Case report

Alpha-1-Antitrypsin Deficiency Associated With the Mattawa Variant

Beatriz Lara, Beatriz Martínez-Delgado, Maria Luisa Torres, Sandra Marín-Arguedas, Ana Bustamante, Marc Miravitlles

α1-Antitripsina Deficiency

Matawa.

Introduction

Normal α1-antitrypsin (AAT) alleles, present in 85%-90% of individuals, are called M, and the most common deficient alleles, S and Z (frequencies: 10 and 1.7% of the Spanish population, respectively). Patients homozygous for the M, S and Z alleles express around 100, 40 and 15% of serum AAT, respectively.

Severe AAT deficiency, defined as serum levels below 35% of the mean expected value, is a rare condition, generally associated with PI*ZZ homozygotes and much less frequently with combinations of Z, S, rare and null alleles. However, in recent years, the Spanish AAT Deficiency Registry (REDAAAT) laboratory has detected rare and null alleles in 1.6% of cases (a rate comparable with that found in Italy, Switzerland, Germany and the USA), mostly Mmalton, but also Mheerlen, Nulclayton, Nullbellingham, Mvhebron and Ybarcelona, among others.

Keywords: Alpha-1-Antitrypsin Case Registry Deficiency

© 2013 SEPAR. Published by Elsevier España, S.L. All rights reserved.

Déficit de alfa-1-antitripsina asociado a la variante Matawa

Resumen

Los alelos deficitarios más frecuentes son los Pi’S y Pi’Z, pero existen también otras variantes deficientes. En la presente nota clínica se describen los 2 primeros casos detectados en España de déficit de alfa-1-antitripsina (DAAT), resultante de la combinación de un alelo nulo Matawa con un normal Pi’M y con un raro Mmalton.

Ambos casos fueron inicialmente diagnosticados como Pi’MM por isoelectrofoque (IEF), pero los valores séricos bajos de AAT hicieron sospechar la existencia de alelos deficientes indetectables por IEF, por lo que se realizó un análisis molecular del gen que proporcionó el diagnóstico correcto.

Las incoherencias entre los valores séricos de AAT y el fenotipo deben hacer sospechar la existencia de uno de estos alelos deficientes.

© 2013 SEPAR. Publicado por Elsevier España, S.L. Todos los derechos reservados.

© 2013 SEPAR. Published by Elsevier España, S.L. All rights reserved.

1579-2129/5 – see front matter © 2013 SEPAR. Published by Elsevier España, S.L. All rights reserved.
**Case report**

**Case 1**

The first patient was a 47-year-old woman, non-smoker, with essential hypertension, recurrent bronchitis since age 25, and exertional dyspnea in the last 3 years.

Her spirometry was normal (FVC 96%, FEV₁ 105%, FEV₁/FVC 84), but her carbon monoxide diffusing capacity (DLCO) and transfer coefficient (KCO) were 68 and 61% of their respective theoretical values. Chest computed tomography (CT) showed an accentuated bronchial pattern with no signs of bronchiectasis or emphysema. Liver function tests were normal. The serum AAT concentration was 73.7 mg/dL (reference values: 103–200), consistent with partial AAT deficiency, but the phenotype labeled as PI′MM did not agree with the AAT concentrations. It was therefore decided to perform gene sequencing of the AAT in peripheral blood, in which a PI′Nullmattawa allele was detected. This mutation is characterized by the insertion of a nucleotide within the coding region of exon 5, and results in a frameshift that creates a premature stop signal at position 376 (p.Leu353PhefsX24). This finally translates into a very unstable truncated protein that is degraded inside the hepatocyte and is undetectable in serum (Fig. 1).

The second allele of the patient contained a normal variant in exon 5, consisting of a substitution of a cytosine (C) for an adenine (A) in nucleotide 1200 of the cDNA, generating the replacement of a glutamic acid (Glu) by an aspartate (Asp) in codon 400 (c. 1200A>C/p.Glu400Asp), which corresponded to an M3 allele. Therefore, this is a PI′M3Nullmattawa heterozygous genotype, with moderately reduced serum AAT levels.

**Case 2**

Another carrier of the Nullmattawa allele was identified from the REDAAT database.

The patient was a 67-year-old woman with a history of pleuropulmonary tuberculosis, with documented bacteriological cure. She suffered frequent respiratory infections. Functional parameters were consistent with severe airflow obstruction (FEV₁: 620 ml and FVC: 1280 ml, 22% and 39% of the theoretical values, respectively). High resolution computed tomography (CT) showed diffuse centrilobular and paraseptal emphysema and diffuse cylindrical bronchiectasis. No result indicating liver involvement was detected at any time.

Her serum AAT concentrations were 43 mg/dL. IEF suggested a PI′MM phenotype, but as it did not correspond with the serum AAT concentrations, a genetic study was performed. This detected a PI′Mmalton allele (deletion of residue 52, p.Phe52del) and a PI′Nullmattawa allele, the combination of which explained the patient’s low serum AAT concentrations.

**Discussion**

The exceptional nature of the null alleles (estimated prevalence 100–200 times lower than the Z alleles) precludes us from having precise knowledge of their clinical impact and real incidence. Nevertheless, it is important to take them into account, as they can create diagnostic confusion if genomic studies are not performed.

The Mmalton allele (also known as Mcagliari and Mnichnan) was first described in 1987 and, like the Z gene, produces a poorly folded protein. Around 80%–90% of this variant polymerizes in the hepatocyte without being secreted into the blood, where it expresses levels less than 15% when in homozygosity. It is associated with a high risk of pulmonary emphysema and liver disease.11,12

The Mattawa allele (and in general any null allele) codes for a truncated protein, with major conformational changes, which is degraded intracellularly without having the opportunity to aggregate, and hence expresses undetectable serum AAT concentrations. This means that homozygotes have a very high risk of emphysema, but not of liver disease.

In conclusion, in our patients, the discrepancy between the IEF phenotype and the serum AAT concentrations led us to suspect the existence of rare alleles. Molecular analysis of the gene finally provided the correct diagnosis, as stated in the recommendations.2

**Conflict of Interest**

The authors declare no conflict of interest.

**Acknowledgements**

The authors thank Dr. Ignacio Blanco for his important contribution to the writing of this article.
References