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Alpha-1 Antitrypsin Deficiency: The Learning Goes On

The pathophysiology of chronic obstructive pulmonary disease (COPD) is widely accepted to reflect an abnormal inflammatory response to the inhalation of toxic agents, especially cigarette smoke. This is supported by the development of multiple transgenic and knockout mice that either develop "emphysema-like" changes spontaneously or become more resistant or susceptible to cigarette smoke exposure.

These studies have their origin in the observation some 60 years ago of several subjects with a circulating deficiency of alpha-1 antitrypsin (AAT) associated with severe early onset basal panlobular emphysema. Once recognized as a clinical and familial entity, targeted testing confirmed the association. Index was the term used for those identified by testing symptomatic subjects and nonindex for those identified by chance or family screening. Nonindex cases were generally younger with better preserved lung function, suggesting an earlier stage of evolution of the disease.

Because AAT was recognized as an inhibitor of neutrophil elastase (NE), which can replicate many of the features of COPD, the concept of an NE/AAT imbalance became, and remains, the cornerstone of the pathophysiology of COPD and, specifically, AAT deficiency.

Logically, supplementation of AAT should restore the normal NE/AAT physiological balance in the lung. In the early 1980s, AAT was purified from human blood and shown to increase recipient AAT in both blood and the lungs (1), falling over seven days to levels still above baseline (~12 μM). It was argued that this was still protective because other AAT variants with levels above this were not at increased risk for COPD (2). *In vitro* experiments confirmed excess connective tissue damage with ZZ plasma was greatly abrogated by MM plasma and decreasing ambient level with SZ; MS and MZ plasma had a similar effect, enabling physiological NE activity to take place while preventing excessive damage (3). The authors concluded a target threshold of 11 μM was largely "protective."

The initial patients with AAT deficiency were homozygous for the Z variant gene and these subjects had typical blood levels of AAT of <8 μM (i.e., below the putative protective threshold).

Although such patients represent the vast majority of subjects receiving augmentation therapy, studies have identified multiple variants of AAT, although most have AAT levels in the normal range (17–47 μM).

The S variant has a mild reduction in blood level and SZ heterozygotes have AAT levels that range from the protective threshold of 11 to 28 μM, suggesting at least some may be at risk and benefit from augmentation therapy. Currently, such patients are being treated (as well as MZ heterozygotes who have even higher AAT levels) at great cost (~$80 million/yr in the United States alone) despite lack of demonstrable benefit.

Whether SZ patients are at increased risk of COPD has long been contentious, with some studies saying yes (4) and some no (5). The problem of perceived risk largely relates to acquisition bias. Patients with established COPD are usually tested if young, with severe disease, and perhaps a limited smoking and/or family history of COPD. Family testing identifies further deficient subjects and more COPD. However, COPD can run in families without AAT deficiency, suggesting unknown genetic concordance as well as common social and environmental risk factors. Thus, whether an abnormal AAT genotype is an association with or cause of COPD remains uncertain.

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In this issue of the *Journal*, Franciosi and colleagues (pp. 73–82) have addressed the uncertainty by a process that overcomes some of these potential confounders using the Irish AAT deficiency registry (6). For the initial risk assessment, index cases were identified and family members invited for testing to identify nonindex SZ siblings by phenotype or genotype. MM and MS family members were also recruited because neither genotype is a recognized risk factor for COPD, resulting in 70 subjects with nonindex SZ and 46 control subjects.

The minimal and never smokers had similar lung function to control subjects and, if performed, no emphysema on computed tomographic scans, unlike never-smoking ZZ homozygotes of whom 25% develop progressive airflow obstruction (7). However, subjects with nonindex SZ with a smoking history (47% of the cohort) had reduced lung function compared with control subjects (though mild), with an odds ratio for spirometric COPD of 4.65 (not statistical significance); and 33% had emphysema on computed tomographic scans but apical distribution (unlike subjects with ZZ in which it is predominantly basal). There was no relationship of lung function to the baseline blood AAT concentration or above and below the protective threshold for the whole cohort ($n = 82$), including the SZ index cases.

Sixty subjects with SZ were followed for a median of approximately five years with 3–5 measurements and had a greater annual decline in lung function not related to smoking but a feature of established COPD.

The summary is that the SZ genotype alone is not a risk factor for developing COPD and is associated with a non–AAT deficiency distribution of emphysema (unlike the ZZ genotype). Smoking has an effect as in control subjects and established COPD has an identifiable effect on subsequent progression. The AAT level itself is not a contributing factor and augmentation therapy is not indicated.

How do we interpret some of the data? In a similar design by the same group, the COPD risk of the MZ genotype was increased (odds ratio, 10.65) in smokers (8). The odds ratio in the SZ smoking cohort was 4.65, which was not significant, possibly reflecting power (a major problem in rare diseases). Subjects with MZ have greater blood, and hence lung, concentrations of AAT but the smoking history was also greater than the current SZ cohort, which may have strengthened the COPD signal. Patients who are AAT-null with no or minimal circulating AAT have worse lung function than individuals with ZZ (9). So, concentration clearly plays a role not thought for SZ or MZ individuals. Smoking, therefore, has a central role for individuals who also carry the Z gene, irrespective of AAT concentration. Perhaps, therefore, concentration is one factor and having no AAT is the worst-case scenario, with levels in individuals with severely deficient ZZ being only partially protective. Smoking interaction with individuals who are SZ and MZ leads to a mild degree of disease above and beyond control patients and, hence, is not a feature of AAT level but more a feature of a common Z gene.

So how might this have an effect?

The Z variants of AAT can spontaneously polymerize and these are proinflammatory, being found in the lung tissues in close proximity to neutrophils. This property may be an amplification factor for the inflammation generated by cigarette smoke or established COPD. This would explain why smokers who are MZ develop mild COPD compared with control subjects and why this, rather than smoking, leads to progressive airflow obstruction. Whether this progression is worse than in a matched MM cohort should be explored (as suggested by the authors) to clarify this concept. So, still more to learn! ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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