Acknowledgments

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https://doi.org/10.1016/j.pulmoe.2020.04.006

A PI*MS is not always a PI*MS. An example of when genotyping for alpha-1 antitrypsin deficiency is necessary

Dear Editor,

Alpha-1 antitrypsin (AAT) is a serum glycoprotein with functions which include neutrophil elastase inhibition in the lung (protecting it from destruction and emphysema), and antioxidant, anti-inflammatory, anti-infectious and immunomodulation effects. Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant disease and is considered one of the most frequent hereditary disorders; however, its epidemiology remains partially unknown owing to underdiagnosis.[1] At least 60 deficient proteinase inhibitor* (PI*) alleles have been described, the most common being PI*S (5%–10% in Caucasians) and PI*Z (1%–3%), which are associated with reduced serum AAT levels of 40 an escalation plan and ceilings care and 10%–20%, respectively. PI*ZZ is the most frequent genotype (95%) among individuals with severe deficiency.[2] Previous studies suggest that some areas of Portugal may have a very high frequency of deficient variants.[3] Other deficient variants (non-S, non-Z) are considered as ''rare'' because of their low frequency, they cannot be identified by the usual allele-specific genotyping methods and cannot always be characterized by isoelectrofocusing (IEF) for phenotyping; therefore they can only be detected by molecular biology techniques, such as genome sequencing.[4] Consequently, in cases with discordant plasma and phenotype results, it is important to continue diagnostic assessment since the identification of a severely deficient genotype supports the possible indication of augmentation therapy and the need for family screening.[1]

The PI*M_{Malton} variant is a rare deficient variant that differs from the normal M allele by deletion of the entire codon (TTC) for the residue Phe at position 51/52 (exon II). It is associated with severely reduced plasma AAT levels and hepatic inclusions by polymers and is characterized by a normal isoelectrophoretic pattern, which may be confounded with a normal M protein on IEF.[4]

Information about the frequency of rare alleles in Portugal is scarce. In a previous study including 1864 subjects, 9.5% of the AATD cases were related to a rare allele and null variants.[2] The majority of rare alleles (n = 64; 15.3%) corresponded to PI*M_{Malton} and PI*$M_{Palermo}$, including n = 16 PI*SM_{Malton} (3.8% of the individuals with AATD). However, the study sample might not be representative of the whole country, because most of the samples had been collected in the North and Central regions of Portugal.

Similarly, the PI*M_{Malton} variant is considered to be the second cause of severe AATD in Spain. A study including 3511 subjects over 12 years showed 1.6% of rare AAT variants, with PI*I (34%) and PI*M_{Malton} (20%) being the most frequent, accounting for 54% of all rare variants.[5] PI*M_{Malton} allele was also very common among the rare variants in other countries: 60% in Tunisia, 35% in Italy (particularly in Sardinia), and 8% in Switzerland. However, it has not been found in Finland, and is rare in Ireland.[4,5]

Augmentation therapy is indicated in severely deficient patients (AAT serum levels < 57 mg/dL) associated with deficient genotypes, including PI*SZ.[1] Since M_{Malton} is associated with levels similar to the Z variant, patients with genotypes such as PI*$M_{Malton}M_{Malton}$, PI*ZM_{Malton}, PI*SM_{Malton} and PI*NullM_{Malton} may be candidates for augmentation therapy. Therefore, it is crucial to identify these genotypes in patients with clinical manifestations, low AAT serum levels and inconsistent phenotypes on IEF.

We had the opportunity to treat the case of a 57-year-old man, ex-smoker of 40 pack-years, with severe chronic obstructive pulmonary disease (COPD) and extensive emphysema on computed tomography scan. He was diagnosed with severe AATD due to a serum AAT level of 46 mg/dL and ful-

filled all criteria for augmentation therapy.[1] However, the phenotype was reported as PI*MS. Due to the inconsistency between the plasma levels and phenotyping, genotyping was performed by SERPINA1 gene sequencing, showing a PI*SM$_{Malton}$ genotype.

This was an example of a patient with severe, early-onset emphysema with severe AATD defined by a serum level of AAT < 57 mg/dL, considered as the protective threshold, but with a PI*MS phenotype, consistent with a mild deficiency.

The patient was referred for evaluation for lung transplantation, and in the meantime was considered for augmentation therapy with intravenous AAT.

In conclusion, among the rare deficient variants of AAT, PI*M$_{Malton}$ is probably the most frequent on the Iberian Peninsula, although it still represents a challenge because it is not detected by the first line diagnostic tests (phenotyping/allele-specific genotyping). An PI*M$_{Malton}$ allele-specific genotyping assay has been developed for faster and cheaper diagnosis,[6] but it is not universally available. A larger registry database is needed for a better understanding of the characteristics and natural history of carriers of this rare variant.[7]

Conflicts of interest

Teresa Martin has received speaker fees from Menarini and GlaxoSmithKline. Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Spin Therapeutics, Verona Pharma, TEVA, pH Pharma, Novartis, Sanofi and Grifols and research grants from GlaxoSmithKline and Grifols. Sofia Tello Furtado has received speaker fees from AstraZeneca, Boehringer Ingelheim, Bial, Novartis, Boehringer Ingelheim, and GlaxoSmithKline.

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18 May 2020

https://doi.org/10.1016/j.pulmoe.2020.06.013

Acute colonic pseudo-obstruction causing Acute Respiratory Failure in Duchenne Muscular Dystrophy

To the Editor,

Duchenne Muscular Dystrophy (DMD) is the most common inherited muscle disease diagnosed in children, with a prevalence ranging between 1.3 and 2.1 per 10,000 live male births. Caused by a mutation of the dystrophin encoding gene located at Xp21, the disease results in a relentless progression of muscle weakness and wasting of the skeletal and cardiac muscle cells. Even though implementing nocturnal and daytime long-term ventilation and cough assistance has reduced the risk of respiratory complications, Acute Respiratory Failure (ARF) is still a common occurrence in DMD patients and a leading cause of death in the very advanced stages of the disease. The pathogenesis of ARF has been attributed to an imbalance between increased respiratory load and reduced diaphragmatic capacity. Well-known aetiologies include pneumonia, otherwise benign