Hereditary hemorrhagic telangiectasia in pediatrics: descriptive study in a specialized unit

Magalí Squitín Tasende[1-2#], Nicolás Guerrero Serravalle[1#], Lucía G. Pérez[3], Ana Braslavsky[4], Marcelo Serra[2]

ABSTRACT

Introduction. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia characterized by bleeding telangiectasias and arteriovenous malformations (AVMs) in the brain, lungs, liver, and gastrointestinal tract. In childhood, its manifestations are often subtle or absent, making it difficult to recognize. The lack of evidence in pediatrics, especially in Latin America, favors underdiagnosis and limits the timely management of its complications. This study describes the epidemiological, clinical, genetic, and therapeutic characteristics of pediatric patients with HHT at a referral center.

Population and methods. Retrospective, descriptive study of pediatric patients evaluated between 2010 and 2022 in the HHT Unit of a referral center. Epidemiological, clinical, genetic, and therapeutic data were collected from the institutional registry.

Results. A total of 158 patients were included, mainly from Buenos Aires and surrounding areas; nearly 70% consulted due to a family history of the disease. The average age at the first consultation was 9 years, with 52% of participants being female. HHT was confirmed in 80 patients using Curaçao criteria and/or genetic testing, with a positivity rate of 50%. Mutations were identified in *ACVRL1* (56%), *ENG* (40%), and *MADH4* (2.7%). Epistaxis was the most common symptom (92%), with an average onset at age 7. Pulmonary (13%), central nervous system (11%), hepatic (8%), and digestive (2%) AVMs were detected.

Conclusion. The importance of early diagnosis of HHT in pediatrics, as well as the need to recognize signs such as recurrent epistaxis or unexplained hypoxemia, is highlighted to facilitate detection and specialized treatment.

Keywords: *Osler-Weber-Rendu disease; child; Latin America; epistaxis; arteriovenous malformations.*

doi: http://dx.doi.org/10.5546/aap.2025-10661.eng

To cite: Squitín Tasende M, Guerrero Serravalle N, Pérez LG, Braslavsky A, Serra M. Hereditary hemorrhagic telangiectasia in pediatrics: descriptive study in a specialized unit. *Arch Argent Pediatr.* 2025;e202510661. Online ahead of print 7-AUG-2025.

[1] Pediatric Clinic Service, Department of Pediatrics, Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina; [2] Hereditary Hemorrhagic Telangiectasia Unit, Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina; [3] Clinical Research Department, Universidad Hospital Italiano, Autonomous City of Buenos Aires, Argentina; [4] Internal Medicine Research Area, Medical Clinic Service, Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina.
 # Contributed equally.

Correspondence to *Magalí Squitín Tasende: magali.squitin@hospitalitaliano.org.ar*

Funding*: None.*

Conflict of interest*: None.*

Received*: 2-5-2025*
Accepted*: 6-11-2025*

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by increasing penetrance with age and variable clinical expression, even among family members.[1,2] Its prevalence is estimated to be between 1 in 5000 and 1 in 10 000 people, making it a rare disease.

HHT is characterized by the presence of telangiectasias and arteriovenous malformations (AVMs), which lack the intermediate capillaries that are typically found in normal blood vessels. The most common manifestation, present in approximately 95% of cases, is spontaneous and recurrent epistaxis, caused by the rupture of fragile telangiectasias in the nasal mucosa, with an average onset around 12 years of age.[4] Telangiectasias are mainly located in the nose, face, lips, tongue, oral cavity, fingers, and digestive tract; however, in childhood, they may be subtle or absent.[5] AVMs mainly affect the lungs, liver, central nervous system (CNS), and digestive tract. In the lungs, they usually take the form of arteriovenous fistulas that generate right-to-left shunts and predispose to complications such as ischemic strokes, brain abscesses, and hypoxemia. Hepatic AVMs, on the other hand, can lead to heart failure, portal hypertension, or biliary necrosis, although these manifestations are rare in children and adolescents.[6,7]

Two main phenotypes of HHT are recognized: type 1, characterized by greater pulmonary and neurological involvement, and type 2, which is predominantly associated with hepatic and digestive manifestations.[3,8,9] There are also less common forms (1-3%), such as HHT-juvenile polyposis (HHT-JP) overlap syndrome, associated with the *MADH4* gene, which may be accompanied by hyperlaxity and arteriopathy.[10] Diagnosis is established by applying the Curaçao clinical criteria (≥3 positive criteria) and/or genetic testing.[1,11,12] In children, the lower penetrance of the disease reduces the sensitivity of the clinical criteria; family history is the most relevant finding.[13-15]

To date, more than 800 pathogenic variants have been identified in genes of the TGF-β/BMP pathway. The most common ones affect the gene *ENG* (endoglin), located on chromosome 9 (HHT type 1), and the *ACVRL*1 gene (Activin A Receptor Type II-Like 1, also known as *ALK1*), on chromosome 12 (HHT type 2); the latter is the most prevalent in our country.[3] Mutations in other genes such as *RASA1*, *EPHB4*, and *GDF2* are associated with clinical phenotypes similar to HHT.[16-19] Clinical management is aimed at preventing hemorrhagic, embolic, and hemodynamic complications. Epistaxis is typically treated with local measures, including nasal lubrication, antifibrinolytic agents, and otolaryngological procedures, as well as, in some cases, antiangiogenic drugs. Pulmonary AVMs are treated by transcatheter embolization, while those in the CNS may require surgery, embolization, or multimodal treatment. In severe cases of liver involvement, intensive hemodynamic management, the use of antiangiogenic therapies, and, in selected situations, liver transplantation may be necessary.[20-23]

Information on HHT in the pediatric population is scarce, especially in Latin America, contributing to an estimated underdiagnosis of around 90% and, consequently, higher morbidity and mortality rates.[13,24,25] Therefore, it is recommended that genetic testing be offered to all children of affected parents, as well as screening for pulmonary AVMs using contrast echocardiography, chest X-ray, or pulse oximetry, and for cerebral AVMs using magnetic resonance imaging, in all children diagnosed with or at risk for HHT.[20,22]

The objective of this study is to describe the epidemiological, clinical, genetic, and therapeutic characteristics of pediatric patients evaluated at the HHT Unit of the Hospital Italiano de Buenos Aires (HIBA), with special emphasis on those diagnosed with HHT.

POPULATION AND METHODS

A descriptive, retrospective study was conducted on pediatric patients (aged 0 to 18 years) evaluated at the HIBA HHT Unit between January 1, 2010, and December 31, 2022. The HHT Unit is a leading Latin American interdisciplinary group comprising healthcare professionals dedicated to providing comprehensive care for patients and families affected by this disease. The diagnosis of HHT was established by a positive genetic test for a pathogenic variant and/or the presence of three or more Curaçao criteria.[12,20] According to these criteria, the clinical diagnosis was classified as "definite" (≥3 criteria), "suspected" (2 criteria), or "unlikely" (≤1 criterion). The clinical criteria considered were (1) spontaneous and recurrent epistaxis; (2) telangiectasias in characteristic locations (lips, oral cavity, fingers, and nose); (3) visceral vascular lesions (gastrointestinal,

pulmonary, hepatic, or central nervous system); and (4) first-degree family history with a diagnosis of HHT.

The interpretation of genetic tests was classified as: positive (pathogenic variant identified), non-informative (no pathogenic variants detected, but with technical limitations that prevent the diagnosis from being ruled out), uncertain (presence of variants of unknown significance), and negative (no detection of the pathogenic variant previously identified in the family).

By international guidelines, genetic testing was offered to all patients descended from a parent with HHT, regardless of the presence of symptoms, as well as to those with clinical findings suggestive of HHT who did not meet full diagnostic criteria (Curaçao ≤2).

To assess the severity of epistaxis in patients with HHT, the Epistaxis Severity Score (ESS) was used, as outlined in the medical criteria (*Appendix 1*).[14] All pediatric patients evaluated by the HHT Unit during the study period were included. Case detection and data collection were performed using the institutional HHT registry and subsequently validated by manual review of electronic medical records by specialists in pediatrics and HHT, to minimize information loss. Given the descriptive nature of the study and the inclusion of the entire population available in the period, no sample size estimation was performed.

A descriptive analysis of the epidemiological, clinical, genetic, and therapeutic characteristics of the population was performed. Categorical variables are expressed as absolute and relative frequencies, with their corresponding 95% confidence interval (95%CI). Continuous variables are described by mean and standard deviation, or median and interquartile range (IQR), depending on their distribution. Statistical analysis was performed using STATA software version 13.0.

The Research Protocol Ethics Committee of the Hospital Italiano de Buenos Aires approved the study.

RESULTS

General characteristics

A total of 158 pediatric patients evaluated at the HHT Unit between 2010 and 2022 were included in this study. Of these, 83 (52.5%; 95%CI: 44.4-60.5) were female. The median age at the time of the first consultation was 9.1 years (IQR: 5.0-12.6). Most individuals resided in the Buenos Aires Metropolitan Area (AMBA, by its Spanish acronym), and the primary means of accessing specialized care was through family referrals (*Table 1*).

Clinical manifestations at the time of the first consultation

Almost half of the patients (66/158; 41.8%; 95%CI: 34.1-49.8) were asymptomatic at the first consultation. Among those who presented

Table 1. Demographic characteristics of patients followed by the Hereditary Hemorrhagic Telangiectasia Unit

Demographic characteristics	Total n = 158 n (%; 95%CI)	Patients diagnosed with HHT n = 80 n (%; 95%CI)
Sex		
Female	83 (52.5; 44.6-60.2)	45 (56.3; 45.0-66.97)
Male	75 (47.5; 39.7-55.3)	35 (43.7; 33.1-54.9)
Age at first consultation		
Average in years (SD)	8.9 (4.9)	9.4 (4.9)
Median in years (IQR)	9.1 (5–12)	9.7 (6-13)
Place of residence		
AMBA	101 (63.9; 56.1-71.1)	52 (65; 53.7-74.8)
Country´s interior	46 (29.1; 22.4-36.7)	25 (31.3; 21.9-42.4)
Outside the country	11 (6.9; 0.4-12.2)	3 (3.7; 1.2-11.2)
Source of referral		
Family	112 (70.9; 63.2-77.5)	35 (22.1; 16.3-29.4)
Medical	35 (22.1; 16.3-29.4)	12 (15; 8.6-24.8)
Social media	11 (6.9; 0.4-12.2)	5 (6.3; 2.6-14.4)

HHT: hereditary hemorrhagic telangiectasia; SD: standard deviation; IQR: interquartile range; AMBA: Buenos Aires Metropolitan Area (by its Spanish acronym); 95%CI: 95% confidence interval.

symptoms, the most common was epistaxis. The manifestations observed in symptomatic patients are described in *Table 2*.

DIAGNOSIS

Genetic studies

Genetic testing was performed in 74 patients. In 37 cases (50.0%; 95%CI: 38.3-61.7%), pathogenic variants were identified: 21 in *ACVRL1* (56.8%; 95%CI: 40.9-71.8), 15 in *ENG* (40.5%; 95%CI: 26.4-56.1) and 1 in *MADH4* (2.7%; 95%CI: 0.1-14.2). No mutations were found in *RASA1* or *GDF2*. Twenty-seven studies were negative (36.5%; 95%CI: 25.8-48.6) and 10 were non-informative (13.5%; 95%CI: 7.1-23.5). *Figure 1* shows the distribution of patients according to diagnostic evaluation and criteria applied.

Application of the Curaçao criteria

During follow-up, 31 patients (19.6%; 95%CI: 13.5-25.8) met one or no clinical criteria; 61 (38.6%; 95%CI: 31.0-46.5) met two criteria; and 66 (41.8%; 95%CI: 34.1-49.8) met three or four criteria. The distribution of criteria is detailed in *Table 3*.

Integrated diagnosis

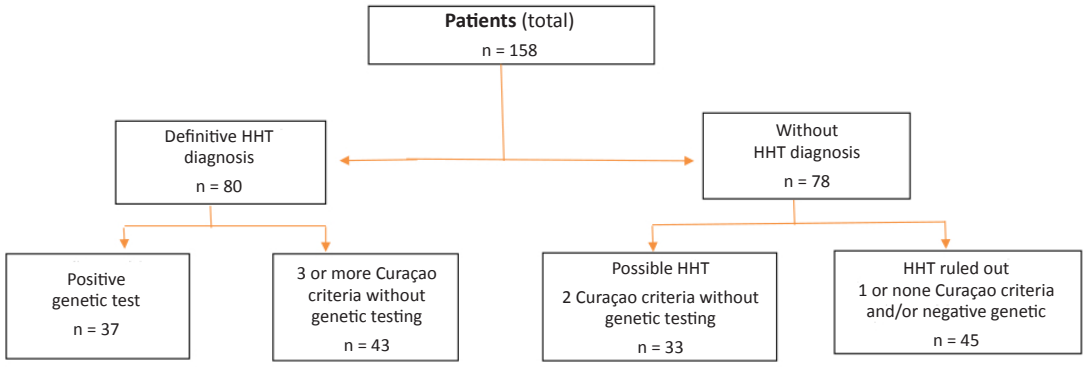
Combining clinical criteria and genetic testing studies, 39 patients with a suspected diagnosis of HHT were identified. Of these, 6 (15.4%; 95%CI: 6.5-30.0) had non-informative genetic results and 33 (84.6%; 95%CI: 70.0-93.5) had not undergone genetic testing. The most common clinical combination was epistaxis plus a first-degree family history in 26 patients (66.7%; 95%CI: 50.4-80.0).

Table 2. Clinical manifestations of symptomatic patients at the first visit*

Clinical manifestations	Symptomatic patients (n = 92) n (%; 95%CI)
Epistaxis	47 (51.1; 40.4-61.5)
Hypoxemia and cyanosis	6 (6.5; 2.4-13.5)
Anemia	4 (4.3; 1.2-10.7)
Headache	2 (2; 0.3-7.7)
Hematoquecia	2 (2.2; 0.3-7.7)
Seizures	2 (2; 0.3–7.7)
Hemoptysis	1 (1.1; 0.1-6.1)
CHF	1 (1.1; 0.1-6.1)
Hemorrhagic stroke	1 (1.1; 0.1-6.1)
Ischemic stroke	1 (1.1; 0.1-6.1)

CHF: congestive heart failure; 95%CI: 95% confidence interval.
**Clinical manifestations are not mutually exclusive; the same patient may have presented more than one symptom, so the percentages do not add up to 100%.*

Figure 1. Distribution of patients according to diagnostic evaluation and criteria applied



HHT: hereditary hemorrhagic telangiectasia.

The diagnosis of HHT was confirmed in 80 patients (50.6%; 95%CI: 42.8-58.4): 43 (53.8%; 95%CI: 42.4-64.9) based on clinical criteria and 37 (46.2%; 95%CI: 35.1-57.6) by genetic testing. During follow-up, 66 patients (82.5%; 95%CI: 72.3-89.6) met >3 Curaçao criteria, while 14 (17.5%; 95%CI: 10.4-27.7) were diagnosed solely by genetic studies.

Clinical manifestations in patients with HHT

Epistaxis was the predominant manifestation, observed in 74 of the 80 patients with HHT (92.5%; 95%CI: 84.4-97.2%). Among the 13 patients with epistaxis and a known genetic variant, 6 (46.2%; 95%CI: 18.9-73.4) had mutations *in ACVRL1*, 6 in *ENG* (46.2%), and 1 in *SMAD4* (7.7%).

The mean age at onset of epistaxis was 6.8 ± 3.4 years. In 36 patients, severity was assessed using the ESS questionnaire, with a median of 1.6 (IQR: 1.1-3.2).

Iron deficiency anemia secondary to epistaxis was documented in 24 patients (32.4%; 95%CI: 22.2-44.3), all of whom were treated with oral iron. Six of these (25.0%; 95%CI: 10.2-46.4) required intravenous iron and 4 (5.4%; 95%CI: 1.5-13.3) required ablative treatment (sclerotherapy, laser, or other).

A total of 47 patients (63.5%; 95%CI: 51.7-74.1) reported adequate nasal care. During follow-up, 64 of the 80 patients (80.0%; 95%CI: 69.9-87.9) presented at least one telangiectasia (*Table 4*).

Screening for pulmonary AVMs was performed in 68 patients with a diagnosis; AVMs were identified in 13 (19.1%; 95%CI: 11.1-31.2) (*Table 5*).

Eight of the 13 patients with pulmonary AVMs (63.0%; 95%CI: 35.4-84.8) had variants in *ENG*. Nuclear magnetic resonance and/or angiography were performed in 68 patients; cerebral AVMs were identified in 12 (17.6%; 95%CI: 10.0–29.2), including four classic AVMs, three arteriovenous fistulas, two micro-AVMs, two capillary AVMs, and one hemangioma. All lesions were intracranial, predominantly in the temporo-occipital region. Hepatic AVMs were detected in 8 patients (10.0%; 95%CI: 5.1–19.0): 6 with telangiectasias and

Table 3. Curaçao criteria for patients treated in the Hereditary Hemorrhagic Telangiectasia Unit

Curaçao criteria	Patients with HHT (n = 80) n (%; 95%CI)	Patients without HHT (n = 78) n (%; 95%CI)
Epistaxis	74 (92.5; 84.4-97.2)	35 (44.8; 33.7-56.5)
First-degree relative affected	75 (93.5; 86.0-98.0)	55 (70.5; 58.8-80.7)
Mucocutaneous telangiectasias	64 (80; 69.9-87.9)	27 (34.6; 24.1-46.5)
AVM	27 (33.7; 23.3-45.7)	8 (10.2; 4.6-19.2)

HHT: hereditary hemorrhagic telangiectasia; AVM: arteriovenous malformation; 95% CI: 95% confidence interval.

Table 4. Location of telangiectasias in patients with HHT*

Location of telangiectasias	Patients with HHT (n = 64) n (% ; 95%CI)
Face	21 (32.8; 21.8-45.4)
Lip	11 (17.2; 9.0-28.7)
Mouth	10 (15.6; 7.9-26.9)
Tongue	7 (11; 4.5-21.5)
Intranasal	18 (28; 17.6-40.3)
Trunk	2 (3; 0.4-10.8)
Extremities	19 (30; 19.0-42.2)
Conjunctiva	2 (3; 0.4-10.8)

HHT: hereditary hemorrhagic telangiectasia.

**The sites of telangiectasias are not mutually exclusive; the same patient may have had multiple locations, so the percentages do not add up to 100%.*

Table 5. Characteristics of patients with pulmonary arteriovenous malformations (n = 13)

Saturation ranges, n (%; 95%CI)		**Type of fistulas,** n (%; 95%CI)	
>95%	6 (46.2; 19.2-74.9)	Single fistula	3 (23.1; 5.0-53.8)
94-90%	2 (15.4; 1.9-45.4)	Multiple and diffuse fistulas	10 (76.9; 46.1-94.9)
89-85	2 (15.4; 1.9-45.4)		
<84%	3 (23.1; 5.0-53.8)		
Clinical presentation, n (%; 95%CI)		**Treatments initiated**, n (%; 95%CI)	
Hypoxemia	7 (53.8; 25.1-80.8)	Lobectomy	1 (7.7; 0.2-36.0)
CVA	3 (23.1; 5.0-53.8)	Pneumonectomy	1 (7.7; 0.2-36.0)
Headache	3 (23.1; 5.0-53.8)	Embolization	9 (69.2; 38.6-90.9)
Hemoptysis	2 (15.4; 1.9-45.4)	Reembolization	5 (38.5; 13.9-68.4)

CVA: cerebrovascular accident; 95%CI: 95% confidence interval.

2 with arteriovenous fistulas. In addition, one case of telangiectasias in the digestive tract, located in the jejunum, was documented.

DISCUSSION

This study describes for the first time the characteristics of a pediatric population with HHT in Argentina and Latin America, considering epidemiological, clinical, and genetic aspects. Most patients came from the AMBA, probably due to the accessibility of our center.

More than 70% of patients who visited our center's HHT unit did so because they had a first-degree relative with the condition. Only 15% were referred by or suspected of having the condition by a healthcare professional. Additionally, 6.3% of patients came to the consultation after finding information on digital platforms, demonstrating the potential impact of these tools in disseminating medical information.

Regarding the first consultation at the HHT unit, the average age was 9 years, and most already had symptoms attributable to the condition. This result suggests that diagnosis was established later than desirable, highlighting the need to increase awareness among adult family members to promote medical consultation for their children at earlier stages, regardless of the presence of symptoms. Genetic testing was performed in almost half of the patients evaluated. The absence of testing in the rest could be explained by difficulties in access, diagnosis defined by the Curaçao clinical criteria, absence of a pathogenic variant in the family, or confirmation of an alternative diagnosis that justified the clinical picture, among other causes. In this context, the usefulness of genetic testing in the pediatric population, where the Curaçao criteria have limited diagnostic sensitivity, is highlighted.[26] A negative genetic result avoids the need for additional testing, especially in young children, which may require anesthesia and hospitalization. Likewise, the diagnosis and early detection of vascular malformations and their timely treatment reduce morbidity and mortality, especially those associated with AVMs.[20] Five patients with asymptomatic HHT were diagnosed with AVMs: two with pulmonary malformations and three with cerebral malformations.

Using the screening protocol, vascular malformations of the CNS were identified in 17.6% of cases, slightly higher than the 10% reported by Al-Saleh et al.[27] and similar to the 16.2% reported by Giordano et al.[25] Pulmonary AVMs were found to have a prevalence of 19.1%, lower than that reported by Giordano et al. (45.4%) and Al-Saleh et al. (30.5%). These differences could be due, in the case of CNS AVMs, to varying degrees of adherence to international guidelines, and in the case of pulmonary AVMs, to a higher local prevalence of type 2 HHT.

During the study period, screening methods and management guidelines for HHT evolved, incorporating recommendations for the pediatric population, which may have influenced the diagnostic and therapeutic strategies implemented. This should be taken into account when interpreting the results, as differences in approaches may have affected the identification and treatment of complications.

Our findings, which are consistent in some respects and divergent in others from those reported in the literature, underscore the relevance of screening protocols in children with HHT. The identification of visceral malformations at an early age may allow for timely interventions, confirming Giordano et al.'s hypothesis that the prevalence of AVM in children tends to resemble that in adults

when strict evaluation criteria are applied.

This study is original in its approach, as it is the first descriptive study on HHT in the pediatric population of Latin America, spanning an extensive 12-year period.

The study has some limitations, such as the concentration of patients in the AMBA, which compromises geographical representativeness and external validity. Furthermore, as this is a retrospective study, there may be biases inherent in this design. However, to minimize this risk and optimize data accuracy, a thorough manual validation of the information was performed using electronic medical records.

CONCLUSION

This study provides a detailed description of the epidemiological, clinical, and therapeutic characteristics of a pediatric population with HHT, highlighting the importance of early diagnosis and timely intervention to prevent serious complications. The clinical diagnosis of HHT in the pediatric population is difficult. Familiarity with the symptoms of HHT, especially recurrent epistaxis or hypoxemia of unclear cause, will facilitate early diagnosis and referral to specialized centers. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2025/10661_AO_Squit%C3%ADnTasende_Anexo.pdf

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