Letter to the Editor

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Dear Editor:

We would like to respectfully make a series of contributions regarding the original article "Diagnosis and treatment of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendú syndrome) at a university hospital in Colombia" by Dr. Mosquera et al.. Our contributions are on genetic diagnosis, clinical manifestations, medical management and endoscopic management.

Osler-Weber-Rendú syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is a disease with an autosomal dominant inheritance pattern characterized by telangiectasias and arteriovenous malformations. (1)

To date, the Curaçao criteria remain the parameters to be considered for diagnosis. It has been reported that these criteria are particularly useful in two situations: unaffected older adults, and young adults and children. This is where genetic testing plays an important role even though it is not widely available and is expensive. It should not be underestimated for making an accurate diagnosis. The alterations described related to endoglin (ENG for type 1 HHT) and the activin type A receptor gene (ACVRL1 for type 2 HHT) genes that account for the majority of HHT cases. They generate protein products that influence signaling TGF-β in vascular endothelial cells. The reported data show detection rates with sensitivity of up to 75% for mutations of ENG and ACVRL1 sequences. (1, 2) We also believe that these tests are relevant because of the different degrees of severity associated with different genotype alterations. Patients with HHT type 1 genotype are more serious and have a higher prevalence of pulmonary arteriovenous malformations and more severe episodes of gastrointestinal bleeding than do patients with HHT type 2. However, no significant changes in the severity of epistaxis, age of presentation and mortality rates have been demonstrated. (3)

On the other hand, more detailed descriptions of clinical manifestations and their frequencies seem relevant since they are data that can help a clinician suspect this disease which otherwise might initially be classified as an orphan disease. At least 90% of patients present nosebleeds, and 80% of HHT patients have gastric or small intestine telangiectasias although only 25% to 30% develop overt bleeding which tends to occur in the fifth to sixth decade of life (rarely before 40 years). (1, 4) These data are similar to those found in the study of Dr. Mosquera et al. It is also important to take into account other manifestations. Cardiac manifestations (acute myocardial infarcts and arrhythmia) have low prevalences. Arrhythmia is the most frequent cardiac manifestation. (5)

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There is also evidence that these patients have a higher prevalence of hepatic focal nodular hyperplasia. (6) We point out these clinical data to complement the article since they were not discussed in the patients of the published series.

As part of the review of the available literature, we would also like to complement the article in regard to clinical and endoscopic management. According to reports in the literature, oral or parenteral iron supplements may be sufficient treatment for mild anemia and chronic bleeding of patients with HHT and could even be defined as the first-line. (1) Among the pharmacological treatments described is hormonal therapy (estrogen/progesterone or danacrine preparations). (7) As a second line, antifibrinolytics (aminocaproic acid or tranexamic acid) have been used, (8) and there are also reports of the use of tamoxifen, interferon, thalidomide and sirolimus. (9)

In endoscopic therapy, Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:Y3Al5O12) lasers and argon plasma coagulation (APC) have been described. The latter is considered to be the most effective method available today. Multiple attempts at local endoscopic therapy are not recommended due to the additive risks of adverse events without additional benefit. (1, 7, 10) There are also data in favor of the use of N-acetylcysteine as an antioxidant. Although prospective controlled studies of its efficacy have yet to be done, it is considered to be a promising management possibility. (11)

We should not put aside recent guidelines which suggest an approach based on five specific measures to optimize care and reduce morbidity and mortality rates: detection of pulmonary arteriovenous malformations (AVM), advice regarding nasal bleeding, evaluation of iron deficiency, antibiotic prophylaxis before dental and surgical procedures, and pregnancy advice. It is known that most pregnancies in women with HHT develop normally. Major complications are rare, but survival is better if HHT is recognized and addressed prior to pregnancy. (10, 12)

The Mayo Clinic currently has the most experience managing HHT-related bleeding with intravenous bevacizumab. In general, it is well tolerated, but a relevant adverse effect is arterial hypertension. It is usually benign course and responds well to medical management. From a cost-benefit perspective that considers transfusions, hospitalization time and iron infusions, in the future biological therapy could become an earlier therapeutic approach. (4) There are reports of the use of pazopanib as an alternative for patients who are refractory to bevacizumab, but more controlled and prospective studies of its efficacy are still needed. (13)

Until 2011, there were no data that favored nutritional measures or lifestyle changes for managing this disease. (1) Despite this, in 2013, Silva et al. suggested that room humidification, nasal lubrication and saline treatments could be beneficial for controllin epistaxis associated with HHT. They also suggested that modifying the intake of foods high in salicylates and those with natural anti-platelet activity (including red wine, spices, chocolate, coffee, certain types of fruit, garlic, ginger, ginseng, and ginkgo biloba) could be beneficial. (14)

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Reply to the letter to the Editor

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Dear Editor:

We thank you in advance for the contributions received by from Dr. Costa Barney and Dr. Castañeda. We are pleased to know that our case series has been reviewed and analyzed by this honorable working group. Their valuable comments can certainly contribute to managing and monitoring these patients who suffer from such a complex condition, and perhaps interesting guidelines can be established for future studies in this field. For us, it is a pleasure that our work has raised concerns that can be discussed in the academic environment of this type of publication.

The Curacao criteria remain the diagnostic gold standard, especially when three or more of its criteria are present (*defined* diagnosis). (1, 2) Confirmation of a *defined* diagnosis is not required because current management recommendations remain unchanged except in the rare situation of the *SMAD4* mutation with the theoretical risk of its association with juvenile polyposis. (3) Incidentally, this is the rarest of the genetic mutations identified in this disease.

We agree that this disease is uncommon in our environment. In fact, it is one of the 2,271 diseases that are officially listed as orphan-rare diseases in Colombia. Because it is an orphan disease, it is mandatory to report all cases to SIVIGILA (Sistema de Información para la Vigilancia en Salud Pública - Public Health Surveillance Information System). This disease's code number is 844 while its ICD-10 code number is I780. Based on the provisions of current regulations regarding the national registry and notification of patients with orphan diseases, we want to clarify that when no confirmatory diagnostic test has been determined for an orphan disease, or when no such test is available in Colombia, notification will be made on the basis of the clinical diagnosis declared by one or more of the treating doctors. The declaration of a clinically confirmed orphan disease will be made based on scientifically accepted classifications, medical history and other patient records that confirm the presence of the orphan disease (Ministry of Social Protection, Resolution 946 of April 22, 2019). We make this clarification because, as mentioned in our study, all patients included therein were diagnosed on the basis of the Curacao criteria. Also, genetic tests are not often available in our environment even though they are part of the procedures of the health benefits plan.

Currently there are only 15 sites in Colombia that can do genetic and metabolic tests for this disease. They are mostly based in Bogotá, and none are in Medellín. In addition, although these sites collect the samples, they are processed in laboratories in the United

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States. The confirmatory genetic tests for this disease available in these centers and suggested by the Ministry are for ACVRL1, ENG, SMAD4, MADH4, GDF2. Each test has an estimated cost of 4 million pesos and average delivery time is 50 days. We reiterate that, in the absence of genetic confirmatory tests, a *defined* clinical diagnosis of Rendu-Osler-Weber syndrome on the basis of the Curaçao criteria is sufficient. Hopefully, a diagnosis will be endorsed by a multidisciplinary group. For this reason, our discussion cites Kjeldsen et al. At follow-ups of more than 7 years, they found no significant differences in the mortality rates of patients related to genetic diagnoses and/or establishment of disease subtype. (4) With the data described, we confirm that our position is only to request these tests in selected patients who do not meet the *defined* criteria of Curaçao. We believe that genetic tests can be useful and may also be requested for asymptomatic first-degree relatives without stigmata of the disease as an initial screening method.

We would like to take advantage of this space to suggest development of a multicenter study that can bring together the majority of patients with this disease in Colombia. Perhaps with more data we can propose a follow-up strategy based on the best currently available evidence.

Regarding clinical manifestations, we agree that extension of this description could be of interest to clinicians. The fact that the patients described in our series had no cardiac manifestations can be explained by the low prevalences described in other series. Four of the six patients with hepatic manifestations had vascular malformations while two had hepatic focal nodular hyperplasia.

We agree with what has been described about medical treatment. The data in our work reflect only the actions performed on the patients treated at our center. (5) For patients with very extensive disease who frequently consulted the emergency department due to bleeding, the approach was almost always to initially stabilize the patient. In cases of severe anemia, blood products were transfused. If endoscopy documented high-risk stigmas or recent bleeding, argon plasma therapy was administered, as described. A retrospective review found no data in the medical records that suggest complications during endoscopic procedures despite multiple interventions.

Regarding the general recommendations provided by the literature review by Dr. Costa Barney and Dr. Castañeda, we can only comment that patients with Rendu-Osler-Weber syndrome are complex and usually require multidisciplinary management. For this reason, any intervention aimed at improving the quality of life or increasing the life expectancy of these patients might be useful, but interventions should be individualized and should weigh risks against benefits. Of course, the context must be analyzed to be fair in terms of the costs and benefits of each intervention, since it is possible that one patient may require multiple interventions during the natural evolution of the disease.

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