

Original Article

Neurologic Complications in Hereditary Hemorrhagic Telangiectasia with Pulmonary Arteriovenous Malformations: A Systematic Review

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ABSTRACT: Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant multi-organ condition occurring with a 1 in 3800 prevalence in Alberta. This genetic disorder leads to vascular malformations in different organs including the lungs and brain, commonly affecting pulmonary vasculature leading to pulmonary arteriovenous malformations (PAVMs). PAVMs lead to right-to-left shunts, which may be associated with neurologic complications. We aimed to evaluate and summarize the reported neurologic manifestations of individuals with HHT with pre-existing PAVMs. **Methods:** We performed a qualitative systematic review to determine available literature on neurological complications among patients with PAVMs and HHT. Published studies included observational studies, case studies, prospective studies, and cohort studies including search terms HHT, PAVMs, and various neurologic complications using MEDLINE and EMBASE. **Results:** A total of 449 manuscripts were extracted including some duplicates of titles, abstracts, and text which were screened. Following this, 23 publications were identified for inclusion in the analysis. Most were case reports ($n = 15$). PAVMs were addressed in all these articles in association with various neurological conditions ranging from cerebral abscess, ischemic stroke, hemorrhagic stroke, embolic stroke, and migraines. **Conclusion:** Although HHT patients with PAVMs are at risk for a variety of neurological complications compared to those without PAVMs, the quality and volume of evidence characterizing this association is low. Individuals with PAVMs have a high prevalence of neurological manifestations such as cerebral abscess, transient ischemic attack, cerebral embolism, hemorrhage, and stroke. Mitigating stroke risk by implementing proper standardized screening techniques for PAVMs is invaluable in preventing increased mortality.

RÉSUMÉ : Problèmes neurologiques dans des cas de télangiectasie hémorragique héréditaire avec malformations artério-veineuses pulmonaires : un examen systématique. **Contexte :** La télangiectasie hémorragique héréditaire (THH) est une maladie autosomique dominante qui touche plusieurs organes et dont la prévalence est de 1 sur 3 800 en Alberta. Cette maladie génétique entraîne des malformations vasculaires dans différents organes, dont les poumons et le cerveau. Elle affecte généralement la vascularisation pulmonaire, ce qui entraîne des malformations artério-veineuses pulmonaires (MAVP). En retour, ces MAVP entraînent des *shunts* de la droite vers la gauche qui peuvent être associés à des complications de nature neurologique. Nous avons donc cherché à évaluer et à résumer ces complications rapportées chez des personnes atteintes de THH et affectées par des MAVP préexistantes. **Méthodes :** Au moyen de MEDLINE et d'EMBASE, nous avons effectué une revue systématique qualitative pour évaluer la littérature disponible au sujet des complications neurologiques affectant les patients atteints de MAVP et de THH. Les études publiées comprenaient des études d'observation, des études de cas, des études prospectives et des études de cohorte incluant les termes de recherche « THH » et « MAVP » ainsi que diverses autres complications neurologiques. **Résultats :** Un total de 449 publications a été extrait, ce qui inclut quelques doublons, des résumés et des textes qui ont été passés au crible. Suite à cela, 23 publications ont été identifiées pour être incluses dans notre analyse. La plupart étaient des rapports de cas ($n = 15$). Les MAVP ont été abordées dans tous ces articles en association avec diverses complications neurologiques allant de l'abcès cérébral à l'AVC ischémique en passant par l'AVC hémorragique, l'AVC embolique et la migraine. **Conclusion :** Bien que les patients atteints de THH et présentant des MAVP soient davantage exposés à des risques de diverses complications neurologiques par rapport à ceux ne présentant pas de MAVP, la qualité et la quantité de preuves caractérisant cette association sont faibles. À cet égard, les personnes atteintes de MAVP donnent à voir une prévalence élevée de complications neurologiques telles que l'abcès cérébral, l'accident ischémique transitoire (AIT), l'embolie cérébrale, l'hémorragie et l'AVC. L'atténuation du risque d'AVC par l'adoption de techniques de dépistage standardisées appropriées pour les MAVP est en définitive inestimable pour prévenir une mortalité accrue.

Keywords: Embolic strokes; Stroke; Transient ischemic attack; Hereditary hemorrhagic telangiectasia; Pulmonary arteriovenous malformation; Cerebral abscess; Migraine; Osler–Weber–Rendu syndrome

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), previously known as Rendu–Osler–Weber disease, is an autosomal dominant genetic disorder with a prevalence of 1:3800 in the province of Alberta.^{1,2,3} HHT is characterized by vascular malformations which can affect different organs, including the lungs and brain leading to what is known as pulmonary arteriovenous malformations (PAVMs) and cerebral arteriovenous malformations (CAVMs), respectively. Both can lead to stroke. The estimated annual cost of stroke in Canada is \$2.8 billion according to a 2012 article published in the Canadian Journal of Neurological Sciences, with other estimates indicating upwards of \$3.6 billion.^{4,5} A better understanding of risk factors for HHT patients who may develop stroke is therefore important. Further, there are other associated neurological manifestations in HHT patients with PAVMs that have been noted in the past such as cerebral abscess, migraine, and transient ischemic attack (TIA).

Inherent in this genetic disorder, patients with HHT often exhibit bleeding from both epistaxis and / or gastrointestinal tract along with liver involvement which can also commonly occur.^{1,2,6} Six different genes have been identified, where pathogenic mutations can result in HHT, most of which involve the endoglin (*ENG*) and *ACVRL* genes. The majority of HHT patients have mutations in the endoglin and activin type-II-like receptor kinase 1 (*ACVRL1*) gene causing HHT type 1 and HHT type 2, respectively.⁷ Molecular genetic testing is often sought for patients who are suspected of having HHT and can reveal the specific mutation (i.e. *ENG*, *ALK1* mutation, *SMAD4* mutation).

Patients diagnosed with HHT are categorized as having “definite,” “possible,” or “suspected” HHT based on the clinical Curaçao criteria. These categories coordinate with the following clinical findings: epistaxis, (ii) telangiectasia (lips, oral cavity, fingers, nose), (iii) visceral AVMs (including the lungs, brain, and liver), and (iv) first-degree family history of HHT.^{2,8} Patients with three or four of the criteria present are said to have definite HHT, while having two of the criteria constitutes possible HHT, and one unlikely.

Pulmonary Arteriovenous Malformations

A PAVM is an abnormal connection between a pulmonary artery and a pulmonary vein, where there is low resistance and high blood flow which bypasses the normal capillary bed.⁷ Such malformed connections may lead to what is known as an intrapulmonary right-to-left shunt which can lead to other life-threatening complications.^{7,9,10,11,12} The etiology of such is due to the lack of proper capillary network between the pulmonary arterial branch and pulmonary venous tributary, whereby blood bypasses the network which serves as functions of gas exchange and filtration. As such, PAVMs left untreated can lead to adverse conditions such as cerebral abscess, stroke, paradoxical emboli, and hypoxemia.¹² PAVMs are estimated to be present in 15–50% of patients with HHT, and approximately 80–90% of patients with PAVMs eventually present with HHT.^{7,9,10} They are more commonly found in patients with HHT1 associated with the *ENG* mutation, though reasons for this propensity remain unknown.^{1,11} Patients who do have PAVMs have a 53–70% likelihood of them being in the lower lobes of the lungs.¹¹

PAVMs can be classified as either simple (80–90%) or complex.¹¹ Simple PAVMs consist of a single feeding artery and a single draining vein, whereas the complex PAVMs may consist of multiple feeding arteries or draining veins.¹¹ Patients with PAVMs often experience no symptoms, whereby the PAVMs can go unnoticed

until further complications arise. International guidelines for the diagnosis and management of HHT underscore the importance of screening for PAVMs while they may be in a treatable phase, prior to becoming life-threatening.^{9,13} Complications from untreated PAVMs include associations with stroke, TIA, cerebral abscess, hemoptysis, and hemothorax.⁹ Due to the lack of filtration that normally occurs in the capillary beds of connecting arterial and venous connections in the lungs, patients with PAVMs are at high risk of developing paradoxical emboli, or a passage of a clot from a vein to an artery, which can develop into embolic strokes or cerebral abscesses.¹⁴

Diagnosis of PAVM

The preferred method of screening for PAVMs, with up to 98.6% sensitivity and relatively low risk, is transthoracic contrast echocardiography (TTCE), which is often referred to as “bubble echocardiography.” The combination of TTCE and chest X-Ray (CXR) provides a 100% pick-up rate.^{7,9,13,14,15} The process involves the injection of an agitated saline solution intravenously and observing for microbubbles (contrast) in the left cardiac cavity – indicative of right-to-left pulmonary shunt.¹⁴ The approximate size of the shunt can be semi-quantified based on the opacification of the left ventricle.¹⁴ The values are (a) Grade 0: no bubbles; (b) Grade 1: occasional filling with less than 30 bubbles; (c) Grade 3: moderate filling with 30–100 bubbles; and (d) Grade 4: complete opacification with more than 100 bubbles.¹⁴ International guidelines for the diagnosis and management of HHT recommend that TTCE be used as the initial screening test for PAVMs and that all patients with either possible or confirmed HHT be screened for PAVMs.^{9,13} There are other methods of screening for PAVMs such as chest radiography, pulse oximetry, arterial blood gas analysis, and CT chest.¹⁵

Treatments for PAVM

Surgery was the only method of treatment for PAVMs between the 1940s and late 1970s, where either ligation, excision, segmentectomy, lobectomy, or pneumonectomy were the standard procedures.¹¹ In 1977, Porstmann first reported using embolotherapy for treatment of a PAVM.¹¹ The procedure consists of the obstruction of the feeding artery by means of inserting steel coils, detachable balloons, polyvinyl alcohols among others.¹¹

Few studies have evaluated secondary neurologic complications in HHT patients with PAVMs, in line with the rarity of the disease. We therefore conducted a systematic review to evaluate and summarize neurologic complications in HHT patients who have PAVMs versus those without PAVMs and to consolidate the available literature on the subject.

Methods

A systematic review was conducted, and search terms and strategy were defined to include records pertaining to HHT and PAVMs as well as any subset of neurologic conditions. A systematic approach was outlined in order to consolidate literature from the following databases: MEDLINE (1946 to the present, which also includes Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Ovid MEDLINE(R) Daily) and EMBASE. The systematic review was then updated with the same search terms both in EMBASE and MEDLINE and included any additional manuscripts as of June 2021. Any discrepancies were resolved by reviewer discussion. The search strategy was reviewed with the assistance of a health sciences librarian. Manuscripts were then

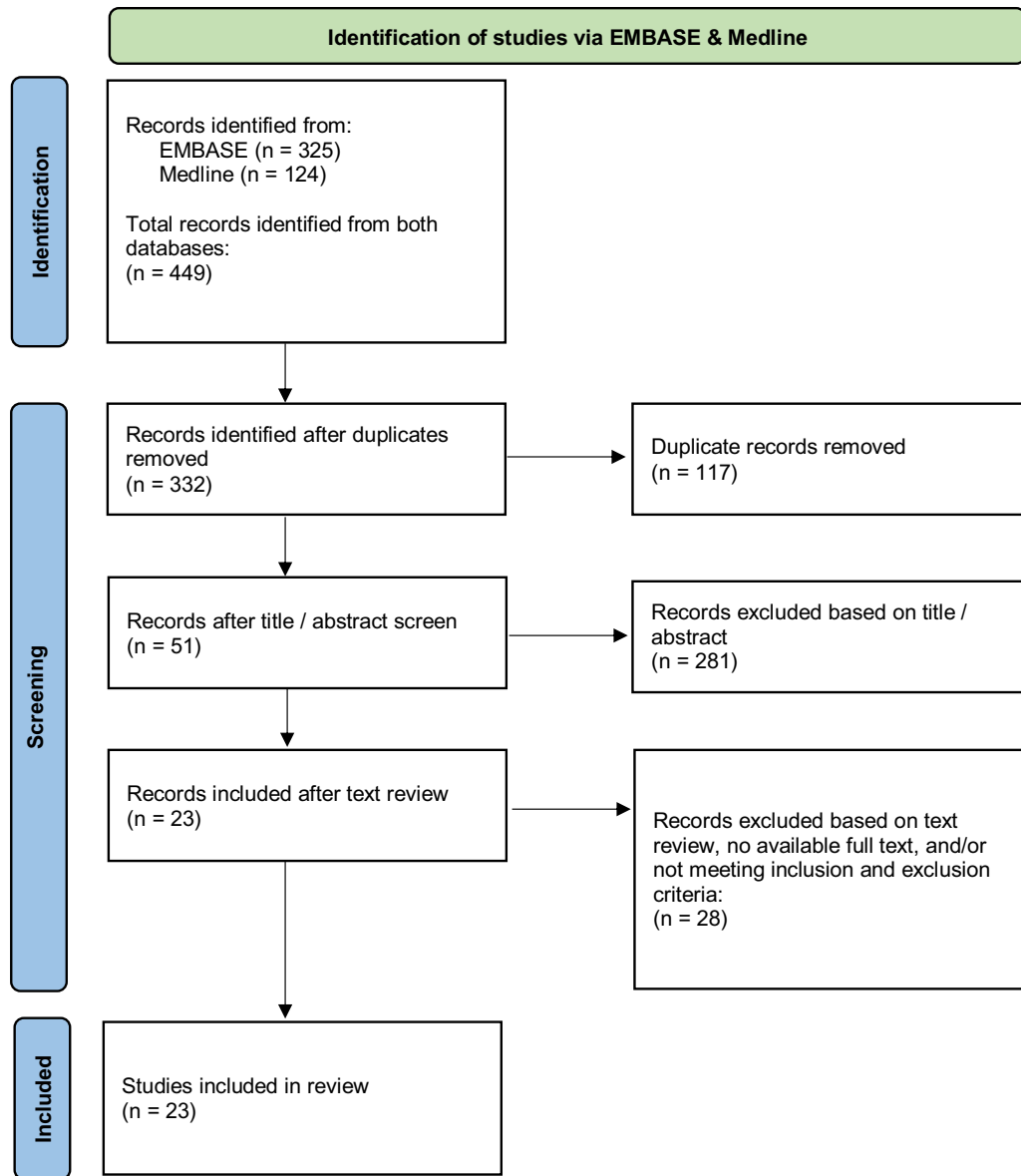


Figure 1: PRISMA flow diagram for identification of studies. Flowchart strategy for HHT patients with PAVMs and neurological complications included a total of 449 citations originally identified and 23 included in the systematic review.

exported into RefWorks where Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods were used to screen records for inclusion in this study (Figure 1).

Inclusion Criteria: We included published observational studies, case studies, prospective studies, retrospective studies, and cohort studies that looked at HHT patients who have PAVMs further complicated with secondary neurologic complications.

Exclusion Criteria: We excluded studies that were not written in English, studies which only included abstracts, review articles, and conference or poster presentations. Studies in which patients had PAVMs but not HHT were also excluded.

Data Analysis: A qualitative analysis was performed on the included manuscripts and summarized in tabulated format (Tables 2 and 3). We rated quality of included studies and risk of bias using the GRADE framework.^{16,17}

Results

We secured a total of 449 records from MEDLINE and EMBASE, which were screened based on title and abstract. Search strategy

including detailed search terms was saved and included in Table 1. Of the total $n = 449$ records, $n = 117$ were identified as duplicate articles from MEDLINE and EMBASE and were subsequently excluded. The first round of screening involved title and abstract review, where $n = 281$ were excluded due to not meeting the inclusion criteria. After text review, a total of $n = 23$ articles were included in the study, and results and major findings were summarized in Tables 2 and 3.

Of the 23 articles included, 15 were case studies, and 8 were non-case studies. PAVMs were addressed in all these articles in association with various neurological conditions ranging from cerebral abscesses, ischemic stroke, TIA, migraine, CAVM and seizure among others.

In summary, there were a total of $n = 15$ case studies with a total of $n = 20$ patients who presented with HHT, PAVM, and some type of neurologic complication. A total of 20 patients resulted from two of the case studies reporting multiple patient cases each, which met our inclusion criteria (Table 3). Ischemic stroke ($n = 13$) was by far the most common neurologic complication. One patient was described to have a stroke, with no detail as to what subtype. Patients also

Table 1: Search strategy used in EMBASE and Medline developed with help of Health Sciences Librarian (UofA, John Scott Library)

Database	Search Strategy
EMBASE	<ol style="list-style-type: none"> 1. exp Rendu Osler Weber disease/ or hht.mp 2. (Hereditary Hemorrhagic Telangiectasia or hereditary haemorrhagic angiomatosis).mp. 3. osler* disease.mp 4. weber osler.mp 5. osler rendu.mp 6. 1 or 2 or 3 or 4 or 5 7. pulmonary arteriovenous fistula/ or pavm.mp 8. pulmonary arteriovenous malformation*.mp. 9. 7 or 8 10. 6 and 9 11. cerebrovascular accident/ 12. (brain ischaemic attack or CAVM or cerebral arteriovenous malformation or brain arteriovenous malformation or brain infarct* or brain attack or cerebrovascular accident* or brain accident*).mp [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 13. (stroke or strokes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 14. 11 or 12 or 13 15. 6 and 10 and 14 <p>Total results: 325</p>
Medline	<ol style="list-style-type: none"> 1. exp Telangiectasia, Hereditary Hemorrhagic/ or hht.mp. 2. Hereditary Hemorrhagic Telangiectasia.mp. 3. osler* disease.mp. 4. weber osler.mp. 5. osler rendu.mp. 6. 1 or 2 or 3 or 4 or 5 7. arteriovenous malformations/ or pulmonary atresia/ 8. pulmonary arteriovenous malformation*.mp. 9. 7 or 8 10. 6 and 9 11. exp Stroke/ or brain arteriovenous malformation.mp. or cerebral arteriovenous malformation.mp. CAVM.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12. (stroke or strokes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 13. 11 or 12 14. 10 and 13 <p>Total results: 124</p>

presented with TIA ($n = 2$), cerebral abscess ($n = 2$), with migraine ($n = 1$), CAVM ($n = 2$), seizure ($n = 2$), epilepsy ($n = 1$), nocturnal headache ($n = 1$), and Todd's Palsy ($n = 1$). Study quality was rated as very low for case series, and therefore, risk of bias was high.

There were a total of $n = 8$ non-case studies (Table 2). Of these, they were cross-sectional studies ($n = 3$), prospective cohort studies ($n = 1$), and retrospective cohort studies ($n = 4$). These eight studies are summarized below by category of methodology. Study quality was rated as low for cross-sectional studies and retrospective cohort studies, and therefore, risk of bias was high. Study quality was rated as moderate for the prospective cohort study with moderate risk of bias.

*Angriman et al., 2014*¹⁸

This cross-sectional study was based on data from 108 patients between 2010 and 2012 accessed through the Institutional records of HHT in Argentina to evaluate for complications related to PAVMs. A primary finding of this study emphasized the disparity between the prevalence of embolic complications (ischemic stroke can be embolic or thrombotic) and between patients with significant PAVMs in comparison to the control group, without significant PAVM. A significant PAVM was defined as those with contrast echocardiography of grade 2 or greater, a PAVM feeding

artery larger than 3 mm, or the patient having had treatment for PAVM in the past. Individuals diagnosed with significant PAVMs indicated a higher risk of developing embolic complications (34.3%) when evaluated with the control group, 9.4% ($p = 0.006$), which was attributed to the potential influence of sex, age, anemia, and age of onset of the PAVM. The most common embolic complication was stroke. Additionally, the study highlighted the increased risk of secondary embolic complications due to PAVMs. Of the 35 patients with significant PAVMs, 9 developed further stroke/TIA, 2 had brain abscesses, and 12 had embolic complications.

This study demonstrated that patients with significant PAVMs are at a higher risk of developing embolic complications. Further, this study also noted that patients with PAVMs were significantly younger ($p = 0.01$) with more pulmonary symptoms (60% vs. 11%, $p < 0.001$) and embolic complications as noted earlier.

*Moussouttas et al., 2000*¹⁹

This cross-sectional study aimed to evaluate the risk of neurological manifestations of 75 patients with PAVMs. Prevalence of brain abscess and seizure was twice as high in patients with multiple PAVMs as compared to those with only one PAVM, though these differences were not statistically significant. Most neurological

Table 2: Summary of non-case study articles included (n = 8)

Study	Study design	N (female)	HHT diagnosis	PAVM diagnosis	Neurological manifestation considered	Genetic testing n (%)	Key results
¹⁸ Angriman, 2014	Cross-sectional	108	Diagnosis based on Curaçao criteria*		Cerebrovascular accident, transient ischemic accident, brain abscess, or peripheral embolism		– Patients with significant PAVM have a higher risk of developing embolic complications than those without significant PAVM
²¹ Boother, 2017	Prospective Cohort	445 (267)	Diagnosis of HHT was made in the presence of PAVMs plus at least 2 of epistaxis, characteristic telangiectasia, family history, and other visceral AVMs, or a positive HHT gene test -403 with HHT		Cerebral abscess	Not captured	– Males with PAVMs were at higher risk of cerebral abscess, estimated as 2.63-fold (95% CI 1.18- to 5.86-fold) – 1 in 16 individuals with PAVMs experienced a cerebral abscess by median age of 48 years, usually before their PAVMs were diagnosed
²² Etievant, 2018	Retrospective Cohort	170	Diagnosis based on Curaçao criteria, and molecular diagnosis		Brain abscess, ischemic stroke	– HHT1/ENG: 120 (70.6), – HHT2/ALK1: 23 (31.5), – SMAD4: 8 (4.7)	– 15 presented with brain abscess, 26 presented with ischemic stroke – Larger feeding artery significantly associated with more ischemic strokes – Largest feeding artery diameter of PAVM significantly associated with frequency of ischemic stroke, and the # of PAVMs with the risk of brain abscess
¹⁹ Moussouttas, 2000	Cross-sectional	75	Diagnosis based on Curaçao criteria	Defined as solitary PAVM with an FA diameter of ≥ 3 mm	Migraine, CVM, cerebral abscess, seizure, ischemic event, cerebral infarct	Not captured	– Strong association between single PAVM and various neurologic manifestations, and greater for multiple PAVM – 64% (29/45) of patients with multiple PAVM and 29% (6/21) of patients with a single PAVM had ischemic involvement (OR 4.5, 95% CI 1.47 to 14, p 5 0.008) – Prevalence of ischemic stroke increased from 14% (patients with one PAVM) to 27% (patients with multiple PAVMs) – Study evaluated the risk determinants for cerebral ischemia and neurologic manifestations in patients with PAVM – Patients with multiple PAVMs had greater prevalence of infarction, cortical infarction, subcortical infarction, abscesses, and seizures – Prevalence of all types of cerebral infarction increased from 32% (patients with single PAVM) to 60% (patients with multiple PAVM)

(Continued)

Table 2: (Continued)

Study	Study design	N (female)	HHT diagnosis	PAVM diagnosis	Neurological manifestation considered	Genetic testing n (%)	Key results
²³ Post, 2005	Retrospective Cohort	538	Diagnosis based on Curaçao criteria	Confirmed with CT scan or pulmonary angiography.	CAVM, brain abscess, TIA, brain infarction, migraine	Not captured	<ul style="list-style-type: none"> – Patients with PAVM had higher prevalence of CAVM compared to those without PAVM (13.0% vs 4.2%, respectively (p < 0.001)) – Patients with PAVM had 9.1% prevalence of brain abscess vs 0% for patients with no PAVM (p < 0.001) – Patients with PAVM had 8.7% prevalence of TIA vs 1.2% for patients with no PAVM (p < 0.001) – Patients with PAVM had 16.8% prevalence of brain infarction vs 1.2% for patients with no PAVM (p < 0.001) – Higher prevalence of migraine in patients with HHT and PAVM is found compared to those without
²⁴ Shovlin, 2008	Retrospective Cohort	323	International criteria: nosebleeds, mucocutaneous telangiectasia, visceral involvement, and family history	All patients with possible HHT were screened for PAVM	Migraine, ischemic strokes, brain abscess	Not captured	<ul style="list-style-type: none"> – Stroke/ abscess risks could not be predicted by respiratory symptoms or PAVM severity in individuals with HHT and PAVMs – PAVM embolization significantly reduced ischemic stroke rate (p = 0.028); no strokes/ abscesses occurred following obliteration of all angiographically visible PAVMs – 74 (33.8%) patients with PAVM had a brain abscess or clinical stroke – All 57 abscess/ischemic stroke patients had underlying HHT (p = 0.023, Fisher's exact test). Only 1 HHT patient had ischemic stroke without PAVMs – No significant association with PAVM and brain abscess
²⁵ Shovlin, 2014	Retrospective Cohort	497 (302)	Clinical diagnosis of HHT	Radiologically confirmed PAVM	Ischemic strokes,	Not captured	<ul style="list-style-type: none"> – Data suggest that patients with PAVM are at increased risk of ischemic stroke if they are iron deficient, likely due to enhanced aggregation of circulating platelets – Study suggests that pts with CT-proven PAVMs, the key biomarker for ischemic stroke risk seems to be iron deficiency rather than the severity of the right-to-left shunt – 61 (12.3%) of individuals experienced at least one stroke (median age 52 ys (IQR 41–63 ys))
²⁰ Velthuis, 2011	Cross-sectional	1038 (608)	Diagnosis based on Curaçao criteria	TTCE	Ischemic stroke, TIA, or brain abscess)	<ul style="list-style-type: none"> – HHT1 218 (21.0) – HHT2 294 (28.3) – SMAD4 6 (0.6) 	<ul style="list-style-type: none"> – Prevalence of cerebral manifestation (TIA, brain abscess or ischemic stroke) in patients with pulmonary RLS was 8.3% vs 1.4% in patients without pulmonary RLS (p < 0.001) – Cerebral manifestation prevalence based on pulmonary shunt grade: 1.4%, 0.4%, 6.5%, and 20.9% for pulmonary shunt grade 0, 1, 2, and 3 on TTCE, respectively – TTCE more sensitive screening tool than pulmonary angiography or chest HRCT scan

HHT = hereditary hemorrhagic telangiectasia; PAVM = pulmonary arteriovenous malformation; CAVM = cerebral arteriovenous malformation; TTCE = transthoracic contrast echocardiography; TIA = transient ischemic attack; RLS = right-to-left shunt; HRCT: high-resolution computed tomography.

*Curaçao criteria consist of 1. epistaxis, 2. telangiectas/es, 3. visceral lesions, and 4. family history. Individuals with three criteria are said to have definite HHT. Individuals with two criteria are said to have possible or suspected HHT. Individuals with fewer than two criteria have unlikely HHT.²

Table 3: Summary of case studies included (n = 15). All patients had a diagnosis of HHT

Study	Case(s)	Age (sex)	PAVM	Neurological manifestation	Genetic testing	Key results	Diseased / cause of death
³⁰ Byrne, 2009	1	56 (m)	- Pt underwent coil embolization of PAVM	Nocturnal headache, generalized seizures, Todd's palsy, recurrent cerebral abscess	No information	- Case underscores importance of life-long follow-up for pts with HHT and treated PAVM - Pt underwent PAVM embolization, was subsequently lost to follow-up, developed cerebral abscess and later died from a pulmonary embolus	Yes: died of pulmonary embolus
³¹ Cappa, 2018	1	32 (m)	- CT angiogram confirmed a 3.1 by 1.8 cm PAVM - Feeding artery to the AVM measured 5 mm - Grade 2 shunt - Pt underwent embolization	Infarct in the left middle cerebellar artery territory (ischemic stroke), and small chronic cerebellar infarcts, epilepsy	<i>ACVRL1</i>	- Case of undiagnosed pulmonary AVM leading to recurrent paradoxical emboli to the brain - Case underscores the need to consider PAVM in the differential diagnosis for cryptogenic stroke - CT scans should be done 6–12 months after embolization then every 3 years thereafter	No information
³² Felix, 2008	1	17 (m)	- TTCE diagnosed right-left shunt (related to untreated PAVM)	Aphasia at presentation which spontaneously resolved in 10 hrs - hyper-intense cortical lesions, ischemic stroke	<i>ALK1</i>	- Pt had stroke episode 48 hours after PAVM embolization - Case suggests further look at use of antiplatelet drug (i.e. low dose aspirin) use after PAVM embolization in pts with HHT in order to prevent potential thrombus formation	No information
³³ Hewes, 1985	Case 1	34 (f)	- CT: small, simple PAVM in left base with single feeding artery and draining vein	- Cerebral embolic occlusion secondary to a paradoxical embolus from the pulmonary AVM (ischemic stroke)	No information	- Pt admitted to hospital for ballooning embolization of PAVM	No information
	Case 2	21 (f)	- Multiple PAVMs seen on chest radiograph	- Seizure	No information		No information
	Case 3	64 (m)	- Successful embolotherapy of a large complex PAVM	- Paradoxical embolism (ischemic stroke)	No information	- Pt underwent successful embolotherapy of large PAVM August 1982. In December of 1982 developed paradoxical embolism - later found more PAVMs which were occluded using angiographic catheters and detachable balloons	No information
	Case 4	35 (f)	- Pulmonary arteriography showed two moderate-sized PAVMs	- Cerebrovascular accident (stroke) with left arm weakness and slurred speech that resolved immediately - CAVM	No information	- Pt admitted to hospital for stroke. Cerebral arteriography revealed an occlusion of the right middle cerebral artery and two AVMs (CAVM) - PAVMs were discovered	No information
	Case 5	26 (m)	PAVM	- Embolic occlusion of the right middle cerebral artery (ischemic stroke)	No information	- After embolic incidence, pt recovered and underwent elective balloon embolotherapy of a single moderate-size PAVM	No information
³⁴ Kane, 2016	1	21 (m)	- Chest CT found several PAVMs	- Acute ischemic stroke	No information	- Patient recovered after stroke and medications. - case study highlights the importance of identifying pts with PAVMs before they lead to neurologic complications such as stroke - iron deficiency is a factor associated with ischemic stroke in patients with HHT	No information
³⁵ Kawaguchi, 1990	1	52 (m)	- Multiple PAVMs	- Multiple CAVMs, brain abscess	No information	- At age 49, pt underwent drainage of brain abscess, at which time a CAVM was detected near the brain abscess - Development of CAVMs and PAVMs “may” have been unrelated - neurological complications secondary to PACMs include 1) hypoxic encephalopathy due to a reduction in the blood oxygen concentration caused by the pulmonary arteriovenous shunt; 2) cerebral thrombosis due to secondary polycythemia; 3) paradoxical embolus; and 4) brain abscess	No information

(Continued)

Table 3: (Continued)

Study	Case(s)	Age (sex)	PAVM	Neurological manifestation	Genetic testing	Key results	Diseased / cause of death
³⁶ Kodati, 2019	1	30 (f)	– CT pulmonary angiography confirmed PAVM	– MRI indicated multiple chronic infarcts in right frontal lobe of cerebellum (ischemic stroke)	No information	– Pt had embolization for PAVM which improved her symptoms – “Family members of patients with HHT should be evaluated for this condition as AVMs may result in life-threatening complications like bleeding, paradoxical embolization, and pulmonary hypertension.”	No information
³⁷ Lu, 2020	1	19 (m)	– Bubble contrast study detected massive right-left shunt. CT pulmonary angiography revealed PAVM – two feeding arteries of 7.43-mm and 4.95-mm diameter in the left lower lobe	– Acute cerebral infarcts and signs of old infarcts (recurring ischemic stroke)	No information	– Pt presented with paralysis of arm. Suffered reoccurring stroke, and large PAVM – Pt underwent embolization for PAVM	No information
³⁸ Morier, 2011	1	67 (f)	– Isolated PAVM surgically removed in 1969	– Embolic stroke (ischemic stroke), migraine with visual aura, TIA		– Pt underwent embolization of eight PAVMs to reduce risk of stroke. After this, dyspnoea was improved; however, migraine frequency was not improved – Risk of stroke recurrence in this pt was estimated to be high due to lack of proper antiplatelet treatment, and incomplete PAVM treatment	
³⁹ Pareés, 2010	1	44 (f)	Cardiothoracic CT and MR angiography reveal one PAVM in lower lobe of the right lung	– Acute ischemic stroke	No information	– First case which reported stroke in a pt with recent air travel associated with PAVM – five days prior to admission, pt traveled by airplane. At admission, pt underwent cerebral MRI which indicated acute ischemic infarction. Plasminogen was given to pt 2 hrs after symptoms – Paradoxical embolism was suspected because of recent air travel – case highlights paradoxical embolism through the PAVM was the most probable pathophysiological mechanism of stroke	No information
⁴⁰ Ribeiro, 2011	Case 1	35 (m)	– PAVM detected. Later embolized	– Left temporal infarction (ischemic stroke)	SMAD4	– Pt presenting with PAVM (asymptomatic) with feeding artery of 2.4 mm. One month later pt. had infarction as detected through MRI – Antiplatelet therapy was started afterwards and no stroke recurrence or complications were observed during 7 years of follow-up	No information
	Case 2	36 (f)	– PAVM in the right pulmonary lobe. Treated by coil embolization	– Anterior-medial thalamic infarctions (ischemic stroke)	ENG	– Pt presented with stroke. Paradoxical embolism thought to be the cause of stroke – After embolization (coil) of PAVM, no complications occurred in the following two years – Long-term follow-up of pts after embolization is critical – Importance of treating PAVMs with transcatheter embolotherapy on a case-by-case basis – regardless of feeding artery diameter	No information
⁴¹ Tabakow, 2005	1	53 (f)	– CT revealed six PAVMs, most with feeding artery >3 mm in diameter	– Cerebral abscess	No information	– Pt admitted with headache, nausea, vomiting. CT and MRI revealed cerebral abscess. Pt underwent surgery for removal and drainage of abscess – PAVM should be considered in case of brain abscess of unknown etiology	No information
⁴² Tsetso, 2013	Patient 4	34 (m)	– Multiple PAVMs	– Stroke with a left hemisindrome (ischemic stroke), seizures – Cerebral CT showed air embolism	No information	– Pt with PAVMs and ischemic stroke – PAVMs were embolized which lead to pt recovery	No information
⁴³ Villa, 2020	1	22 (m)	– Chest CT revealed multiple PAVMs	– Transient ischemic attack (TIA)	ENG	– HHT should be considered in young patients with unknown cause of cerebral ischemic events	No information
⁴⁴ Yassi, 2014	1	57 (m)	– PAVM	– Ischemic stroke	No information	– Pt diagnosed with HHT at 32 yrs. MRI detected stroke – Catheter occlusion of PAVMs is well-established treatment for prevention of neurological complications	No information

complications were higher in patients with multiple PAVM as compared to patients with a single PAVM, except for cerebral vascular malformation (or CAVM) possibly suggesting that PAVMs and CAVMs occur independently. The following is a summary of these results: migraine was present in 50% of those with a single PAVM versus 63% of those with multiple PAVMs (OR 1.7, 0.66–4.51, $p = 0.267$); seizure 4% versus 20% (OR 6.4, 0.77–53.20, $p = 0.054$); ischemic stroke 38% versus 47% (OR 1.4, 0.54–3.73, $p = 0.482$); cerebral infarct 32% versus 60% (OR 3.2, 1.20–9.44, $p = 0.030$); and cerebral abscess 8% versus 16% (OR 2.3, 0.46–11.94, $p = 0.295$). On the other hand, cerebral vascular malformation was found in 19% of those with one PAVM versus 11% in those with multiple PAVMs (OR 0.5, 0.11–2.76, $p = 0.456$).

Velthuis et al., 2013²⁰

This cross-sectional study compared cerebral complications between patients with HHT and differing pulmonary shunt grading associated with PAVMs. The findings suggest that there was a higher prevalence of cerebral complications (either ischemic stroke, TIA, or brain abscess) among patients with a pulmonary right-to-left shunt (8.3%), as compared to patients without a pulmonary right-to-left shunt (1.4%; $p < 0.001$). Further to this, the percentage of patients with cerebral manifestations differed significantly depending on the grade of the pulmonary shunt (pulmonary shunt grade 0, 1, 2, and 3 corresponding to 1.4%, 0.4%, 6.5%, and 20.9%, respectively). This finding differs from *Shovlin, 2014* wherein shunt severity was not found to have an impact on neurologic complications. Findings from this study indicate that shunt size needs to be taken into consideration when determining potential development of neurological complications.

Boother et al., 2017²¹

This prospective cohort study analyzed the data from a total of 445 patients, all of whom had CT-confirmed PAVMs. They evaluated whether previously recommended measures (including judicious dental hygiene, antibiotic prophylaxis prior to dental and surgical procedures, and embolization of asymptomatic PAVMs) had led to reduced morbidity from cerebral abscess. Cerebral abscess poses a serious risk for patients as it is often associated with right-to-left shunting, where infected material can enter the brain. Previous literature analyzed in this study suggested that cerebral abscess affects 7–9% of PAVM patients, due to lack of proper filtration through the normal diameter (7–10 μm). It was noted that 8.3% of these patients experienced a cerebral abscess (confirmed through neurosurgical drainage). Additionally, of these patients 37% reported having untreated infections in their mouth (dental infection) when assigned to their associated groups based on presentation data where case notes were documented to capture patient-specific variables. This provides insight into the preventative measure, of dental hygiene, and its significance as an effective precautionary method of preventing cerebral abscesses. Males with PAVMs were found to have an increased risk of developing cerebral abscess, estimated as 2.63-fold higher, indicating a greater than double assessment of PAVM diagnosis in males compared to females. Overall, the role of PAVMs on cerebral abscess had not yet been defined; however, the importance of screening is stressed for patients who have experienced cerebral abscess. Further research needs to be evaluated to analyze a broader range of preventative measures to suggest more effective mechanisms to reduce morbidity from PAVMs.

Etievant et al., 2018²²

This retrospective cohort study in HHT populations determined the associations of PAVMs with cerebral abscess and ischemic strokes. Of the 170 patients included in the study, 8.8% presented with cerebral abscess. Impressively, these patients with cerebral abscess were exclusively in the group who had non-treated PAVMs, highlighting the importance of proper screening and treatment. Further, 16.5% of the total patients had ischemic stroke, which is marginally high compared to expected. Most of these stroke patients were also non-treated for PAVMs and further had significantly larger feeding artery (4.9 mm versus 3.2 mm; $p = 0.009$). Significant correlations were found between the prevalence of neurological complications and CT imaging of PAVMs. This study further subclassified the types of PAVMs and found that there was an increased risk of cerebral abscess in those with multiple, diffuse, or disseminated PAVM. Along with cerebral abscesses, the study highlighted the statistically significant relationship between diameter of the largest feeding artery of the PAVM and frequency of ischemic stroke. The authors urge clinical practice to treat PAVMs by embolotherapy at the soonest notification of cerebral complications in order to decrease further risk. Causality amongst these fascinating correlations remains speculative or unaddressed.

Post et al., 2005²³

A total of 538 HHT patients were included in this retrospective cohort study, and the findings suggest that migraine is more common in HHT patients with PAVM, as well as more common in HHT patients as compared to the general population. Migraines occur in 10–12% of the population, and studies show a higher prevalence in HHT patients. The current study indicated that migraine was present in 88 of the 538 (16.4%) patients who had HHT. Migraine prevalence was higher in HHT patients who had PAVM (21.2%) as opposed to those without PAVM (13%) and interestingly, significantly more prevalent in women with PAVM than men (65.4% vs 34.6%; $p = 0.009$). Further to migraines, the percentage of patients developing other neurological conditions with PAVMs as opposed to without PAVMs respectively was as follows: CAVMs (13% vs 4.2%), brain abscess (19% vs 0%), TIA (18% vs 4%), and brain infarctions (35% vs 4%) all with $p < 0.00$. The study further attempted at describing possible reasons for the linkage between migraines and PAVMs. One such speculation considers that due to the possibility that HHT and some subtypes of migraines are autosomal dominant disorders, a genetic reason may be involved in providing an explanation. However, a more plausible explanation is the possibility of “trigger” substances passing through the right-to-left shunt and inducing cerebral instabilities which can lead to migraines. This study postulates that PAVMs play an important role in the pathogenesis of migraines, and further work is needed to develop this understanding.

Shovlin et al., 2008²⁴

In this retrospective cohort study, 323 individuals with PAVMs were included where 74 (33.8%) with PAVMs had a brain abscess or stroke. Interestingly, univariate analysis found no significant relationship between brain abscess and the markers of PAVM severity. A large proportion of those with brain abscess and PAVMs had events which are known to have associations with bacteremia in the weeks prior to the cerebral abscess (three with scale

and polish procedures, and four with occlusive braces and fillings). This study also found no significant relationship between PAVM parameters and ischemic stroke incidents.

Shovlin *et al.*, 2014²⁵

In another retrospective cohort study with 497 individuals, they were able to identify that the strongest risk factor for stroke in patients with HHT and PAVMs was iron deficiency rather than the severity of the right-to-left shunt. No statistically significant association was found between PAVM and stroke when looked at in isolation. This is an important finding that the authors hypothesize is related to a model which suggests that iron deficiency is associated with platelet aggregation.²⁶ This needs to be further studied to better understand the physiological underpinnings.

Discussion

The aim of our systematic review was to consider HHT patients and identify their risk of developing neurologic complications in those who have PAVMs as compared to those without PAVMs. This is the first comprehensive review of this topic in an HHT population to our knowledge.

The findings of this review suggest that HHT patients with PAVMs have a high prevalence of neurological manifestations such as cerebral abscess, TIAs, cerebral embolism, hemorrhage, and stroke. Strokes were highlighted most often in literature analyzed within this review; however, a positive correlation between PAVMs and the risk of cerebral abscess was also indicated, with one study indicating males at a higher risk.²¹ HHT patients with PAVMs are at risk of life-threatening complications and require proper screening and diagnosis. Review of the available literature indicates a clear need for HHT patients to be screened for PAVMs to prevent this risk.^{27,28,29}

Risk of cerebral complications which arise because of right-to-left shunting in patients with PAVMs remains. Interestingly, there was conflicting data regarding the risk of neurological complications based on the PAVM right-to-left shunt grade. Shovlin *et al* were able to demonstrate the risk factor for stroke in patients with HHT, and PAVM was more strongly associated with iron deficiency rather than the severity of the right-to-left shunt, which was in direct opposition to the findings of Velthuis *et al* who demonstrated a higher percentage of neurologic complications as the shunt grade increased from 0 to 3.^{20,25} This was also demonstrated by Etievant *et al*, who showed a significant relationship between diameter of feeding artery and frequency of ischemic stroke.²² Moussouttas *et al* demonstrated that brain abscess and seizure were two times as high among those with multiple PAVMs as compared to those with only one PAVM.¹⁹ Shovlin *et al* hypothesize that iron deficiency among patients with PAVMs can lead to platelet aggregation thus increasing the risk for stroke and indeed demonstrated this. The lack of studies on this topic given the prevalence of disease indicates there is further research needed to better understand the physiologic underpinnings of risk of cerebral events, and further work is needed to better understand the role of iron among patients with HHT and PAVMs.

Neurologic manifestations can arise when bacteria or other larger fragments pass through a PAVM and into the brain causing a cerebral abscess. The pathophysiology of PAVMs is a cause of concern for the patient in many regards. The irregular arterial to venous connection of a PAVM may lead to right-to-left shunting leading to inadequate oxygenation of the surrounding tissue as well

as improper filtration. Patients with PAVMs must be careful especially when receiving dental work, to reduce the risk of infections. Boothe *et al* demonstrated 37% of those with cerebral abscess had untreated infections in their mouth.²¹ Patients with PAVMs should be especially careful in such situations, and healthcare workers should be aware of these risks. Boothe *et al* also described the bacterial isolates indicating that most cerebral abscess cultures were microaerophilic and anaerobic bacteria, and culture negative.²¹ Etievant *et al* studied this relationship between PAVMs and cerebral abscess and found that the number of PAVMs strongly positively correlated with risk of cerebral abscess, and that the larger the feeding artery was, the more strongly related with risk of ischemic stroke.²² Small sample size was noted in many reports due to HHT being a rare disease. One study included a large number of patients ($n = 445$) and found similar results with strong associations between PAVMs and cerebral abscesses.²¹ Of these, 10 cases included PAVMs which were diagnosed because of a cerebral abscess. The study further identified that low oxygen saturation and intravenous iron may be associated risk factors involved in cerebral abscess. Through multiple regression analysis, association of cerebral abscess was found to be insignificant with number of PAVMs. The prospective cohort studies which are likely to provide the most accurate measures of prevalence quote a variable cerebral abscess risk from 8.3% to 33.8%.^{21,24} There is need for better understanding of the pathophysiological mechanism for cause of cerebral abscess, especially in HHT patients who have PAVMs.

It is clear through this review that PAVMs and migraines are not reported commonly. Studies have found an increase in migraine frequency in cardiac right-to-left shunts; however, Post *et al* described this phenomenon in pulmonary right-to-left shunts. They were able to find a modest (21.2%) increase in the prevalence of migraine in PAVM patients than in non-PAVM patients (13.3%), $p = 0.02$. This is not necessarily unexpected, as a right-to-left shunt is often associated with undesired particles passing through. The study describes a more plausible possibility of the passing of a “trigger” substance through the right-to-left shunt, which may induce cerebral vascular instability.²³ Though this is plausible, there is need for further research for any definitive answers. Further, there are potential further research opportunities considering the correlation between the specific genetics an HHT patient with a PAVM has in relation to risk of migraine.

A recent study looked at the links between strokes and HHT in Alberta and found there to be a significantly higher risk than compared to the general global population (450 per 100,000 versus 260 per 100,000, respectively).³ There may very well be an increased prevalence of stroke among those with PAVMs in this same HHT population. Our work underscores the need for appropriate screening for PAVMs within HHT Centres. The risk of cerebral events associated with PAVMs demands that this be done consistently to reduce such incidents. According to the most recent international guidelines for the diagnosis and management of HHT patients, there is strong emphasis on flagging pregnant women with PAVMs or CAVMs as being high risk for hemorrhagic and neurologic complications.^{13,45} This also applies to those patients who have not yet been screened.

The strength of this narrative review is that it addresses an important gap in the literature in regard to the neurological manifestations of HHT patients with pulmonary AVMs and identifies areas for future work. The review is limited by the low volume of studies and the relatively low quality of evidence available. There is

overall need for further research considering the prevalence of neurologic complications among the various types of HHT and genotype-phenotype correlations within this population.^{1,11}

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