Provider Education in Alpha 1 Antitrypsin Deficiency: Try Again, Fail Again, Fail Better

Suzanne Roche, Tomás P. Carroll, and Noel G. McElvaney

Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

ORCID ID: 0000-0002-0152-4370 (N.G.M.)

Alpha-1 antitrypsin (AAT) deficiency (AATD) was first described by Laurell and Eriksson in 1963 (1). During the following 60 years, our understanding of the pathogenesis of this condition has increased exponentially, and various treatment strategies have been developed (2). Lagging behind this is our ability to identify people with AATD in a timely manner before the onset of irreversible lung and liver destruction. The diagnosis of AATD is simple, with an initial step of quantifying AAT levels in the blood, preferably with a measurement of C-reactive protein to out rule an acute-phase response. A low level should be further clarified by phenotyping and/or genotyping, and gene sequencing as required (3). It is clear, however, that a very significant percentage of the AATD population remains undiagnosed or is diagnosed too late (4).

In this issue of *ATS Scholar*, Schumacher and colleagues evaluated whether a targeted provider education module would improve AATD screening (5). More than 11,000 healthcare providers, including eight pulmonologists, opened the educational module, with one third completing the entire module. Confidence in identifying patients at high risk for AATD improved significantly after completion of the module, with the rate of screening of patients at high risk doubling after the intervention. Among patients screened for AATD in this cohort, 27% had a genotype/phenotype or low AAT level consistent with AATD. The study was helped by a simple message that every patient with chronic obstructive pulmonary disease (COPD) needs an AATD screening at least once in their lives. These data suggest the potential for the implementation of this or a similar program at other centers. However, the authors also noted problems with this approach to AATD screening. Much of the improvement in screening was driven by the testing of AAT levels alone, not by genotype or phenotype testing, in contrast to the recommendations of the American Thoracic Society and European Respiratory Society. The authors note quite rightly that the variability in selecting the appropriate test—not just "any test"—needs to be explored in future studies. Despite the investigators' best efforts, the

Author contributions: S.R., T.P.C., and N.G.M. conceptualized, wrote and reviewed the draft

ATS Scholar Vol 4, Iss 4, pp 396–399, 2023

DOI: 10.34197/ats-scholar.2023-0128ED

overall rates of screening patients at high risk for AATD remained low in their center. This points to significant, multifaceted problems in AATD detection.

The two largest screening programs to date in AATD screened 200,000 neonates in Sweden (6) and 107,038 neonates in Oregon (7). In the Swedish study, the number of babies with the ZZ AATD genotype was one in 1,639, whereas the Oregon study detected a frequency of one in 5,097, suggesting an estimated 66,000 individuals with the ZZ ATD genotype in the United States and 6,000 in Sweden. Most of these people with AATD were never identified, partly because some had no signs or symptoms, but a significant cohort were almost certainly symptomatic but misdiagnosed. This deficit was recognized by the World Health Organization, the American Thoracic Society and European Respiratory Society, and the Alpha-1 Foundation. The consensus from these groups was in favor of targeted detection programs in which AATD testing is undertaken for patients with COPD, asthma with irreversible airflow obstruction, liver disease of unknown etiology at any age, panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis (8, 9). It was also recommended that parents, siblings, children, and extended family of individuals identified with an abnormal gene for AAT be tested.

Targeted detection can make a difference. In the National Detection Program for AATD in the United States, Z homozygotes were computed to comprise 0.4% of the targeted population, compared with a population prevalence of 0.02% (10). This is an undoubted improvement in detection, but it still falls well short of detecting the majority of people with AATD in the United States as a partly as a result of poor adherence to screening guidelines. Similarly, in the general Irish population, one in 2,104 individuals are ZZ homozygotes, which equates to approximately 3,000 individuals in Ireland (11). The Irish National Targeted Detection demonstrated a fourfold increase in Z frequency compared with the general population, but, to date, only 500 ZZ individuals have been diagnosed. Similar scenarios exist with other programs (10).

Why is testing important and how can we improve it? The diagnostic delay in AATD is between 5 and 8 years across many studies, with respondents with attributable symptoms reporting having seen at least three doctors before diagnosis (3). Delayed diagnosis is associated with worse COPD-related symptoms and functional status (12), more rapid decline in lung function, and decreased overall and transplant-free survival (13). Although there is a definite need to improve testing in general, pulmonologists, and primary care providers, the groups most likely to test for AATD across all genotypes (10) also need to increase and improve their testing practices.

Targeted detection programs should form part of the guidelines for COPD management. There is a need to challenge the overemphasis on screening only White populations (14). In a recent study in cystic fibrosis, an autosomal-recessive genetic disorder with a Northern European origin, >12% of the 982 participants enrolled were a race other than non-Hispanic White (15). With this as background, it is inevitable that the number of AATD individuals who are Black, Hispanic, or multiracial will increase, and our screening guidelines should reflect this. With an increasing understanding of pulmonary and liver risks for MZ and SZ AATD genotypes, these individuals should also be actively sought as part of screening programs and counseled after diagnosis, as

lifestyle changes such as smoking cessation or obesity reduction measures may have significant, inexpensive positive effects.

Even then, targeted screening will not detect all people with AATD because, even with the most robust screening programs, the age at diagnosis is too late when significant lung or liver disease has been established, and uptake is still generally poor (9, 13). This raises the question of neonatal screening. We now understand more about the natural history of the various forms of AATD, and we are developing therapies for the most severe forms of this condition. We need to address the psychological and social implications of early diagnosis of a genetic disorder that must be weighed against the enormous potential benefits of early lifestyle interventions made possible by that early diagnosis.

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

REFERENCES

1. Laurell CB, Eriksson S. The electrophoretic α1-globulin pattern of serum in α1- antitrypsin deficiency. *Scand J Clin Lab Invest* 1963;15:132–140.
2. Strnad P, McElvaney NG, Lomas DA. Alpha$_1$-antitrypsin deficiency. *N Engl J Med* 2020;382: 1443–1455.
3. Franciosi AN, Carroll TP, McElvaney NG. Pitfalls and caveats in α1-antitrypsin deficiency testing: a guide for clinicians. *Lancet Respir Med* 2019;7:1059–1067.
4. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. *Lancet* 2005;365:2225–2236.
5. Schumacher R, Chiu CY, Lubarda J, Aboulsaoud P, Bomberger J, Wells M. A novel provider education module to enhance detection of alpha-1 antitrypsin deficiency. *ATS Scholar* 2023;4: 490–501.
6. Sveger T. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med* 1976;294:1316–1321.
7. O'Brien ML, Buist NR, Murphey WH. Neonatal screening for alpha1-antitrypsin deficiency. *J Pediatr* 1978;92:1006–1010.
8. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society Statement: standards for the diagnosis and management of Individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003;168:818–900.
9. Sandhaus RA, Turino G, Brantly ML, Campos M, Cross CE, Goodman K, *et al.* The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis (Miami)* 2016;3:668–682.
10. Brantly M, Campos M, Davis AM, D'Armiento J, Goodman K, Hanna K, *et al.* Detection of alpha-1 antitrypsin deficiency: the past, present and future. *Orphanet J Rare Dis* 2020;15:96.
11. Carroll TP, O'Connor CA, Floyd O, McPartlin J, Kelleher DP, O'Brien G, *et al.* The prevalence of alpha-1 antitrypsin deficiency in Ireland. *Respir Res* 2011;12:91.
12. Tejwani V, Nowacki AS, Fye E, Sanders C, Stoller JK. The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: the association between diagnostic delay and worsened clinical status. *Respir Care* 2019;64:915–922.

13. Fraughen DD, Ghosh AJ, Hobbs BD, Funk GC, Meischl T, Clarenbach CF, *et al.* Augmentation therapy for severe alpha-1 antitrypsin deficiency improves survival and is decoupled from spirometric decline-a multinational registry analysis. *Am J Respir Crit Care Med* 2023;208:964–974.

14. Riley L, Sriram A, Brantly M, Lascano J. Testing patterns and disparities for alpha-1 antitrypsin deficiency. *Am J Med* 2023;136:1011–1017.

15. Goss CH, Heltshe SL, West NE, Skalland M, Sanders DB, Jain R, *et al.*; STOP2 Investigators. A randomized clinical trial of antimicrobial duration for cystic fibrosis pulmonary exacerbation treatment. *Am J Respir Crit Care Med* 2021;204:1295–1305.