Asymptomatic pulmonary arteriovenous malformations in children with hereditary hemorrhagic telangiectasia

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Abstract

Background: Children with Hereditary Hemorrhagic Telangiectasia (HHT) may have pulmonary arteriovenous malformations (AVMs), which can lead to symptoms of shortness of breath, exercise intolerance, clubbing, cyanosis and hemoptysis. However, some patients with pulmonary AVMs may be asymptomatic, placing them at risk for complications such as stroke or brain abscess if they are not identified and treated. This study examines the incidence of signs and symptoms associated with pulmonary AVMs in children with HHT known to have pulmonary AVMs.

Method: Sixty-one children with HHT and documented pulmonary AVMs were questioned for any symptoms possibly associated with their pulmonary AVMs, prior to embolization.

Results: The results show that the majority of these children were asymptomatic (56%), and their AVMs were discovered by routine screening. Those who did experience symptoms most often complained of shortness of breath and exercise intolerance, although there was a tendency to blame other conditions, such as asthma or deconditioning (being out of shape), for these symptoms. Migraine headaches were common in those with pulmonary AVMs, regardless of whether they were symptomatic or not (17 of 61 children, 28%), although they were more common in those who were symptomatic (10 of 27, 37%) versus those who were asymptomatic (7 of 34, 21%).

Conclusion: Children with HHT and pulmonary AVMs are often asymptomatic. Routine screening for the presence of AVMs should be performed regardless of symptomatology.

KEYWORDS
hereditary hemorrhagic telangiectasia (HHT), pulmonary arteriovenous malformations (PAVM), pulmonary vascular disorders

1 | INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT) is a vascular disease, inherited in an autosomal dominant fashion.1 Manifestations range from dilation of postcapillary venules to arteriovenous malformations (AVMs).2 The prevalence of HHT ranges from 1:5000 to 1:10 000,1,3,4 with no difference with race, ethnicity, or sex.2,5,6

HHT demonstrates incomplete penetrance and increased expressivity with age.7–9 Most clinical signs appear between the 4th and 6th decades of life.10 However, by 16 years of age approximately 70% of patients will show some signs of HHT, while by 40 years of age over 90% will manifest signs.6 In children, family history is an important indicator of HHT as the clinical manifestations typically become noticeable in adulthood.11 The clinical criteria lack sensitivity in children and underestimate the presence of this disease in this age group.7,12–15

Ten percent of patients with HHT will suffer major disability or die prematurely, primarily as a result of pulmonary AVMs and cerebral AVMs.6 In patients with HHT, pulmonary AVMs are most often diagnosed in the 2nd and 3rd decades of life.4,16 However, AVMs may be present early in life, sometimes resulting in serious, life-threatening complications.12,17 Pulmonary AVMs have even been reported in newborns.18–21

Symptoms typically associated with pulmonary AVMs include dyspnea on exertion and other symptoms of hypoxemia (cyanosis, clubbing, polycythemia), as well as hemoptysis and neurological
complications (stroke, cerebral abscess).\textsuperscript{6,22–24} Migraines also occur more frequently in patients with pulmonary AVMs than in the general population.\textsuperscript{25–28} Unfortunately, the majority of HHT patients with pulmonary AVMs are undiagnosed at the time of a pulmonary AVM-associated ischemic stroke (66.7\%) or cerebral abscess (64.3\%).\textsuperscript{29} In one study, mortality as a result of pulmonary AVM-related events occurred in 11\% of untreated patients.\textsuperscript{9} Therefore, prevention of morbidity and mortality relies upon identifying patients with HHT who have pulmonary AVMs.

It is estimated that pulmonary AVMs are present in 40-55\% of patients with HHT, including those who develop or present with symptoms during childhood.\textsuperscript{14,15,30,31} While patients of any age may be asymptomatic at the time of diagnosis,\textsuperscript{32,33} general practice is to screen for pulmonary AVMs only in those children who are symptomatic. Screening is often deferred in children given the variability of clinical features,\textsuperscript{13} unclear practice guidelines, and the belief that children with pulmonary AVMs must necessarily be symptomatic. This leads to potential avoidable risk.\textsuperscript{34} The purpose of this study is to examine the presence or absence of signs and symptoms in children with HHT who have known pulmonary AVMs.

\section{METHODS}

A retrospective review was performed on children with definite HHT and documented pulmonary AVMs to assess for the presence or absence of signs and symptoms typically associated with pulmonary AVMs. Pediatric patients with HHT are enrolled into the local HHT database, which was queried for the presence of definite HHT as defined by the Curaçao criteria and the presence of pulmonary AVMs.\textsuperscript{1} The charts of those patients were reviewed in detail for the presence of any signs or symptoms associated with pulmonary AVMs, including shortness of breath, exercise intolerance, hypoxemia, cyanosis, clubbing, hemoptysis, as well as migraine. In addition, the presence or absence of cerebral AVMs in this study was determined using brain MRI/MRA. All signs and symptoms were recorded and tabulated.

Exercise intolerance was divided into true exercise intolerance as well as intolerance due deconditioning, anemia, asthma, as well as neurologic causes. Exercise intolerance is subjective and due to several possible factors. The exercise intolerance classification given to patients in this study reflect the symptoms of which they complained. In addition, a few patients had exercise stress tests that either supported or refuted the presence of true exercise intolerance. Similarly, the diagnosis of migraine was made clinically and was confirmed by the examining physician based on history.

\section{RESULTS}

Sixty-one children with a known diagnosis of HHT and documented pulmonary AVMs were identified and included in the study. Small pulmonary AVMs were included in the analysis. Only 53\% of patients had pulmonary vessels large enough to embolize, which is generally considered to be feeding vessels with a diameter of 3 mm or larger.\textsuperscript{5}

Of these 61 children, 34 (56\%) had no symptoms to suggest the presence of a pulmonary AVM, whereas 27 (44\%) did experience symptomatology (Table 1). Of those children who were symptomatic, the most common symptom was exercise intolerance, which occurred in 16 of the 27 children. Interestingly, seven of those who were exercise intolerant either failed to recognize this as a symptom or had attributed the exercise intolerance to another cause, such as being out of shape or having asthma (Table 2). Other symptoms included blue lips or fingertips in eight children, hemoptysis in five, and chest pain in four. The complication of stroke occurred in two, and myocardial ischemia in one. Physical examination signs suggestive of pulmonary AVMs were present in some patients, including hypoxemia in eight, clubbing in two, and orthodeoxia in one. Thirteen children had more than one symptom or sign, and a few children had several symptoms.

Of the 27 children who had classic symptoms of pulmonary AVMs, 11 (41\%) experienced headaches (Table 3). Of these 11, only one had non-migraine headaches, whereas 10 had headaches that could be described classically as migrainous (Table 3). Of the 34 children who were asymptomatic, 17 (50\%) experienced any form of headache (Table 3). Ten of these children experienced non-migraine headaches and seven experienced migraine headaches (Table 3).

Re-assessing the data for the presence of symptoms, but including migraine headaches in the analysis, 27 of the 61 (44\%) children would still be considered asymptomatic, while 34 (56\%) would be defined as symptomatic for pulmonary AVMs (Fig. 1). Of note, 22\% of patients without headache and 21\% of patients with headache had brain MRI positive for cerebral AVMs. Eighteen percent of patients with migraine headaches had cerebral AVMs, while 27\% of patients with non-migraine headaches had cerebral AVMs.

\begin{table}[h]
\centering
\caption{Symptom incidence}
\begin{tabular}{|l|c|}
\hline
\textbf{Symptom} & \textbf{\# Patients} \\
\hline
Exercise intolerance & 16 \\
Cyanosis & 8 \\
Hypoxemia & 5 \\
Hemoptysis & 4 \\
CP & 2 \\
SOB & 1 \\
Clubbing & 2 \\
Orthodeoxia & 1 \\
Adverse event & 3 \\
Stroke & 2 \\
Cardiac ischemia & 1 \\
\hline
\end{tabular}
\end{table}
4 | DISCUSSION

International treatment guidelines published in 2011 advocate for the screening for and treatment of pulmonary AVMs. They recommend that physicians screen all patients with possible or confirmed HHT for pulmonary AVMs using chest CT and/or contrast echocardiography. Although less evidence exists in children, the expert panel included children in the screening recommendation, since they are also at risk of life-threatening complications. In patients with negative initial screening, repeat screening should be considered after puberty, after pregnancy, within five years preceding planned pregnancy, and otherwise every 5-10 years. However, current practice by many physicians is to only screen children for pulmonary AVMs if they present with symptoms or signs of pulmonary AVMs. The same guidelines suggest treating asymptomatic children only on a case-by-case basis, but they acknowledge that the safety and efficacy of treatment with transcatheter embolization are similar in children and adults. Consensus guidelines for screening as well as treatment of pediatric patients are lacking.

In this study, the majority of children with definite HHT and pulmonary AVMs were completely asymptomatic. Complications of visceral AVMs, while rare in children, may be severe and may lead to substantial morbidity or mortality. Thus, regardless of the presence of symptoms, radiographic screening for occult pulmonary AVMs should be considered in all children with HHT to decrease the likelihood of complications from unrecognized pulmonary AVMs.

While headache itself is a common complaint in both children and adults, migraine headache is associated with the presence of a pulmonary AVM. Even if headaches are included in the study analysis as a symptom indicative of pulmonary AVM, most children would still be described as asymptomatic. In addition, cerebral AVMs do not appear to be correlated with the presence of headache in our patients.

It is important to acknowledge, however, that underreporting is a limitation of this study given the retrospective nature of the study. Another limitation is that the definitions of exercise intolerance and migraine are made clinically and based primarily on patient testimony. Symptoms of exercise intolerance are vague, subjective and may be misinterpreted.

In conclusion, the majority of children with pulmonary AVMs and HHT are asymptomatic. This reinforces the importance of screening children with HHT for the presence of pulmonary AVMs regardless of symptomatology. This study also raises the question as to whether migraine headache should be considered a symptom indicative of pulmonary AVMs. Prospective registries of pediatric patients with HHT will be integral to creating more definitive guidelines for screening and treatment.

CONFLICT OF INTEREST

Nothing to disclose.

REFERENCES


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<th>Types of exercise intolerance</th>
<th># Patients</th>
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<tr>
<td>True intolerance</td>
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<tr>
<td>Deconditioning</td>
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<tr>
<td>Anemia</td>
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</tr>
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<td>Neurologic</td>
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*Classifications reflect symptoms of which patients complained.

<table>
<thead>
<tr>
<th>Headache type</th>
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<th>Non-migraine</th>
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<td>PAVM symptoms</td>
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<td></td>
<td></td>
</tr>
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<tr>
<td>Total</td>
<td>17</td>
<td>11</td>
<td>28</td>
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</table>

TABLE 3 Headache incidence relative to PAVM* symptomatology

PAVM, pulmonary arteriovenous malformation.

FIGURE 1 Symptomatic children, +/- inclusion of migraine


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