ORIGINAL ARTICLE

UNDERDIAGNOSIS: A LIMITATION TO THE FOLLOW-UP OF PATIENTS WITH COPD ASSOCIATED WITH ALPHA-1 ANTITRYPSIN DEFICIENCY

Subdiagnóstico: uma limitação ao seguimento dos pacientes com DPOC associados à deficiência de alfa-1

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is a rare autosomal codominant hereditary disorder that primarily affects the lungs and liver. The only Brazilian study reporting the prevalence of AATD estimates that 2.8% of patients with chronic obstructive pulmonary disease (COPD) have this disorder. Thus, this case report aimed to demonstrate the need to investigate AATD in patients with COPD, as the underdiagnosis and subsequent lack of prevention and treatment lead to unfavorable prognostic outcomes.

Keywords: Alpha-1-Antitrypsine; COPD; Genotyping techniques; Neutrophil elastace; Spirometry

RESUMO

A deficiência de alfa-1 antitripsina (DAAT) é um distúrbio hereditário codominante autossômico raro que afeta principalmente os pulmões e o fígado1. O único estudo brasileiro que relata a prevalência de DAAT estima que 2,8% dos pacientes com doença pulmonar obstrutiva crônica (DPOC) apresentam essa deficiência. O objetivo deste relato de caso consiste em demonstrar a necessidade de investigar a DAAT em pacientes portadores de DPOC, evitando o subdiagnóstico e a não realização de medidas preventivas e de tratamento específico, que quando não implementados leva a desfechos prognósticos desfavoráveis.

Palavras-chave: DPOC; Alfa-1-antitripsina; Técnicas de genotipagem, Espirometria; Elastase neutrofílica

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a rare hereditary autosomal codominant disorder that affects mainly the lungs and the liver.[1] Alpha-1 antitrypsin (AAT) is part of the superfamily of serine protease inhibitors, and it is encoded by the SERPINA1 gene, located on the long arm of chromosome 14 (14q32.1). The main function of AAT is to inhibit several enzymes, including trypsin, neutrophil elastase, and protease-3.[1,2]

The AAT deficiency causes pulmonary emphysema due to an imbalance in the protease-antiprotease relationship, as reduced serum levels of this protein (or dysfunctional molecules) are insufficient to protect the lungs from the elastolytic action of neutrophil elastase and other damages.[2,4] Thus, the lung lesion would be a consequence of increased damage factors (smoking, infections, and occupational factors), or reduced protection (i.e., serum AAT levels) (or both), accelerating lung damage.[3]

In Brazil, the underdiagnosis of AATD is mainly due to poor medical knowledge about the condition, the diagnostic tests required, and their limited availability. The diagnosis is confirmed when the test detects reduced AAT serum levels, followed by the identification of specific alleles via phenotyping or genotyping (or both). The normal serum AAT levels range between 120 and 220 mg/dL; levels below 50 mg/dL characterize severe deficiency.[2,3,4]

AAT is an acute phase reactant, similar to C-reactive protein (CRP) and amyloid A, and its plasma levels increase in response to inflammation or infection. A normal CRP level confirms that AAT levels are elevated. However, AAT levels could be falsely increased when CRP is elevated, requiring a new test during clinical stability.[5]

Protein phenotyping uses isoelectric focusing electrophoresis to identify the most common AAT variants (S, Z, and M). Although this test is the gold standard for detecting AATD variants, it requires expertise in interpretation and has limitations. When the diagnosis is inconclusive (null, rare, or very rare variants), genotyping is performed.[5]

Genotyping uses CRP to identify the most common AATD alleles, mainly S and Z. Gene sequencing may be needed when null or deficient variants besides S and Z are suspected to be present. Fast genotyping methods can be used to detect the most common alleles (PiS and PiZ); however, misdiagnosis may occur since these tests do not include rare or null alleles. The molecular analysis by direct SERPINA1 gene sequencing may be used to identify rare alleles and null variants and characterize novel mutations.[5]

One of the tests available in Brazil is the A1AT genotyping, which simultaneously analyzes the 14 most prevalent AATD mutations using DNA extracted from buccal swabs or blood collected on filter paper.[5] Nearly 80% of patients are identified via investigation of respiratory symptoms, whereas only 3% of diagnoses are attributed to liver disease.[3]

Given that AAT gene mutations are found in about 1.0% to 3.0% of patients with COPD, this case report presents several clinical and imaging aspects of a patient with a long-standing, early-onset COPD diagnosis who had never been screened for AATD.[1]

This case report aimed to highlight the need to investigate AATD in patients with COPD, preventing underdiagnosis and ensuring proper prevention and treatment to avoid poor prognostic outcomes.

CASE REPORT

Male patient, 63 years old, with a medical history of systemic arterial hypertension, mild obstructive sleep apnea syndrome, and significant exertional dyspnea. He was diagnosed with COPD 30 years ago, was a former smoker with an 80-pack-year history, and was abstinent for 10 years. The patient was referred on 12/03/2019 to the Emergency Department of the State Public Servants' Hospital.

In the emergency, the dyspnea of the patient worsened, and he presented a productive cough with increased yellow or green sputum . On physical examination, the patient was dyspneic (2+/4+), with SpO_2: 89% to 90% on room air; HR: 116 bpm; BP: 190 X 110 mmHg; and temperature: 37.5ºC. Pulmonary auscultation revealed universally reduced vesicular breath sounds, rhonchi at the bases, and discrete diffuse expiratory wheezing.

His medical history included four previous hospitalizations for COPD exacerbations in the past year; the most recent occurred two months prior. He was under the care of a pulmonologist and was using inhaled Salmeterol (50 mcg) and Fluticasone (500 mcg) twice a day, along with Tiotropium 2.5 mcg (two inhalations once daily). He also used a short-acting bronchodilator as needed, reporting daily use of four to six doses.

A chest tomography (CT) from October 2019 showed centrilobular and paraseptal emphysematous changes in the upper lung, along with multiple emphysematous alterations in the lung bases, architectural distortion in the lower lobes, middle lobe, and lingula, as well as cicatricial atelectasis and bronchiectasis in the lower lobes.

A spirometry performed in September 2019 showed FVC: 1.32 L (34%), FEV_1: 0.65 L (21%), and FEV_1/FVC: 49.2 (62%) pre-bronchodilator; and FVC: 1.39 L (36%), FEV_1: 0.77 L (25%), and FEV_1/FVC: 55.4 (69%) post-bronchodilator. These results characterized a severe obstructive ventilatory disorder with reduced FVC and no significant bronchodilator response.

With a presumptive diagnosis of COPD exacerbation, the patient was admitted and started on broad-spectrum antibiotic therapy with piperacillin-tazobactam due to the history of previous hospitalizations, alongside other standard measures for an infectious COPD exacerbation. Given the CT findings and the severity of the disease progression, a genotyping test for AATD and serum AAT measurement were performed using an oral swab sample.

During hospitalization, the patient improved in dyspnea, returning to his baseline level with moderate exertion (mMRC: 3). He also reduced cough and sputum production. He was discharged in good general condition, without signs of infection or complaints, maintaining preserved physiological habits and adequate oral food intake.

At a follow-up appointment on 12/26/2019, serum AAT levels and genotypic testing results confirmed the diagnosis of AATD with the PI*-ZZ genotype. After reassessment, a weekly intravenous AAT replacement therapy was added to his treatment regimen. Over one year of follow-up, the patient remained clinically stable, with no further exacerbations.

This case report was approved by the research ethics committee of the Faculdade de Medicina de Olinda (CAAE: 50086721.3.0000.8033).

COMMENTS

ATTD is considered the most important genetic cause of respiratory disorders in adults, particularly COPD with an emphysematous phenotype. Several mutations on the SERPINA1 gene cause it and have several clinical implications.[1]

The rate of lung function decrease among smokers with COPD associated with AATD is significantly higher than in COPD cases with normal AAT levels. This results from the combined effects of cigarette smoke, reduced antiproteinase activity of the AAT, and persistent pulmonary inflammatory infiltration.[6]

The global database of individuals affected by AATD is limited, and for a long time in Europe, researchers considered that this disease affected only white individuals and their descendants. However, recent studies demonstrated that this disease is present among many populations, including Black Africans, Arabs, and Jews in the Middle East, white individuals in Australia/New Zealand, Europe, and North America, as well as Central, East, and Southeast Asians.[7]

Epidemiological studies estimate that AATD affects about 1 in 2,000 to 5,000 live births. Moreover, the only Brazilian study reporting AATD prevalence estimated that 2.8% of patients with COPD present this disorder. The Platino study revealed that 15.8% of patients aged 40 years or older had COPD in the city of São Paulo, suggesting a significant number of AATD underdiagnosis.[3]

The criteria for suspecting and investigating AATD include any patient diagnosed with COPD, especially those with early-onset emphysema (before age 45); bronchiectasis of unknown cause; adults with asthma exhibiting a progressive obstructive pattern of evidence of emphysema; consanguineous relatives of AATD patients; individuals with family members with chronic cough and dyspnea; and individuals with chronic liver disease of unknown origin, lacking an alpha-1 glycoprotein peak, or with panniculitis or vasculitis of unknown cause.[1,8,9]

The patient analyzed in this case had been diagnosed with COPD at age 33, presenting severe symptoms and a chest CT scan showing widespread emphysema, especially in the basal lung. Nevertheless, he was never screened for AATD, leading to a missed diagnosis for 30 years.

Since COPD alone and COPD with AATD affect the body differently, they lead to different disease progressions, outcomes, and treatment responses. Therefore, early diagnosis of AATD changes the natural history of the disease, improving patient outcomes by allowing preventive measures and identifying those who may benefit from specific therapy. [5]

Thus, upon early identification of COPD-AATD, standard therapy (i.e., smoking cessation, vaccination, bronchodilator use, pulmonary rehabilitation, and long-term home oxygen therapy when indicated) should be implemented. Additionally, specific therapy involving AAT replacement via the administration of purified, concentrated human plasma-derived AAT may be needed in selected patient groups.[9] Therefore, a thorough investigation of clinical history and AATD as a potential diagnosis is essential.[6]

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