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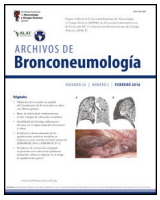

Letter to the Director

Diagnostic Difficulties in Hemorrhagic Hereditary Telangiectasia Presenting With Respiratory Failure and a *De Novo* Mutation in ENG Gene

To the Director,

Hemorrhagic hereditary telangiectasia (HHT) is a hereditary autosomal dominant disease associated with mutations in the genes encoding endoglin (ENG) and ALK1 receptor (ACVRL1). Loss of function of these proteins results in altered angiogenesis that leads to formation of vascular malformations in different organs, including the lungs. The development of pulmonary arteriovenous malformations (PAVMs) can lead to a right-to-left shunt, which impairs gas exchange causing hypoxemia, and puts the patients at risk of severe neurological complications.[1] We present the case of a 15-year-old female who developed hypoxemic respiratory failure due to a right-to-left shunt related to multiple PAVMs, that was eventually diagnosed of HHT with a *de novo* mutation in ENG gene and discuss the diagnostic difficulties in pediatric and adolescent patients, especially when family history is absent.

We present the case of a 15-year-old female without family or personal history of interest, except for isolated episodes of mild epistaxis in her early childhood. She presented with a 2-year history of worsening exertional dyspnea and fatigue. Physical examination revealed a baseline O_2 saturation measured by pulse oximetry of 88% and 2 lingual telangiectasias. Arterial blood gas values were in the range of respiratory failure. Chest X-ray, lung function tests, electrocardiogram, and echocardiogram were normal. Thoracic computed tomography (CT) without contrast showed multiple bilateral nodular opacities. A new echocardiogram with contrast confirmed the passage of multiple bubbles into the left heart chambers. CT angiography of the pulmonary arteries revealed the presence of multiple bilateral PAVMs. Selective embolization of the larger PAVMs was performed using coils and microvascular plugs, with good angiographic results and clinical improvement. Genetic study showed the variants c.279_280delinsGGA and c.284T>G in ENG, not described in the literature but classified as probably pathogenic and of uncertain significance, respectively. Neither of the variants was found in the study of her parents.

Diagnosis of HHT is based on the Curaçao criteria, which include (1) spontaneous and recurrent epistaxis, (2) telangiectasia, (3) family history, and (4) visceral vascular malformations. It is considered "definite" if at least 3 of the 4 criteria are fulfilled and "probable" if at least two are present. If only 1 criterion is present the diagnosis is considered "unlikely".[2,3] Many clinical manifestations of HHT develop with age, therefore the Curaçao criteria are not as helpful in children and adolescents as they are in adults.[4,5] On the other hand, it has been noticed that a significant proportion of patients with genetically confirmed HHT, with or without PAVMs, do not meet diagnostic criteria for definite HHT.[6] In these cases, family history may provide an important clue for early diagnosis. Due to limitations of Curaçao criteria, especially in children and adolescents, current guidelines advocate genetic testing in patients with one or more PAVMs, even in the absence of family history.[6,7] Our case represents a very unusual presentation of HHT with isolated respiratory failure, without family history, significant epistaxis, or evident telangiectasia, and highlights the importance of considering HHT in the differential diagnosis of patients with PAVMs.

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Conflict of interest

The authors declare to have no conflict of interest directly or indirectly related to the manuscript content.

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