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Ischemic strokes due to pulmonary arteriovenous malformations: A systematic review

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Abstract:

BACKGROUND: Pulmonary arteriovenous malformations (PAVMs) can cause acute ischemic strokes (AISs) through paradoxical embolism. The clinical and imaging features of AIS due to PAVMs have not been studied. We report a case and perform a systematic review of the clinical and imaging characteristics of patients with AIS due to PAVMs. This may provide clues to screen patients with AIS for PAVMs and treat them appropriately to prevent further strokes.

MATERIALS AND METHODS: MEDLINE, EMBASE, and Web of Science databases were searched from inception to October 2023. We included patients of any age with AIS attributed to PAVM. Studies without clinical data were excluded. Demographics, AIS characteristics (location and arterial territories), and PAVM characteristics (location, size, and treatment) were recorded.

RESULTS: A 47-year-old female presented with acute vertigo and gait imbalance. Magnetic resonance imaging showed AIS in the right cerebellum. CT chest confirmed a PAVM in the right lower lobe. Endovascular coil closure was performed. We identified 102 patients from 96 records. The mean age was 47.4 ± 17 years (67% female). Seventy percent had single AIS and 30% had multiple. The location was anterior circulation in 50%, posterior in 37%, and both in 13%. The most common arterial territory was middle-cerebral (51%), followed by posterior-cerebral (25%). PAVMs were mostly single (78%) and in the lower lobes (66%). Thirty-three had hereditary hemorrhagic telangiectasia (HHT) (33%).

CONCLUSIONS: PAVM-related strokes occur at a young age and may have a high propensity for multifocality and posterior circulation location. Patients with PAVMs and AIS should be screened for HHT and venous thromboses.

Keywords:

Embolic stroke, ischemic stroke, paradoxical embolism

Introduction

A pulmonary arteriovenous malformation (PAVM) is an abnormal communication between a pulmonary artery and vein devoid of intermediate capillaries. As a result, they are low-resistance conduits with high flow that shunt deoxygenated blood continuously from the right-sided circulation to the left.[1] The shunt, similar to a patent foramen ovale (PFO), serves as a path for thrombi and infectious material from the periphery to reach the intracranial vasculature and results in complications such as ischemic stroke and intracranial abscess.[1,2] PAVMs are most commonly genetic (70%), seen with vascular dysplasias such as the autosomal dominant hereditary hemorrhagic telangiectasia (HHT), but they can also be sporadic.[1] The incidence of respiratory symptoms and neurological complications is related to the number and size of PAVMs, and they are found to be silent in most patients until the occurrence of an acute ischemic stroke (AIS).[3]

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In patients with AIS, the prevalence of PAVMs is estimated to be quite low (0.02%) in large nationwide samples.[4] However, compared to clinical strokes, patients with PAVMs have a higher prevalence of silent infarcts on imaging (1.13:1), which carry long-term clinical implications such as impaired cognition and mood.[5,6] Although the rate of diagnosis of PAVMs in stroke patients has increased recently, their prevalence is likely underestimated due to the lack of routine pulmonary imaging in patients with embolic-appearing AIS.[7] Currently, there are no studies on the imaging features of AIS in patients with PAVM to guide patient selection for pulmonary screening. In this study, we report a case of AIS due to PAVM and perform a systematic review of the stroke imaging characteristics in patients with PAVMs. This may provide clues to select AIS patients for PAVM workup or inform future studies.

Methods

We searched MEDLINE, EMBASE, and Web of Science databases from inception to October 1, 2023. Search terms included a combination of the keywords "pulmonary," "arteriovenous," "fistula," "malformation," "AVM," "stroke," and "ischemic stroke." An example of a search term was "Pulmonary arteriovenous AND stroke" (MEDLINE). Preset search filters in these databases were used to exclude duplicates. Inclusion criteria were any patient age, AIS and pulmonary AVM both confirmed on imaging, and studies with patient-level data, such as case reports or case series. Both HHT-related and non-HHT sporadic PAVMs were included. Exclusion criteria were studies without patient-level data such as retrospective/prospective studies and systematic reviews. Transient ischemic attack was excluded as the goal of the study was to analyze the imaging features of strokes due to PAVM. Patients with concurrent PFO were not excluded if PAVM was deemed to be the etiology of stroke by the authors based on cardiopulmonary testing. AISs that occurred immediately following PAVM closure were not excluded.

Demographic variables such as age (years), sex (male/female), and race were recorded. Race was not inferred from the country of origin of the case report but from specific reporting. The following AIS characteristics were recorded: imaging modality used, first versus recurrent stroke, number (single or multiple), side (right, left, or bilateral), circulation (anterior, posterior, or both), vascular territory (arterial supply), specific brain regions involved, and location of the past strokes. Arterial territory and brain regions involved were recorded based on direct author report in most cases. In some cases, we inferred the above based on images provided in the case report.

PAVM characteristics recorded were number, side (right, left, or bilateral), lobe involved, size (in mm), whether previously treated, and current modality for closure. The modality of closure was recorded verbatim as per the authors' report. Other cardiopulmonary testing data such as transcranial Doppler or bubble echocardiogram were recorded where available. The presence or absence of HHT and genetic mutation were also noted. The presence of systemic thromboembolism and systemic illness such as cancer or prothrombotic states was also recorded. Descriptive data are reported as numbers, percentages, ranges, and mean (standard deviation) or median (interquartile range) based on the normality of distributions. The Chi-square test and independent samples *t*-test were used to estimate associations between variables. Data were collected by coauthors independently, and adjudication for inclusion into the study was performed by S. R. Since this was an exploratory study without meta-analysis, the systematic review was not registered, and a review protocol was not uploaded before the study.

Results

Case report

A 47-year-old female presented to our institution with acute onset vertigo, nausea, vomiting, and imbalance for several hours. She was a mother of 10 children with no history of pregnancy-related complications. She did not have other traditional vascular risk factors. A neurological examination showed direction-changing horizontal nystagmus and gait instability. An initial noncontrast computed tomography (CT) scan showed hypodensity in the right cerebellum consistent with AIS. CT angiography of the head-and-neck vessels was normal. The patient was outside the time window for intravenous thrombolysis. Magnetic resonance imaging (MRI) brain confirmed AIS in the posterior inferior cerebellar artery territory, and a chronic silent ischemic stroke was noted in the right occipital lobe in the posterior cerebral artery (PCA) territory [Figure 1]. Transesophageal echocardiogram revealed abundant late-appearing bubbles (>5 cardiac cycles) in the left atrium without Valsalva maneuver, suggestive of intrapulmonary right-to-left shunting. A PAVM in the lower lobe of the right lung was confirmed on CT pulmonary angiography [Figure 2a]. Venous Doppler of the extremities was negative for deep-vein thrombosis. Atrial fibrillation was not detected on telemetry during her 1-week hospital stay. Laboratory investigations ruled out hematological abnormalities or hypercoagulable states. There was no family history of HHT. She denied a prior history of nasal or other bleeding in self or family members, so HHT was thought to be unlikely, and testing was not considered. The AIS was attributed to the PAVM and closure was performed using endovascular coiling for secondary prevention [Figure 2b]. The patient was started on anticoagulation postprocedure and then transitioned to an antiplatelet agent on an outpatient basis for secondary stroke prevention. Outpatient bubble transthoracic echocardiogram was negative for residual shunt. The patient has not had a recurrent stroke over 3 years of follow-up and has minimal residual ataxia that does not impair her daily activities.

Systematic review

Six hundred and thirty-six abstracts were identified using the search terms. Using inclusion and exclusion criteria, abstracts were screened for full-text review and then for inclusion in the final analysis. Ninety-six records were included with a total of 102 patients with AIS due to PAVM [Figure 3]. The mean age of patients was 47.4 ± 17 years. Sixty-eight were women (67%). Information on race was specified in reports only for four patients (4%) (3 Asians and 1 Caucasian).

Characteristics of AIS and PAVM are described in Tables 1 and 2, respectively. Patients most frequently had single AIS (70%) in the anterior-circulation (50%) middle cerebral artery (MCA) distribution [Table 1]. Multiple

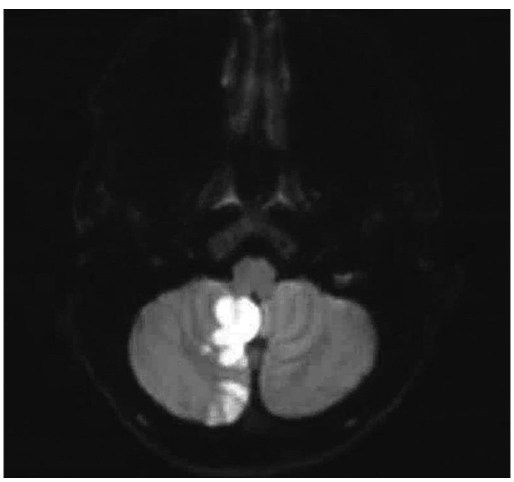

Figure 1: Magnetic resonance imaging of the brain: Acute ischemic stroke in the posterior inferior cerebellar artery territory on diffusion-weighted imaging

AISs in both anterior and posterior circulations or in both hemispheres were seen in 15% and 21%, respectively. Of note, nearly one-third (30%) had concurrent conditions that could predispose to thrombo-embolic phenomena such as cancer, deep-vein thromboses, or congenital prothrombotic states [Table 1]. Thirteen patients (13%) had a prior clinical stroke or silent stroke identified on MRI. PAVMs were most commonly single (78%) and in the lower lobes (66%). Multiple PAVMs were seen in 20%.

Thirty-three patients had HHT (33%), with the majority diagnosed clinically (67%). Eleven had mutations [Table 2]. Patients with HHT were younger [mean 42 (±18) years] than non-HHT patients (49 [±16] years) (P = 0.04). Patients with HHT had a higher prevalence of multiple PAVMs compared to non-HHT patients (χ^2 [1, n = 100] = 13, P = 0.0003), but did not have a higher occurrence of multifocal AIS (χ^2 [1, n = 102] = 1.9, P = 0.2).

Discussion

We report a case of AIS due to PAVM and discuss findings from our systematic review of the characteristics of AIS due to PAVM. To the best of our knowledge, this is the first systematic review exploring the imaging characteristics of AIS in patients with both HHT- and non-HHT-related PAVMs. In our study, patients with AIS due to PAVM were younger, with a strong female preponderance compared to the general stroke demographics.[7-10] Although anterior circulation strokes were the most common in this study, we noted a high prevalence of multiple territory and posterior circulation AIS compared to overall stroke estimates.[11,12] HHT-associated PAVMs and underlying conditions with risk for thromboembolism were commonly seen.

Patients in our systematic review were of lower mean age (47 ± 17 years) than the global mean for AIS patients (62 ± 14 years), consistent with case series of AIS due to PAVM which reported a mean age of 47–51 years but only included patients from 2017 to 2021 or only

Figure 2: (a) Pulmonary arteriovenous malformation in the right lung lower lobe (arrows) on computed tomography pulmonary angiography. (b) Catheter angiogram showing coil placement in the pulmonary arteriovenous malformation

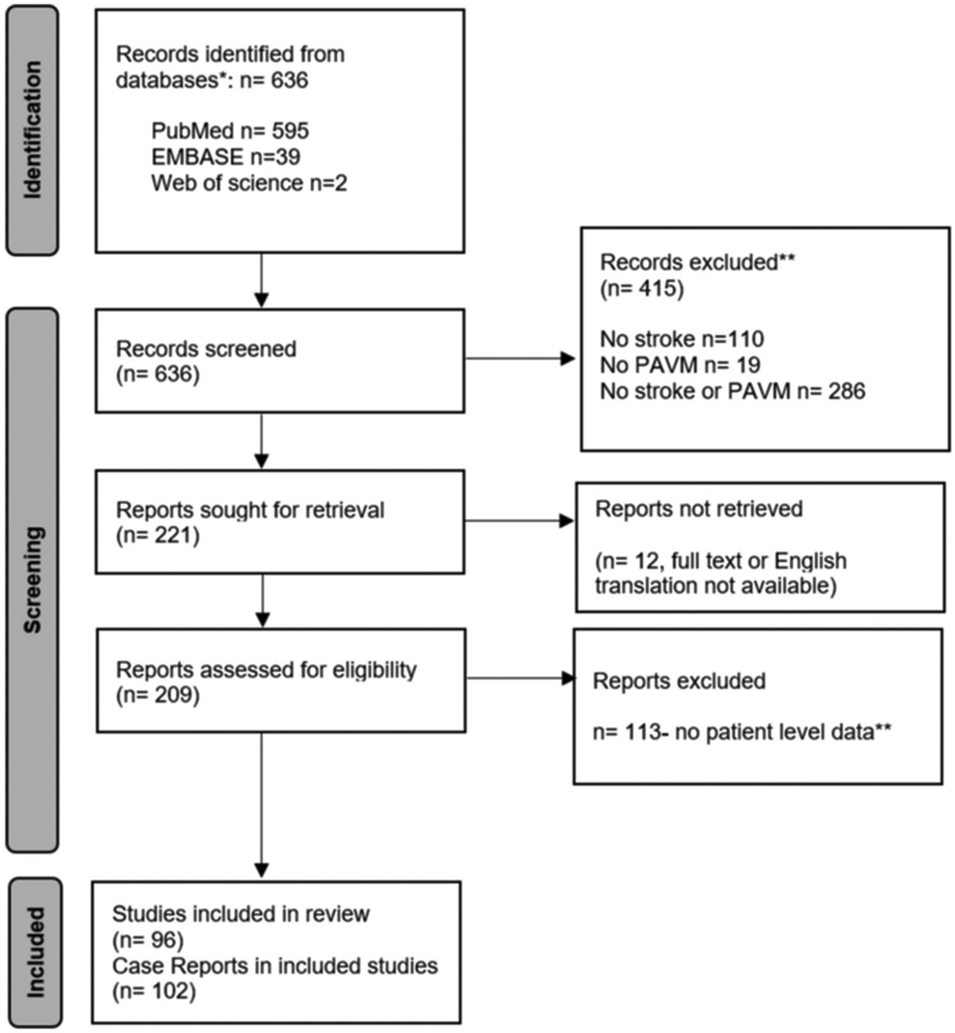

Figure 3: PRISMA flow diagram for new systematic reviews which included searches of databases. *Records in EMBASE and Web of Science that were duplicates from PUBMED were excluded based on the filter function in the search engine of the databases. **Retrospective/prospective studies, translational studies, systematic reviews, or case reports/series without sufficient patient-level data for inclusion in the final analysis

those with HHT.[7-9] A national inpatient sample that studied the prevalence of PAVM in AIS patients in the United States reported a higher mean age of 58 years; however, it is not clear whether the PAVM was causative or incidental in these patients.[7] AIS due to PAVM, therefore, appears to occur at a lower age than non-PAVM AIS and may confer higher disability-adjusted life years lost due to young stroke.[7] In our study, 67% were women, a significantly higher proportion compared to population data for AIS (40% female), but similar to the general female sex preponderance reported for PAVMs without AIS (1.5–1.8:1 female to male).[8,10]

AISs in our systematic review were most commonly in a single arterial territory (83%). The prevalence of multiple-territory AIS ranges from 4.6% to 37.1% in various studies.[13] In patients with cardioembolic strokes, it is noted to be higher, close to 40%.[14] We found a lower prevalence of multiple-territory AIS (17%). Perhaps, this could be due to potentially higher embolic burden related to atrial fibrillation and left atrial thrombosis. AISs in our study were more commonly left sided (45% vs. 34%). Prior studies of stroke laterality have also reported a slight left-sided preponderance (54%-57%).[15] In our study, we found a higher prevalence of bilateral AIS (20%) compared to prior reports (~10%).[16] Posterior circulation strokes were seen in 37%, higher than previous general estimates of 20%-30% in AIS patients.[11,12] The MCA was the most common arterial territory in our study followed by PCA. This is similar to data from other studies such as TOAST (n ~ 3000), wherein the MCA was the most common territory; however, basilar strokes were found to be more common than PCA.[14] Basilar artery strokes were not as frequent in our study, possibly due to a lower chance of penetrating paramedian artery strokes related to embolic phenomena.[17] The frontal lobe followed by the parietal lobe and the cerebellum were the most common AIS locations. Embolic strokes have a higher

Table 1: Characteristics of acute ischemic strokes due to pulmonary arteriovenous malformations

Variable	Results, *n* (%)
Confirmatory imaging modality (*n*=97)	
MRI	81 (84)
CT	16 (16)
Number of patients with AIS (*n*=102)	
Single lesion	71 (70)
Multiple lesion	31 (30)
Circulation (*n*=101)	
Anterior	50 (50)
Posterior	37 (37)
Both	14 (13)
Side (*n*=97)	
Left	44 (45)
Right	33 (34)
Bilateral	19 (21)
Vascular territory (*n*=115)	
Single territory	78 (83)
Multiple territory	16 (17)
Middle cerebral	59 (51)
PCA	29 (25)
Posterior inferior cerebellar	7 (6)
Basilar	7 (6)
Anterior cerebral	5 (4)
Superior cerebellar	5 (4)
Internal carotid	1 (1)
Vertebral	1 (1)
Anterior inferior cerebellar	1 (1)
Brain regions (*n*=145)	
Frontal	41 (28)
Parietal	24 (17)
Cerebellum	19 (13)
Temporal	15 (10)
Occipital	14 (10)
Thalamus	12 (8)
Basal ganglia/internal capsule	11 (8)
Pons	4 (3)
Midbrain	3 (2)
Medulla	2 (1)
Prior stroke location (*n*=18)	
Cerebellum	8
Frontal	3
Parietal	3
Temporal	2
Basal ganglia/internal capsule	2
Associated conditions (*n*=30; 30%)	
PE	8
DVT	7
Both DVT and PE	3
AIS post-PAVM closure	3
Cancer	4
Hypercoagulable state	4
APLAS	1
MTHFR mutation	1
Protein S deficiency	1
Factor 5 deficiency	1
Pregnancy	1

PE: Pulmonary embolism, DVT: Deep vein thrombosis, MRI: Magnetic resonance imaging, CT: Computed tomography, PAVM: Pulmonary arteriovenous malformation, AIS: Acute ischemic strokes, PCA: Posterior cerebral

rate of hemorrhagic transformation and intracranial hemorrhage compared to nonembolic strokes.[18,19] We could not estimate the rate of hemorrhage in the systematic review due to insufficient reporting and missing data in the case reports.

PAVMs in our review were more commonly solitary (78%). In general, PAVMs are solitary and unilateral in non-HHT patients (90% and 97%, respectively) compared to HHT patients.[20] Given the high prevalence of HHT patients in our sample (33%), the number of multiple (22%) and bilateral PAVMs (16%) was accordingly higher.[21] PAVMs were present in the lower lobes in 66% of our patients, identical to prior studies of PAVMs which showed a two thirds predilection for the lower lobes.[22,23] Data on the size of PAVMs in our sample were quite limited. The mean PAVM size, reported in 1–3 dimensions, was 27, 21, and 16 mm, respectively; however, the size is likely to be measured heterogeneously across these reports and may not be reliable. Information on feeding and draining vessels was sparsely reported. One-third of patients in our study had HHT, and the mean age of AIS was lower in these patients (42 ± 17 years) than non-HHT patients (47 ± 17 years). We also found a higher prevalence of multiple PAVMs in HHT patients which is characteristic of the disease.[21] While HHT-related PAVM can facilitate strokes, there has not been reported an increased risk of lung or other malignancy, and no such trend was found in our study.[24]

Approximately one-third of the sample had underlying conditions that could predispose to paradoxical embolism. Of note, 18% had concurrent deep-vein thrombosis and/or pulmonary embolism. In patients with AIS due to PFO or PAVM, clinical practice should include an extremity Doppler scan to exclude venous thromboembolism. In patients with young strokes, evaluation for a right-to-left shunt using bubble echocardiogram (class 2a indication) or transcranial Doppler should be considered.[25] The timing on the arrival of the bubbles in the left-sided circulation may help distinguish an intrapulmonary shunt such as a PAVM, which demonstrates late bubble arrival (>4 cardiac cycles), as compared to an intracardiac shunt which demonstrates early bubbles.[26] However, it should be noted that the predictive value of bubble studies for intrapulmonary shunt is suboptimal. In patients with embolic-appearing strokes with no obvious cause, contrast CT chest may be considered part of the workup to identify intrapulmonary shunting with optimal sensitivity.[27]

There are several limitations of our study. Data obtained from case reports, such as AIS characteristics, may not be reliable due to heterogeneous assessments and reporting by different authors. In addition, for a few cases, arterial territory or brain region data were extrapolated based on depicted images. As a result, the quantitative results

Table 2: Characteristics of pulmonary arteriovenous malformations in patients with acute ischemic strokes

Variable	Results, *n* (%)
Confirmatory imaging modality (*n*=100)	
CT pulmonary angiography	95 (95)
Conventional catheter angiography	5 (5)
Time of diagnosis (*n*=102)	
Concurrent with stroke	96 (96)
Prior to stroke	5 (4)
Number (*n*=100)	
Single	78 (78)
Multiple	22 (22)
Side (*n*=98)	
Right	45 (46)
Left	37 (38)
Bilateral	16 (16)
Location (side, lobe) (*n*=94)	
Left lower	33 (35)
Right lower	27 (29)
Bilateral multiple	13 (14)
Right upper	6 (7)
Right middle	5 (5)
Left upper	5 (5)
Bilateral lower	2 (2)
Right multiple	2 (2)
Left multiple	1 (1)
Size (mm), mean (range)	
Dimension 1 (*n*=29)	27±18 (2–74)
Dimension 2 (*n*=17)	21±12 (6–50)
Dimension 3 (*n*=3)	16±1 (15–17)
Treatment modality* (*n*=75)	
"Embolization"	27 (36)
"Coil embolization"	24 (32)
Amplatzer occluder	15 (20)
"Surgical"	4 (5)
"Endovascular"	2 (3)
"VATS"	2 (3)
"Clipping"	1 (2)
HHT (*n*=33; 33%)	
Clinical diagnosis	22 (67)
Mutations	11 (33)
Actinin A	1
ALK1	1
ENG	5
GDF2	1
SMAD4	2

*Recorded as reported by the authors since specific treatment modality under embolization or endovascular was not specified. HHT: Hereditary hemorrhagic telangiectasia, CT: Computed tomography, VATS: Video assisted thoracoscopic surgery

we have reported for these variables may not be entirely accurate. Larger prospective studies with well-defined, standardized protocols are required. We were unable to include patients from studies which did not include patient level data, and those that did not have English language translation or full text (n = 12). This could be a potential source of literature bias.

Conclusions

This study alerts the clinician to PAVM as an etiology of embolic-appearing strokes in young patients. PAVM-related strokes more commonly appear to be multifocal and posterior in location compared to typical overall stroke patterns. Targeted workup, including a CT chest, may be required to promptly identify PAVMs and offer appropriate surgical secondary preventive measures. Stroke may be the first manifestation of HHT-related PAVM as patients may otherwise be asymptomatic.

Author contributions

Srinath Ramaswamy: Conceptualization, Data curation, Data analysis, Statistical Analysis, Manuscript Draft, Manuscript Revisions; Izabela Marczak: Data curation, Data analysis; Yohannes Mulatu: Data curation, Data analysis; Mohamed Eldokmak: Data curation, Data analysis; Alon Bezalel: Data curation, Data analysis; Ariana Otto: Data curation, Data analysis; Steven R. Levine: Conceptualization, Manuscript Draft, Manuscript Revisions.

Ethical approval

Not applicable.

Declaration of patient consent

This manuscript does not contain any personal health information (PHI) such as name, medical record number, photographs, or identifying features. Patient consent was therefore not required in accordance with ICJME guidelines.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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