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Epidemiology of Hereditary Haemorrhagic Telangiectasia (HHT) in Spain

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Abstract

Aim: To describe epidemiological characteristics of a wide cohort of Spanish patients with hereditary hemorrhagic telangiectasia (HHT) and Rendu-Osler-Weber disease.

Methods and Results: Between 1 January 2002 and 31 December 2013, 667 Spanish patients with suspected HHT were evaluated in the reference HHT Unit in Hospital Sierra del la and 449 were diagnosed by clinical Curaçao criteria and/or genetic test. The diagnostic sensitivity of Curaçao clinical criteria in the population studied was 94.59%. Prevalence was 1:5,936 people and lethality rate of 0.16%. Type 2 HHT was the most prevalent and in total 147 different mutations were identified. Epistaxis was the most prevalent symptom (96.88% of cases) while 95.18% of patients showed typical telangiectasias. Pulmonary involvement was present in 28.25% of patients by (computed tomography) mainly in women and HHT1 cases while liver infection was more prevalent in HHT2 cases. Brain involvement was disclosed in 28.35% of cases. Telangiectasias in conjunctival mucose were very frequent mainly in HHT1 elderly patients.

Conclusion: This is the first representative series of epidemiological data on a non-previously evaluated population, showing results about prevalence, genetic distribution and organ infection and disclosing new observations that can help guide the diagnostic and screening procedures for these patients.

Keywords: Hereditary haemorrhagic telangiectasia (HHT); Rendu-Osler; Epidemiology; Spain

Introduction

Hereditary haemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease (CIE10 178.0/ ORPHA774) is an autosomal dominant genetic disorder characterized by the development of abnormal vascular structures (telangiectasias and/or arteriovenous malformations (AVM)) in the skin, mucous membranes, and internal organs. The penetrance of the symptoms is variable, and usually increases with age, reaching 90% at 45 [1]. Epistaxis is the most frequent clinical manifestation: up to 96% of the patients have nosebleeds and it is normally the first symptom to be observed [2]. HHT is a rare disease and is therefore an under-diagnosed pathology [3]. The average worldwide prevalence is estimated to be 1:5,000-8,000 persons [4]. Due to the founder effect there are isolated populations where this index is higher, for example, Jura in France, Funen in Denmark, and the Netherlands Antilles [5,6]. HHT has significant morbidity and mortality [7] associated and has no definitive cure.

The diagnosis is based on the Curaçao clinical criteria. These are epistaxis, telangiectasia, dominant familial aggregation, and internal organs alteration (three or four criteria need to be fulfilled for the diagnosis to be determined [8]). Also acceptable is the detection of the causative mutation through a molecular study. Three genes are implicated in this disease. The first, ENG, is located on chromosome 9 (9q33-q34) and it encodes for the endoglin protein. A mutation in this gene causes type 1 HHT [9,10]. A mutation in the ACVRL1 gene causes type 2 HHT. This gene is located in the 12q11-q14 region of chromosome 12 [11,12] and encodes for ALK1 (activin receptor-like kinase 1). A small percentage of patients have juvenile polyposis/hereditary HHT syndrome (JPHT) due to mutations in the MADH4 gene located in chromosome 18. Recently a new syndrome has been described, known as capillary malformation-arteriovenous malformation syndrome with a phenotype similar to that of HHT and caused by mutations in the gene encoding for BMP9 (bone morphogenetic protein 9) [13]. Mutations in ENG are more frequent than in ACVRL1 (61% vs. 37%) while mutations in MADH4 are observed only in 2% of the cases. There seems to be a geographic variability in the prevalence of type 1 HHT (higher in North American, Anglo-Saxon, and North European countries) while HHT 2 is more common in the area of the Mediterranean and in South America [4,14-16]. Patients with HHT 1 are more likely to have vascular malformations in the lungs and in the central nervous system. Patients with type 2 HHT are more affected in the hepatic and gastrointestinal systems [17,18].

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Valdecilla was established in 2002; it is coordinated by the Department of Internal Medicine and listed by the International HHT Foundation in Monkton, USA (www.hht.org). This Unit has its own multidisciplinary team that provides with genetic diagnoses, prevention protocols, diagnostic screening, and support treatment, all according to international recommendations. The HHT Unit also collaborates in basic research with the Biological Research Center (CSIC) of Madrid and with the activities of the Spanish Association of HHT patients (www.asociacionhht.org).

Patients and Methods

This is a transversal, observational, descriptive study that includes those patients with a clinical and/or genetic diagnosis of HHT evaluated in the HHT Unit of the Sierrallana Hospital from January 1st 2003 to December 31st, 2013. During this time, the HHT Unit served as a reference national unit in Spain for a population of 46,507,760 according to data from the National Statistics Institute (INE, January 1, 2014). A screening protocol was performed in all cases consisting of the series of tests described in Table 1.

The SPSS program, v22.0, was used to analyze the diagnostic quality of the data resulting from the different tests. Informed consent was acquired from all patients included in the study, according to the principles set forth by the Helsinki declaration.

Results

In the cited period, 667 patients were studied in the HHT Unit of the Sierrallana Hospital. HHT was confirmed in 449 cases (Table 2).

Two hundred and twenty seven patients (34.03%) were evaluated in the outpatient clinic, while 32.28%, 216 were seen as inpatient basis and 33.58%, (224) were only studied through genetic study (this group was not included for the evaluation of the clinical variables except genetics and prevalence as the follow up was performed in external centers).

Most patients were either from Cantabria and neighbour Autonomous Communities, or from the most highly populated areas of Spain: Andalucia, Catalonia, and Madrid.

The diagnostic sensitivity of Curacao clinical criteria in the population studied, when taking as gold standard a positive result in a genetic study was 94.59%. This sensitivity increased with age, reaching almost 100% in the eldest patients.

Estimate of disease prevalence and lethality rate

Taking the Cantabria population as a reference, the prevalence of HHT in the community was 1:5,936 people. Extrapolated nationally, this would correspond to 7,835 persons affected in Spain (3841 females and 3994 males). The estimated lethality rate for the period under study was 1.78% (accumulated) or 0.16% annually.

Analysis of the genotypic distribution

Type 2 HHT was the most prevalent, with 229 cases (51.00%), followed by HHT type 1, with 192 patients (42.76%). Only 3 patients had mutations in the gene (0.67%). Causative mutations were not detected in 5.8% of the patients. Using classical sequencing techniques, 89.53% of the patients were molecularly diagnosed. In addition, 22 patients (4.90%) were diagnosed via multiple ligation dependent probe amplification (MLPa) techniques. Therefore, the rate of coverage via genetic identification was 94.43%.

In total, 147 different mutations were identified: 74 in ENG, 71 in ACVR1, and 2 in MADH4. Of these, 93 (47 in ENG and 46 in ACVR1) had already been described and incorporated into the International registry. The majority were missense or nonsense mutations. However, there were 4 large deletions: 3 of these were in ENG and 1 was in ACVR1. Alterations in exon coding regions predominated, while a relatively small number were found in introns. In two cases, mutations were found in the promoter of ENG.

Epistaxis

Of the 353 treated patients, 342 (96.88%) had episodes of nose bleeds. There were no significant differences when comparing genetics or gender. Nevertheless, males were primarily affected. The average age of patients starting with epistaxis was 15.56. This average was similar in females and males, but was significantly earlier in patients with HHT2.

Telangiectasias

Of the 353 patients studied, 336 (95.18%) had typical telangiectasias in characteristic locations. Lesions were typically located in labial and lingual/oral areas with no differences when considering gender or genetics except a higher presence of facial telangiectasias in males (p=0.045). Labial telangiectasias appeared earlier in time in all cases while the frequency of all types of telangiectasias significantly increased with age.

Pulmonary findings

A contrast echocardiography (ECC) with saline solution was performed on 312 of the 353 inpatient and outpatient cases (88.93%) while thorax computed tomography (CT) was performed on 269 patients (76.20%). The ECC gave a positive result in 222 patients (71.15%) while images compatible with pulmonary arteriovenous malformations (MAVP) were achieved in 76 cases (28.25%) using CT. In both cases females and HHT1 patients showed higher rates.
of pulmonary involvement (Table 3). Males with pathological results in either ECC or CT were significantly younger than those who were unaffected.

Out of 222 patients with a positive ECC result, 120 (54.05%) were considered grade 1, 49 (22.07%) were considered grade 2, 31 (13.96%) were considered grade 3, and 22 (9.91%) were considered grade 4.

Out of 76 patients with MAVps detected by CT, 33 (43.42%) presented with a single malformation and multiple MAVps were observed in the remaining 43 (56.58%). One hundred and six MAVps (56.99%) were located on lower lobes and 80 (43.01%) were located on upper lobes. At the time of diagnosis, 118 lesions (63.44%) had afferent arteries with a diameter of less than 2 mm; 27 lesions (14.52%) had afferent arteries of between 2 and 3 mm in diameter and 41 (22.04%) lesions had afferent arteries greater than 3 mm in diameter.

Thirty-three MAVs were embolized with platinum coils (17.74% of the total and 48.53% of those greater than 2 mm in diameter). The recanalization rate was 39.40%, corresponding to 13 of the treated patients.

Of the patients with positive ECCs, 17 (6.97%) presented frequent migraine episodes (7 of these were grade 1, considering ECC, 4 were grade 2, 3 were grade 3, and 3 cases were grade 4).

Twelve patients of this same group (4.92%) had a history of ischemic cerebrovascular accidents and 5 (2.05%), had suffered from a cerebral abscess.

One HTT1 patient and one HTT2 patient needed surgery because of an aneurism in the thoracic aorta. The first was a case involving a dissection.

Abdominal findings

An abdominal CT was performed on 245 patients. As a result, hepatic arteriovenous malformations (MAVh) were observed in 177 cases (72.24%), being more frequent in females and HHT2 patients (p<0.001).

The most common lesions were telangiectasias and confluent vascular masses. Of the 64 patients with hepatic fistulas, 41 (62.69%) had arterioporal fistulas, 19 (31.34%) had systemic artery fistulas, and 3 (5.97%) had porto-hepatic fistulas. Meanwhile, 1 patient had simultaneous arterioporal and systemic arterial fistulas.

Non-pathological anatomical vascular variations were observed in 35.01% of the patients. Images consistent with focal nodular hyperplasias were produced in 6 cases (2.45%).

Fifteen patients had pancreatic vascular malformations (6.12%) (Figure 1) while there were 5 cases of splenic malformations (2.04%), and 1 case of a renal malformation. There was also an isolate case of a malformation in the gastric wall and another case of a malformation in the cecum wall.

When considering abdominal ultrasound, this was performed on 279 patients with pathological findings observed in 80 of them (26.67%) being the most common the presence of an increase in the perimeter of the hepatic artery.

A case was documented of a female 45-year-old patient with HHT2 whose MAVh showed hepatic fistulas. This patient presented congestive heart failure that required a hepatic orthotopic transplant performed in 2005 with the patient remaining asymptomatic in December 2013. Although routine screening for gastro-intestinal telangiectasias was not

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### Table 3: Distribution of patients according to findings in the MAVp, MAVh and MAVc screening.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Shunt in ECC n=222</th>
<th>MAVp in thoracic TAC n=76</th>
<th>MAVh in abdominal TAC n=177</th>
<th>MAVc n=13</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>71.15</td>
<td>28.25</td>
<td>0.08</td>
<td>72.24</td>
<td>6.5</td>
</tr>
<tr>
<td>Average age (SD)</td>
<td>44.21 (15.96)</td>
<td>41.63 (15.97)</td>
<td>48.37 (14.58)</td>
<td>47.64 (7.75)</td>
<td>0.94</td>
</tr>
<tr>
<td>Gender %</td>
<td>-</td>
<td>0.04</td>
<td>-</td>
<td>0.58</td>
<td>-</td>
</tr>
<tr>
<td>Females</td>
<td>127 (57.21)</td>
<td>48 (63.16)</td>
<td>98 (55.37)</td>
<td>7 (53.8)</td>
<td>-</td>
</tr>
<tr>
<td>Average age (SD)</td>
<td>44.53 (15.06)</td>
<td>44.67 (14.17)</td>
<td>48.65 (15.15)</td>
<td>41.29 (14.81)</td>
<td>-</td>
</tr>
<tr>
<td>Males</td>
<td>95 (42.79)</td>
<td>28 (36.84)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average age (SD)</td>
<td>43.79 (17.17)</td>
<td>36.43 (17.74)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Genetics %</td>
<td>0.77</td>
<td>0.17</td>
<td>0.006</td>
<td>0.08</td>
<td>-</td>
</tr>
<tr>
<td>HHT 1</td>
<td>106 (47.75)</td>
<td>58 (76.32)</td>
<td>57 (32.20)</td>
<td>9 (69.23)</td>
<td>-</td>
</tr>
<tr>
<td>HHT 2</td>
<td>104 (46.85)</td>
<td>15 (19.74)</td>
<td>114 (64.41)</td>
<td>4 (30.87)</td>
<td>-</td>
</tr>
<tr>
<td>Smad4</td>
<td>1 (0.45)</td>
<td>1 (1.32)</td>
<td>1 (0.56)</td>
<td>0 (0.00)</td>
<td>-</td>
</tr>
<tr>
<td>No fill</td>
<td>11 (4.96)</td>
<td>2 (2.63)</td>
<td>5 (2.82)</td>
<td>0 (0.00)</td>
<td>-</td>
</tr>
</tbody>
</table>

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![Figure 1: Telangiectasias in pancreas (left) and in gastric fundus (right).](image-url)
performed in the unit, 83 patients underwent an endoscopy or capsule endoscopy. Lesions were detected in 57 (68.67%) cases. These lesions did not vary significantly according to the gender or genetic profile of the patients. However, they were more common in females with HHT2. The 3 patients with mutations in Smad 4 were specifically referred for a digestive study and monitoring at their home healthcare centers.

Telangiectasias were observed in 48 of the 76 patients (63.16%) who had undergone an upper digestive endoscopy. Sixteen patients underwent a capsule endoscopy and 15 of these (93.17%) were found to have telangiectasias in the small bowel. In 13 out of these 15 patients, concomitant gastric telangiectasias were observed. In the remaining two cases, gastroscopy was not available. Finally, a colonoscopy was carried out on 34 patients with 11 cases (32.35%) showing colon telangiectasias.

Cerebral findings

A brain magnetic resonance (MR) was performed on 201 patients. Types of cerebral arteriovenous malformations (MAVc) found considering gender and genetic type and other non-vascular cerebral changes are documented in Table 4.

There was a higher prevalence of vascular malformations in patients with HHT1, however, this result was not significant. Meanwhile, bilateral basal ganglia hyperintensity was more frequently observed in HHT2 patients, as were multiple foci of white matter hyperintensity. This lesions were also more common in females, but with no significant differences.

Finally, a lumbar MR study was carried out on 17 females who were of fertile age to disclose the presence of spinal arteriovenous malformations with negative result in all cases.

Ophthalmological findings

Data were collected from 243 patients who underwent an ocular examination of the conjunctiva and iris, as well as a direct ophthalmoscopy after pupil dilation, a slit lamp exam and a contact free lens exam.

Some effects were observed in 57.61% of cases. There were no significant differences due to gender. In all of these cases, telangiectasias of the conjunctiva, either isolated or multiple, were observed (Figure 2). Meanwhile effects on the retina were not observed.

The prevalence of lesions increased with age: 28.57% of affected patients were less than 31 years old, 55.67% were between 31 and 50 years of age, 67.90% were between 51 and 65 of age, and 70.00% were above 65 years of age (p=0.001). Ocular lesions were significantly more prevalent in HHT-1 patients than in HHT-2 patients (p=0.017). Four patients reported episodes of ocular bleeding.

Discussion and Conclusion

This series is the first of its kind, both in terms of sample size and number of variables performed in Spain, and also one of the largest in the literature showing new data on a non-previous evaluated population [19-21].

Estimation of prevalence

The prevalence of this disease in the population studied was found to be similar to that previously reported in European and American series. However, it was far from the maximum described for high aggregation areas like the Netherlands Antilles [6]. We want to highlight the increase observed in the number of cases with respect to the initial series by Morales C and cols. [19] in 1997 that established a prevalence of 1/12,200 in Cantabria. This type of increase is commonly observed once a reference unit has been established and more cases are detected as a consequence. This result shows that, in the absence of reference units, there are delays in the diagnoses and a high degree of under-diagnosis [3,22].

According to these data nationally, the population affected by HHT amounts up to 7835 people. Nevertheless, recent studies of populations with a greater risk of isolation, such as one conducted in Gran Canaria, show a higher prevalence of about 1:3000 [23] probably due to a founder effect.

Not many data are available about the rate of mortality associated with HHT. Some studies appear to indicate that life expectancy is slightly reduced, by 3 years [24,25] affecting more to HHT1 patients [26]. Recent comorbidity studies in HHT patients show differences in the incidence of concomitant neoplasias, with a lower incidence in lung and a higher incidence in breast. These studies also show that infections are more common in patients with the disease. Therefore, evaluating the mortality directly derived from HHT is difficult [27,28].

Genotypic characteristics

Genotypically, there were a greater percentage of mutations in ACVR1I than in ENG. This result is consistent with series from other Southern European and Latin American countries [29,30]. The low percentage of patients with mutations in the ENG gene can be explained in part by the fact that sequencing of the gene began in 2007. has been linked to thoracic aortic aneurisms (above all in the aortic root) [31]. Significantly, the two patients treated by the Unit suffering this type of aneurism were HHT1 and HHT2.

The high rate of causative mutation detection is significant [17,18]. This is due to the cautious selection done by the health practitioners involved, who carefully chose the cases to refer for genetic analysis (according to Curacao criteria). Another factor was the systematic

<table>
<thead>
<tr>
<th>Cerebral Changes n=70</th>
<th>n</th>
<th>%</th>
<th>HHT1/HHT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic MAV (n=5)</td>
<td>5</td>
<td>2.49</td>
<td>3/2</td>
</tr>
<tr>
<td>Venous anomalies (n=7)</td>
<td>7</td>
<td>3.48</td>
<td>6/1</td>
</tr>
<tr>
<td>Cavernomas (n=1)</td>
<td>1</td>
<td>0.50</td>
<td>1</td>
</tr>
<tr>
<td>Global MAVc</td>
<td>13</td>
<td>6.5</td>
<td>7/6</td>
</tr>
<tr>
<td>Hyperintensive basal ganglia</td>
<td>24</td>
<td>11.94</td>
<td>15/9</td>
</tr>
<tr>
<td>Ischemic Encephalopathy</td>
<td>4</td>
<td>1.99</td>
<td>3/1</td>
</tr>
<tr>
<td>Polymicrogyria</td>
<td>2</td>
<td>0.99</td>
<td>1/1</td>
</tr>
<tr>
<td>Hyperintensive white matter</td>
<td>27</td>
<td>13.43</td>
<td>14/13</td>
</tr>
<tr>
<td>All other alterations</td>
<td>57</td>
<td>28.35</td>
<td>33/24</td>
</tr>
</tbody>
</table>

Table 4: Types of cerebral changes and distribution by gender and genetics.
use of molecular assays. HHT is a monogenic disease; however there are a wide variety of possible mutations, making diagnosis difficult. For example, there are pathologic alterations in introns and at the promoter as well as many kinds of deletions/insertions in the gene [32,33]. Significantly, during the period of study, the Unit carried out preimplantation embryonic diagnoses (PGD) [34] for three couples which allowed them to have disease-free children.

Epistaxis

Epistaxis is the most commonly observed symptom in our series and in literature [35,36]. However, we have to take into account that 50% of the general population can also have this symptom while 2% of the healthy population can have epistaxis together with telangiectasias [37].

Telangiectasias

As in other studies, most telangiectasias are labial [38]. These occur most frequently in younger patients. The frequency of mucocutaneous telangiectasias increases with the age of the patient.

The differences are not linked to gender, with the exception of more frequent facial lesions in males. This could indicate a small hormonal influence on the development of facial lesions.

Pulmonary alterations

Checking for a left-to-right pulmonary shunt or short circuit using an agitated saline serum ECC, was initially described by Shub et al. [39] in 1976 as a good screening method for detecting MAVp in HHT patients. This method was shown to be highly sensitive and to have a highly negative predictive value [40]. This method was also shown to have a low probability of complications [41] and that it could be used as a grading system for calculating the probability of having a MAVp large enough to be embolized [42]. Screening is necessary because of the high prevalence of MAVp in this population and to the high risk of a stroke or an infection (brain abscess) in the un-treated lesions [43]. Nevertheless, 6% to 28% of the population without HHT have a grade “one” lesion detectable by ECC [40,42]. Therefore, a second grade lesion is needed to increase sensitivity of the test. In our series, the percentage of cases with pulmonary involvement could be estimated according to the detection method used. If estimated using the ECC with agitated saline serum method (including all grades) the value is 71.15%. If estimated according to the TAC screening method, it was 28.25%. Using ECC probably leads to an over-diagnosis of pulmonary effects. According to recent studies, there is a minor risk of neurological events in patients with a positive grade 1 ECC result [40]. Our results confirm that pulmonary effects predominate in patients with HHT1 and that these patients have more lesions in their lower pulmonary lobules. This phenomenon is a consequence of an increase in hemodynamic pressure.

On the other hand, the rate of previously embolized MAVp rechannelling is slightly higher than seen in previous series. This result is probably due to the exclusive use of platinum coils for embolization procedures while other healthcare centers use ball mechanisms combined with coils [44]. Here, the rate of cases with neurological effects is slightly higher compared with past series (nearly 6%) probably because data about minor subclinical events were not registered in the study. The rate of patients who had migraines and a positive ECC result in the series was higher than the 6%, a result consistent with past reports that link this clinic with incidences of right-left shunts [45].

Abdominal alterations

The practice of screening for liver alteration is controversial because of the low percentage of associated symptomatology [46]. However, recent prospective studies of the HHT population, revealed a high rate of morbidity and mortality (1.1% and 3.6% yearly, respectively) related with liver disease. This suggests that this type of screening is advisable and that a monitoring protocol should be established [47]. There is a higher prevalence of cases showing liver alterations when CT is used for screening. The high percentage of fistulas (26.12%) is notable when comparing with reports of 8.8 and 16.9% [47,48] and the majority of these lesions are mainly to portal and systemic veins. This result is probably a consequence of the prevalence of HHT2 patients in the population but another factor is that many fistulae lesions are difficult to be evaluated using CT. Fistulas were mainly found in HHT2 patients and females [17,29] and this suggests that hormonal factors may play a part in the development of fistulas.

Anatomical variants were found mainly at the start of the hepatic artery and its branches in the celiac trunk and upper mesenteric artery [49]. Vascular alterations in HHT patients supported the development focal nodular hyperplasia foci. This result was observed less frequently than in other series in which a rate of 16% was reported [48].

Effects on the gastrointestinal tract mucosa are frequently observed. However, active bleeding is observed in only 25% of these cases [50]. In the series reported here, there is higher frequency of changes in the upper tract.

Cerebral alterations

According to the two largest series published until now [51,52], about 10% to 20% of these patients have AVMc. The frequency increases with mutations in ENG [17,53]. The low percentage revealed here, 6.5%, could be a consequence of the type of population and of the lower proportion of HHT1 patients. Even so, of the 13 cases described in the Unit, HHT1 was involved with a ratio of 2:3:1. In previous series nearly 40% of HHT patients presented multiple AVMc, and in contrast only 1% of the non HHT population with AVMc showed more than one lesion [54,55]. We saw a similar tendency on our series: 3/13 was cases of multiplicity. 69.23% of the AVMc were supratentorial, a result consistent with past reports [51]. There were not enough data to estimate the bleeding rate of the lesions.

In non-HHT patients with liver pathologies, magnesium deposits in basal ganglia are associated with the neurological symptomatology. Since nearly 35% of HHT patients with hyper intensity T1 MR signals, we appreciate as previously described [56] a link between MAVh and hyper intensity T1 MR results. This could potentially be worsened by anaemia [57,58]. Nearly 10% of our neurological findings are similar and were observed primarily in females and HHT2 patients. In all the cases, liver was involved as well. There were no effects on the spine observed in fertile females.

Ophthalmology findings

Little has been reported about the ocular effects in series that show that nearly 40% of cases involved telangiectasias of the subconjunctiva, while few changes were observed in the retina [59,60]. We show here, that there is a high rate of changes in the conjunctive mucosa, more prevalent in patients with HHT1 and increased with age.

Study limitations and bias control

Probable selection biases: There were a few pediatric patients due to the characteristics of the hospital.

Probable information biases: For some patients, not all the screening could be performed in the Unit, and had to be completed in
their home healthcare centers. The MLPA technique and sequencing of the gene were not available from the start of the study. In spite of the possible limitations, the size of the sample and its overall characteristics seem to be sufficiently representative.

Conflict of Interest
All authors of the manuscript declare lack of conflicts of interest.

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References


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