EDITORIAL

Iron deficiency and pulmonary hypertension

Déficit de hierro e hipertensión pulmonar

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Iron deficiency is frequent in patients with pulmonary hypertension, with an estimated prevalence of 43% to 56%. (1-3). Regardless of the presence of anemia, iron deficiency is an adverse prognostic factor which has been associated with lower functional class, distance walked in the 6-minute walk test and increased mortality, especially in patients with pulmonary arterial hypertension (PAH). (1, 2, 4) Due to multiple diagnostic criteria, the prevalence and association with prognostic factors is very variable. Consequently, current international guidelines include continuous monitoring and iron replacement in case of deficiency in patients with PAH. (5)

The study of Atamañuk A. et al. (6), published in this issue of the Argentine Journal of Cardiology, prospectively evaluated patients with diagnosis of group I and IV pulmonary hypertension from July 2015 to July 2017. The purpose of the study was to establish the incidence of iron deficiency and its importance as prognostic factor, comparing pulmonary hypertension patients with healthy controls and patients with left-sided heart failure. The study included 60 patients with pulmonary hypertension, 26 with heart failure and 21 healthy controls.

The analysis showed a high prevalence (78.3%) of iron deficiency, without significant differences in the incidence of anemia, and with similar results in the subgroup of patients in functional class I and II. In addition, serum iron and transferrin saturation were correlated with the distance walked in the 6-minute walk test (r: 0.35; p <0.01 and r: 0.34; p <0.01), with no difference with iron deficiency, functional class and NT-proBNP. In the subgroup analysis, no differences were found between groups with group I pulmonary hypertension.

The study results are in accordance with those reported in other populations, indicating the high prevalence and importance of the study of iron deficiency associated with pulmonary hypertension. The incidence of iron deficiency in pulmonary hypertension is variable according to the diagnostic criterion used (9.9% to 38.9%). (7) The study of Atamañuk a. et al. used serum ferritin <100 ng/ml or between 100 ng/ml and 300 ng/ml with transferrin saturation <20% as diagnostic criteria. The criteria associated with a bad prognosis are: serum ferritin <100 ng/ml associated with transferrin <20% or increased transferrin saturation/(log) ferritin ratio. (7)

Iron deficiency is correlated, independently of the severity of the disease, with decreased functional class, reduced distance walked in the 6-minute walk test, higher serum levels of NT-proBNP, and there is limited evidence correlating iron deficiency with higher mean pulmonary artery pressure (63.3±12.2 mmHg vs. 38.8±16.7 mmHg), lower cardiac index (1.3±0.2 l/min/m2 vs. 2.5±0.4 l/min/m2) (8, 9) and reduced survival. (4) As mentioned by the authors, the low number of patients might explain the absence of correlation with functional class and NT-proBNP.

Cotroneo et al. (10) demonstrated in an animal model with rats that iron deficiency was associated with pulmonary vascular remodeling, medial hypertrophy, perivascular inflammation and cellular infiltration, in association with increased pulmonary artery pressure and right ventricular hypertrophy. Reduced mitochondrial activity, increased HIF1-α, HIF2-α and NFAT expression and STAT3 activation, which promotes vascular cellular proliferation and resistance to apoptosis, were observed at the molecular level. These alterations, similar to those observed in PAH, reverted after iron supplementation.

There is evidence demonstrating the multifactorial nature for the development of iron deficiency in pulmonary hypertension. The mechanisms involved are a reduction in iron absorption caused by gastrointestinal edema associated with systemic venous congestion, increased iron consumption due to secondary polycythemia and chronic hypoxemia (11), blood loss

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as a consequence of chronic anticoagulation and abnormal hepcidin serum levels. (12)

Hepcidin metabolism is altered independently of inflammation markers such as IL-6 and it acts through a BMP dependent pathway. Subgroup analyses have shown greater deficiency in premenopausal women and with BMPR2 gene mutations, suggesting an interaction between BMPR2 function loss, IL-6 and iron metabolism, findings that have not been reproduced in patients with chronic thromboembolic pulmonary hypertension.

Iron deficiency has a high prevalence in pulmonary hypertension and is associated with adverse cardiovascular outcomes. Atamañuk et al. present for the first time Latin American results, which is particularly relevant as iron deficiency is frequent in developing countries. It is important to unify diagnostic criteria due to the variability of prevalence and association with prognostic factors. The mechanisms involved and their relationship with these markers, as well as the effect of iron supplementation should be further studied. The development of genetic research is a priority, using models that allow establishing which genes promote the association between pulmonary hypertension and iron metabolism disorders.

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