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# Screening for pulmonary and cerebral arteriovenous malformations in children with hereditary haemorrhagic telangiectasia

**S. Al-Saleh*,#,¶,**, M. Mei-Zahav*,#,**, M.E. Faughnan*,+,§, I.B. MacLusky*,#, S. Carpenter*,#, M. Letarte*,f and F. Ratjen*,#,¶**

**ABSTRACT: Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterised by vascular dysplasia complicated by visceral arteriovenous malformations (AVMs). To date, the diagnostic yield of screening procedures for pulmonary and cerebral AVMs in children with definite or potential HHT is not well defined. The aim of the present study was to prospectively evaluate the diagnostic yield of a screening protocol for pulmonary and cerebral AVMs in children with either a definite or potential HHT diagnosis.**

**All children referred for evaluation for HHT between 1996 and 2008 were included in the present analysis. Screening tests for AVMs included chest computed tomography and brain magnetic resonance imaging.**

**61 children with a definite clinical and/or genetic diagnosis of HHT were asymptomatic for visceral AVMs at their first baseline assessment (mean±SD age 8.7±4.7 yrs; range 0–17.0 yrs). Of these, 15 (25%) had pulmonary and/or cerebral AVMs diagnosed on initial screening tests. Pulmonary AVMs predominated in paediatric HHT patients (14 out of 15 patients) and were found in eight children aged <10 yrs. 55 children had a potential HHT diagnosis as they fulfilled only one or two HHT clinical diagnostic criteria and did not have a confirmatory genetic diagnosis (age 10.9±4.8 yrs; range 0–17.9 yrs). None of these children had pulmonary or cerebral AVMs on initial screening tests.**

**The present data suggest that children with a definite HHT diagnosis have a high frequency of pulmonary AVMs even when clinically asymptomatic. In contrast, no AVMs were observed in children not fulfilling HHT diagnostic criteria. Genetic testing appears to be useful in defining an at-risk group for pulmonary AVMs in childhood.**

**KEYWORDS: Arteriovenous malformations, diagnosis, hereditary haemorrhagic telangiectasia, Rendu–Osler–Weber, screening**

Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber syndrome, is an autosomal dominant vascular disorder with an estimated prevalence ranging 1 in 5,000 to 1 in 16,000 depending on the population studied [1–4]. Germ-line mutations in the endoglin (*ENG*) gene on chromosome 9 and the activin receptor-like kinase1 (*ACVRL1*, or *ALK1*) gene on chromosome 12, are responsible for most HHT cases, referred to as HHT type 1 (HHT1) and HHT2, respectively [5–8]. Most mutations are unique and distributed throughout the genes and, therefore, diagnostic testing requires full sequencing of both genes [9, 10]. SMAD family member 4 (*SMAD4*) gene mutations are found in a small percentage (2%) of cases and can be associated with a combined syndrome of juvenile polyposis and HHT (JPHT) [9, 11]. Two additional loci, one on chromosome 5 and one on chromosome 7, have been assigned to HHT3 and HHT4, respectively [12, 13], although the genes remain to be identified. The overall yield of genetic testing for mutations in *ENG*, *ALK1* and *SMAD4* in clinically confirmed cases is high, ranging 78–93% [9, 14, 15].

The pathophysiology of HHT has been reviewed elsewhere [10, 16], and is related to impaired transforming growth factor-β (TGF-β) signalling pathways critical to angiogenesis and the regulation of vascular tone [17]. Mutations in *ENG* or *ALK1* genes result in a significant reduction in the level of functional endoglin and activin receptor-like kinase1 proteins, which are mediators of

AFFILIATIONS
*University of Toronto,
#Division of Respiratory Medicine, Hospital for Sick Children,
¶Physiology and Experimental Medicine, Research Institute, Hospital for Sick Children,
fMolecular Structure and Function Program, Hospital for Sick Children,
+Dept of Medicine, St Michael's Hospital,
§Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada.
**Both authors contributed equally to this study.

CORRESPONDENCE
S. Al-Saleh
Division of Respiratory Medicine,
Dept of Paediatrics
Hospital for Sick Children
555 University Ave
Toronto
ON
M5G 1X8
Canada
E-mail: suhail_alsaleh@hotmail.com

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TGF-β signalling pathways. Such mutations lead to disrupted and abnormal angiogenesis and the formation of focal vascular lesions [10, 16].

Clinically, HHT is characterised by skin and mucosal telangiectases, epistaxis and signs caused by visceral arteriovenous malformations (AVMs). Epistaxis is the most common presenting symptom in adults and occurs in up to 98% of patients with HHT [18–21]. However, almost half of these patients are not symptomatic before adulthood [18, 20, 21]. Skin telangiectases can be seen in 74–89% of cases, but their onset often occurs after epistaxis [20, 21]. Therefore, an early diagnosis during childhood cannot always be achieved based on these clinical features [21].

Visceral HHT manifestations are well described in patients with HHT, and larger series in adults suggest their frequency to be 25–38% [7, 20–22]. Pulmonary, gastrointestinal and cerebral AVMs are more common than spinal and other visceral AVMs [5, 7, 21]. Pulmonary and cerebral AVMs can cause complications, such as intracranial bleeding, brain abscess, ischaemic stroke and pulmonary haemorrhage, and screening of at-risk populations has been advocated [23–32]. Studies in adult patients have demonstrated that significant pulmonary and cerebral AVMs can be detected in asymptomatic patients [5, 6, 22, 31–39], and that preventative treatment can reduce the rate of complications [32]. This is less well established in children, and recent studies have suggested that the overall rate of complications is low in this age group [23, 32]. Whether this is due to a lower rate of pulmonary and cerebral manifestations in children is unclear. To date, frequency estimates of pulmonary and cerebral AVMs are based on case reports and small series [8, 24, 26, 27, 40–51], and the diagnostic yield of initial diagnostic screening procedures in asymptomatic children has not been systematically evaluated.

Therefore, the main objective of the present study was to assess the prevalence of pulmonary and cerebral AVMs detected by routine screening procedures in children with either a definite or potential diagnosis of HHT who do not have symptoms related to pulmonary and cerebral AVMs. The secondary objective was to assess the prevalence of pulmonary AVMs among children with different HHT gene mutations.

## METHODS

### Patient cohort

A systematic review of data from the prospective study of children referred to the HHT clinics at the Hospital for Sick Children and St Michael's Hospital in Toronto (ON, Canada) was performed for the years 1996–2008. The study was approved by the Research Ethics Board of the Hospital for Sick Children and St Michael's Hospital. Children were referred for evaluation for HHT based on either a positive family history of HHT or symptoms and signs of clinical manifestations of HHT. The data review included: 1) children with a definite HHT diagnosis (*i.e.* children with either a definite clinical diagnosis or a confirmed genetic diagnosis) who were asymptomatic for visceral AVMs when they underwent their first baseline assessment; and 2) children either in whom HHT was suspected clinically (epistaxis and telangiectasia) or who had a first-degree relative with HHT asymptomatic for visceral AVMs when they underwent their first baseline assessment; as well as 3) children with symptoms related to visceral AVMs at first assessment. Children who had not been evaluated or had not undergone screening tests for visceral AVMs at the time of the present analysis were not included in this review. Children from parents with a confirmed genetic diagnosis but who tested negative for the familial mutation and children with neither a clear family history of HHT nor clinical signs consistent with HHT were also excluded.

### Study protocol

A standardised protocol was developed for screening for pulmonary and cerebral AVMs within the Toronto HHT programme at the Hospital for Sick Children and St Michael's Hospital in 1996. Screening tests included an unenhanced computed tomography (CT) scan of the chest and magnetic resonance imaging (MRI) of the brain. Although transthoracic echocardiography with agitated saline has been shown to be an important screening tool for pulmonary AVMs, experience in children is rather limited. Therefore, CT was used as part of the screening process in children. A diagnosis of pulmonary AVMs was established by chest CT. Pulmonary AVMs were considered for transcatheter embolotherapy when the feeding artery diameter was $\geqslant$3 mm, based on recommendations for adult HHT patients [52, 53]. Transcatheter embolotherapy was also recommended for patients with signs and symptoms related to pulmonary AVMs (*e.g.* congestive heart failure, cyanosis or haemoptysis) regardless of the diameter of the feeding artery (*i.e.* even if the size of the feeding artery was $<$3 mm) as the symptomatic presentation justified the need for intervention. A diagnosis of cerebral AVMs was established and the embolisation therapy considered when there were characteristic findings of AVMs on brain MRI [23]. Screening for liver AVMs was not included in the programme as patients with large liver AVMs present with symptoms such as heart failure, whereas smaller AVMs do not lead to complications that would need to be addressed by interventions.

### Diagnostic criteria for HHT

A clinical diagnosis of HHT was established according to the Curaçao criteria [54]. These include the following: 1) a history of recurrent spontaneous epistaxis, 2) the presence of multiple skin telangiectases at characteristic locations, 3) a first-degree relative diagnosed with HHT, and 4) the presence of visceral AVMs. A definite clinical diagnosis is established if the patient fulfils three or more of these criteria. A clinical diagnosis is possible if two criteria are present and unlikely if less than two are present. Owing to the limitations of this classification in the paediatric population, and given the age-related expression of HHT symptoms, screening procedures were also performed in children if they fulfilled only one criterion as their risk of developing HHT in the future was unclear. Children with one or two HHT criteria are referred to as the ''potential HHT'' group.

### Genetic testing

Mutation analysis is currently being performed as a clinical diagnostic test at the Hospital for Sick Children, by sequencing both *ENG* and *ALK1* genes. In cases in which a mutation is not found, sequencing of *SMAD4* is performed.

### *Statistical analysis*

Descriptive statistics, including range, frequency, mean and SD, were used to describe the study population. Comparisons between groups were performed using Fisher's exact test, with a p-value of $<0.05$ being considered significant.

## RESULTS

### *Study population*

Of 219 children referred to the HHT clinics at the Hospital for Sick Children and St Michael's Hospital between January 1996 and December 2008, 82 met predefined exclusion criteria as their screening tests have not been completed to date (n=35) or the diagnosis was ruled out clinically (n=10) or through genetic testing (n=37). Thus 137 children (65 females) were included in the present analysis (fig. 1). This group consisted of 61 children with a definite clinical and/or genetic diagnosis of HHT who were asymptomatic for visceral AVMs, 55 with a potential diagnosis of HHT and 21 who were symptomatic for visceral AVMs at their first assessment. Only asymptomatic children with a definite or potential HHT diagnosis were included for assessing the yield of screening, but both symptomatic and asymptomatic patients with genetically confirmed HHT were combined in the genotype–phenotype analysis.

### *Asymptomatic children with a definite diagnosis of HHT*

61 children with a definite diagnosis of HHT did not exhibit any signs or symptoms of pulmonary or cerebral AVMs at the time of their first assessment (mean$\pm$SD age of 8.7$\pm$4.7 yrs; range 0–17.0 yrs). This group consisted of 46 patients with a documented disease-causing mutation and 15 children with a definite clinical diagnosis of HHT (positive family history, recurrent epistaxis and telangiectases). Their demographics and clinical characteristics are described in table 1. Baseline screening test results were positive in 15 (25%) out of 61 children, with the majority showing evidence of pulmonary AVMs alone (n=13) or in combination with cerebral AVMs (n=1). One patient gave positive screening results for a cerebral AVM only. After the initial screening, eight children fulfilled four clinical diagnostic criteria. Of the 14 children with positive screening results for pulmonary AVMs, nine met the criteria for embolisation therapy (AVMs of $\geqslant$3 mm), of whom seven received embolisation therapy as the parents of the remaining two did not consent to the procedure. Owing to the risk of bleeding from the AVMs, the two children with positive screening results for cerebral AVMs underwent embolisation therapy. Eight (57%) of the 14 children with positive screening results for pulmonary AVMs were aged $<$10 yrs.

### *Asymptomatic children with a potential diagnosis of HHT*

55 children had clinical signs (telangiectasia and/or epistaxis) and/or a positive family history, but did not fulfil the clinical diagnostic criteria, of HHT (age 10.9$\pm$4.8 yrs; range 0–17.9 yrs).

**TABLE 1** Summary of 61 children with genetically or clinically confirmed hereditary haemorrhagic telangiectasia (HHT) who were asymptomatic for visceral arteriovenous malformations at their first assessment

| | |
|---|---|
| **Female sex** | 30 (49) |
| **Positive family history** | 61 (100) |
| **Positive genetic testing** | 46 (75) (24 *ALK1*; 20 *ENG*; 2 *SMAD4*) |
| **Positive family genetics**[#] | 1 (2) (*ENG*) |
| **Telangiectasia** | 42 (69) |
| **Epistaxis** | 46 (75) |
| **Diagnostic criteria** | |
| Three | 37 (61) |
| Two | 14 (23)[¶] |
| One | 10 (16)[¶] |

Data are presented as n (%). *ALK1*: activin receptor-like kinase1 gene; *ENG*: endoglin gene; *SMAD4*: SMAD family member 4 gene. [#]: children untested; [¶]: positive family history of HHT and positive test result for the familial disease-causing mutation.

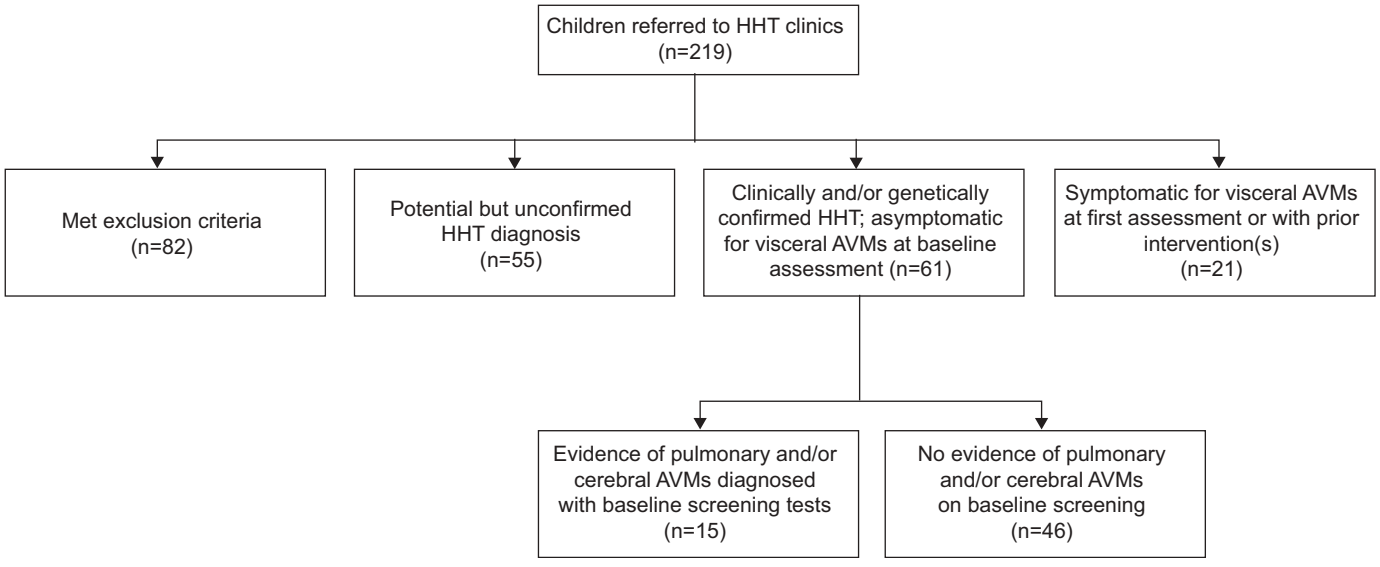


**FIGURE 1.** Patients referred to hereditary haemorrhagic telangiectasia (HHT) clinics at the Hospital for Sick Children and St Michael's hospital (both Toronto, ON, Canada) and their subgroups. AVMs: visceral arteriovenous malformations.

Their demographics and clinical characteristics are described in table 2. This group consisted of patients with uninformative genetic test results in the familial index case, as well as patients for whom genetic test results were not available. Of these children, 34 had first-degree relatives with a positive history of HHT, 19 had affected relatives only within the extended family and two had no family history but clinical signs of HHT. All of the 55 children were asymptomatic on initial assessment and all gave negative baseline screening test results for pulmonary or cerebral AVMs.

### *Children symptomatic for visceral AVMs*

21 children were symptomatic for visceral AVMs at their baseline assessment and/or had already undergone intervention for visceral AVMs (age 6.3±5.7 yrs); their demographic data are summarised in table 3. Nine of the patients had pulmonary AVMs, of whom six presented with cyanosis and/or hypoxia, one with hypoxia and congestive heart failure, one with haemoptysis and one with hypoxia and transient ischaemic attacks, as well as haemoptysis. Two children showed both pulmonary and cerebral AVMs, of whom one presented with cyanosis and the second with intracranial haemorrhage. Five children exhibited cerebral AVMs and presented with either intracranial haemorrhage (n=3) or headaches (n=2). Two patients exhibited spinal AVMs with signs and symptoms of spinal haemorrhage on presentation. Three patients showed hepatic AVMs and presented with signs and symptoms of congestive heart failure. Of the 21 children, 10 (45%) were aged <7 yrs at the time of symptomatic presentation.

### *Gene–phenotype association*

The link between mutations in *ENG* and *ALK1* genes and manifestations of pulmonary or cerebral AVMs was also evaluated in both symptomatic and asymptomatic patients with genetically confirmed HHT. Among 28 children with *ENG* mutation, 19 (68%) had either pulmonary (n=15) or cerebral AVMs (n=2), and two had both pulmonary and cerebral AVMs. Among 32 patients with *ALK1* mutation, six (19%) had pulmonary (n=4) or cerebral AVMs (n=2). Pulmonary AVMs were significantly more frequent among children with *ENG* mutations than with *ALK1* mutations (17 out of 28 *versus* four out of 32; $p<0.0001$ (Fisher's exact test)).

**TABLE 2** Summary of 55 children with a potential hereditary haemorrhagic telangiectasia diagnosis who were asymptomatic for visceral arteriovenous malformations at their first assessment

| | |
|---|---|
| **Female sex** | 25 (45) |
| **Positive family history** | 34 (62) |
| **Negative or unknown family genetics** | 46 (84) |
| **Telangiectasia** | 26 (47) |
| **Epistaxis** | 19 (34) |
| **Diagnostic criteria** | |
| Two | 24 (44) |
| One | 31 (56) |

Data are presented as n (%).

## DISCUSSION

To our knowledge, this is the first prospective analysis of a screening programme for pulmonary and cerebral AVMs in asymptomatic children with either confirmed or potential HHT. In children with a definite diagnosis of HHT, confirmed by either genetic diagnosis or clinical criteria, a high frequency (23%) of pulmonary AVMs was found, with a significant proportion of the children being aged <10 yrs. In contrast, pulmonary or cerebral AVMs were not detected in patients not fulfilling diagnostic criteria. Genetic testing was not only helpful in defining a subgroup at greater risk of AVMs, compared to patients with uncertain HHT diagnosis, but also confirmed significant differences in the prevalence of pulmonary AVMs between children with HHT1 *versus* HHT2.

The reported frequency of pulmonary and cerebral AVMs among HHT patients varies according to the population studied and the diagnostic methods used. In large adult cohorts, the prevalence of pulmonary and cerebral AVMs in patients who were not systematically screened were 4–14 and 3–4%, respectively [20, 21, 23], but the prevalence was higher (up to 19–52% for pulmonary AVMs and 6–9% for cerebral AVMs) if asymptomatic patients were systematically assessed using screening procedures [5, 6, 22, 31–36]. Experience in children is limited, but one smaller series reported an even higher prevalence of pulmonary and cerebral AVMs in both symptomatic and asymptomatic children with HHT [8]. These differences may be due to ascertainment bias as the present report provides a prospective analysis of all eligible patients referred to the Toronto HHT clinics rather than a subgroup of patients considered at high risk. Nevertheless, the combined evidence would suggest that presymptomatic screening gives positive results in a significant proportion of children with a clinically or genetically confirmed diagnosis of HHT.

Although screening for cerebral AVMs in children with HHT is considered the standard of care in North America, practices related to screening for pulmonary AVMs vary widely. Routine screening for pulmonary AVMs has been advocated in the adult population [24–27, 31, 36] as embolisation of pulmonary AVMs is safe and reduces the risk of stroke and brain abscess, as shown in interventional studies [28, 30, 32, 55]. In addition, embolisation therapy has been shown to be safe and effective in children [44]. Although the size of the feeding vessel has been used to define the at-risk population, recent evidence would suggest that this may not be a useful predictor of subsequent complications, which makes it challenging to define the target population for interventional procedures [32]. The same study suggested that the risks of complications related to pulmonary AVMs are very low in young children, which would advocate against early screening in childhood [32]. This is contradicted by the report of several cases of serious complications, including pulmonary haemorrhage, ischaemic stroke and brain abscess, in children with HHT as early as during the neonatal period [8, 24, 26, 27, 31, 40–42, 44, 51], which was also shown in the present data in children who presented with symptoms related to visceral AVMs. In our opinion, these cumulative cases justify screening for pulmonary AVMs in children with a definite diagnosis of HHT.

In the present predefined protocol, patients with a potential diagnosis of HHT were also screened when a disease-causing

**TABLE 3** Summary of 21 symptomatic children with visceral arteriovenous malformations (AVMs)

| | |
|---|---|
| **Female sex** | 10 (48) |
| **Positive family history** | 17 (81) |
| **Positive genetic testing** | 12 (57) (5 *ALK1*; 6 *ENG*; 1 *SMAD4*) |
| **Positive family genetics**[#] | 4 (19) (3 *ALK1*; 1 *ENG*) |
| **Telangiectasia** | 8 (38) |
| **Epistaxis** | 14 (67) |
| **AVMs** | |
| Pulmonary | 9 (43) |
| Cerebral | 5 (24) |
| Pulmonary and cerebral | 2 (10) |
| Spinal | 2 (10) |
| Hepatic | 3 (14) |
| **Diagnostic criteria** | |
| Four | 4 (19) |
| Three | 10 (48) |
| Two | 7 (33)[¶] |

Data are presented as n (%). *ALK1*: activin receptor-like kinase1 gene; *ENG*: endoglin gene; *SMAD4*: SMAD family member 4 gene. [#]: children untested; [¶]: six children had a positive family history of hereditary haemorrhagic telangiectasia and one child had a positive test result for a disease-causing gene mutation.

mutation could not be detected in the index case, since a diagnosis of HHT cannot be excluded by genetic testing in this scenario. In addition, the development of telangiectases and epistaxic symptoms can occur after puberty [20, 21], which makes it difficult to rely solely on clinical diagnostic criteria (Curaçao criteria) [54]. Therefore, these patients were included in the current analysis. None of the children with a potential clinical HHT diagnosis gave positive screening test results for visceral AVMs. It is not surprising that screening gave a lower diagnostic yield in this group, in which diagnostic suspicion was lowest, and it could be speculated that a high proportion of children in this group may indeed turn out not to have HHT. The very low yield of the screening tests among this population is different from that previously described in adults [6, 7]. However, in the adult studies, the patient population described with negative genetic test results fulfilled the clinical criteria of HHT, which was not the case in the present paediatric group with a potential HHT diagnosis. The present data, therefore, indicate that the risk of AVMs is lower in this group of children and may suggest that the risk/benefit ratio for screening in these children does not favour routine screening. However, a subgroup of these children could potentially fulfil diagnostic criteria of HHT in the future, and long-term follow-up is required in order to clarify the overall incidence of HHT in this population.

Overall, a higher prevalence of AVMs was observed in patients with HHT1, putting them at greater risk of early disease manifestations. This difference was largely due to a higher frequency of pulmonary AVMs. This increased frequency of pulmonary AVMs in children with HHT1 compared to those with HHT2 observed in the present study is in agreement with previous studies in adult subjects [5–7], and may be helpful for risk stratification of children with a known HHT mutation.

Finally, screening for liver vascular malformations (VMs) was not part of the routine screening protocol. Liver VMs were found to be more common if systematically screened for in both adults [5, 56] and children [8], but most of these cases are clinically asymptomatic and do not require intervention. Since clinically silent complications have not been described, there is currently no documented clinical value in routine screening for liver VMs in otherwise asymptomatic children. Conversely, finding liver VMs may clarify that children (or adults) have HHT by adding one more clinical criterion. Therefore, screening for liver VMs as part of diagnostic HHT screening might be of value. Further research is required in order to evaluate this hypothesis.

In conclusion, among paediatric patients with HHT, a high proportion showed evidence of pulmonary AVMs, detected in screening tests, including in children aged <10 yrs. As there is ongoing controversy regarding the complication rate of pulmonary AVMs in early childhood, further evidence is required in order to clarify whether or not this high prevalence justifies screening for pulmonary AVMs as early as possible in children with HHT.

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## STATEMENT OF INTEREST

None declared.

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