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Case Report

Isolated pulmonary arteriovenous fistula: insights from diagnosing young-onset stroke

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Abstract: Paradoxical embolism (PE) is considered one of the main causes in young stroke patients. The right-to-left shunt (RLS) including both intracardiac and intrapulmonary shunt is the most common cause of paradoxical embolism. Intracardiac shunt through a patent foramen oval (PFO) has already been widely reported. Rarely, paradoxical embolism can also develop at pulmonary level, such as in patients with pulmonary arteriovenous fistula (PAVF). Here we reported a case of a 43-year-old woman who presenting with an ischemic stroke and got a RoPE score of 7. She was found to have a five-degree RLS on contrast transcranial Doppler (cTCD). Intrapulmonary shunt was implied by delayed appearance of microbubbles, observed on transthoracic contrast echocardiography (TTCE). Further pulmonary angiography confirmed a PAVF. After percutaneous transcatheter embolization (TCE), RLS together with the risk of recurrent stroke was removed. As a treatable cause of ischemic stroke in the young onset stroke, PAVF should not be ignored. An optimized process is recommended to screen and confirm PAVF in young cryptogenic stroke (CS) patients.

Keywords: Pulmonary arteriovenous fistula, paradoxical embolism, right-to-left shunt, ischemic stroke, RoPE score, contrast transcranial Doppler

Introduction

Paradoxical embolism (PE) is one of the main causes of stroke in young patients. Rarely, PE can develop at the pulmonary level, such as in patients with pulmonary arteriovenous fistula (PAVF). As a treatable cause of young-onset ischemic stroke, PAVF should not be ignored. Here, we reported a case of a 43-year-old ischemic stroke patient who experienced a paradoxical embolic event caused by PAVF. An optimized process for the screening and diagnosing PAVM was summarized.

Case report

A 43-year-old woman who suffered a stroke presented with transient loss of consciousness and quadriplegia. Brain magnetic resonance imaging (MRI) revealed a pontine infarction. She had no known medical or family history, took no medication or illicit substances, drank occasionally and was a non-smoker. Her complete thrombophilia work-up (including protein C, protein S, anticardiolipin antibodies, antithrombin III, factor V Leiden gene mutation, prothrombin gene mutation and methylenetetrahydrofolate reductase gene mutation) was negative. Cranial CT angiography (CTA) showed no stenosis except for basilar artery occlusion. A routine transcranial Doppler (TCD) was negative for abnormal blood flow. Doppler ultrasound found neither carotid atherosclerosis nor any potential source of venous thrombosis. The transthoracic echocardiography and Holter monitoring showed normal cardiac structure, function and rhythm patterns. The patient had a Risk of Paradoxical Embolism (RoPE) score of 7; therefore, a paradoxical embolization was suspected [1]. Microbubbles appeared on cTCD approximately 8-9 seconds after contrast injection. A five-degree right-to-left shunt (RLS) was observed both at rest and during the Valsalva maneuvre (VM) (**Figure 1**). Transthoracic contrast echocardiography (TTCE) demonstrated a

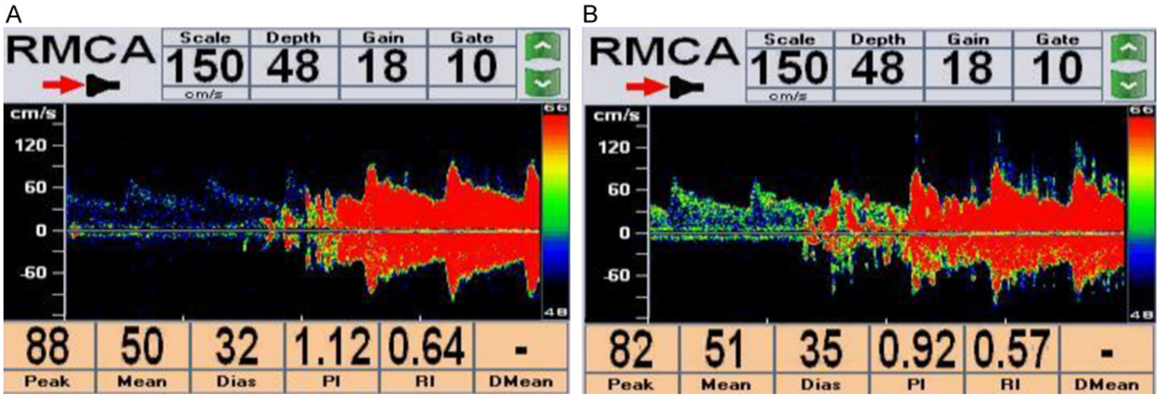

Figure 1. Contrast transcranial Doppler (cTCD) revealed a five-degree right-to-left shunt during both rest (A) and the Valsalva maneuvre (B).

Figure 2. (A) Pulmonary CT angiography showed a single PAVF approximately 1.78 cm × 1.72 cm in size (↑) with the feeder (⟵) and drainer (⟶) blood vessels in the right lower lobe. (B, C) Fluoroscopy showed the arteriovenous fistula before (B) and after (C) coil embolization.

delayed RLS (on the fourth cardiac cycles) into the left atrium, suggesting intrapulmonary shunt. Pulmonary CTA showed a simple PAVF approximately 1.78 cm × 1.72 cm in the right lower lobe. The feeding artery was approximately 2.1 mm in diameter (**Figure 2A**). Further pulmonary angiography (PA) also confirmed that the PAVF involved a large sac with afferent supply from a single artery. The efferent limb of PAVF communicated with one branch of the pulmonary vein.

We concluded that the isolated PAVF was responsible for ischemic stroke. To remove the risk of recurrent stroke, transcatheter embolization (TCE) was performed using a NESTER 8-mm device (**Figure 2B** and **2C**). No sign of RLS was observed on cTCD after embolization. The patient had no recurrence of ischemic stroke during the 6-month follow-up.

Discussion

PE is considered one of the main causes of stroke in young patients. PE can arise from RLS at either the cardiac or pulmonary level. Intracardiac RLS through a patent foramen ovale (PFO) has already been widely reported. Rarely, PE can also develop in PAVF patients with intrapulmonary RLS (Supplemental Table 1).

PAVF is an abnormal vascular structure that bypasses the normal capillary bed and results in an intrapulmonary RLS. Most PAVFs (80-95%) are associated with hereditary haemorrhagic telangiectasia (HHT). Isolated PAVF (i.e., without HHT) is rare and is diagnosed in only 4 of 747 (0.5%) ischemic stroke patients [2]. Hypoxemia and paradoxical emboli due to compromised capillary bed filtration lead to the main complications of PAVF [3]. The presence

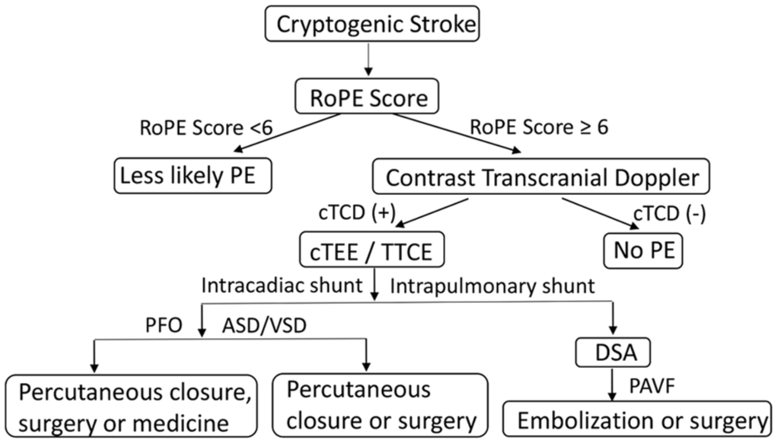

Figure 3. Optimized process for the screening and diagnosis of PAVM.

of a cerebral manifestation is more common in patients with the higher-grade shunts [4]. Patients developing PE may present with transient ischaemic attack (TIA), stroke, migraine or brain abscess. At least 25% of untreated PAVF patients will experience at least one clinical stroke by 65 years [5]. Paradoxical emboli due to RLS is deemed as the main pathogenesis of PAVF [6].

Our patient was between 40-49 years of age and had no documented medical history, such as hypertension, diabetes, smoking or previous stroke history. She had a RoPE score of 7. After complete coagulation work-up and vascular assessment, PE was suspected.

Instead of semi-invasive TEE, cTCD is now recommended as the initial screening for RLS due to its high sensitivity, specificity, simplicity and non-invasive character [7]. RLS revealed by cTCD can imply either intracardiac or intrapulmonary RLS. An intracardiac shunt, which is most commonly seen in PFO, can also be found in other congenital heart diseases, such as atrial septal defect (ASD) or ventricular septal defect (VSD). PAVF is the most representative of an intrapulmonary shunt. The sensitivity of TCD in identifying a PAVM was 98% at rest and 100% during VM. Specificity was 58% and 35%, respectively, presumably due to pulmonary shunts that are too small to recognize on CT [8]. In this case, RLS was revealed by cTCD. Furthermore, 4 TCD characteristics including persistent shunt (appear during both resting and VM phrase), early shunt (appear soon after contrast injection), vast shunt (shower effect), constant shunt (be less affected by VM) were summarized from this PAVF patient. We assume that identifying all the 4 cTCD characteristics present at the same time is important, as it suggests the possibility of PAVF.

For cTCD-positive patients, further evaluation is needed to discern between intracardiac or intrapulmonary shunt. The gold standard method for diagnosing intracardiac shunt is contrast transoesophageal echocardiography (cTEE) in cooperation with the VM [6]. Furthermore, the appearance of microbubbles visualized in the left atrium within one to two cardiac cycles implies an intracardiac shunt rather than an intrapulmonary shunt on cTEE.

In this case, we combined positive cTCD results with previous auxiliary examinations and concluded that the PE due to RLS was responsible for stroke. For dysphagia caused by pontine infarction, we opted for TTCE instead of cTEE as a further test. During the TTCE test, this patient was suspected to have an intrapulmonary shunt due to the delayed appearance of microbubbles in the fourth cardiac cycles [9, 10].

Though TCD and cTEE/TTCE are non-invasive examinations designed to detect RLS, they do not provide anatomic information. CTA is recommended in all cTEE/ TTCE-positive cases to offer detailed anatomic information, such as PAVM location, size, feeding artery and draining vein, which are critical for treatment decisions and planning. CTA was reported to have higher sensitivity but slightly lower specificity compared with digital subtraction angiography (DSA) [11]. Similar to CTA, contrast-enhanced-magnetic resonance angiography (CE-MRA) can also provide anatomic information on PAVF. Although there are inherent limitations in detecting PAVMs < 5 mm, MRA has still shown itself to have excellent applications in the life-long follow-up of treated PAVMs, benefiting from its radiation-free nature. PA remains the reference standard for inconclusive PAVF diagnosis; furthermore, it is also reserved for therapeutic purposes.

Paradoxical embolic events such as TIA and stroke are more common in patients with PVAF than others with PFO [12]. Treating PAVF can eliminate the risk of paradoxical embolic events and other complications associated with PAVM. The previously proposed "3 mm rule", which suggests that any PAVM with a feeding artery ≥ 3 mm in diameter should be considered for therapy, was withdrawn. The literature now advocates treatment for any PAVF, especially in patients who have already experienced a paradoxical embolic event [13]. Regardless of symptoms, any PAVF large enough for CT detection or with a pulmonary shunt on grade 3 should be considered for therapy [5]. Embolization with the use of TCE is the first-line treatment of PAVM. Surgical techniques, including local excision, segmental resection, lobectomy, ligation, and even pneumonectomy, is used only if TCE fails or as an emergency procedure to control bleeding. In our case, PAVF was treated by percutaneous TCE. There was no sign of RLS detected on cTCD on post-operative check.

Though rare, PAVF should be considered in all young onset strokes. In this case, we optimized the diagnostic process for PAVF. A series of tests, including RoPE score, cTCD, TTCE/cTEE and CTA, were combined to screen and confirm PAVF in cryptogenic stroke (CS) patients. An initial RoPE score should be derived in all CS patients. Further cTCD is taken to detect RLS in patients with a high RoPE score (≥ 6 points). If the patient turns out to be positive for RLS, cTEE or TTCE could help discern intracardiac shunt from intrapulmonary shunt. CTA is recommended in all cTEE/TTCE-positive cases to offer detailed anatomic information. PA remains the reference standard for inconclusive PAVF diagnosis. Once PAVM is confirmed, TCE is the first-line treatment. Thus, cTCD, which helps in detecting RLS, could be used in post-operative follow-up (**Figure 3**).

Acknowledgements

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Disclosure of conflict of interest

None.

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Supplemental Table 1. Previous Similar Cases

Isolated Pulmonary Arteriovenous Fistula in a Patient with Recurrent Stroke.	Acta Cardiol Sin.	2013 Jan; 29 (1): 107-9.
An isolated fistula between the right pulmonary artery and the right pulmonary vein: an unusual cause of stroke in a young female.	Cardiol J.	2011; 18 (1): 73-6.
Paradoxical brain embolism in a young man with isolated pulmonary arteriovenous fistula.	Neurol Sci.	2008 Jun; 29 (3): 169-71.
Diagnosis of isolated pulmonary arterio-venous fístula using contrast transcranial Doppler.	Neurologia.	2006 Jan-Feb; 21 (1): 40-3.
Clinical characteristics of paradoxical brain embolism associated with isolated pulmonary arteriovenous fistula.	Rinsho Shinkeigaku.	2002 Sep; 42 (9): 849-54.