Alpha-1-Antitrypsin Deficiency Associated With Null Alleles

Déficit de alfa-1-antitripsina asociado a alelos nulos

To the Editor,

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant disorder that predisposes carriers to early development of chronic obstructive pulmonary disease (COPD) and/or liver disease. It is caused by the inheritance of 2 severe deficiency alleles in the SERPINA1 gene, and a plasma concentration of alpha-1 antitrypsin (AAT) below 50 mg/dl is representative of a significant deficiency. Up to 95% of clinical cases related with AATD are associated with the PI*ZZ genotype, while the other 5% are associated with PI*SZ and PI*MZ genotypes or combinations of PI*S or PI*Z with other extremely rare deficiency or null alleles. These rare alleles account for 4.6% of the deleterious variants recorded in the Spanish Registry of Patients with AAT Deficiency, and null variants are very rare indeed. Although around 25 null variants have been discovered in the last 20 years or so, little information is available on their clinical impact. We report 2 cases of patients referred to the respiratory medicine clinic with a diagnosis of AATD associated with the PI*Q0amersfoort and PI*Q0cardiff allele.

The first was a 47-year-old woman, native of the former republic of Yugoslavia, with a smoking history of 15 pack-years, referred to the respiratory medicine clinic for a 1-year history of dyspnea on moderate exertion (mMRC 2). Lung function tests results were as follows: FEV1/FVC 0.5; FEV1 1.801 (55%); FVC 3.401 (77%); DLCO 53%; KCO 52%. High-resolution computed tomography revealed centrilobular emphysema, predominantly in both lower lobes. Complete blood count, IgA, IgM, IgG, IgE and transaminases were within normal levels. Plasma AAT determined by nephelometry was 18 mg/dl, so a genetic study to detect deficiency alleles S and Z was performed using real-time PCR (FRET, LightCycler 2.0, and TIB MOLBIOL probes), which detected heterozygosity for the PI*Z allele, while the presence of PI*S alleles was ruled out. In view of the discordance between the genotype obtained and AAT plasma levels, a molecular study was performed of all exonic coding regions and of the intronic sequences flanking the SERPINA1 gene, using Sanger sequencing (BigDye™ Terminator v3.1 Cycle Sequencing, Thermo Fisher Scientific). In this study, in addition to the PI*Z described above, heterozygosity for the PI*Q0amersfoort allele was detected (Fig. 1).

The second case was a 42-year-old man with no clinical history of interest, who was referred to our clinic for a family history of AATD. He had severe AAT deficiency (41 mg/dl), and heterozygosity for the PI*Z allele was detected. Molecular study of the SERPINA1 gene revealed a Z/Q0cardiff genotype (Fig. 1). The patient had no respiratory symptoms or liver disease. Lung function test results were within normal limits: FEV1/FVC 0.79; FEV1 4.821 (109%); FVC 5.601 (112%); DLCO 109%; KCO 106%. Chest radiograph and general laboratory tests were unremarkable.

AAT is an antiprotease, produced mainly by the hepatocytes, which inhibits the elastase activity of the neutrophils, with the elastase activity of the neutrophils. Normal plasma levels range between 120 and 200 mg/dl. Although the Z mutation (p.Glu342 Lys) deficiency allele is the most common and leads to very low AAT levels in plasma (around 10%–15% of the normal level), serum AAT levels in null mutations are extremely low or undetectable, which is involved in this outcome, including errors in protein synthesis or post-translational degradation. For this reason, genotypes consisting of null homozygotes or accompanied by other deficiency alleles of the SERPINA1 gene carry a particularly high risk of very early onset pulmonary emphysema, even earlier than would be expected in the ZZ genotype.

With regard to PI*Q0amersfoort, the limited literature available suggests that both heterozygous and homozygous forms lead to COPD at an early age, as observed in our female patient, with no liver involvement whatsoever. This mutation causes a stop codon at position 184 of the protein, resulting in a severe deficiency when associated with other deficiency variants, such as PI*Z. Like other null alleles, the PI*Q0amersfoort variant does not cause liver disease because the protein is not polymerized in the liver, as occurs in mutations caused by amino acid switches, in which deficiencies exist that alter protein structure and folding, giving rise to accumulation in the endoplasmic reticulum of the hepatocytes, resulting ultimately in tissue damage.

In the case of PI*Q0cardiff, the amino acid aspartate is replaced by valine at position 256 of the ATT protein. This substitution causes a severe deficiency when it occurs in homozygosis or in association with other deficiency variants such as PI*Z. Some authors argue that homozygous Q0cardiff patients are not at risk for emphysema, although there may be a risk if it occurs in heterozygosity with the PI*Z allele or other null alleles. In our case, the male patient was asymptomatic. In our opinion, PI*Q0cardiff cannot be
considered a null allele, since it is not a mutation that causes a premature stop codon, nor does it produce complete protein degradation, a mechanism usually observed in null deficiency alleles. Some authors define the PI*Q0cardiff variant as PI*(lowell), since the genetic variation consisting of the switch of an aspartic acid to valine causes degradation of the intracellular protein, which leads to reduced, but undetectable, levels of protein. It seems likely that these residual protein levels, along with those produced by the PI*Z allele, caused our patient to present AAT levels higher than those found in patients with null alleles.

References
The Utility of Diaphragmatic Ultrasound in the Radiological Diagnosis of Systemic Lupus Erythematous Patients With Shrinking Lung Syndrome

Diagnóstico radiológico en el shrinking lung syndrome en pacientes con lupus eritematoso sistémico. Utilidad de la ecografía diafragmática

To the Editor,

We report the case of a 30-year-old woman, native of Bolivia, with no cardiovascular risk factors or toxic habits, diagnosed in December 2012 with systemic lupus erythematosus (SLE) and Sjögren's syndrome. She was receiving treatment with methotrexate, prednisone, and hydroxychloroquine.

She attended the systemic disease clinic in November 2015 due to dyspnea on moderate exertion, accompanied by orthopnea with no associated clinical evidence of infectious disease. Of note on examination were tachypnea and tachycardia with no tolerance to the decubitus position. She was hospitalized for further examinations and treatment.

Additional tests produced the following results:

- Clinical laboratory tests revealed anemia with leukopenia and mild thrombocytosis, and no other changes.
- Lung function tests showed a restrictive pattern and her maximum inspiratory and expiratory pressures were low, particularly maximum inspiratory pressure at 18.4% predicted value.
- Tests to detect heart disease were normal, including electrocardiogram, echocardiography, pro-BNP values, and enzymes for myocardial insult.

The following radiological tests were performed:

1. Chest radiograph showing elevation of both hemidiaphragms, with no other significant changes.
2. High-resolution computed tomography (HRCT), which showed laminar atelectasis in the right middle and lower lobe.
3. CT-angiogram revealed no evidence of acute or chronic pulmonary thromboembolism.
4. Initial ultrasonography of the chest and diaphragm showed limited diaphragmatic amplitude, both at rest and during deep breathing and voluntary sniff maneuvers, reduced inspiratory time and diaphragmatic cycle, and increased diaphragmatic contraction speed. Table 1 lists these parameters on admission and during the follow-up performed 3 months after discharge.

Based on these findings, shrinking lung syndrome in a patient with SLE and Sjögren's syndrome was diagnosed. Treatment began with theophylline, salbutamol, and high-dose prednisone. Clinical and ultrasound findings confirmed the patient's good progress, and she was discharged after 15 days of hospitalization.

Lung involvement in SLE is very common, and can occur in up to 60%–80% of cases,\(^1\) often in the form of pleurisy with or without pleural effusion, pneumonia, interstitial fibrosis, acute lupus pneumonitis or pulmonary hypertension.\(^2\)

A rarer, less common form of lung involvement in SLE is shrinking lung syndrome (SLS): less than 100 cases have been reported in the literature, and the prevalence among lupus patients is estimated to be less than 1%.\(^3\) Although an increasing number of authors are now claiming that this entity is underdiagnosed in mild cases.\(^4\) The first authors to describe this syndrome were Hoffbrand and Beck in 1965,\(^5\) in a study of 24 patients with lupus, 8 of whom developed unexplained dyspnea. They found that all patients had progressive reduction of lung volumes, and a restrictive ventilatory pattern on spirometry, associated with loss of ventilated lung volume on chest radiograph, leading the authors to propose the term “shrinking lung syndrome”.

This syndrome is generally diagnosed 4 years after onset of SLE,\(^5\) although cases have been published in which SLS was the first respiratory manifestation of the disease.\(^6\)-\(^10\)

The SLS triad is formed by elevated hemidiaphragms, dyspnea with normal lung parenchyma and restrictive pattern on spirometry.

Dyspnea with chest pain is the most frequent complaint among SLS patients, along with orthopnea and intolerance to the decubitus position.

The causes of the SLS are not entirely clear, although a number of hypotheses have been put forward; for example, the syndrome is caused by secondary microatelectasias due to a pulmonary surfactant deficiency, or it is caused by lupus myopathy due to T-cells infiltrating the diaphragm and the muscles of the chest wall.\(^11\)

Diagnosis is derived from clinical suspicion, lung function tests showing a restrictive pattern, and radiological tests ruling out other diseases.

Treatment is not well established, but immunosuppressive drugs are the most widely used and prognosis is generally favorable.

Our case meets the criteria of SLS that have been described to date, since this was a patient diagnosed 3 years previously with SLE\(^2\) who had Sjögren's syndrome with anti-Ro\(^+\) antibodies that are often associated with the presence of SLS. Our patient's clinical manifestations were typical, with dyspnea on exertion, chest pain, and orthopnea with intolerance to decubitus position, possibly related with weak respiratory muscles. To reach the presumptive diagnosis, other causes of dyspnea in lupus patients must be ruled out: the diagnosis of SLS is initially reached by exclusion of other entities.

In this respect, we would like to highlight the usefulness of ultrasonography of the diaphragm and the chest when SLS is suspected.\(^12\)-\(^15\) This is a relatively simple and non-invasive examination that can be performed at the patient's bedside, and only minimal collaboration is needed to perform forced inspirations

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