

one second (FEV1) diffusion capacity of the lungs for carbon monoxide, and cardiopulmonary exercise testing.⁶ In our setting, during the study period, the preoperative functional assessment protocol was based on the European Respiratory Society and European Society of Thoracic Surgeons 2009 guidelines on radical treatment of lung cancer, although 1 of our patients (case 1) did not meet the respiratory function criteria, due to limiting physical circumstances (patient with tracheostomy).

Due to the scant evidence, no specific recommendations are available on the role of adjuvant treatment in patients operated for MPLC. In patients with synchronous MPLC, the tumor with the most advanced staging will determine the need for adjuvant treatment; the situation is unclear when a patient has 2 synchronous or metachronous stage I lesions, since, although the prognosis is worse than in patients with a single stage I NSCLC tumor, the absolute benefit of adjuvant cisplatin-based chemotherapy has not been demonstrated.⁷ Factors that could be considered when deciding whether or not to use adjuvant chemotherapy include the time interval between the cancers, certain unfavorable histologic characteristics (degree of differentiation, vascular and lymphatic invasion, solid and micropapillary pattern), tumor size, comorbidities, and the functional assessment of the patient.

Despite the limited number of patients in our series, we believe that a second lung lobectomy is a feasible technique, with zero mortality but with significant morbidity. Of the 3 cases that developed a complication, 2 patients had Grade III postoperative complications according to the Clavien–Dindo scale⁸ (complication that requires intervention without general anesthesia); and another had a Grade IV (life-threatening complication due to single organ dysfunction). To avoid major intraoperative bleeding in the event of an ipsilateral resection, complex dissection of the hilum should be anticipated, and intrapericardial dissection may be a surgical option to be taken into account in this group of patients.

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Alpha-1 Antitrypsin Deficiency Associated with the PI*QO_{Ourém} Allele in a 2-Year-Old Girl and Family Study. An Unusual Case[☆]



Descripción de la deficiencia de alfa-1-antitripsina asociada al alelo PI*QO_{Ourém} en una niña de 2 años de edad y su estudio familiar. Un caso infrecuente

To the Editor,

Alpha-1 antitrypsin (AAT) is a medium-sized circulating glycoprotein encoded by the SERPINA1 gene, located on the short arm of chromosome 14, in the 14q32.13 region.¹ AAT mainly acts as a protease inhibitor, and protects lung tissue from the proteolytic action of neutrophil elastase. Other characteristics, such as the inhibition of other serine proteases, and anti-inflammatory, immunomodulatory, and antimicrobial activity have also been described.² AAT deficiency (AATD) is one of the most common genetic disorders in

the Caucasian population. An AAT level below 80 mg/dl, determined by nephelometry, increases the risk of pulmonary emphysema in adulthood,³ the most common form of disease associated with AATD. Other manifestations include various types of hepatitis in children and adults, panniculitis and vasculitis. An association with other inflammatory disease has been posited in recent years.

AAT exhibits simple, autosomal, codominant Mendelian inheritance. Around 85%–90% of the population has an MM genotype, formed from the inheritance of an allele from each parent, which synthesizes normal amounts of functioning protein. The most common deficient alleles are Pi*S and Pi*Z, which occur in the Spanish population at an estimated prevalence of 10.4% and 1.72%, respectively, and express 40% and 15% of normal AAT levels, also respectively. In clinical practice, 96% of AATD disease occurs in ZZ homozygotes, and the remaining 4% occur in SZ and MZ heterozygotes and in the uncommon rare and null genotypes or their combinations with alleles Pi*S and Pi*Z.

We describe the case of a family carrying a QO_{Ourém} gene,⁴ a null allele identified for the first time in the central region of Portugal, very few cases of which have been described in the literature.

A 2-year-old girl with a history of ferropenic anemia, mild gastroesophageal reflux, and mild-moderate persistent asthma with several hospital admissions due to exacerbations. She was receiving treatment with inhaled fluticasone, montelukast and salbutamol

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Fig. 1. Distribution and estimated frequency of rare and null genotypes in the Iberian Peninsula, Switzerland, Italy and Tunisia.⁷

on demand. After an admission at the age of 11 months, she was investigated in the Pediatric Department for anorexia and growth retardation after the age of 8 months. Tests for anti-transglutaminase antibodies, immunoglobulins, skin prick tests for egg, fish, wheat and cow's milk protein (CMP), and viral serologies were negative. Thyroid function and chlorine in sweat were normal. AAT levels: 40 mg/dl. Genetic study by sequencing of the SERPINA1 gene identified the Pi*SQO_{Ourém} genotype.

The family study was completed with AAT determinations in the patient's parents. The father is a 33-year-old man, smoker of 10–15 cigarettes a day (pack-year index: 16.5), welder by profession. He had no history of lung disease nor was he receiving regular treatments. Physical examination was normal. Clinical laboratory tests were normal except for AAT 34 mg/dl (116–232 mg/dl/21–41 $\mu\text{mol/l}$).⁵ The gene sequencing study identified genotype Pi*SQO_{Ourém}. Lung function tests were normal. High-resolution computed tomography (HRCT) showed panlobular emphysema in anterior fields and bases with no signs of centrilobular emphysema. The patient is being monitored in the Respiratory Medicine outpatient clinic and has given up smoking. His lung function remains normal.

The mother was a 30-year-old woman with no significant medical history. AAT levels: 119 mg/dl with PiMS phenotype.

The low number of cases with a null allele in patients with AATD (100–200 fold lower prevalence of allele Pi*Z) limits the understanding and evaluation of the prevalence of these variants (Fig. 1). The null alleles give rise to a structurally dysfunctional protein, causing AAT to degrade within the cell, leading to undetectable levels in serum. For this reason, they are associated with a very high risk of emphysema but not of liver disease, due to the lack of polymerization.

Our 2 patients are heterozygous carriers of an QO_{Ourém} allele, first described in 2002 in a very specific area in Portugal,⁴ and

later in La Palma, Canary Islands, Spain.⁶ The QO_{Ourém} mutation is characterized by the insertion of a thymine nucleotide in the coding region of exon 5 within a small microsatellite (T)₅, on a normal M3 genetic background. The resulting frameshift creates a premature stop codon that shortens the carboxy-terminal end of the 19-amino acid protein, that includes a proline residue essential for AAT secretion. The mutation, while not affecting the size or stability of the messenger RNA, causes the altered protein to be retained in the endoplasmic reticulum, where it is degraded.⁷ This mutation is identical to QO_{Mattawa} mutation, but the latter originates from an M1 genetic background.⁸ In a review of the historical evolution and clinical and functional impact of AAT deficiency caused by the QO_{Ourém} allele, published in 2012,⁹ 41 individuals carriers of this allele were identified among 4 families in the central area of Portugal. Of these, 8 were homozygous, 5 had Pi*SQO_{Ourém} and 28 had Pi*MQO_{Ourém}. None of the 5 individuals with Pi*SQO_{Ourém} were smokers and all patients had normal lung function and chest X-ray results. HRCT was not performed in any of these cases. In our adult patient, the finding of emphysema in the HRCT at the age of 33 years may be associated with the high susceptibility of individuals with severe AAT deficiency to the effects of smoking. This underlines the importance of an early diagnosis of AATD, in order to avoid the patient starting smoking, or to encourage cessation in those who already smoke.

Five individual carriers of the Pi*QO_{Ourém} allele were identified in La Palma. The index case had Pi*SQO_{Ourém}, 3 had Pi*MQO_{Ourém} and 1 had Pi*ZQO_{Ourém}.

This mutation is estimated to be comparatively recent, having emerged 650 years ago, in the 14th century. The origin of the variant has been established as the center of Portugal. The geographical proximity of this area with Galicia would explain the presence of this allele among the population of Galicia, but to our knowledge,

these are the 2 first cases of this mutation published in Galicia, in 2 members of the same family.

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Prognosis of Obesity Hypoventilation Syndrome With and Without Concomitant Obstructive Sleep Apnea Syndrome[☆]



Pronóstico del síndrome de hipoventilación-obesidad con y sin síndrome de apnea obstructiva asociado

Dear Editor,

Obesity hypoventilation syndrome (OHS) is a clinical entity characterized by the coexistence of obesity and hypercapnia during waking hours. However, the lack of a universally accepted definition creates confusion, since no distinctions are made between patients with different grades of severity and forms associated, or not associated, with sleep apnea-hypopnea syndrome (SAHS).^{1–3} Cabrera et al. proposed a severity stratification for OHS based on daytime PaO₂, PaCO₂, the apnea-hypopnea index (AHI), body mass index, and comorbidities, but this classification has not been associated with differences in prognosis. An earlier study published by our group in patients with a severe form of OHS, in which global respiratory failure was detected at diagnosis, found a 5-year mortality rate of 15.5%, and a 2-fold risk of death compared to patients with SAHS without diurnal hypoventilation.⁴ Similarly to other studies,^{5–7} the main cause of death was cardiovascular disease (CVD).

Masa et al. classified OHS patients in tertiles according to the number of desaturations of $\geq 3\%$ per hour of recording (oxygen desaturation index, ODI). Although it differs from the AHI, the ODI should reflect the severity of the underlying SAHS, and a higher prevalence of CVD could be expected among patients with more

severe SAHS, but the authors found exactly the opposite.⁸ They speculated that this may be because patients with more severe disease might seek medical intervention earlier, and so would receive earlier treatment for their cardiovascular risk factors. They also referred to a mechanism called “ischemic preconditioning”, in which repeated episodes of subclinical ischemia, triggered by nocturnal hypoxemia, may lead to angiogenic stimulation and the development of collateral circulation. Aside from this, the study shows that the stratification of OHS is associated with significant clinical consequences. However, no difference was made between patients with and without SAHS, who could constitute different phenotypes. Ojeda et al.,⁹ in contrast, did distinguish between OHS with and without SAHS, and identified more OHS patients without SAHS (OHS-nonSAHS) than with SAHS (OHS-SAHS). This study found no differences in mortality between the 2 groups (about 28% at 5 years), but a trend toward improved survival in OHS-SAHS was identified. The study was criticized for not reporting cardiovascular comorbidities in both groups before and after treatment, since this might explain the improved (but non-significant) survival among the OHS-SAHS group.

Our group designed a retrospective chart review to compare the prognosis of OHS-SAHS and OHS-nonSAHS patients (approved by the Ethics Committee of Galicia: Reg. No. 2017/079). We reviewed the medical records of 124 patients diagnosed with OHS between 1995 and 2017 using restrictive criteria: global respiratory failure at time of diagnosis and pH ≥ 7.34 . Patient were matched 1:2 by date of diagnosis ± 3 years, sex, and an age range of ± 10 years. A total of 11 patients with OHS-nonSAHS (AHI <5) and 22 with OHS-SAHS were finally included. At baseline, there were no significant differences between patients with OHS-nonSAHS and OHS-SAHS in mean age (67 vs 68.5 years; $P=.88$), female sex (77.7% vs 77.1%; $P=.1$), average body mass index (43 kg/m² vs 42.5 kg/m²; $P=.81$), FVC (59.5% vs 49% predicted; $P=.96$), baseline PaO₂ (51.5 \pm 9.5 mmHg vs 48 \pm 7.6 mmHg; $P=.25$) and baseline PaCO₂ (54.7 \pm 9.1 mmHg vs 60.6 \pm 13.2 mmHg; $P=.38$). Obviously, AHI was greater in OHS-SAHS patients with in OHS-nonSAHS

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