Unravelling the risk of (intermediate) antitrypsin deficiency

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The seminal observation of severe deficiency of alpha-1-antitrypsin (AAT) with premature emphysema over 50 years ago led to the elastase–antielastase hypothesis of lung disease. Subsequent research identified alpha-1-antitrypsin deficiency (AATD) as an inherited metabolic genetic condition caused by mutations on the *SERPINA1* gene, resulting in a reduction in the serum concentration of AAT.[1] The role of AAT is to act as an inhibitor to the enzyme neutrophil elastase, and it is crucial in the homeostasis of elastase–antielastase activity, with an imbalance in this activity causing lung disease via a cycle of inflammation and proteolytic damage leading to premature emphysema, disability and death. There are over 100 mutations of *SERPINA1* described in the literature, some of which are associated with AATD. The normal genotype is designated PiMM; the most common genotype resulting in severe deficiency is designated PiZZ. AATD is an autosomal codominant condition so heterozygosity can also create in genotypes resulting in mild and intermediate deficiency, such as PiMZ and PiSZ. The prevalence of AATD worldwide is estimated between 0.02% and 0.05%. Normal AAT serum concentration would be in the range 20–53 µmol/L, while deficient genotypes express varying levels, from 55% for PiMZ to 40% for PiSZ and <15% for PiZZ. While the risk of developing premature emphysema in PiZZ is beyond doubt, there has been considerable debate regarding the risk of SZ genotype (intermediate deficiency) and emphysema severity.[2]

The study carried out by Franciosi *et al*[3] in this journal is a welcome addition to the area aiming to further understand the PiSZ genotype and its effect on lung disease. Their results imply that it is closer in phenotype to mild AATD from PiMZ than a PiZZ (severe deficiency). They attempted to assess differences in a range of clinical outcomes between PiMZ (n=156), PiSZ (n=117) and PiZZ (n=213) patients by retrospective study of the National Irish AATD Registry. Included subjects had data available on age, smoking history, AAT serum concentration and ascertainment (ie, how the patient was diagnosed). The authors' preliminary analysis found that those diagnosed due to lung disease, irrespective of genotype, had a significantly lower $FEV1_{pp}$ (15% lower on average). However, there was no significant correlation between age, pack-years and FEV_{1pp} within PiMZ and PiSZ patients who had smoked. The OR indicated that the likelihood of PiMZ and PiSZ patients being ascertained due to their lung disease was no different. However, a significant difference was found between pack-year history and FEV_{1pp} between PiSZ and PiZZ: −0.39% per pack-year. PiZZ patients were almost twice as likely (OR 2.11) to be diagnosed due to lung disease than PiSZ individuals. In their final analysis, the authors looked for the difference in effect of PiMZ and PiZZ genotypes on lung function and emphysema relative to PiSZ. They found no difference in any PFT value between PiMZ and PiSZ, regardless of smoking history and age. Conversely, PiSZ and PiZZ patients exhibited significant differences, with PiZZ patients being more severely affected. The authors also analysed 448 CT reports for evidence of emphysema (n=136 PiMZ, n=102 PiSZ, n=210 PiZZ). Emphysema was much more common in PiZZ than PiSZ patients (OR 13.51) but no different between PiMZ and PiSZ individuals (OR 1.18, 95% CI 0.49 to 2.80). Furthermore, emphysema did not occur in any PiMZ or PiSZ never smoker.

The authors were able to demonstrate that the PiSZ genotype presents phenotypically closer to PiMZ than to PiZZ, and therefore significantly lower risk of lung disease than PiZZ. This has been shown in other cohorts previously,[4] but Franciosi *et al*[3] were able to go further by demonstrating no significant difference between PiMZ and PiSZ, implying that the development of emphysema in some PiSZ individuals is more likely to be due to a cofactor such as smoking. The importance of smoking exposure when it comes the PiSZ phenotype is well recognised from a case control study that showed no significant difference in spirometry between never smoker PiSZ cases and similar controls, but a significant decrease in $FEV1_{pp}$ (−14.3%) for ever smokers.[5] These findings support those of a larger study involving PiSZ cases that found a significant negative correlation between pack-year history and FEV_1, and that in the absence of smoke exposure, PiSZ cases had similar levels of emphysema to PiMZ. This suggests that PiSZ cases should be treated as almost two separate phenotypes with the presence or absence of smoke exposure.[6]

Although this study was beneficial in establishing evidence of the PiSZ genotype presenting phenotypically closer to PiMZ, and thus more like smoking induced 'usual' chronic obstructive pulmonary disease (COPD), as is common in many studies in rarer diseases, there were some limitations. Lack of longitudinal data makes the conclusion stated less robust; examining lung function decline between the different genotypes would make for a stronger comparison. In addition, it was not possible to assess emphysema distribution in the cohort; relative upper versus lower zone dominance would have been a useful addition given that upper zone dominance is more typical in usual COPD, and reported in prior PiSZ cohorts in up to half of patients. Furthermore, liver disease was not analysed in this study, which can still be a considerable comorbidity for individuals with deficient variants, which have a tendency to aggregate in the liver.

The importance of the putative protective threshold—a minimum serum concentration of AAT required to adequately protect the lung from adverse effects of proteolysis—when it comes to deciding treatment for AATD has posed difficulties when assessing PiSZ cases who may exhibit levels either above or below this amount. It has been a source of debate, and some might argue controversy that an AAT serum concentration of <11 µmol has been used to gauge whether patients should receive AAT augmentation therapy in countries where this is licensed and funded.[7] The authors therefore analysed lung disease severity and method of diagnosis in PiSZ patients on either side of the threshold; no differences were seen. Taken together with the absence of difference between PiSZ and PiMZ patients, this suggests that the current accepted threshold may be incorrect and not as relevant relative to genotype and smoke exposure when it comes to deciding about benefit of augmentation therapy.

In the UK, augmentation therapy remains under consultation by NICE, with the initial decision being not to fund mainly due to concerns over cost-effectiveness, since assessment of the effect

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on emphysema progression, disability and mortality in this less common condition is based on meta-analyses and observational data.[8 9] The importance of this study highlights that therapy should only currently be considered in more severely deficient patients, which may lower the size of the population eligible and thus limit the cost burden to the NHS.

While this study demonstrated that lung disease in PiSZ cases is milder than PiZZ, the exposure of smoking has been demonstrated to add a significant burden. Therefore, clinicians can be more reassuring to PiSZ individuals who have never smoked that the risk of significant emphysema is much lower than PiZZ. It is the task for clinicians now to not treat AATD as a homogenous disease but as a complex, varied condition and accordingly to facilitate patient access to specialist advice on risk, therapies or lifestyle changes to make sure patients and their families have the best possible outcomes.

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