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Original Article

Factors Associated With the Evolution of Lung Function in Patients With Alpha-1 Antitrypsin Deficiency in the Spanish Registry☆

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ABSTRACT

Introduction: The present study intends to describe the characteristics of patients diagnosed with severe alpha-1 antitrypsin deficiency (AATD) in Spain, to observe the rate of decline in forced expiratory volume in 1 s (FEV1) with and without substitutive therapy, and to identify factors associated with a rapid rate of decline in FEV1.
Method: A retrospective study of the evolution of individuals with AATD was carried out based on data collected from the Spanish registry. The primary response variable was the annual rate of decline in FEV1, calculated using the baseline and last postbronchodilator FEV1 values in an endpoint analysis.
Results: Three hundred and three patients with severe AATD and Pi ZZ phenotype were identified. Follow-up spirometric data were collected for 117 subjects. Being a smoker or ex-smoker vs never smoker (odds ratio [OR]=10.31; 95% confidence interval (CI)=1.8–58.8; *P*=.008) and having a higher baseline postbronchodilator FEV1 (% predicted) (OR=1.03; 95% CI=1.005–1.06; *P*=.018) were independently associated with a more rapid rate of decline in FEV1. There was also a trend towards a relationship between low body mass index (BMI) and a greater rate of deterioration in lung function (OR=1.14; 95% CI=0.98–1.33; *P*=.085).
Conclusion: Being a smoker or ex-smoker, greater baseline lung function, and low BMI were the main risk factors associated with an accelerated rate of decline in FEV1. This finding warrants the close observation of younger patients with a better-preserved FEV1.

Factores asociados a la evolución de la función pulmonar en pacientes con déficit de alfa-1-antitripsina del registro español

Palabras clave:
Déficit de alfa-1-antitripsina
Registros
Función pulmonar
Tabaquismo

RESUMEN

Introducción: El presente estudio pretende describir las características de los pacientes diagnosticados de déficit grave de alfa-1-antitripsina (AAT) en España, calcular la tasa de descenso del FEV1 con y sin tratamiento sustitutivo, e identificar factores asociados a una tasa de descenso acelerada del FEV1.
Método: Estudio retrospectivo de la evolución de los individuos con déficit de alfa-1-antitripsina (DAAT) incluidos en el registro español. La variable principal evaluada en el estudio fue la tasa anual de descenso del FEV1.

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Resultados: Se identificaron 303 pacientes con DAAT grave y fenotipo Pi ZZ. Se dispuso del seguimiento espirométrico de 117 pacientes. Ser fumador activo o ex fumador frente a nunca fumador (odds ratio [OR] = 10,31; intervalo de confianza (IC) del 95% = 1,8–58,8; *P* = 0,008) y tener un mayor FEV1(%) posbroncodilatador (OR = 1,03; IC del 95% = 1,005–1,06; *P* = 0,018), se asociaron de manera independiente a una tasa más acelerada de descenso del FEV1. Se apreció una tendencia entre tener un índice de masa corporal (IMC) bajo y experimentar una mayor tasa de deterioro del FEV1 (OR = 1,14; IC del 95% = 0,98–1,33; *P* = 0,085).

Conclusiones: Ser fumador o ex fumador, tener una función pulmonar preservada y un bajo IMC fueron los principales factores de riesgo asociados a una tasa acelerada de descenso del FEV1. Este hallazgo justificaría la necesidad de efectuar un seguimiento estrecho de los pacientes jóvenes con un FEV1 más preservado.

Introduction

Alpha-1 antitrypsin (AAT) is a highly pleomorphic glycoprotein belonging to the serpin superfamily, with more than 100 varieties and whose main characteristic is its antiprotease function, especially anti-neutrophil elastase.[1,2]

The normal allele, present in more than 90% of the population, is called PI*M. The most frequent deficient allelic variants are PI*S and PI*Z, which are responsible for the production of abnormal proteins that polymerize within the hepatocytes; thus, the plasma levels are markedly reduced in subjects who are carriers of at least one and especially two Z deficiency alleles.[3,4] AAT deficiency (AATD) is one of the most common genetic disorders. It is the main genetic factor that contributes to the development of pulmonary emphysema in adults, as the absence of AAT causes an imbalance favoring proteases, which cause tissue damage.

AATD, defined by serum concentrations of AAT less than 35% normal values, is a rare condition that affects one out of every 2000–5000 Caucasian individuals, descendants of Northern, Central, and Western Europeans.[5] As occurs in other rare diseases, patient registries have been developed in order to compile information and, in this manner, improve the understanding of the disease. Although clinical assays are considered the gold standard for establishing the most effective interventions, the information found in the registry and from other observational studies can be used to fill in important gaps that, if not, would be left uncovered because clinical assays do not deal with real-life situations.[6]

The world-wide AATD population registries (Alpha One International Registry [AIR], the registry of the National Heart, Lung, and Blood Institute [NHLBI] in the United States and the Alpha One Foundation Research Network Registry [AOF-RNR]) have demonstrated that the main clinical characteristic of this disease is effort dyspnea.[7,8] They have also shown that the majority of patients are diagnosed when they have already developed severe lung disease, generally at an earlier age than patients with chronic obstructive pulmonary disease (COPD) without AATD.

The evolution in clinical terms and life expectancy are both directly related with the accelerated loss of forced expiratory volume in 1 s (FEV1), and it has been reported that the lung function deterioration is faster in individuals with AATD than in COPD patients without AATD.[9–13]

Several studies have shown that smoking and respiratory exacerbations are the main factors related with the deterioration of FEV1. They have also suggested that substitutive treatment (intravenous administration of purified AAT from blood donors, capable of maintaining AAT plasma levels above 80 mg/dl) could stop the decline of FEV1, reduce the frequency of the exacerbations and even stop the loss of lung density.[14–17]

The natural history of AATD is not well known. Its clinical and functional impacts are not homogeneous in all individuals and the existing series include very diverse populations that are occasionally very limited.[18] Health-care institutions and scientific societies recognize that the creation of rare disease registries is an essential strategy in order to be able to develop clinical studies and clarify the natural history of these diseases. The Spanish registry of patients with alpha-1 antitrypsin deficiency, or REDAAT, compiles the clinical and functional data of the Spanish population with AATD. REDAAT is a Spanish national registry and was founded in 1993 as a workgroup of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[19]

The present study describes the evolution of FEV1 in patients belonging to REDAAT, centered on the parameters that could potentially have a predictive value for a fast deterioration in lung function.[20]

Methods

Based on the information compiled in the REDAAT database, we carried out a retrospective study in patients with AATD. The objectives of this study were: (a) to describe the characteristics of the patients diagnosed with AATD in Spain; (b) to observe the rate of decline in FEV1 of the patients who had been or currently were receiving substitutive treatment and those who had/were not; and (c) to identify the factors associated with a greater rate of descent in FEV1.

Participants

The data included in this study come from subjects with AATD included in REDAAT. REDAAT can be accessed through its web page (www.redaat.es), which meets all the requirements related with the protection of personal data in accordance with Spanish legislation. Its page is certified as an Accredited Medical Web by the commission of the College of Physicians of Barcelona. Although the recommendation of REDAAT is to include data on the follow-up visits biannually, information on the evolutional follow-up of the majority of the registered individuals is not available. In order to achieve the objectives of the study, we contacted all the doctors who collaborated with the registry by mail, e-mail and/or telephone requesting them to provide data related to the follow-up of their patients. The data obtained were included anonymously in a database in Access format, and the quality was checked, as was the frequency of absent data. The study was done in accordance with the principles of the Declaration of Helsinki, the guidelines for good practice in epidemiological research and the local regulations for the use of study databases.

The inclusion criteria for the study were: (a) severe AAT deficiency, demonstrated by serum levels of AAT lower than 50 mg/dl with phenotype Pi ZZ or other deficient allelic variants, such as $Pi_{Barcelona}$[21]; and (b) to have at least 2 spirometries available over a time period of more than 6 months in order to analyze the rate of