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Editorial

First Argentine Study on Alpha-1 Antitrypsin Deficiency in Dried Blood Spot Samples From COPD Patients☆

Primer estudio argentino del déficit de alfa-1-antitripsina en muestras de sangre seca de pacientes con enfermedad pulmonar obstructiva crónica (EPOC)

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We welcome the cross-sectional, observational, case-finding study on alpha-1 antitrypsin deficiency (AATD) in 1002 individuals with COPD conducted by Sorroche et al. in Buenos Aires. This is the first study of its kind in Argentina.[1]

The authors set out to identify all genotypes associated with severe AATD (namely, Pi*ZZ and Pi*SZ) using an effective screening technique based on the quantification of alpha-1 antitrypsin (AAT) in dried blood. This was followed by hybridization probe genotyping to detect S and Z mutations in individuals with COPD and AAT concentrations below a cut-off level of 100 mg/dl (measured by immunonephelometry).

The diagnostic technique enabled the investigators to detect nearly 22% of individuals with AAT levels below the cut-off value. Of these, 15 (1.5%) presented severe AATD associated with Pi*ZZ (12 cases, 1.3%) and Pi*SZ (3 cases, 0.2%) genotypes. The remaining 20% (60 cases) presented mild or moderate AATD associated with MS, SS, MZ genotypes and various uncharacterized heterozygous genotypes. Although these latter are not in themselves known to increase the risk of developing AATD-associated diseases, they can pass down S and Z and rare deficiency alleles.

The results of this study suggest that far from being rare in Argentina, AATD is simply vastly under-diagnosed, as it is in nearly every other country in the world.[2] The estimated incidence of Pi*S and Pi*Z in the Argentine population, made up of 97% of individuals with Spanish or Italian blood and 3% with Amerindian or mixed blood, is 33 and 6 per thousand inhabitants, respectively,[3] a rate very similar to that found in Italy for these same alleles (Pi*S: 31 and Pi*Z: 8 per 1000).[4]

Although the study carried out by Sorroche et al. clearly has more strengths than weaknesses, some confounding variables acknowledged by the authors could, in aggregate, have partially distorted the findings. These include the failure to perform serial lung function tests to correctly classify COPD patients, the loss to follow-up of some subjects, and the bias inherent to the diagnostic method used. Specifically, the loss of some patients prevented the investigators from obtaining an accurate diagnosis in 13% of subjects with low AAT levels. Obtaining a diagnosis in 87% of the remaining patients, however, amply compensates for this limitation.

The technique of screening for AATD in dried blood samples is reliable and minimally invasive and facilitates processing and delivery of samples to the laboratory. Although real-time allele-specific PCR genotyping is a fast, cost-effective and very safe method of diagnosing S and Z alleles, it cannot detect other deficiency or normal alleles.[5] This means that once a case of severe AATD is detected, the results must be confirmed through quantitative determination of AAT and phenotype characterization in serum samples using isoelectric focusing. In some, albeit rare, cases the SERPINA1 gene must be sequenced in whole blood samples to characterize rare or null genotypes.[6]

In the Argentine study, some cases were left undiagnosed, including 2 M-rare heterozygous genotypes. This is an important factor, as the prevalence of rare and null genotypes (approximately 50) among Caucasians is around 1×10^{-4} and 2.5×10^{-5}. These subjects have a serum level of AAT of between 1% and 15%, and are at high risk for developing emphysema, particularly when combined with other rare and null genotypes or with common S and Z deficiency alleles. Indeed, in Spain and Italy, null and rare alleles are more common than thought, and account for nearly 5% and 16%, respectively, of patients entered in the National Patient Registers of these countries.[7–9]

Given that the main aim of diagnostic screening studies is to detect all ZZ and SZ individuals, we believe that the findings of this valuable study should be taken closely into consideration. Apart from the need to correct some weaknesses detected in the study and implement systematic isoelectric focusing and sequencing techniques, this study should encourage others to develop similar screening programs in other regions in Argentina. Such initiatives would lead to the detection of individuals with AATD in risk groups (particularly those with COPD or chronic liver disease

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of unknown origin, and also in cases of systemic vasculitis and neutrophilic panniculitis).[10] Diagnosis of severe AATD will prompt clinicians to issue critical warnings to affected individuals, such as avoiding exposure to tobacco smoke and industrial, agricultural and domestic contaminants, and also hepatotoxins. They could also recommend performing AATD screening in first-degree relatives, give genetic counseling, and order replacement therapy in certain cases, in accordance with the Argentine AATD diagnosis and treatment guidelines.[3]

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