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10.4103/bc.bc_66_21

Ischemic stroke due to sporadic and genetic pulmonary arteriovenous malformations: Case report

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Abstract:

Pulmonary arteriovenous malformations (PAVMs) encompass congenital and genetic vascular anomalies characterized by complex interlacing of arteries and veins connected by fistulas, which allow rapid and continuous extracardiac right-to-left shunting (RLS). Presenting neurologic manifestations of PAVM include brain abscess and stroke, as the consequence of paradoxical embolism. Although rare, PAVM represents an overlooked cause of cryptogenic ischemic stroke in young adults, being misdiagnosed as patent foramen ovale and a preventable trigger of silent cerebral ischemic changes. In the emergency clinical setting, the recommended ischemic stroke workup in patients with RLS should include the influence of postural changes and the effect of Valsalva maneuver on the entity of the RLS on contrast-enhanced transcranial color Doppler ultrasound and the delay in the right inferior pulmonary vein and left heart opacification on contrast-enhanced transthoracic echocardiography. This is in addition to the evaluation of chest X-rays or thoracic computed tomography. We here describe two patients with ischemic stroke due to sporadic and genetic PAVM-associated paradoxical embolism.

Keywords:

Arteriovenous malformation, cerebrovascular disorders, computerized tomography angiography, echocardiography, hereditary hemorrhagic telangiectasia, novel ENG mutation

Introduction

Evaluation of the young adult with cryptogenic ischemic stroke (which accounts for 20%–25% of ischemic strokes) requires an accurate history taking, clinical, imaging, and laboratory workup. This is aimed at establishing the location of the potential embolic sources and at excluding covert atherosclerosis, hypercoagulability disorders, cardiac sources, paradoxical embolism, genetic conditions, and small vessel diseases. Recently, the category of “embolic stroke of undetermined source” has been introduced, which includes nonlacunar strokes without proximal arterial stenosis or a definite cardioembolic

source, overall accounting for about 16% of acute ischemic strokes.^[1,2]

Paradoxical embolism, or the passage of thromboemboli from the venous system into the arterial circulation, represents a well-known cause of stroke often associated with patent foramen ovale (PFO) and atrial septal defects, and less commonly, to pulmonary arteriovenous malformations (PAVMs). The reported prevalence of PAMVs in patients admitted with acute ischemic stroke is 0.02%;^[2] however, this percentage may be underestimated owing in part not only to underrecognition but also to misdiagnosis as PFO. Indeed, canonical contrast-enhanced transcranial color-Doppler ultrasound (c-TCCD) and contrast-enhanced transthoracic

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Submission: 13-09-2021

Revised: 28-11-2021

Accepted: 16-12-2021

Published: 21-03-2022

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How to cite this article: Tagliapietra M, Turri G, Bortolotti F, Mansueto G, Monaco S. Ischemic stroke due to sporadic and genetic pulmonary arteriovenous malformations: Case report. *Brain Circ* 2022;8:57-60.

echocardiography (c-TTCE) do not differentiate between intra or extracardiac right-to-left shunt (RLS), unless the influence of postural changes and the effect of Valsalva maneuver on the entity of the RLS, in addition to the delay in the right inferior pulmonary vein and left heart opacification, are assessed.

We here present two patients in whom the diagnosis of sporadic and genetic PAVM was not considered at clinical presentation.

Case Reports

Case 1

A 44-year-old woman presented to the emergency department with sudden onset headache, vertigo, and postural instability. On examination, gait ataxia with retropulsion, dysarthria, left-beating horizontal nystagmus, and mild right facial paresis were observed. Computerized tomography (CT) scan and angio-CT were negative for bleeding and large artery occlusion. An abrupt worsening occurred after systemic thrombolysis, with right hemiplegia and marked dysarthria, followed by a near-complete recovery within a few hours except for mild right facial paresis. Headache resolved 2 days later, its features being consistent with her long-standing monthly attacks of migraine with aura. The previous medical history was otherwise unremarkable, except for a reported pulmonary malformation incidentally detected at chest X-rays 25 years earlier. Brain MRI demonstrated unilateral left pontine infarction, while cardiovascular workup revealed a hypermobile interatrial septum at transthoracic echocardiography and a substantial (Grade 4) RLS at c-TCCD, a finding which was attributed to PFO. Blood chemistries excluded coagulopathies or rheumatologic diseases. The patient asked for a second opinion at our institution, where chest X-rays and a chest CT angiogram confirmed the presence of a right lower lobe PAVM. Reevaluation of c-TCCD showed an RLS incrementing while the patient assumed the erect posture and was not modified by the Valsalva maneuver. c-TTCE showed a 3–4 beats long opacification of the right inferior pulmonary vein, left atrium, and ventricle, starting at 6–7 beats from the infusion. Valsalva maneuver did not modify this pattern. Chest X-rays showed a single right lower lobe lesion of 35 mm diameter, identified at CT angiogram as a “simple” (i.e., having a single feeding artery) PAVM [Figure 1]. Oxygen saturation by pulse oximetry was 93%. At pulmonary angiography, PAVM closure was achieved with the use of coilings (2 × COOK Nester 8 mm) and a plug (Medtronic MVP-9Q 13 mm). Persistent occlusion with PAVM shrinkage was observed at a follow-up of angio-CT obtained 7 months later. Genetic screening for hereditary hemorrhagic telangiectasia (HHT) revealed no mutations in *ACVRL1*, *ENG*, *GDF2*, and *SMAD4*

genes. During 18 months of follow-up, the patient did not experience further neurological events and intriguingly, did not incur in other migraine attacks.

Case 2

A 45-year-old woman with lip telangiectases presented to the emergency department with a single short-lasting episode of speech disturbance and left arm weakness. A brain CT scan was unremarkable, whereas on brain MRI an incongruent small acute ischemic lesion was detected in the left occipitoparietal region. Medical history was relevant for panic attacks and for a recently discovered iron deficiency anemia.

Head-and-neck angio-CT and transthoracic echocardiography were negative, while c-TCCD showed a Grade 4 RLS, a finding deemed consistent with possible PFO.

Reevaluation of c-TCCD at our institution showed an RLS incrementing while the patient assumed the erect posture and not modified while a Valsalva maneuver was performed. The patient also reported a history of recurrent epistaxis. Thoracic angio-CT showed at least two PAVMs at the right inferior and left inferior pulmonary lobes with multiple afferents at pulmonary angiography [Figure 2]. Genetic analysis showed the presence of a novel heterozygous *ENG* mutation (c. 1214_1219del; p. Leu405_Ser407delinsCys) also detected in an affected first-degree relative with HHT and a single asymptomatic PAVM. A diagnosis of definite HHT according to “Curaçao criteria” was achieved, and the patient successfully underwent occlusion of both

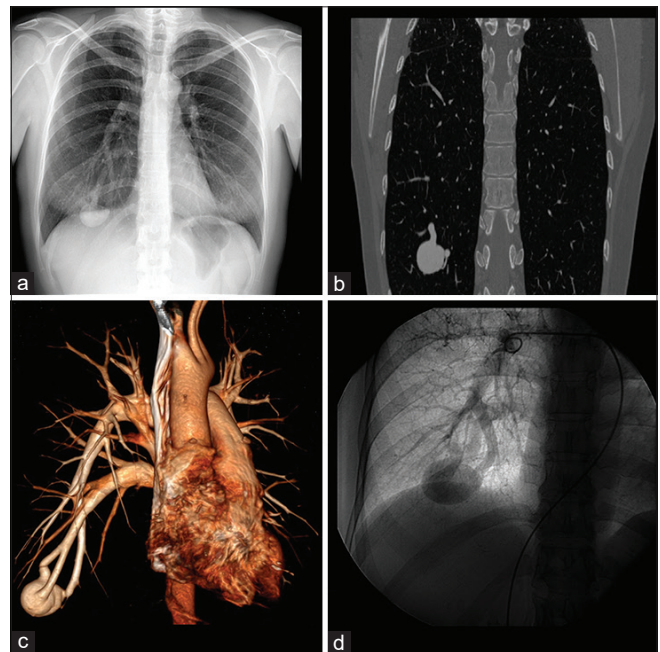


Figure 1: Right lower lobe pulmonary arteriovenous malformations as depicted at (a) chest X-rays; (b) chest angio-computerized tomography on coronal slices and (c) three-dimensional reconstruction; (d) pulmonary angiography

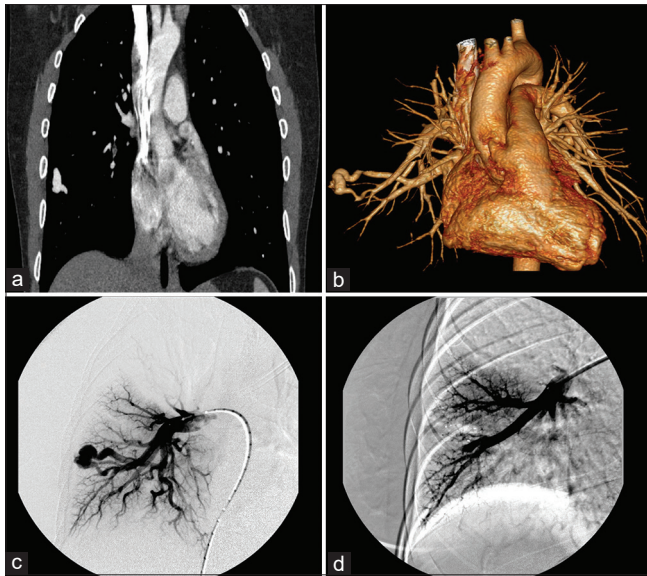


Figure 2: Right lower lobe pulmonary arteriovenous malformations as depicted at (a) chest angio-computerized tomography on coronal slices and (b) three-dimensional reconstruction; pulmonary angiography (c) before and (d) after the embolization procedure

pulmonary lesions with micro-Amplatzer devices and coilings. RLS was reduced at control c-TCCD while angio-CT was negative for PAVM reperfusion, a finding suggestive for residual flow through radiologically undetectable small PAVMs.

Discussion

PAVMs are aberrant communications between pulmonary arteries and veins that, in the absence of an intervening capillary bed, result in an anatomic and continuous RLS.^[3] Patients with small lesions are usually asymptomatic, whereas patients with larger lesions may present with dyspnea, pulmonary hemorrhage, chest pain, and hemoptysis. Intrapulmonary RLS is responsible for migraine and respiratory disorders, whereas paradoxical embolization causes stroke, cerebral and systemic abscesses, and endocarditis.^[4] Typical features of PAVM-related cerebrovascular events include the occurrence of symptomatic smallsize cerebral infarcts (so-called partial anterior and posterior circulation syndromes according to the Oxford/Bamford classification)^[5] in patients who, on average, are 15 years younger than those without PAVMs, with large-vessel occlusions being characteristically uncommon.^[2] Beyond that, PAVMs are also an underlying cause of silent strokes, which cumulatively represent a preventable contributor to cognitive impairment.^[2] Ischemic stroke is often accompanied by a migrainous headache in HHT,^[6] as particulate paradoxical embolism of sort provokes migraine in patient with PAVMs.^[7]

Respiratory disturbances are described in 20% of the patients,^[4] often presenting as a particular dyspnea

worsening in the upstanding position (platypnea), as an effect of increasing RLS owing to gravitational blood redistribution to lower pulmonary lobes, a favorite site for PAVMs.^[8]

RLS and thrombus formation in the aneurysm sac can lead to systemic embolization and ischemic stroke, with an annual incidence of 14/1,000 patients.^[4] The occurrence of this event is affected by the diameter of the largest feeding artery, with a reduced risk for smaller lesions.^[9]

The total flow through the RLS, as determined by PAVMs size and number, impairs the immunological function of the pulmonary capillary system. The risk of invasive infective complications is proportional to total RLS, with an annual incidence of brain abscesses of up to 7/1,000 patients.^[9]

In the emergency setting, neither clinical clues pointing to HHT (spontaneous recurrent epistaxis and mucocutaneous telangiectasia) are seldom investigated nor the clinician could not rely on routine, low-yield investigations as chest X-rays, pulse oximetry, or arterial blood gases.^[10]

Recommended ischemic stroke workup in young adults requires a c-TCCD to rule out the presence of a PFO. c-TCCD uses the quantification of the passage of air bubbles from an agitated saline solution administered through a peripheral vein and visualized in an intracranial vessel to characterize RLS, whereas in physiologic conditions, these are trapped in pulmonary capillaries and do not reach the systemic circle. In the case of PFO, under resting conditions, RLS is inhibited by a higher blood pressure in the left atrium if compared to the right. Valsalva's maneuver reduces this gradient, thus increasing the RLS. Being confined to the pulmonary system, PAVMs are less affected by the change of pressure gradient related to Valsalva.^[11]

To differentiate between PAVMs and PFO, TTCE also adds a time analysis of opacification of the left structures due to the diverse length of the short circuit with a maximum opacification of the left ventricle 3–4 beats after right atrium in PFO, >6 beats in PAVMs.^[9,12] In patients with a single PAVMs, the feeding artery size correlates with both timing on TTCE and RLS grade (quantified in a previously described 3-point scale),^[9] with earlier and stronger opacification in bigger PAVMs.^[12]

Although TTCE can discern intracardiac from intrapulmonary shunts based on the right atrium opacification timing, in a number of cases, including coexisting shunts or PAVM mimics, the degree and

timing of opacification may not be straightforward. Under these circumstances, contrast-enhanced transesophageal echocardiography of the pulmonary veins provides clear-cut results in assessing the level of shunting, whereas a CT chest has been reported to have 100% specificity at both distinguishing pulmonary PAVM from its mimics and identifying all PAVMs that are amenable to embolization.^[13]

All patients with PAVMs should be offered genetic consultation for the suspicion of HHT. To date, rare mutations in *ENG*, *ACVRL1*, and *SMAD4* genes, which encode a signaling protein and cell-surface receptors involved in transforming growth factor- β signaling pathway, have been associated with inheritance of HHT. Vascular anomalies including PAVMs have also been recently reported in patients carrying *GDF2* mutations, in phenotypical overlap with HHT.^[14] If appropriately based on Curaçao criteria, a diagnosis of HHT should be applied even in the absence of a known mutation.^[8]

Angio-CT is mandatory both for quantitative measures and structural assessment for comorbid pathologies and lung abnormalities before intravascular therapies, as only patients with angio-CT-visible PAVMs are to be selected to outweigh the procedural risks.^[8] Intravascular embolization is a safe procedure with approximately 1% complication rates and >95% success rate in centers with due expertise.^[15] Each radiologically detectable PAVMs is eligible for embolization treatment, regardless of symptoms.^[10]

Spontaneous reperfusion is seldom observed, instead of up to 20% of cases with multiple PAVMs show a trend for the remaining untreated lesions to grow in size after the intervention.^[15]

As expected, successfully treated cases with negative follow-up do not incur new events. In the absence of conclusive evidence, there is no definite recommendation for thrombolysis. The safety of secondary prevention with antiplatelet drugs and statins has been ascertained and is recommended even after successful PAVMs closure based on usual stroke management.^[8]

Declaration of patient consent

The authors declare that they have obtained consent from patients. Patients have given their consent for their images and other clinical information to be reported in the journal. Patients understand that their names will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

M. Tagliapietra reports a training grant from Pfizer and received support for attending scientific meetings from Alnylam.

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