Clinical Reasoning:

A 43-year-old woman with right limb weakness

Siying Li, MD
Jingjing Zhang, MD
Ping Liu, MD
Ruili Wei, MD, PhD
Huaiwu Yuan, MD, PhD
Qing Ke, MD, PhD

Correspondence to
Dr. Ke:
keqing2003@126.com

SECTION 1

A 43-year-old woman presented with a 4-day history of right limb weakness. While biking 4 days earlier, she felt a weakness in her right hand and leg. She had a history of hypertension for more than 2 years, and was taking extended-release nifedipine tablets (40 mg) and perindopril (4 mg) daily, but her blood pressure was difficult to control (fluctuations of 150–180/90–115 mm Hg). The patient did not smoke or drink alcohol, and had no family history of similar diseases.

Clinical examination revealed a blood pressure of 154/98 mm Hg, facial acne, abdominal obesity, and ecchymosis on the upper limbs (figure, A and B).

The Medical Research Council power was 4/5 on the flexor and extensor of the right hip, knee, and ankle. No other nervous system abnormalities were observed. The random blood glucose level was 14.38 mmol/L. Brain MRI revealed acute infarctions in the left thalamus and right occipital lobe, subacute infarctions in the left cerebellum, and old infarctions in the periventricular and centrum semi-ovale (figure, C and D).

Questions for consideration:

1. Which type of cerebral infarction should first be considered as the etiology?
2. Which examinations should be performed next?

[GO TO SECTION 2](#)

Supplemental data
at [Neurology.org](#)

From the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases (S.L.) and Department of Neurology (P.L., R.W., H.Y., Q.K.), The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou; and the Department of Neurology (J.Z.), The Sixth Hospital of Ningbo, China. S.L. is also currently with the Department of Infectious Diseases, Hangzhou First People's Hospital, Hangzhou, China.

Go to [Neurology.org](#) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

(A) Facial acne. (B) Abdominal obesity and ecchymosis on the upper limbs. (C) MRI diffusion-weighted imaging sequence reveals significant hyperintensities in the left thalamus. (D) MRI scan reveals T2/fluid-attenuated inversion recovery hyperintensities in the left thalamus and both sides of the lateral ventricle. (E) Transcranial Doppler with saline contrast medium shows numerous microembolic signals from the left middle cerebral arteries during normal breathing. Results indicate the presence of a continuous right-to-left shunt. (F, G) Real-time 3D transesophageal echocardiography reveals a secundum atrial septal defect with an area of about 0.125 cm², and the atrial septal echo interrupts for 0.26 cm at 85° (F: 2D modality; G: 3D modality). (H) Sagittal T1-weighted enhanced MRI scan presents a sheet of a weakly enhanced lesion in the right side of the pituitary, which surrounds 3/4 of the internal carotid artery. (I) Axial T1-weighted image shows abnormal soft tissue signal on the right side of the pituitary. The signal is slightly less than the normal pituitary signal, and the internal carotid artery is surrounded by an abnormal signal. (J) A large number of tumor cells exhibit a patchy distribution (low magnification, hematoxylin & eosin stain). (K) Tumor cells are similar in size, the nucleus is round or oval, much of the nuclear chromatin is deeply stained and uniform, and a large amount of the chromatin is lightly stained (high magnification, hematoxylin & eosin stain).

SECTION 2

A middle-aged woman presented with primary symptoms of right limb weakness. Brain MRI revealed multiple infarctions involving bilateral, anterior, and posterior cerebral circulation, as well as old and new lesions, suggesting recurrent cerebral infarction. Thorough examinations were needed to determine the cause of illness.

According to the Trial of Org 10172 in Acute Stroke Treatment criteria, acute ischemic stroke is classified into the following 5 subtypes: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion (lacune), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology.¹ Ischemic stroke caused by atherosclerosis or heart disease comprises more than 60% of patients, and diagnosis is easily established by routine examinations, including basic laboratory testing, brain CT and MRI, echocardiogram, and ultrasonography of the carotid arteries. However, for young stroke patients (<50 years of age) without traditional vascular risk factors and a large clot burden, some relatively rare etiologies should be considered, such as thrombophilia, paradoxical embolism, arterial dissection, and unusual arteriopathies.^{2–4} To exclude large-artery atherosclerosis, carotid artery CT angiography was utilized, which revealed no significant findings. Twenty-four-hour

Holter cardiac rhythm monitoring indicated no atrial fibrillation. Transcranial Doppler (TCD) with saline contrast medium suggested a right-to-left shunt (figure, E). Therefore, transesophageal echocardiography was conducted, revealing a small secundum atrial septal defect (ASD) in the patient's heart (figure, F and G). In patients with ischemic stroke of undetermined origin, cardiac right-to-left shunt occurs when there is a heart defect (i.e., patent foramen ovale or ASD), suggesting cerebral paradoxical embolism.⁵ Although the patient underwent an arteriovenous ultrasound scan of the 4 limbs, no embolism was found. However, CT image of the abdomen showed thrombosis in the left portal vein branch. Other diagnostic evaluations suggested hypokalemia (2.96 mmol K⁺/L). According to current relevant information, the following diagnoses should be considered: (1) multiple cerebral infarction, (2) atrial septal defect, (3) paradoxical embolism, (4) hypertension, (5) diabetes, and (6) hypokalemia. However, the mechanisms of thrombosis remain unclear.

Questions for consideration:

1. Why did this patient easily develop thrombosis?
2. Is thrombosis related to other representations, such as hypertension, diabetes, hypokalemia, acne, or obesity?

GO TO SECTION 3

SECTION 3

In cases where refractory hypertension is associated with diabetes, hypokalemia, facial acne, abdominal obesity, and other metabolic syndromes, secondary hypertension should initially be ruled out. Secondary hypertension is common in Cushing syndrome (CS), primary aldosteronism syndrome, pheochromocytoma, and renovascular and renal parenchymal hypertension. CS is characterized by protracted exposure to glucocorticoids, and the clinical signs and symptoms include moon facies, centripetal obesity, glucose intolerance, hypertension, hypokalemia, skin bruising, acne, hyperlipidemia, hypercoagulable states, and kidney stones.⁶ The diagnosis is usually established by measuring urinary free cortisol, as well as the overnight low/high-dose dexamethasone suppression test, adrenal CT, and pituitary MRI. Lung CT and PET-CT are needed to diagnose ectopic adrenocorticotrophic hormone (ACTH) syndrome.

To support our hypothesis, new evaluations were performed, resulting in the following: 24-hour urinary free cortisol excretion of 1,003.8 $\mu\text{g}/24$ hours (reference value: 20.9–292.3 $\mu\text{g}/24$ hours); plasma cortisol levels: 15.6 $\mu\text{g}/\text{dL}$ at 8 AM and 21.8 $\mu\text{g}/\text{dL}$ at 4 PM (reference value: 5–25 $\mu\text{g}/\text{dL}$ at 8 AM, plasma cortisol levels at 4 PM should be about half of levels at 8 AM); ACTH levels: 104 $\mu\text{g}/\text{dL}$ at 8 AM and 102 $\mu\text{g}/\text{dL}$ at 4 PM (reference value: 0–46 $\mu\text{g}/\text{dL}$); overnight low-dose (1 mg) dexamethasone suppression test: suppression of serum cortisol 16.2 $\mu\text{g}/\text{dL}$ (reference value <1.8 $\mu\text{g}/\text{dL}$ is suppressed); high-dose (8 mg) dexamethasone suppression test: plasma cortisol levels before and after suppression were 15.6 and 5.87 $\mu\text{g}/\text{dL}$, respectively, suppression ratio was 62% (reference value >50% is suppressed) (table e-1 at Neurology.org). Together, these results suggested that hypercortisol correlated with excessive ACTH from the pituitary, and Cushing disease was considered. To identify Cushing disease and ectopic ACTH secretion, the desmopressin test during inferior petrosal sinus sampling was conducted. In this test, ACTH ratios of inferior petrosal sinus to peripheral venous blood were calculated at each time point: right IPS: $p > 2$ (basal ACTH), right IPS: $p > 3$ (poststimulation ACTH), suggesting excessive ACTH secretion may be from a pituitary tumor; right IPS: left IPS >1.4, suggesting the tumor was located in the right pituitary (table e-2).⁷ Then, enhanced MRI of the pituitary showed abnormal signal lesions on the right side of the pituitary, suggesting a pituitary tumor (figure, H and I); the enhanced adrenal CT image showed bilateral adrenal hyperplasia and multiple stones in the kidneys; PET-CT and chest CT revealed no ectopic ACTH tumors.

According to these symptoms, as well as laboratory and imaging examinations, a new clinical diagnosis of Cushing disease was made. The hypercoagulable state caused by Cushing disease could account for the venous thrombosis; when accompanied by an ASD, these patients are likely to have cerebral embolisms. According to clinical practice guidelines for treating CS, removal of the pituitary tumor is an effective treatment. However, the hypercoagulable state will remain for at least 1 year after surgery, especially in the first 4 weeks, resulting in an increased risk of venous thrombosis.^{8,9} Boscaro et al.¹⁰ found that adequate anticoagulant treatment after surgery can significantly decrease the incidence of venous thromboembolism in patients with CS. In addition, for cryptogenic stroke patients with patent foramen ovale (PFO), the updated guidelines recommend life-long antithrombotic therapy other than PFO closure, because it is impossible to define the causal relationship between PFO and stroke. However, in some circumstances, PFO closure may be considered for patients with recurrent strokes who are taking adequate medical therapy and no other etiologies can be identified.^{e1} Therefore, our patient underwent surgery to remove the pituitary tumor (pathology suggested a pituitary adenoma, figure, J and K) and was administered anticoagulation therapy postsurgery. We recommend ASD closure if the patient has recurrent strokes during anticoagulation treatment. The final diagnosis is acute ischemic stroke, caused by a paradoxical embolism through an ASD, in a patient with a hypercoagulable state due to Cushing disease.

DISCUSSION Stroke is the leading cause of adult disabilities. Routine examinations, such as basic laboratory testing, parenchymal brain imaging (CT and MRI), ECG, echocardiogram, ultrasonography of the carotid arteries, and noninvasive intracranial vascular imaging, can identify most causes of ischemic stroke, such as proximal occlusive atherosclerosis, lacunar strokes due to cerebral small artery disease, and major-risk cardioembolic sources.^{e2} The etiology in approximately 25% of strokes has not been determined after comprehensive evaluation for the most common causes; these cases have been diagnosed as cryptogenic stroke and are more frequent in younger patients.^{e2} Once cryptogenic stroke is diagnosed, the etiology and pathogenesis should be explored to determine the best treatment strategy for secondary prevention. Advanced diagnostic techniques, including long-term monitoring, agitated saline TCD monitoring, transesophageal echocardiography, high-resolution MRI, and coronary CT angiography, are helpful for diagnosing atrial fibrillation, paradoxical embolism, PFO, aortic atherosclerosis, and other potential causes.^{e3}

Patients with CS have been reported to have a >10-fold increase in the incidence of venous thromboembolism compared with the normal population, and this risk remains for at least 1 year post-surgery. Mechanisms of hypercoagulability in CS may be due to hypercortisolism, which can induce the release of procoagulant factors, such as fibrinogen, factor VIII, and von Willebrand factor, impair fibrinolytic capacity, and increase plasma concentrations of plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor, and α 2-antiplasmin. Combined, these changes shorten activated partial thromboplastin time and lead to a hypercoagulable state.⁹ In particular, when CS is accompanied by heart defects, venous thrombosis forms easily and Valsalva-provoking activity (coughing, bending) makes it easier for an embolism to enter arterial circulation through heart defects,⁶⁴ eventually leading to recurrent strokes. For a young patient (<50 years of age) with no traditional stroke risk factors, it is crucial to determine the uncommon causes and assess the risk of recurrence.⁴

AUTHOR CONTRIBUTIONS

Siyang Li: drafting and revising the manuscript for content, analysis and interpretation of data. Jingjing Zhang: drafting and revising the manuscript for content, analysis and interpretation of data. Ping Liu: collection, analysis, and interpretation of clinical data. Ruili Wei: revising the manuscript for content. Huaiwu Yuan: drafting and revising the manuscript. Qing Ke: revising the manuscript for content, analysis and interpretation of data, and accepts responsibility for conduct of research and final approval.

ACKNOWLEDGMENT

The authors thank Dr. Haiyan Lou and Dr. Xiaodong Teng for their contributions.

STUDY FUNDING

Supported by Health Bureau grant of Zhejiang Province 2013KYA074, National High Technology Research and Development Program (863 Program) 2015AA020513, and Natural Science Foundation of Zhejiang Province LY16H090007.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Adams HJ, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41.
2. Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol* 2013;70:51–57.
3. Schwamm LH, Jaff MR, Dyer KS, Gonzalez RG, Huck AE. Case records of the Massachusetts General Hospital (case 13-2016): a 49-year-old woman with sudden hemiplegia and aphasia during a transatlantic flight. *N Engl J Med* 2016;374:1671–1680.
4. Maaajwee NA, Rutten-Jacobs LC, Schaapsmeeders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: risk factors and long-term consequences. *Nat Rev Neurol* 2014;10:315–325.
5. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–625.
6. Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. *Lancet* 2015;386:913–927.
7. Castinetti F, Morange I, Dufour H, et al. Desmopressin test during petrosal sinus sampling: a valuable tool to discriminate pituitary or ectopic ACTH-dependent Cushing's syndrome. *Eur J Endocrinol* 2007;157:271–277.
8. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:2807–2831.
9. Van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)* 2013;78:481–488.
10. Boscaro M, Sonino N, Scarda A, et al. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. *J Clin Endocrinol Metab* 2002;87:3662–3666.

Neurology®

Clinical Reasoning: A 43-year-old woman with right limb weakness

Siying Li, Jingjing Zhang, Ping Liu, et al.

Neurology 2017;88:e103-e107

DOI 10.1212/WNL.0000000000003743

This information is current as of March 20, 2017

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/88/12/e103.full
Supplementary Material	Supplementary material can be found at: http://n.neurology.org/content/suppl/2017/03/20/WNL.0000000000003743.DC1
References	This article cites 10 articles, 3 of which you can access for free at: http://n.neurology.org/content/88/12/e103.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Stroke in young adults http://n.neurology.org/cgi/collection/stroke_in_young_adults
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.