

# A 38-Year-Old Woman With Global Aphasia and Migraine



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**CASE PRESENTATION:** A 38-year-old right-handed woman presented to the hospital with subtle right facial palsy and global aphasia of 4 days' duration. She found that she had aphasia when she suddenly woke up at midnight and reported a headache lasting for several hours. She had no fever, vomiting, seizures, or limb paralysis. She had had migraines with an occasional visual aura for > 10 years. She was not taking any medication and was a nondrinker and nonsmoker. She had no other significant medical background and family history.

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## Physical Examination Findings

The patient was conscious and oriented. She had a temperature of 36.5°C, respiration of 19 breaths/min, BP reading of 105/77 mm Hg, and pulse rate of 78 beats/min. Other than the abnormal neurologic signs already mentioned, findings on general examination were unremarkable.

## Diagnostic Studies

Laboratory results revealed an erythrocyte sedimentation rate of 39 mm/h (normal, 0-20 mm/h), a C-reactive protein level of 10.9 mg/L (normal, 0-10 mg/L), and a hypersensitive C-reactive protein level of 6.79 mg/L (normal, 0-3 mg/L). Other laboratory workup revealed neither coagulation disorders nor polycythemia. The lactate concentrations were normal at rest and after moderate exercise. Tumor markers and antineutrophil cytoplasmic antibody and antinuclear

antibody levels were normal. The arterial blood gas analysis included the following: pH, 7.43 (normal, 7.35-7.45), PaCO<sub>2</sub>, 29.0 mm Hg (normal, 35-45 mm Hg), PaO<sub>2</sub>, 80.7 mm Hg (normal, 83-108 mm Hg), and pulse oximetric oxygen saturation of 97.7% on room air.

An initial brain CT scan was negative for cerebral bleeding. Brain MRI showed an increased T1/T2 and diffusion weighted imaging/apparent diffusion coefficient signal in the left cerebral hemisphere (Fig 1). Carotid duplex ultrasonography, CT angiography, and digital subtraction angiography demonstrated no significant findings. The chest radiograph was normal. Twenty-four-hour Holter electrocardiography showed no arrhythmia. Peripheral Doppler scanning was negative for deep vein thrombosis. Transcranial Doppler ultrasonography showed that the left middle cerebral artery demonstrated microbubble signals with bubble-containing saline injection, even without a Valsalva maneuver (Fig 2).

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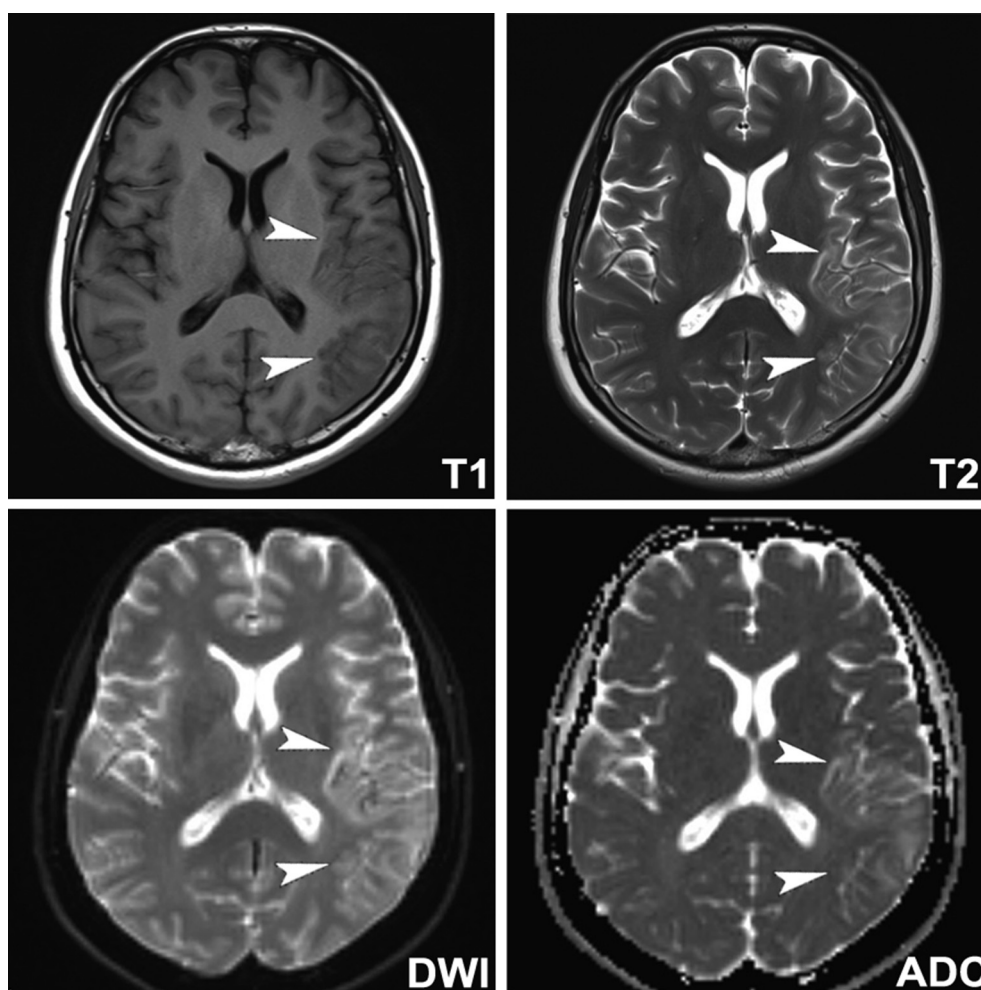


Figure 1 – MRI of brain showed increased T1/T2 and diffusion weighted imaging/apparent diffusion coefficient signal in the left cerebral hemisphere (arrowheads). ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging.

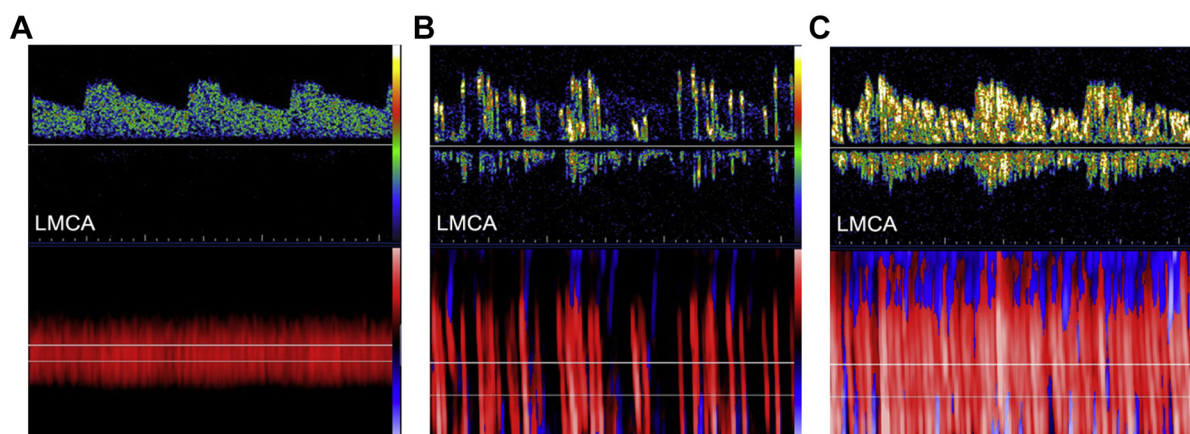


Figure 2 – Contrast transcranial Doppler ultrasonography in left middle cerebral artery showed (A) blood flow signal without agitated saline injection, (B) several microbubble signals in normal respiration, and (C) considerable microbubble signals with Valsalva maneuver. LMCA = left middle cerebral artery.

*What is the diagnosis?*

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**Diagnosis:** Isolated pulmonary arteriovenous fistula and left frontal/temporal/parietal lobe infarction

## Discussion

Pulmonary arteriovenous fistula (PAVF) results in anatomic right-to-left shunts, allowing systemic venous blood to bypass alveolar capillary gas exchange units. During fetal life, pulmonary arteriovenous shunts act as functional pressure relief valves to protect thin-walled perialveolar vasculature by regulating pulmonary blood flow. However, almost all pulmonary arteriovenous shunts close during the normal development of the lung and pulmonary circulations.

PAVFs usually coexist with other arteriovenous malformations at multiple sites, including nasal, hepatic, GI, mucocutaneous, spinal, and cerebral vasculature. Due to mutations in *ENG/ACVRL1/SMAD4*, hereditary hemorrhagic telangiectasia (HHT) accounts for about 80% of PAVFs. HHT should be taken into consideration when patients present with epistaxis, lip or oral cavity telangiectasia, and iron deficiency anemia from chronic bleeding. As HHT is transmitted from parent to child as an autosomal dominant trait, a family history of first-degree relatives with the disease can also provide clues for a clinical diagnosis. However, non-HHT-related PAVFs are relatively rare and may be idiopathic or secondary to infections, trauma, Fanconi syndrome, and bidirectional cavopulmonary shunt. Isolated PAVFs are usually misdiagnosed, especially in patients without pulmonary and cardiac symptoms and signs, such as dyspnea on exertion, hemoptysis, chest pain, palpitations, orthodeoxia, episodes of cyanosis, clubbing, and bruit or murmur over the PAVFs. The pulmonary capillary bed acts as a sieve measuring about 9  $\mu\text{m}$  in diameter, filtering blood coming from systemic veins. Due to compromised capillary bed filtration and subsequent paradoxical embolism, PAVFs increase the risks for neurologic complications, such as stroke, transient ischemic attack, brain abscess, migraine, decompression illness, and seizure. These neurologic complications can be the first or only clinical presentation for PAVFs.

Since cryptogenic stroke accounts for 25% of ischemic stroke, with an even higher percentage in young adults, the diagnosis identifying its cause is of great importance. Most cryptogenic ischemic strokes are embolic in origin. Paradoxical embolism caused by patent foramen ovale, atrial septal defect, and PAVF is much less common

than cardiogenic and arteriogenic embolism. However, more attention should be paid to paradoxical mechanisms when migraine coexists. Migraine with aura (MA) roughly doubles the risk of ischemic stroke and is strongly associated with the presence of a right-to-left shunt. MA and PAVFs are mutual independent predictors in patients with HHT. Paradoxical microembolism triggers a reduction of cerebral blood flow and cortical spreading depression, which is a biological substrate for MA. The compromised elimination of 5-hydroxytryptamine in the lung further increases the vulnerability of cerebral hypoperfusion. Thus, migraine can be regarded as a red flag for a screening of right-to-left shunt. The complex association between PAVFs, ischemic stroke, and migraine suggests that migraineurs with cryptogenic stroke should be prioritized for PAVF screening and highlights the importance of distinguishing migraine as a primary disorder from that secondary to other disorders that can by themselves lead to ischemic stroke.

A stepwise approach to a PAVF diagnosis should be carried out. Chest radiography and arterial blood gas analysis at rest in room air can be an initial step for suspected PAVFs. Thoracic CT imaging and contrast CT imaging can be used for further evaluation. However, normal findings on radiography, CT imaging, and contrast CT imaging cannot exclude PAVFs. Transcranial Doppler ultrasonography and transesophageal echocardiography (TEE) with agitated saline are usually performed to detect right-to-left shunts with high sensitivity and specificity. In contrast TEE, the time that bubbles enter the left atrium after they are seen in the right atrium is used to distinguish intracardiac and extracardiac shunts. However, the commonly used “three-beat rule” cannot provide solid proof for the differentiation between patent foramen ovale and PAVF. The early appearance of contrast in the left side of the heart in PAVFs may be due to the size or anatomy of the feeder artery and drainer vein. Pulmonary angiography remains the gold standard for those inconclusive cases.

There is no indication for supplementary oxygen, bed rest, or exercise limitation for asymptomatic patients. However, embolization is recommended for symptomatic cases, and “3-mm rule,” which states that a feeding artery  $< 3$  mm does not require interventional therapy, has been challenged, because smaller PAVFs can also result in severe complications. Surgical resection or lung transplantation is rarely adopted. Clinical trials regarding the use of antiplatelet and

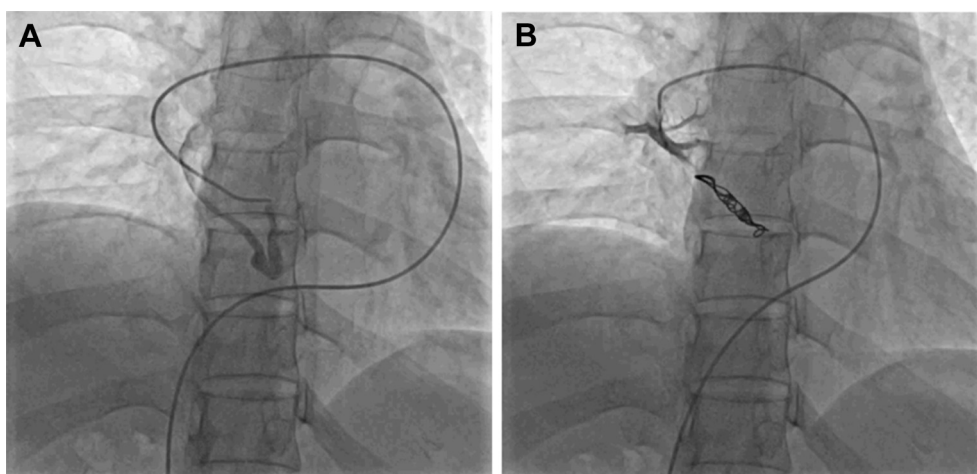


Figure 3 – Pulmonary angiography showed the fistula connecting the right inferior pulmonary artery and vein (A) before and (B) after coiling embolization.

anticoagulation agents for ischemia in patients with PAVFs are still under way, and the safety of thrombolysis is not well established. Since PAVFs can be asymptomatic for years and cause life-threatening complications, screening for suspected PAVFs and follow-up for those who have already been diagnosed or treated is recommended.

### Clinical Course

Stroke was diagnosed, and aspirin and clopidogrel were administered when the patient was hospitalized. Language rehabilitation training was carried out. Color Doppler echocardiography showed a suspected intracardiac right-to-left shunt, but TEE was normal. Further pulmonary angiography revealed a fistula connecting the right inferior pulmonary artery and vein. The patient underwent coiling embolization (Fig 3) and was treated with dabigatran etexilate instead of antiplatelet drugs. At the 6-month follow-up, CT angiography showed no PAVFs. The patient had only mild speech impairment and no longer experienced migraines.

### Clinical Pearls

1. Isolated PAVFs can present without pulmonary symptoms and signs. Neurologic complications can be the first or only manifestations of PAVFs.
2. Migraines can be regarded as a red flag for a screening of right-to-left shunt. Migraineurs with cryptogenic stroke should be prioritized for PAVF screening.
3. PAVFs cannot be ruled out with the early appearance of bubbles in the left side of the heart with contrast

TEE. Pulmonary angiography is necessary for inconclusive cases.

4. Embolization of symptomatic PAVFs is usually effective, and a feeding artery of 3 mm cannot be used as the cutoff for the requirement of interventional therapy.
5. Screening for suspected PAVFs and follow-up for diagnosed or treated PAVF is recommended.

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### Suggested Readings

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