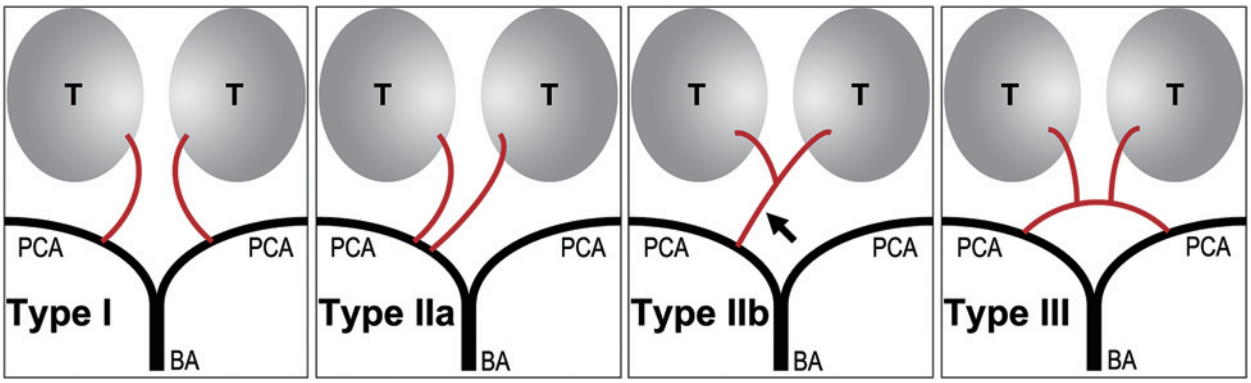

Fig. 2 Paramedian variants of thalamoperforating arteries (in red). Type I: normal anatomy; Type IIa: both paramedian arteries arise from one side of the P1 segment; Type IIb: the artery of Percheron arises from one side of the P1 segment and bifurcates to supply bilateral thalami (arrow); Type III: an arterial arcade connects the P1 segments of both sides and then supplies bilateral thalami.
B: basilar artery, PCA: posterior cerebral artery, T: thalamus

level of 103 mg/dL. The CSF cryptococcal antigen titer was 1:128, and a CSF culture later grew *Cryptococcus neoformans*. Intravenous amphotericin B liposome treatment was started for cryptococcal meningitis. The CSF cryptococcal antigen titer improved from 1:128 to 1:8 and CSF glucose level increased from 24 to 53 mg/dL in serial tests during the following 3 weeks. The serum cryptococcal antigen titer observed 6 weeks after initial treatment was 1:2. The patient's consciousness and muscle power gradually improved after cryptococcal meningitis was controlled. However, she later developed severe pneumonia and died of sepsis during the 11th week of hospitalization.

Patient 2

A 68-year-old woman with a history of hypertension was sent to the emergency department for treatment of acute conscious disturbance followed by delirium. GCS fluctuated between E1V2M5 and E3V4M5-6, without eyeball movement limitation. At her highest level of consciousness she was able to follow one-step commands but was disoriented to time and person, and irritable. No focal limb weakness or fever was noted. Electrocardiography revealed atrial fibrillation. A brain CT revealed hypodense bilateral medial thalamic lesions (**Fig. 1E**). A brain MRA showed acute bilateral paramedian thalamic infarctions (**Fig. 1F-H**). Aspirin was administered to the patient to treat acute stroke. Owing to the unusual disturbance of consciousness, additional laboratory tests were performed and showed elevated levels of free thyroxine (FT4; 2.33 ng/dL; normal, 0.74-1.64 ng/dL), anti-TPO Ab (>13,000 U/mL; normal, 0-60 U/mL), and anti-TG Ab (384.9 U/mL; normal, 0-60 U/mL) and a reduced level of thyroid-stimulating hormone (TSH; 0.006 μIU/mL; normal, 0.5-5.5 μIU/mL). Electroencephalography revealed moderate diffuse slow waves without epileptiform discharge. The cortisol level, cryptococcal antigen titer, and tumor markers and antibodies for autoimmune and paraneoplastic encephalitis were within normal limits. After tentative diagnosis of HE, she underwent a 3-day course of steroid pulse therapy with intravenous methylprednisolone (500 mg/day) infusion, followed by oral prednisolone and methimazole. Consciousness gradually improved after treatment and she was discharged 2 weeks after admission. Follow-up serum titers of FT4 and TSH were within normal limits and levels of anti-TPO Ab and anti-TG Ab were lower after 2 months.

Discussion

Blood is supplied to the thalamus by four main arteries: the polar artery (anterior territory), thalamoperforating arteries (paramedian territory), thalamogeniculate artery (inferolateral territory), and posterior choroidal artery (posterior territory). Four major variants of the paramedian territory were described by Gerard Percheron, and the AOP corresponds to the type IIb variant, which arises from the unilateral P1 segment of the PCA and then bifurcates to supply the bilateral paramedian thalami and rostral midbrain (**Fig. 2**)[4]. Lazzaro et al. identified a midbrain "V" sign on the axial section in a diffusion-weighted image, which improved recognition of AOP infarction[5]. Although no midbrain involvement was observed in our patients, coronal T1-weighted images revealed a similar "V"-shaped, enhanced lesion corresponding to bilateral paramedian thalamic infarctions. Cerebral angiography has low sensitivity for AOP, and a diagnosis of AOP occlusion is mostly based on clinical suspicion[5]. We could not identify the AOP by MRA in the present cases. The symmetric infarctions in the bilateral

paramedian thalami were regarded as identical to the typical pattern of AOP occlusion.

Impaired consciousness in patients with AOP occlusion ranges from drowsiness to deep coma. Coma usually resolves rapidly, whereas other abnormalities can persist. Hemiparesis might be present but is not a major clinical manifestation in AOP occlusion. Although two case serial studies reported motor deficit in 33% and 67% of patients with AOP occlusion, respectively, the severity of hemiparesis was usually milder than that of the major symptoms, including mental status and ocular movement disturbances[6,7]. The ventral anterior, ventromedial, and ventrolateral nuclei are commonly call "motor" nuclei of thalamus. The ventral ventrolateral nucleus (mainly supplied by inferolateral territory) is linked with the motor cortex and is likely responsible for ataxia and mild motor weakness after thalamic stroke[8]. Given the complexity of thalamic nuclei and blood supply, hemiparesis can occur in AOP occlusion. The etiology of AOP occlusion has been classified as cardioembolism or small-vessel disease. Some studies have reported atypical causes of AOP occlusion, including tuberculous meningitis, cryptococcal meningitis, and complications from an iatrogenic endovascular procedure[9,10]. In the present study, the cause of stroke was classified as cardioembolism in patient 2 and as an infectious process related to cryptococcal meningitis in patient 1.

Cerebral infarction is seen on MR images of up to 57% of patients with tuberculous meningitis and in 13% to 21% of patients with cryptococcal meningitis[11]. The mechanisms of cerebral infarction in tuberculous and cryptococcal meningitis are similar and include inflammation and strangulation of vessels, meningeal inflammation of vessel walls that causes thrombosis, and stretching of inflamed vessels due to dilated ventricles[12]. The inflammatory basal exudates of chronic meningitis are more severe at the circle of Willis and hence affect the perforating arteries. This results in infarction involving the basal ganglia, internal capsule, and thalamus. Infiltrative, proliferative, and necrotizing vasculitis was reported to be the main vascular pathologic change causing hemodynamic hypoperfusion due to a variable combination of vasospasm, intimal proliferation, and thrombosis. An infection-related hypercoagulable state might also increase the risk of infarction[13,14]. AOP occlusion rarely occurs in patients with cryptococcal meningitis. Nevertheless, chronic meningitis should be considered a possible cause of AOP occlusion. Two retrospective studies over a 12-year period at the same hospital found that 18 of 88 patients (21%) with cryptococcal meningitis had concomitant ischemic stroke; only two had acute/subacute infarcts in the bilateral thalami[11]. However, no images were available to identify whether the infarctions corresponded to AOP occlusion. Peng et al. reported a patient who initially had normal brain MR findings but suddenly became somnolent because of AOP occlusion 10 days after cryptococcal meningitis treatment[9]. The neurological deficits and outcomes were worse in patients with cryptococcal meningitis-associated strokes. In the present report, the cause of stroke in patient 1 was multifactorial. She was believed to be immunocompromised at stroke onset because of a preceding lumbar spinal surgery, acute cholecystitis, and a subsequent severe abdominal abscess with sepsis associated with prolonged antibiotic treatment. Reduced verbal output was possibly caused by the insidious onset of cryptococcal meningitis. Meningitis was ultimately discovered during further examination for acute stroke from AOP occlusion. Although concomitant stroke and cryptococcal meningitis were adequately controlled by appropriate treatment, the patient died, which indicates that presence of another concomitant neurologic disorder can be life-threatening, either because of cryptococcal meningitis or associated immunocompromised status.

HE is an uncommon autoimmune-related encephalopathy characterized by high titers of anti-TPO Ab and anti-TG Ab. The prevalence of HE is approximately 2.1 per 100,000 people. Mijajlovic et al. divided the clinical manifestations of HE into a vasculitic type, with multiple relapsing-remitting stroke-like episodes, and a diffuse progressive type, with dementia and psychiatric symptoms[15]. Thyroid hormone status ranges from hypothyroid to hyperthyroid. Hypotheses regarding HE include small-vessel vasculitis and direct harm due to antineuronal autoantibodies. Brain MR findings include a normal appearance (approximately 50%), ischemic change, demyelination, and vasogenic edema. No previous case study reported coexisting bilateral paramedian thalamic infarctions due to AOP occlusion and HE. Yeh et al. reported a patient with HE and tiny infarctions in the left midbrain and left thalamus, which were believed to be caused by occlusion of the thalamoperforating arteries or AOP branches[16]. In our patient 2, HE was diagnosed and appropriately treated soon after hospitalization. Recovery from AOP occlusion and a satisfactory response to steroid treatment for HE resulted in rapid improvement of consciousness. Acute conscious disturbance in patient 2 is believed to have been caused by acute stroke due to AOP

occlusion. The subsequent delirium with irritable behavior and varying GCS could have been partially influenced by pre-existing HE. Subclinical symptoms of diffuse progressive HE, such as dementia, might not be observed before stroke. A sudden onset of bilateral paramedian thalamic infarctions could be a trigger for the psychiatric symptoms of HE. The presence of anti-NH2-terminal of α-enolase (anti-NAE) autoantibody was reported to be a highly specific diagnostic biomarker for HE and approximately half of assessed HE patients carry anti-NAE antibodies[17]. We did not check anti-NAE autoantibody in patient 2. It is difficult to distinguish HE from AOP occlusion on the basis of initial symptoms of altered consciousness. Although anti-TPO Ab can be detected in as much as 10% of general population[18], the high titer of anti-TPO Ab (usually over ten-fold the normal level) detected in patient 2, in conjunction with her clinical features and good response to steroid therapy, support a diagnosis of HE.

To avoid delays in diagnosing AOP occlusion, Ranasinghe et al. proposed a comprehensive evaluation pathway, including brain MRI in the emergency department to meet the therapeutic time window for thrombolysis[19]. In the present case study, AOP occlusion was diagnosed rapidly by brain MRA in the two patients, despite its manifestation as a stroke chameleon. However, other concomitant life-threatening diseases are likely overlooked because of the diagnostic complications. Further serum cryptococcal antigen, anti-TPO Ab, and anti-TG Ab surveys are helpful in excluding cryptococcal meningitis and HE. A study of CSF is warranted when central nervous system infection is strongly suspected. Attention should thus be paid to this "Percheron artery-plus syndrome", which comprises multifaceted disorders beyond the stroke chameleon.

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