Reply to the letter to the Editor

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Received: 29/07/19
Accepted: 30/07/19

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

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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