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Conservative Pulmonary Arteriovenous Malformation Screening in Children: Re-Evaluation of Safety

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ABSTRACT

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disease and screening to detect pulmonary arteriovenous malformations (PAVMs) is important to prevent complications. In adults, transthoracic contrast echocardiogram (TTCE) is used to screen PAVMs. In children, a conservative screening method seems to be sufficient to rule out major PAVMs and prevent them from PAVM-related complications. This study reevaluates the conservative noninvasive screening method using a larger cohort of children screened for HHT.

Methods: This single-center observational cohort study includes children screened between December 1998 and December 2022. The screening consisted of medical history, physical examination, pulse oximetry, and chest radiography. Data regarding screening, PAVM presence and complications (including transient ischemic attack, stroke, brain abscess and hemoptysis) were collected using the Dutch HHT-patient database.

Results: In total, 600 children, mean age 9.9 years (SD 4.3) were screened for the presence of PAVMs. None of the 600 children screened suffered any PAVM-related complications after a total of 7102 years of patient follow-up (251 children [42%] with a definite HHT-diagnosis, accounting for 3232 years of follow-up). In 32 patients (13% of children with HHT), a treatable PAVM was found during childhood.

Conclusion: This study confirms that a conservative PAVM screening method in children is safe to prevent complications related to PAVMs. Small PAVMs will be missed using this conservative approach, but without an increased risk of complications.

1 | Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease, with an estimated prevalence of 1:5000 inhabitants, characterized by vascular abnormalities: telangiectases and (visceral) arteriovenous malformations [1, 2].

In most patients, the disease is caused by a pathogenic mutation in the ENG gene (HHT type 1) or the ACVRL1 gene (HHT type 2) resulting in a haploinsufficiency of Endoglin and Activin receptor-like kinase 1 (ALK1) respectively. These play a pivotal role in angiogenesis, particularly in neo-angiogenesis, vessel maturation and stabilization [3, 4]. Insufficient levels of Endoglin or ALK1 can result in pathological angiogenesis manifesting as arteriovenous malformations and telangiectasia [5].

HHT is clinically diagnosed using the Curaçao criteria and/or confirmed with genetic testing [6]. The Curaçao criteria

include presence of spontaneous recurrent epistaxis, mucocutaneous telangiectases, visceral vascular malformations, and presence of a first-degree relative with a definite HHT diagnosis. Definite HHT is diagnosed if three out of four criteria are met and a HHT diagnosis is possible if 2 criteria are met. If less than two of these criteria apply, an HHT diagnosis is considered unlikely. Symptoms become more prominent with age, and establishing a clinical diagnosis at child age is often challenging. Therefore, the Curaçao criteria might be less applicable in children, especially in primary school age [7, 8].

Pulmonary arteriovenous malformations (PAVMs) lead to a right-to-left shunt (RLS), caused by a direct connection between a pulmonary artery and vein [9]. As blood bypasses pulmonary capillaries there is an increased risk of cerebral complications including cerebral infarction or brain abscess. Most PAVMs are asymptomatic, but larger PAVMs can result in dyspnea due to hypoxemia, and migraine [10–17]. To reduce the risk of complications, screening and treatment for PAVMs is recommended in the international guidelines for HHT [18]. The first-line screening in adults consists of a transthoracic contrast echocardiography (TTCE), followed by a computed tomography (CT) chest scan when indicated [9, 18, 19]. Children of a parent with known HHT are screened every 5 years, even if they are asymptomatic, unless HHT has been excluded with genetic testing. If the diagnosis has been established on the basis of the Curacao criteria, or with genetic testing, rescreening is performed every 5 years, because small PAVMs (missed in first screening) can increase in size over time [18, 20]. If HHT and therefore the presence of (small) PAVMs cannot be excluded in children, the use of antibiotic prophylaxis in advance of all procedures with a risk of septic emboli is recommended to prevent brain abscesses in all children, unless HHT was ruled out based on exclusion of the presence of a known mutation causing HHT in the family.

In the Netherlands, a low-impact conservative screening method is used in children to detect larger PAVMs. In a previous study more than 400 children with a parent with HHT were described, including 175 children with a definite HHT diagnosis, 125 children with a possible HHT diagnosis and 136 children without HHT [21]. The study showed that this conservative screening method was sufficient to rule out major PAVMs and prevent children from PAVM-related complications. There is no direct comparison performed between first-line screening of children with TTCE (as in adults) and the conservative method with chest X-ray and saturation measurement and therefore both protocols are currently mentioned in the guidelines.

The aim of this study is to reevaluate whether PAVM screening in children using this conservative screening method is indeed safe to prevent them from PAVM-related complications in a larger cohort of patients.

2 | Methods

This study is an observational cohort study evaluating the safety of a conservative screening method. The study was performed at the HHT Center of the St Antonius Hospital (Nieuwegein), the HHT referral center for the country. The Medical Research Ethics Committees United concluded that the Dutch Research Involving Human Subject Act was not applicable (identifier: W22.251) and the study was approved by the local research and development department (Z23.004). This study includes patients from the report of Hosman et al. [21]

2.1 | Study Population

Children up to 18 years of age who underwent conservative screening in the St. Antonius Hospital (Nieuwegein, the Netherlands) between December 1998 and December 2022 were screened for inclusion. Embolotherapy performed before the first HHT screening resulted in exclusion. Children with an "adult" screening with TTCE as first screening (just before the age of 18), were neither included, because this study is focused on the safety of our conservative screening.

Children were divided into four different categories based on the presence of Curaçao-criteria and/or performed genetic testing. Firstly, definite HHT based on the presence of three or more Curaçao criteria or when the diagnosis was confirmed with genetic testing. Secondly, a possible diagnosis of HHT was made when a patient met two out of four Curaçao criteria. Thirdly, children with none or only one Curaçao criterion were considered HHT unlikely (but certainly not excluded), including children with negative DNA-testing for HHT-related genes but no known family mutation. Patients from the previously mentioned three categories are invited every 5 years for re-screening. The fourth category is no HHT, based on confirmed absence of the known family mutation, and follow-up is not indicated.

2.2 | Screening Method Children

The screening consisted of medical history taking, including epistaxis occurrence, dyspnea, (reduced) exercise tolerance, and headache/migraine. Physical examination included capillary microscopy and pulse oximetry. Chest X-ray was performed to detect visible PAVMs. In children with an abnormal chest X-ray suspected of PAVM(s), and/or decreased pulse oximetry (< 96%) and/or clinical abnormalities, an additional chest CT scan was performed. All chest CT-scans were reviewed in a multidisciplinary meeting to discuss both the treatability of the PAVMs found and the follow-up.

All children were counseled about the possibility of DNA testing of the known family mutation or to identify one of the known causative HHT mutations in the ALK1, ENG or SMAD4 gene. The advantages and disadvantages of DNA testing were discussed with children and their parents.

Children suspected of HHT were evaluated in the outpatient clinic at 5-year intervals according to HHT international guidelines. Excluded from follow-up were children with negative genetic testing of the known family mutation.

2.3 | Adult Screening

In adults, rescreening consisted of medical history, physical examination, and TTCE, as recommended in the HHT international guidelines. Sometimes patients are invited for adult screening just before the age of 18 years, to avoid extra costs due to health insurance issues: before the age of 18, all care is insured, while after the age of 18 an excess applies. TTCEs were performed according our standard protocol, as previously published [9, 22]. Chest CT was performed in those adults in whom the TTCE showed shunting grade 2 or more.

2.4 | Outcomes

Data were collected from the Dutch HHT-database, which includes all patients who visited the St. Antonius Hospital for HHT-screening. The primary outcome evaluated in this study consisted of the occurrence of PAVM-related complications (transient ischemic attack, stroke, brain abscess and hemoptysis). The secondary endpoint consisted of treated PAVMs. All children who became adults and yet not have had an adult screening had a consultation from the HHT team by telephone, to collect information about the occurrence of PAVM-related complications since their last formal screening consult.

2.5 | Data Analysis

Categorical data are presented as number (percentage). Continuous data are presented as mean (standard deviation, SD) in case of normally distributed data, and as median (interquartile range, IQR) in case of non-normally distributed data. Patient follow-up years are defined as the number of years from the date of first screening to the date of data collection. SPSS version 27 was used to analyze descriptive statistics.

3 | Results

A total of 621 children were screened for inclusion. Twenty-one patients were excluded, seven due to PAVM embolization before the first visit, and 14 underwent a first HHT screening with TTCE just before the age of 18. Therefore, 600 children could be included, with a mean age of 9.9 years (SD 4.3) at first screening. The median follow-up time was 11 years (IQR 6.6-18) with a total of 7102 patient follow-up years. The inclusion details are displayed in Figure 1. A second screening during childhood was conducted in 76 out of the 251 children (30%) with a definite HHT diagnosis. The mean age of these 76 children at their second screening was 12.8 years (SD 2.4). Baseline characteristics can be found in Table 1.

3.1 | Diagnosis

At the time of data evaluation (February 2023) 251 children (42%) had a definite HHT diagnosis, accounting for 3232 patient follow-up years. In 61/251 (25%) patients, this diagnosis was based on both the Curacao criteria and a confirmed pathogenic mutation. HHT was clinically diagnosed in 137/251 (55%) patients and in 53/251 based on genetic testing only (21%). In 244/251 HHT patients the family genetic mutation was known (97%), including 168 patients with HHT type 1 (mutation in Endoglin). Of the 251 definite HHT patients, 54 had an initial unlikely or possible HHT diagnosis that changed to a confirmed definite HHT during follow-up, as clinical features became more evident with age or when genetic testing verified the presence of a pathogenic mutation.

In 111 children (19%), a possible HHT diagnosis was made based on two Curaçao-criteria. In 128 children (21%), HHT was considered unlikely based on no or 1 Curaçao criterion present. In 110 children (18%), HHT was excluded based on the absence of the family mutation.

3.2 | Screening Children

In total, chest radiography was performed in 586/600 children (98%). The chest x-ray showed a possible PAVM in 50/586 children (9%). An additional chest CT scan was performed in 54 children; because of abnormal x-ray only in 29/54 patients, because of abnormal x-ray and decreased oxygen saturation in 12/54 patients, because of symptoms of dyspnea and/or migraine in 6/54 patients, because of research purposes in 1/54 patient and other reasons in 6/54 patients. A PAVM was visualized in 40/54 children. The screening results can be found in Table 2 and Figure 2.

In the subgroup of definite HHT patients, 244/251 children underwent chest radiography (97%), of which 40 showed possible PAVMs (16%) including 34 patients with HHT type 1. A chest CT scan was performed in 46 definite HHT patients (19%). Of those, 24/46 were performed because of abnormal chest X-ray only (52%), because of abnormal x-ray and a decreased oxygen saturation in 10/46 (22%) patients, because of symptoms dyspnea ($n = 4$), migraine ($n = 2$) or decreased exercise

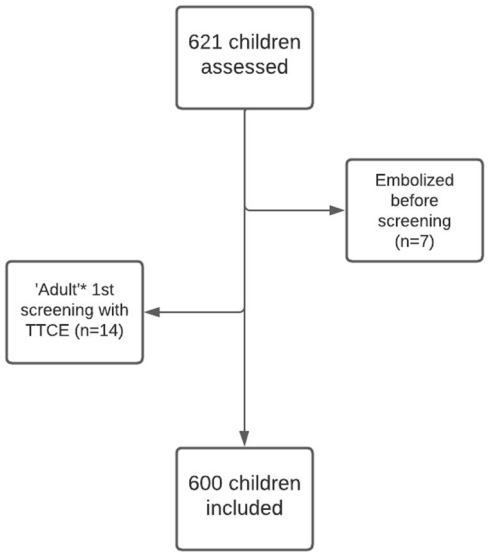

FIGURE 1 | Inclusion chart. TTCE = transthoracic contrast echocardiography. * = adult screening performed at the age of 17 years (see method: screening).

TABLE 1 | Baseline patient characteristics.

Group classification[a]	Definite HHT ($n = 251$)	Possible HHT ($n = 111$)	HHT unlikely ($n = 128$)	No HHT ($n = 110$)	Total (600)
Mean age first screening (± SD)	9.9 (± 4.4)	8.7 (± 3.5)	10.1 (± 4.3)	11.0 (± 4.6)	9.9 (± 4.3)
Range (years)	0–17	0–17	1–18	0–18	0–17
Sex, female n (%)	125 (50)	51 (46)	62 (48)	56 (51)	294 (49)
Classification based on					
Clinical criteria, n (%)	137 (55)	111 (100)	116 (91)	N.A.	364 (61)
Genetics, n (%)	53 (21)	N.A.	N.A.	110 (100)	163 (27)
Both, n (%)	61 (24)	N.A.	12 (9)	N.A.	73 (12)
Family mutation					
Endoglin, n (%)	168 (67)	49 (44)	48 (38)	67 (55)	332 (55)
ACVRL1, n (%)	62 (54)	47 (42)	45 (35)	42 (34)	196 (33)
SMAD4, n (%)	14 (6)	0 (N.A.)	2 (2)	0 (0)	16 (3)
Unknown, n (%)	7 (3)	15 (14)	33 (26)	1 (1)	56 (9)

Abbreviations: ACVRL1, activin receptor-like kinase 1; HHT, hereditary hemorrhagic telangiectasia.
[a]classification as following: definite HHT = presence of three Curaçao-criteria, possible HHT = presence of two Curaçao-criteria, unlikely HHT = presence of 0/1 Curaçao-criteria, no HHT = known family mutation not present at genetic analysis.

TABLE 2 | Screening children results.

Evaluation	Definite HHT ($n = 251$)	Possible HHT ($n = 111$)	HHT unlikely ($n = 128$)	No HHT ($n = 110$)	Total (600)
Chest radiography, n (%)	244 (97)	110 (99)	125 (98)	107 (97)	586 (98)
Possible PAVM on Chest radiography, n (%)	40 (16)	4 (4)	4 (3)	2 (2)	50 (8)
Chest CT performed, n (%)	46 (18)	2 (2)	3 (2)	3 (3)	54 (9)
PAVM on chest CT, n (%)	38 (15)	0	1[a]	1[b]	40 (7)
Treatable PAVM, n (%)	32 (13)	0	1	1	34 (6)

Abbreviations: CT, computed tomography; HHT, hereditary hemorrhagic telangiectasia; PAVM, pulmonary arteriovenous malformation.
[a]1 patient with an isolated PAVM, no other signs of HHT and no HHT in the family. No DNA-testing performed.
[b]1 non-HHT patient with a PAVM secondary to hepatopulmonary syndrome in the presence of an Abernethy malformation.

tolerance ($n = 2$) in eight patients (17%), because of other reasons in 3/46 (6.5%): because of a severely affected sibling/family member causing great worry and in one patient because of a borderline-normal oxygen saturation of 96%. In the 46 HHT patients who underwent chest CT, a PAVM was detected in 38/46 (83%).

In the subgroup of possible HHT-patients, 110/111 children underwent chest radiography (99%). Two x-rays showed possible PAVMs for which two additional chest CT scans were performed on which the presence of a PAVM was excluded. In another two patients, the x-ray showed a subtle abnormality in which a small PAVM could not be excluded. In the presence of a normal oxygen saturation of 98%–99%, there was refrained from additional chest CT.

In the subgroup of patients with unlikely HHT, chest radiography was performed in 125/128 children (98%). Four chest x-rays showed possible PAVMs. Three chest CTs were performed which in one patient showed a PAVM, who also had a decreased oxygen saturation.

In the subgroup of patients without HHT, chest radiography was performed in 107/1110 children (97%) and showed possible PAVMs in two children. In three children, an additional chest CT was performed, including one patient who underwent chest CT for research purposes (not related to this study). In one patient with a decreased oxygen saturation and abnormal chest x-ray, a PAVM was found on chest CT.

3.3 | Pulmonary Arteriovenous Malformation Embolization

In 38 patients with HHT, a PAVM was detected on chest CT (38/251, 15%). Thirty two patients had a treatable PAVM and underwent embolization (13%), including 12/32 patients with a decreased oxygen saturation. Of these, one patient underwent embolization in another hospital. Of those who underwent embolization in our hospital, 15/31 (48%) underwent embolization as a child only and 16/31 (52%) underwent embolization sessions in both childhood and adulthood. 6/31 (19%) patients

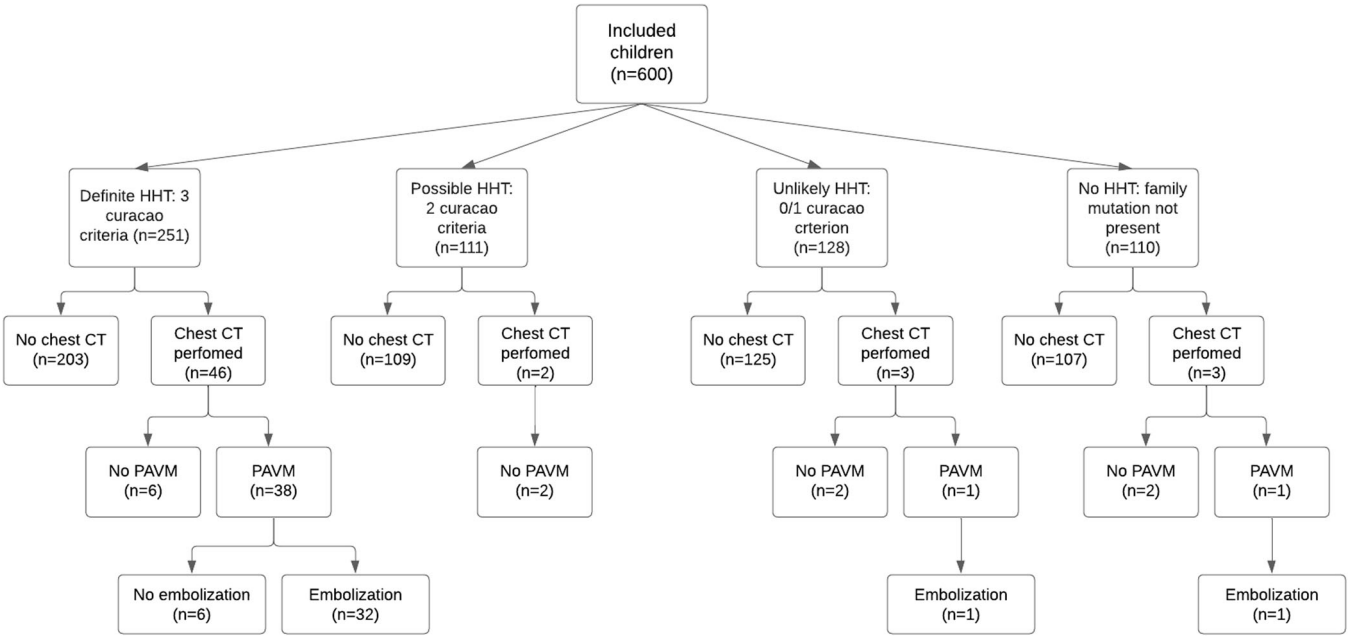

FIGURE 2 | Flow chart depicting results screening children. Chest CT = chest computed tomography scan. HHT = hereditary hemorrhagic telangiectasia. PAVM = pulmonary arteriovenous malformation. TTCE = transthoracic contrast echocardiography.

underwent one embolization procedure, whilst the majority 25/31 (81%) underwent multiple embolization procedures for either newly detected PAVMs (5/25) in follow-up, because of persistent perfusion or reperfusion of previously treated PAVMs (7/25) or both (13/25). These included complex PAVMs in 13/20 patients and multiple (> 20, including complex) PAVMs in 7/20 patients. In total 115 embolization procedures were performed in 31 HHT children. The six children in whom the PAVM was too small for embolization, were monitored.

In two children without HHT-diagnosis, a treatable PAVM was found and embolized. One patient only had an isolated PAVM, no other signs of HHT (yet) or among family members and HHT was considered unlikely. DNA-testing was declined, and the patient is regularly seen for follow-up after embolization and monitoring of the development of other HHT-signs. The other patient had a PAVM secondary to hepatopulmonary syndrome in the presence of an Abernethy malformation (congenital portosystemic shunt), and later underwent a liver transplantation. This patient was considered to have no HHT, because of negative genetic testing for HHT-genes and a good alternative explanation for the formation of macroscopic PAVMs.

3.4 | Adult Screening

In February 2023, 221 children with a definite ($n = 177$) or possible ($n = 44$) HHT diagnosis had reached adulthood. Of these, 25 adults are being monitored after embolization. Rescreening was done in 119 adults (using TTCE in 116 adults), including 111 patients with definite HHT and eight patients with possible HHT. In total, 54/116 (47%) of the possible ($n = 3$) or definite ($n = 51$) HHT patients had a grade 2 or 3 RLS and 57 patients underwent chest CT. A PAVM was visible in 37/111 (33%) patients with a definite HHT diagnosis of which 20/111 (18%) underwent embolization. In the other 17/37, the PAVMs were not treatable, and these patients are being monitored. No PAVMs were detected in the patients with possible HHT. The adult screening results can be found in Figure 3.

In total 77 adults who reached adulthood have not yet been rescreened, 16 patients of which had a last screening less than 5.5 years ago, 31 patients were contacted by phone and had no complications or symptoms (including migraine), two patients moved abroad and were followed-up elsewhere and 28 patients were lost-to-follow-up. Contributing to these numbers, at the time of data analysis we experienced a long waiting list for follow-up visits due to 2 years with reduced care during the COVID-19 pandemic.

Of the 128 children with an unlikely HHT diagnosis, 55 had reached adulthood. Of these, 11 patients have been rescreened using TTCE. In none of these 11 adults a grade 2 or 3 RLS was detected and none of these rescreened children (now adults) underwent chest CT.

3.5 | Complications

None of the 600 screened children suffered any PAVM-related complications including hemoptysis, stroke, brain abscess, or ischemic attack.

4 | Discussion

In this Dutch cohort of 600 children conservatively screened for the presence of PAVMs and HHT, none of the children, including 251 with a definite HHT diagnosis, suffered PAVM-related complications, such as transient ischemic attack, stroke,

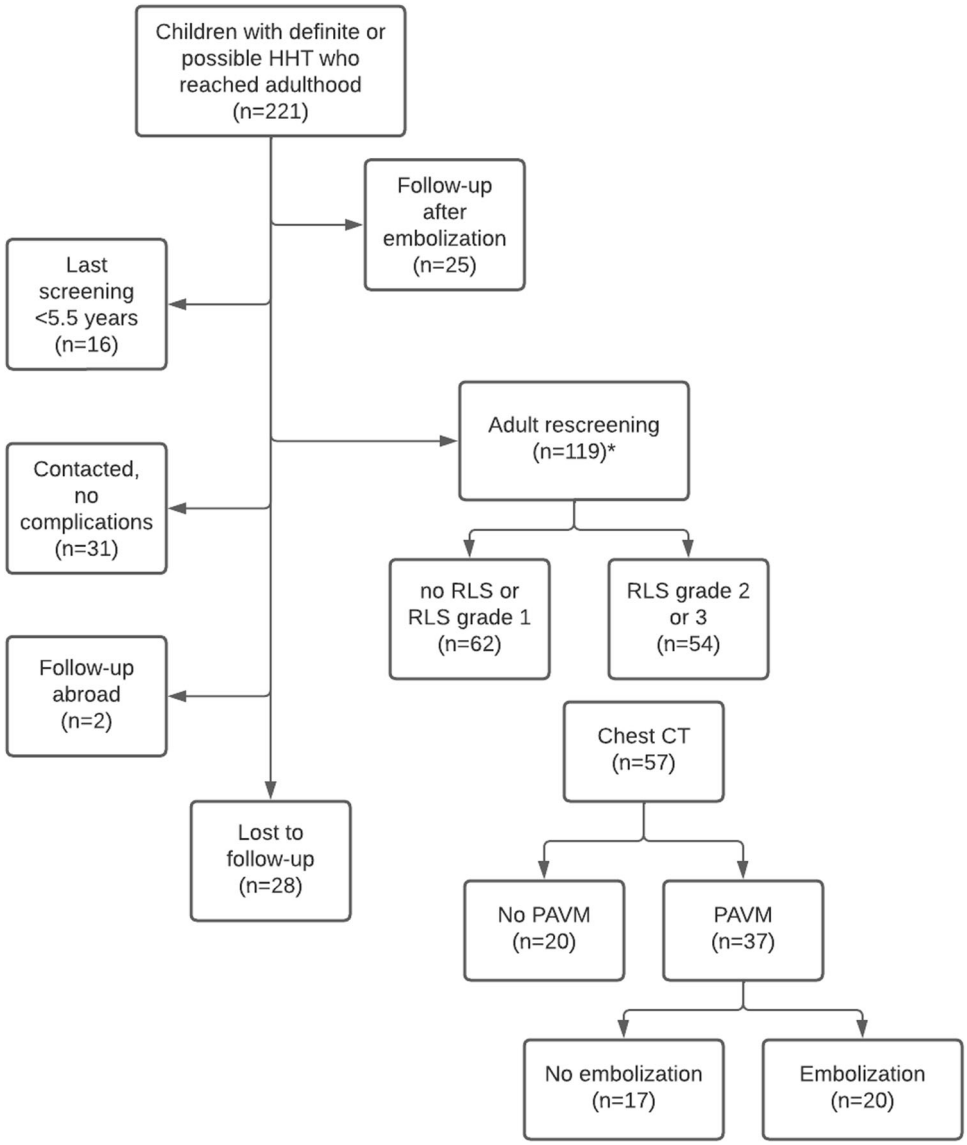

FIGURE 3 | Flow chart depicting results adult screening possible and definite HHT. CT = Computed tomography. HHT = hereditary hemorrhagic telangiectasia. RLS = right-to-left shunt. *Rescreening with TTCE in 116 adults.

brain abscess or hemoptysis. This study reconfirms that a conventional screening approach for PAVM in children with (possible) HHT can be considered safe.

The findings are in line with the previous cohort of 436 children screened until 2015 described by Hosman et al. who also found no complications [21]. Previous studies have shown that it can be assumed that the presence of PAVMs can be excluded in children with TTCE grade 0 or 1 [23]. Karam et al. found that in a cohort of 94 HHT children, implementation of chest CT in the screening approach for HHT in children with grade < 2 pulmonary shunt was not necessary as none of the children with a shunt grade 0 or 1 on TTCE showed a PAVM on chest CT. However, chest CT was still performed in 53% because of TTCE grade 2 or 3, whilst only 14% of the cohort needed embolization. In another study, a cohort of 129 children was examined following a similar practice of screening: a PAVM was detected in 52% and embolotherapy was performed in 38 patients (29.5%) [24]. In comparison, with our conservative screening protocol a CT scan was performed in only 19% of children with HHT, resulting in less radiation exposure. In 52%–53% of the patients of the cohort by Karam and Mowers et al. a PAVM was found, compared to 17% in our cohort. The number of children who eventually underwent an embolization was quite comparable: 14% in the cohort of Karam et al., versus 13% in our cohort. In the cohort of Mowers, a larger proportion of children underwent embolization. The proportion of patients with HHT type 1 (Endoglin mutation) could play a role here: 81% in their cohort versus 62% (Karam) and 67% (our cohort).

The risk of exposing children to ionizing radiation through CT scans is debatable, especially since Mathews et al. showed that children who were exposed to CT scans before the age of 18 years have increased incidences of all types of cancer during adulthood [25]. On the other hand, low dose CT scan protocols in children have considerably decreased the cumulative radiation dose over the last decades.

TTCE is considered the screening test of choice for the detection of PAVMs in adults due to its high sensitivity, great

reproducibility, no use of radiation, and low risk of complications [18, 26]. Chest CT is proven valuable to characterize PAVMs and evaluate the feasibility of embolotherapy [27]. In addition, previous studies have shown that the pulmonary shunting grade forecasts the probability of treatable PAVMs [9, 28].

The number of detected PAVMs in our study is much lower than in current literature [23, 24], which is caused by the conservative method: while clinically relevant PAVMs are detected, the smaller PAVMs are missed. The aim of our study was not to evaluate the sensitivity and specificity of the conventional screening method for PAVM diagnosis but to reassess the safety of our approach to detect the presence of relevant PAVMs in children, which can cause potentially life-threatening complications. Both screening methods, our conventional approach, and the method of using TTCE supplemented by chest CT if indicated seem to be safe as none of the studies reported severe complications. Nevertheless, the risk of exposing children to CT radiation doses is considerably higher in the standard screening method which may also be more detrimental for children. And even though TTCE seems the most optimal technique to detect PAVMs in both adults and children, placing an intravenous access needed to perform TTCE might be stressful for children [29–32].

For interpretation of the results of our study, it should be noted that all children in whom an HHT diagnosis could not be excluded based on the Curaçao criteria and/or genetic testing, were recommended to prophylactically use antibiotics before any procedures risking bacteremia [18], which might have influenced PAVM complication risk. During counseling of parents of children in whom the diagnosis could not be excluded, it was emphasized that though there are no signs of HHT, there is still a 50% chance that the child has HHT.

The most important limitation includes the retrospective nature of the study, possibly leading to missing data and report bias. It is a single-center study including the only HHT expert center in the Netherlands, which results in the advantage that all Dutch patients with HHT are screened in our hospital—reducing the risk of selection bias. Only 28 patients were lost to follow-up and could not be reached. However, the Netherlands is a small country with only one HHT expert center and very short lines between different hospitals and general practitioners and during follow-up visits we always ask explicitly if there have been any problems, signs of complications, and also discus family members. Based on our experience as the only HHT expert center, we expect to be contacted in case of a PAVM-related complication: either by the patient or family member or by the treating physician. Lastly, data on the race of children were not systematically reported in the standard of care and could therefore not be included in this study. Race has been shown to possibly influence the oxygen measurements, which could lead to a possible overestimation in patients of black, Hispanic or Asian race [33, 34]. We assume that these races could be underrepresented in our Dutch cohort, based on the available data of the general Dutch population: in 2023 ($n = 17{,}811{,}291$), 73% of the population was from Dutch origin ($n = 12{,}978{,}154$), 6.5% of the population was from Asian origin ($n = 1{,}150{,}222$), 5.1% of the population was from African, Dutch Caribbean or Surinam origin ($n = 913{,}304$), 4.9% was from Turkish or Moroccan origin ($n = 369{,}363$) and 11% of the population was from other origin ($n = 1{,}900{,}248$) [35]. This could influence the external validity of the study results, and we can imagine that it might be appropriate to adjust the cutoff value slightly.

In conclusion, this study reconfirms that in children below 18 years of age undergoing screening for HHT and PAVMs, a conservative method consisting of history taking, physical examination (including saturation measurements), and chest X-ray, without TTCE, is safe in preventing children from PAVM- related complications.

Author Contributions

Fleur ten Berg: conceptualization, investigation, writing–original draft, methodology, formal analysis, visualization, data curation. **Josefien Hessels:** conceptualization, investigation, writing–original draft, methodology, project administration, formal analysis, visualization, data curation. **Anna Hosman:** methodology, conceptualization, writing–review and editing, resources, supervision, data curation. **Sanne Boerman:** conceptualization, writing–review and editing, methodology, supervision, resources. **Marco C. Post:** conceptualization, investigation, methodology, writing–review and editing, supervision, resources. **Walter A. F. Balemans:** conceptualization, investigation, methodology, writing–review and editing, supervision, resources. **Hans-Jurgen Mager:** conceptualization, investigation, writing–review and editing, formal analysis, methodology, visualization, supervision, resources.

Ethics Statement

This study includes original research and was considered that the Dutch Research Involving Human Subject Act was not applicable, as verified by the Medical Research Ethics Committees United (Identifier: W22.251). Therefore, no informed consent was obtained.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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