

Alpha-1 Antitrypsin Deficiency Associated With the Mmalton Variant. Description of a Family[☆]



Déficit de alfa-1-antitripsina asociado a la variante Mmalton. Descripción de una familia

Dear Editor,

Up to 95% of cases related with alpha-1 antitrypsin deficiency (AATD) are associated with the PI*ZZ genotype, while the other 5% are associated with PI*SZ and PI*MZ genotypes or other extremely rare combinations of PI*S or PI*Z with other deficiency or null alleles. These rare alleles account for 1.6% of the deleterious variants recorded in the Spanish Register of Patients with AAT Deficiency, and the most common of these is the PI*Mmalton variant.¹ The clinical manifestations of this variant are similar to those of the PI*Z phenotype, and diagnosis is typically delayed by its structural similarity to the Pi M2 allele. We report the case of 2 members of the same family group (Table 1) with a diagnosis of AATD associated with homozygous deficiency PI*Mmalton allele.

The index case was a 47-year-old man, native of the island of Gomera (Canary Islands, Spain), with a clinical history of spontaneous pneumothorax in 2005, and former smoker of 30 pack-years, referred to the respiratory medicine clinic due to a 1-year history of dyspnea on moderate exertion (mMRC 2). Lung functional tests showed FEV₁/FVC: 0.5; FEV₁: 1.73 l (51%); FVC: 3.38 l (77%); DLCO: 73%; and KCO: 75%. High-resolution computed tomography (HRCT) revealed centrilobular and paraseptal emphysema, predominantly in the upper fields. Abdominal ultrasonography found no signs of chronic liver disease, despite mildly elevated transaminases. Complete blood count and IgA, IgM, IgG and IgE levels were within normal limits. Alpha-1 antitrypsin (AAT) was determined by nephelometry, revealing severely reduced levels (16 mg/dl), so DNA testing was performed to determine the presence of PI*S and PI*Z alleles, but the result was negative. Given the absence of these

deficiency variants and the low AAT levels in serum, we performed a molecular analysis of the SERPINA1 gene, amplifying both coding exonic regions and flanking intronic sequences of exons 4, 5, and 6. This analysis revealed the presence of the homozygous PI*Mmalton (F52del) allele.

The patient's sister, 42 years old, former smoker of 35 pack-years denied any respiratory symptoms. Lung functional tests showed FEV₁/FVC: 0.74; FEV₁: 2.68 l (96%); FVC: 3.62 l (110%); DLCO: 81%; and KCO: 82%. HRCT, abdominal ultrasonography, and general laboratory tests were all normal. AAT determination revealed severely reduced levels (19 mg/dl), and molecular analysis of the SERPINA1 gene detected the homozygous PI*Mmalton allele.

Various AADT patient registries describe the PI*Mmalton allele as the third most common deficiency variant in Spain,² although this is the first report of its existence in the Canary Islands. Like the Z gene, the Mmalton allele produces improperly folded protein, of which 80%–90% is polymerized in the hepatocyte, expressing levels of less than 15% in blood. The co-existence of emphysema and hepatic cirrhosis is often described in patients with homozygous PI*Mmalton,^{3,4} although this was absent from our cases; however, the behavior of the heterozygous forms appears to be far more variable. Most PI*M/Mmalton patients have no changes in lung or liver function, in contrast to the PI*Z/Mmalton genotype that appears to be associated with an increased risk of emphysema.⁵ With regard to liver involvement, Canva et al. described the case of a PI*Mmalton/M patient who developed end-stage liver disease despite no history of hepatitis, alcohol abuse or liver disease in childhood.⁶ Similarly, Piras et al., found that less than 13% of subjects with either the homozygous or heterozygous PI*Mmalton variant showed evidence of chronic liver disease.⁷

Our case is remarkable because of the clinical differences observed in our patients, despite their consanguinity and similar exposure to tobacco smoke at a similar intensity, demonstrating different patterns of clinical manifestations of the same PI*Mmalton/Mmalton genotype.

Table 1
Characteristics of Study Family.

Family	Smoking History	AAT Levels (mg/dl)	Genotype	Forced Spirometry	Liver Function
Case 1	Yes	16	Mmalton/Mmalton	Obstructive	Altered
Sister 1 of case 1	Yes	19	Mmalton/Mmalton	Normal	Normal
Sister 2 of case 1	No	84.3	M/Mmalton	Normal	Normal
Daughter of case 1	No	83.4	M/Mmalton	Normal	Normal
Son of case 1	No	85.8	M/Mmalton	Normal	Normal
Father of case 1	No	77.3	M/Mmalton	Obstructive	Normal
Mother of case 1	No	90.3	M/Mmalton	Normal	Normal

AAT: Alpha-1 antitrypsin.

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Hering-Breuer Reflex and Non-invasive Mechanical Ventilation. Does it Also Occur During Expiration?*



Reflejo de Hering-Breuer y ventilación mecánica no invasiva ¿también durante la espiración?

Dear Editor:

Interpreting and evaluating the importance of patient-ventilator asynchronies in non-invasive mechanical ventilation (NIMV) is an extremely difficult task. Some of the experiences published in the literature suggest that some asynchronies detected in clinical practice are directly induced by the ventilator, as muscles respond to mechanical stimuli. For example, the phenomenon known as “reverse triggering”¹ has been described in profoundly sedated adult patients receiving invasive ventilation and may be a new form of diaphragmatic neuromechanical coupling, induced by a reflex mediated by the stretch receptors during inspiration (Hering-Breuer reflex). This phenomenon has only been described in sedated patients receiving invasive ventilation, and to date no cases of muscle response to mechanical stimuli have been described in patients receiving NIMV.

We report the case of a 62-year-old woman with amyotrophic lateral sclerosis, with predominant upper neuron involvement and significant hyperreflexia. NIMV was indicated due to forced vital capacity below 50% predicted value, mild hypercapnia (PaCO₂ 46 mmHg) and incipient intolerance to a decubitus position. Titration began with a nasal interface and chinstrap for periods of 1–2 h on consecutive days with a Lumis® 150 pressure ventilator (ResMed, North Ryde, Australia). Parameters at the end of the first session were: IPAP 18 cmH₂O, EPAP 5 cmH₂O, rise time 150 ms, Timin 0.6 s and Timax 1.5 s, triggering and cycling settings at mean values. Unintentional leak was maintained at acceptable values after a chinstrap was placed (less than 10 l/min overall), and breathing rate was around 18–20 bpm. During real time monitoring of pressure-time and flow-time curves, deflection was observed at the start of flow-time waveform expiration, despite good initial tolerance (Fig. 1A).

Since deflection occurred at the start of expiration, with persistent exertion during this phase (premature cycling asynchrony²), the cycling setting was modified, prolonging rise time to 250 ms (in order to delay maximum flow, and thus, cycling), and Timin of 0.8 was superimposed, but the abnormality persisted. Finally, while previous rise time values were maintained without superimposing the time criterion, the deceleration ramp was modified from inspiration to expiration, and was set at 250 ms, with subsequent resolution of the disorder (Fig. 1B).

The abnormality could be resolved only by modifying the descent time in this patient with marked hyperreflexia, suggesting that the visible alteration in flow-time curves might be due to an automatic response of the patient’s respiratory system. This is similar to the situation described by Akoumianaki et al.,¹ although these authors described the phenomenon in patients receiving sedation and relaxation. Instead of being a chest expansion reflex, the response appears to be associated more with a deflation reflex that remains relatively constant from cycle to cycle.

Not all ventilator models record deceleration. To date, its use in clinical practice has not been reported in the literature, although, theoretically at least, it should improve tolerance to the sudden flow inversion that occurs during the transition from inspiration to expiration. Most of the time this flow inversion, that may be as high as 80 lx’ [although in our patient it was around 60 lx’ (20–40 lx’)] does not produce any symptoms, but some patients might report discomfort. In our patient, the flow inversion appeared to trigger an automatic respiratory response, intensified by concomitant generalized hyperreflexia. Amyotrophic lateral sclerosis may present in different forms, not only in terms of muscle topography, but also in the degree of spasticity and hyperreflexia. Thus, predominant lower motor neuron involvement produces weakness and atrophy, while upper motor neuron involvement produces basically spastic hypertonia and hyperreflexia that can affect any muscle group. Reflecting findings made first in animal models and later in patients,³ our patient’s diaphragm may have been activated due to deflation in the presence of vagal nerve integrity. This anomaly can also be observed on spirometry in forced expiratory maneuvers, when cough is induced by maximum expiration (Fontana reflex).⁴

In conclusion, patient-ventilator asynchrony observed in our patient does not appear to be the same as cases previously described in the literature, since it does not meet the characteristics of premature cycling (it is not modified by prolonging inspiratory time or cycling settings) or reverse triggering (the cycle before the asynchrony is not controlled). For this reason, diaphragmatic

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