Case report

Alpha-1-Antitrypsin Deficiency Associated with the Mattawa Variant

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

Servicio de Neumología, Hospital Universitario Arnau de Vilanova, Lleida, Spain
Servicio de Genética Molecular, Área de Genética Humana, Instituto de Investigación en Enfermedades Raras, Instituto de Salud Carlos III, Madrid, Spain
Servicio de Neumología, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain
Servicio de Neumología, Hospital Dos de Maig, Barcelona, Spain
Servicio de Neumología, Hospital de Sierrallana, Torrelavega, Cantabria, Spain
Servicio de Neumología, Hospital Universitario Vall d’Hebron, Barcelona, Spain

ARTICLE INFO

Article history:
Received 4 April 2013
Accepted 9 May 2013
Available online 20 November 2013

Keywords:
Alpha-1-antitrypsin deficiency
Mattawa
Spanish Registry of patients with alpha-1-antitrypsin deficiency

ABSTRACT

The most common deficiency alleles for alpha-1-antitrypsin deficiency (AATD) are Pi*S and Pi*S, but there are also other deficiency variants.

This case report describes the first two cases of AATD detected in Spain resulting from the combination of a null Mattawa allele with a normal Pi*M, and a rare Mmalton.

Both cases were initially diagnosed as Pi*MM by isoelectric focusing (IEF), but the low serum AAT values led us to suspect the existence of rare deficiency alleles that were undetectable using this technique, and to performing molecular analysis of the gene, which provided the correct diagnosis.

Inconsistencies between serum AAT values and the phenotype should make one suspect the existence of one of these rare alleles.

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

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

RESUMEN

Los alelos deficientes 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 Mattawa con un normal Pi*M y con un raro Mmalton.

Ambos casos fueron inicialmente diagnosticados como Pi*MM por isoelectrofofoque (IEF), pero los valores séricos bajos de AAT hicieron sospechar la existencia de alelos deficientes infrecuentes 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 infrecuentes.

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

Introduction

Normal alpha-1-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 (REDAA) laboratory has detected rare 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, Nullclayton, Nullbellingham, Mvhebron and Ybarcelona, among others.
Case report

Case 1

The first patient was a 47-year-old woman, non-smoker, with essential hypertension, recurrent bronchitis since age 25, and ex- 
tional 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*M3 did not 
agree with the AAT concentrations. It was therefore decided to per- 
form 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 serum9 (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 
adene (A) in nucleotide 1200 of the cDNA, generating the replace- 
ment 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.10

The patient was a 67-year-old woman with a history of pleuro- 
pulmonary tuberculosis, with documented bacteriological cure. 
She suffered frequent respiratory infections. Functional param- 
eters were consistent with severe airway obstruction (FEV1: 620 ml 
and FVC: 1280 ml, 22% and 39% of the theoretical values, respec- 
tively). High resolution computed tomography (CT) showed diffuse 
centilobular 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*M2 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)11 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 preva- 
ience 100–200 times lower than the Z alleles) precludes us from 
having precise knowledge of their clinical impact and real inci- 
dence. 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 Mnichi- 
nan) was first described in 1987 and, like the Z gene, produces a 
poorly folded protein. Around 80%–90% of this variant poly- 
merizes 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 aggre- 
gate, 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 contri- 
bution to the writing of this article.
References


