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Diagnosis and treatment of patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) at a university hospital in Colombia

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Abstract

Introduction: Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome) is a hereditary vascular disease characterized by recurrent epistaxis, gastrointestinal bleeding and chronic anemia. Many cases have arteriovenous malformations of solid organs. Diagnosis is based on clinical data, endoscopy and imaging. Early detection and treatment of complications with a multidisciplinary approach impacts the disease's morbidity and mortality. **Objectives:** The objective of this study was to describe the demographic, clinical and outcome characteristics of patients diagnosed with HHT at a university hospital. **Methods:** This is a case series of patients evaluated between 2012 and 2017. **Results:** Records of 18 cases were obtained. The patients were from Colombia and other Caribbean countries. All diagnoses were established using the Curaçao criteria. Eleven patients 11 (61.1%) were men, and the median patient age was 56 years (IQR 52-64). The median number of hospital admissions was 6 (33.3%) (IQR 2.5-20.5), and all admissions were related to bleeding. Sixty-one percent of patients required transfusion of blood products, and the compromises of solid organs were found in the same number of patients by imaging studies. **Conclusions:** The clinical expression of THH varies, but in our study gastrointestinal manifestations were the most frequent causes of hospital admission. They frequently required transfusion of blood products and patients required multiple studies to identify the extent of the disease, and solid organ compromise. Treatment was based on endoscopic and medical management, especially administration of bevacizumab and octreotide.

Keywords

Hereditary hemorrhagic telangiectasia, hemorrhage, epistaxis, melena.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease (OWRD) is an autosomal dominant inherited vascular disease with various clinical manifestations. Patients usually present epistaxis, gastrointestinal bleeding and iron deficiency anemia due to mucocutaneous telangiectasias. Patients with HHT are also said to be at risk of developing arteriovenous malformations which can cause serious organ damage especially in cerebral, pulmonary and hepatic circulation. (1) Initial detection of HHT is based on clinical data, and the Curacao criteria are often used (Table 1). These consist of recurrent epistaxis, telangiectasias, visceral vascular malformations and a first-degree relative with HHT (the diagnosis is established with three or more of these criteria). (2, 3) Treatment of this entity consists of managing symptoms and complications. (3)

The estimated prevalence of HHT is 1.5 to 2.0 people per 10,000. (4, 5) Some authors think that variable penetrance (complete and incomplete) could have impact recognition and notification of the disease since not all patients present symptoms at an early age. (3, 4) This entity has a higher prevalence in certain populations including the Afro-Caribbean population of Curaçao and Bonaire. (5) To date, there have been very few case series published in Latin America, but there are reports of isolated cases in which variable clinical manifestations and involvement of solid organs due to arteriovenous malformations have been described. (6-8)

Table 1. Curacao diagnostic criteria for hereditary hemorrhagic telangiectasia

Criteria	Epistaxis or spontaneous and recurrent nosebleed.
	Telangiectasias at multiple characteristic sites (lips, oral cavity, fingers and nose).
	Visceral lesions, telangiectasias in the gastrointestinal tract (with or without bleeding) or pulmonary, hepatic, cerebral and spinal arteriovenous malformations.
	Family history: first-degree relative with a diagnosis of HHT.
Diagnosis	Definitive if 3 or more criteria are met.
	Possible or presumed if 2 criteria are met.
	Unlikely if less than 2 criteria are met.

The objective of this work is to describe demographic and clinical characteristics as well as outcomes of patients diagnosed with HHT at a university hospital.

MATERIALS AND METHODS

This is a case series study of patients older than 18 years of age with diagnoses of HHT established in the hospital from January 2012 to July 2017. The protocol was approved by the ethics and research committee of the Hospital Pablo Tobón Uribe in Medellín, Colombia. No written authorization was required since no names, personal identity data, or photos which would allow recognition of any individuals are included in the published data. According to National Resolution 8430 of 1993, this is a minimum risk study that does not jeopardize the integrity or identity of any patients.

The review of the medical records and procedures performed on the individuals under study was carried out between January 2012 and July 2017.

Data Collection and Analysis

Variables were loaded into a database by the researchers, and descriptive statistics such as measures of central tendency including means, medians and ranges were used for analysis.

RESULTS

Records of 18 cases were obtained (Tables 2 and 3). There were 11 men (61.1%) and 9 women (29.9%) with a median age of 56 years (interquartile range [IQR]: 52-64). Six were from Antioquia (33.3%), four from Chocó (22.2%), two from Caldas (11.2%), one from Quindío (5.5%), one from

Table 2. Demographic and clinical characteristics of patients with HHT.

Case	Age/sex	Place of Origin	Family history	Symptoms at consultation	Minimum platelet count	Minimum hemoglobin level	Solid organ compromise
1	58/M	Riosucio, Caldas	Yes	Asthenia, adynamia, fatigue, dyspnea, epistaxis, melena, hematochezia	88,000	3.7 g/dL	Yes (liver)
2	62/F	Cali	ND	Hematochezia, asthenia, adynamia, dyspnea	144,000	6.3 g/dL	Yes (liver, lung, pancreas)
3	52/M	Curaçao	Yes	Epistaxis, gastrointestinal bleeding	125,000	5.4 g/dL	Yes (liver)
4	41/F	Medellín, Antioquia	No	AUH, spontaneous ecchymosis	359,000	12.6 g/dL	None
5	77/M	Andes, Antioquia	No	Melena	166,000	5.1 g/dL	None
6	54/F	Riosucio, Caldas	Yes	Epistaxis, melena, hematochezia	208,000	7.4 g/dL	None
7	63/M	Curazao	Yes	Hemoptysis, melena, epistaxis	231,000	5.3 g/dL	Yes (lung)
8	59/F	Lloró, Chocó	Yes	Epistaxis, melena, hematochezia	ND	8.7 g/dL	None
9	56/F	Lloró, Chocó	No	Asthenia, adynamia, epistaxis	131,700	7.6 g/dL	Yes (liver, lung, brain)
10	78/M	Bonaire	ND	Epistaxis, asthenia, adynamia, fatigue, paleness	224,000	7.4 g/dL	Yes (lung)
11	67/M	La Unión, Antioquia	No	Melena	110,000	3.6 g/dL	Yes (lung)
12	58/M	Bonaire	No	Melena	416,000	8.9 g/dL	None
13	52/M	Bello, Antioquia	Yes	Epistaxis	241,000	16 g/dL	Yes (liver)
14	56/F	Quibdó, Chocó	Yes	Melena, epistaxis	134,000	4.9 g/dL	None
15	27/M	Lloró, Chocó	Yes	Epistaxis	ND	ND	Yes (lung, brain)
16	72/M	Riosucio, Caldas	Yes	Asthenia, adynamia	262,000	7.1 g/dL	None
17	48/F	Medellín, Antioquia	No	Epistaxis	264,000	ND	Yes, (lung, brain)
18	55/M	Medellín, Antioquia	Yes	Epistaxis, abdominal pain	234,000	6 g/dL	Yes (liver)

F: female, AUH: abnormal uterine hemorrhaging, M: male, ND: no data.

Table 3. Clinical data on treatment of cases with HHT

Cases	Hospital admissions	Peripheral stigmas: mucocutaneous	Digestive tract telangiectasias	Medical therapy	Endoscopic procedures	Transfusion of blood products (units)
1	74	Nose, hands	Esophagus, stomach, duodenum, jejunum, ileus, colon	Endoscopy, bevacizumab	UDE 8, enteroscopy 1, EVC 1	Yes (179 U)
2	40	ND	Esophagus, stomach, duodenum	Endoscopy, bevacizumab	UDE 10, EVC	Yes (2 U)
3	15	Tongue	Duodenum, jejunum	Endoscopy, bevacizumab, thalidomide, tamoxifen	UDE 2, EVC 1, enteroscopy 1	No
4	11	Hands and trunk	ND	None	ND	No
5	9	Face	Esophagus, stomach, duodenum, jejunum	Endoscopy	UDE 6, colonoscopy 1, EVC 1, enteroscopy 1	Yes (35 U)
6	37	Tongue and fingers	Stomach, colon	Endoscopy	UDE 19, colonoscopy 2, EVC 1	Yes (1 U)
7	46	Tongue, lips Hands	Esophagus, stomach, duodenum, jejunum	Endoscopy, bevacizumab	UDE 5, colonoscopy 1, enteroscopy 1, EVC 1	Yes (6 U)
8	7	Tongue, palate	Hypopharynx, stomach, duodenum, jejunum	Endoscopy	UDE 2, colonoscopy 1, EVC 1	ND
9	8	ND	Stomach, duodenum	Endoscopy	UDE 1, colonoscopy 1, EVC 1	Yes (2 U)
10	5	ND	Stomach, duodenum	Endoscopy	UDE 2, EVC 1, enteroscopy 1	Yes (1 U)
11	3	Lips, palate, nose	Stomach	Endoscopy	UDE 19, colonoscopy 2, EVC 1	Yes (13 U)
12	4	ND	Stomach, duodenum, jejunum, ileus	Endoscopy, octreotide	UDE 3, EVC 1, enteroscopy 1	No
13	3	Tongue	None	None	UDE 1	No
14	3	Tongue, lips	Stomach, duodenum, jejunum	Endoscopy	UDE 8, colonoscopy 1, EVC 1, enteroscopy 1	Yes (32 U)
15	1	ND	ND	Bevacizumab	ND	ND
16	1	Nose, tongue, lips	Stomach, duodenum, jejunum	Endoscopy, octreotide	UDE 1, colonoscopy 1, enteroscopy 1, EVC 1	Yes (2 U)
17	1	ND	Stomach	None	UDE 1	ND
18	1	Tongue, lips	Stomach, duodenum, jejunum	Endoscopy	UDE 1	Yes (2 U)

UDE: upper digestive endoscopy; U: units; EVC: endoscopic videocapsule.

Valle (5.5%), three from Bonaire (16.7%) and one from Curacao (5.5%).

First-degree family histories of HHT reported by 55.55%, six cases (33.33%) were spontaneous. There were no background data on the medical history of only two people (11.11%). The two patients from Riosucio,Caldas; one patient from Curaçao and one patient from Bonaire had first-degree family histories, and three of the four patients (75%) from Chocó had family histories of HHT.

Symptoms at admission were epistaxis (66.7%), melena (50%), hematochezia (22.22%), asthenia-adynamia (27.8%), fatigue (11.11%), dyspnea (11.11%). One patient had hemoptysis, and another patient had ecchymosis and abnormal uterine bleeding.

Endoscopy was performed and registered in the medical histories of 16 patients (88.8%), but there were no records of endoscopy in the clinical histories of the other two patients. All patients who underwent endoscopic studies had upper digestive endoscopy, endoscopic videocapsules had been used in 13/16 (81.25%), enteroscopy in 50% and colonoscopy in 50%.

Ten of the patients (55.55%) were admitted to the hospital for emergencies related to digestive bleeding manifested by melena or hematochezia. The minimum hemoglobin

levels in this group of patients ranged from 3.6 to 8.9 g/dL. All endoscopic studies including video capsules were performed on these ten patients (Table 3). Seven of them (70%) required enteroscopy for argon plasma coagulation of bleeding lesions or those at risk of bleeding (Figure 1).

Bevacizumab was administered in 27.7% of the cases, octreotide in 11.1%, thalidomide in 5.55% and tamoxifen in 5.55%.

The median hospital stay was six days (IQR: 2.5-20.5). All of these cases were patients hospitalized for digestive bleeding, and 61% of these patients required transfusion of blood products (Table 3). In 61% of these patients, solid organ involvement was identified due to arteriovenous malformations in the liver, lung, brain or pancreas. Four (22.2%) had exclusive liver compromises, three (16.7%) had exclusive lung compromises, and the others had multiorgan compromises: one patient in the liver, lung and pancreas; another patient in the liver, lung and brain; and two other patients in the lung and brain.

Table 2 describes the sex, age, blood test results during hospitalization (minimum platelet count and hemoglobin), and solid organ involvement due to arteriovenous malformation. Table 3 shows clinical manifestations, visible physical findings, distribution of telangiectasias in the digestive tract (Figure 2), and treatments and transfusions received.

DISCUSSION

Most patients in our series had minor bleeding episodes at early ages that were underestimated. Several reviews describe that more than half of these patients have symptoms before 20 years of age and say that the prevalence of epistaxis may be even greater than 90% of cases. (9, 10) The most frequently described symptom was epistaxis. It was followed by melena, hematochezia and general symptoms of blood loss such as asthenia, adynamia, fatigue and even dyspnea. The majority had severe anemia with varied related symptoms and were in need of blood transfusions as

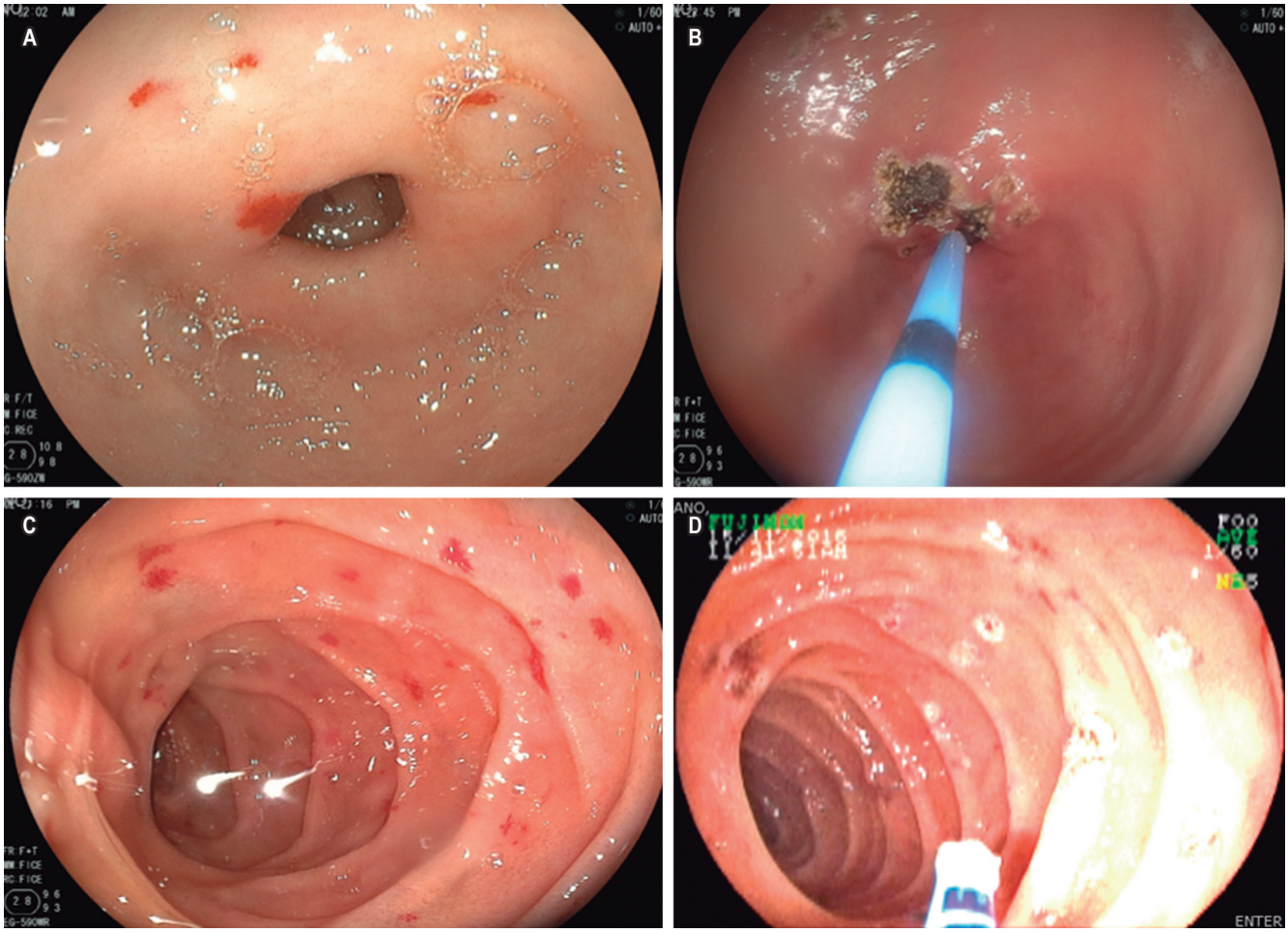

Figure 1. A. Telangiectasias in the antrum. B. Argon plasma therapy on lesions in the antrum. C. Telangiectasias in the small intestine. D. Argon plasma therapy.

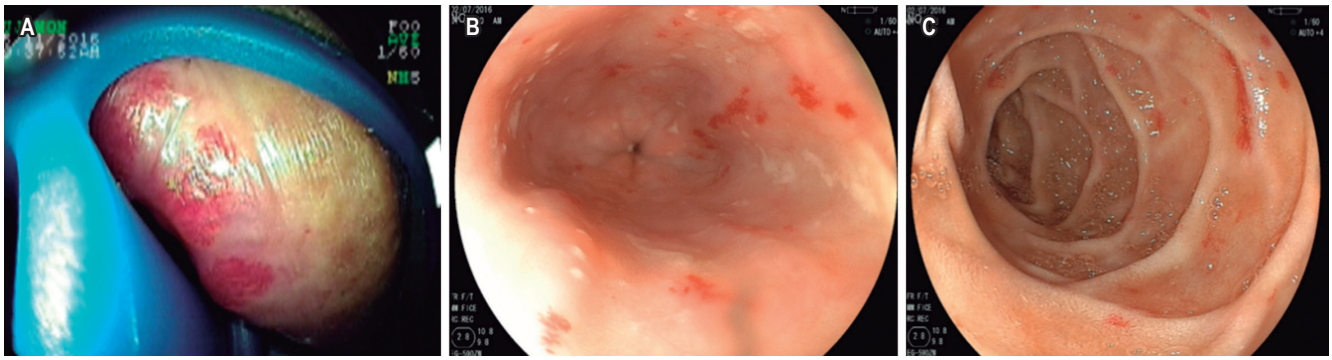

Figure 2. Extensive compromise by HHT. **A.** Lips. **B.** Multiple telangiectasias in the stomach. **C.** Telangiectasias in the duodenum.

described in a recent systematic review. (3) The number of units of red blood cells transfused had a clear relationship with the extent and severity of the disease.

In our series, no patient underwent genetic studies to determine the presence of HHT-related genes. These exams are not widely available in our environment and they are expensive. In addition, there is controversy over variable clinical expression. In a recent study, no significant differences in mortality were found in a period greater than 90 months between HHT Types 1 and 2. (11)

In patients with documented telangiectasias in the digestive tract, the lesions were mostly found in proximal locations. The stomach, duodenum and jejunum were the most common sites. In most cases, EVCs were used as a non-invasive method to assess compromises in the small intestine and define the need for endoscopic therapy. These data are similar to those described in the systematic review by Jackson et al. (3) In cases where bleeding in the small intestine was evidenced, double balloon enteroscopy was used to apply argon plasma therapy, with or without systemic therapy.

Systemic therapy was used in cases with refractory bleeding. Given descriptions in the literature of increased production of vascular endothelial growth factor in patients with this entity, there could also be an imbalance between anti-angiogenic and pro-angiogenic factors. (12, 13) This has allowed the use of drugs such as bevacizumab whose mechanism of action is to inhibit the growth factor of the vascular endothelium. There are multiple case reports of adults such as by Combariza et al. (14) of Hospital Pablo Tobón Uribe in Medellín. Bevacizumab has also been used in small series of cases that highlight good results in terms of effectiveness and safety. (15, 16) However, the costs and profile of adverse events with bevacizumab is not negligible, (17) so an appropriate patient choice must be made in order to opt for this drug. Nevertheless, we believe bevacizumab could be a promising medicine in the scenario of multiorgan involvement and refractory bleeding.

Arteriovenous malformations compromising one or more solid organs was identified in more than 60% of the cases. Most of them had pulmonary or hepatic involvement but a few also had cerebral involvement. The methods described in the literature for detecting these malformations vary. Jackson et al. found that thematic experts recommend studying pulmonary arteriovenous malformations with transthoracic contrast echocardiography and complementing it with high-resolution thoracic computed tomography if there are any abnormal findings. (3) Hepatic vascular malformations are studied in patients with confirmed HHT when they have abnormal liver function tests, cholestasis, portal hypertension or right heart failure. The study of these cases is performed by hepatic ultrasound with Doppler or three-phase helical CT. (18-20) In our series, all cases were studied by means of magnetic resonance imaging (MRI) of the abdomen. Our hospital has good high experience with this exam, and there is less risk of nephrotoxicity than with the use iodinated contrast.

Cerebral arteriovenous alterations were identified in three patients (16.6%) which is very similar to the 10% prevalence found by Fulbright et al. with cerebral MRI. (21) This is the method most often used in asymptomatic patients with possible or confirmed HHT who are 18 years of age or older. (3)

The majority of individuals with HHT who have good access to health services have normal life expectancy in relation to the general population. (3) Distribution of mortality is bimodal with peaks at 50 years and between 60 and 79 years. Acute complications related to arteriovenous malformations are the main cause of death, especially in the context of inadequate health care since these patients play a fundamental role. (3, 22)

We believe that more population studies are required to determine actual local prevalence: Prospective studies in which treatment alternatives aimed at reducing morbidity rates and number and durations of hospital stays are also

needed as are proposals for follow-up of asymptomatic first-degree relatives.

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