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EDITORIAL COMMENT

When an affliction doesn't come alone

Quando um mal não vem só

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Neurofibromatosis type 1 (NF1), also known as peripheral neurofibromatosis or von Recklinghausen disease, is an autosomal dominant genetic condition with an estimated incidence of 1 in 2500-3000 individuals,[1] caused by a mutation in or a deletion of the *NF1* gene, located on the long (q) arm of chromosome 17, at band 11.2 (17q11.2).

The *NF1* gene product is a cytoplasmic protein called neurofibromin 1. It has a guanosine triphosphatase (GTPase)-activating protein domain that causes downregulation of proto-oncogenes. As a result, disproportionate cell proliferation occurs, leading to an increased risk of neoplasms.[2]

The NF1 phenotype results from loss-of-function mutations of the *NF1* gene leading to a lack of neurofibromin 1. This genetic mutation is innate, and clinical symptoms appear early in life and continue over many years.[3]

The diagnosis of NF1 is clinical, based on criteria proposed by the National Institutes of Health Consensus Development Conference.[4] Cutaneous, musculoskeletal and neurological involvement is frequent. In the spectrum of thoracic manifestations, abnormalities in pulmonary vasculature and parenchyma are rarely seen.[2]

Diagnosis by genetic testing is possible but is usually not required because of the typical clinical features of the disease and of the great variety of mutations of the neurofibromin 1 gene.[2]

Diagnosing pulmonary arterial hypertension (PAH) in NF1 is difficult in many cases as it is not a common manifestation of NF1, and therefore not recognized early on. Patients will typically present with classic signs and symptoms of NF1, such as café-au-lait spots, axillary freckling, cutaneous neurofibromas and optic glioma. Dyspnea and signs of right heart failure are the principal symptoms leading to assessment for associated PAH, which is frequently assigned to other pulmonary disorders because of the very low incidence of PAH in NF1 patients. PAH in NF1 is classified as Group 5 PAH, defined as 'PAH with unclear and/or multifactorial mechanisms'.[2,5]

Patients with PAH and pulmonary arteriopathy associated with NF1 usually have a relatively poor long-term prognosis.[6] In addition to malignant peripheral nerve sheath tumors, vasculopathy is one of the most important causes of early death in patients with NF1.[7]

In spite of this unfavorable prognosis, there are specific treatment options for PAH, and supportive management can achieve some improvement in symptoms. Because of the complexity of the condition, patients should be managed at a tertiary care center or institution that specializes in PAH.

Timely recognition of this unusual and severe association between NF1 and PAH is imperative in prolonging survival in this patient population.

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The case report by Santos and Pereira published in this issue of the *Journal*[8] is a rare clinical case of a patient with NF1 complicated with PAH. An exhaustive investigation was performed to identify the main etiology of the patient's PAH, which was classified as Group 5 PAH. In general, such patients have a poor long-term prognosis due to the lack of proven effective treatment.

Take-home messages

- NF1-associated PAH is often under-reported due to difficulty in diagnosis and in distinguishing it from other more common pulmonary disorders.
- Most reported patients with PAH associated with NF1 will typically present with classic signs and symptoms of NF1 in advanced stages of the disease, probably related to the indolent nature of symptoms, their chief complaint often being progressively worsening dyspnea.
- The available treatments for PAH in NF1 have shown discouraging results.
- Early recognition and diagnosis of the life-threatening association between NF1 and PAH should be managed at a tertiary care center or institution that specializes in PAH to enable early referral of eligible patients for lung transplantation.

Conflicts of interest

Dr. Alberto Mello e Silva has received consultancy and speaker fees from Bayer, Daiichi-Sankyo, Menarini, Mylan, Novartis, Servier and Tecnimede.

There is no conflict of interest for this editorial.

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