Bench to Bedside and Back: The Evolving Story of Alpha-1 Antitrypsin Deficiency

More than half a century ago, Laurell and Eriksson, working in their clinical biochemistry laboratory, noted anomalous findings in some of the samples sent for serum protein electrophoresis. In a minority of electrophoreses, the alpha-1 protein band was faint to nonexistent. Such a finding might easily have been dismissed as population variance, but Laurell and Eriksson left the confines of the lab to determine the clinical phenotype associated with the anomaly they observed. In doing so, they described what we now recognize as alpha-1 antitrypsin deficiency (1). Individuals with markedly reduced serum levels of this protective glycoprotein were predisposed to develop severe emphysema early in life, often with little or no tobacco smoke exposure. The basal predominant, panlobular emphysema was distinctive. Moreover, there was a predilection for the development of cirrhosis. That this disorder was genetic was established early; much later, the most common severe variant was localized to an abnormality on the *SERPINA1* gene. The initial family kindreds had what we now understand to be the most common genotype associated with a severe deficiency of alpha-1 antitrypsin, the ZZ genotype.

These bench-to-bedside findings have been of great importance in several ways. Scientifically, they described the foundations of the protease/antiprotease theory of the of emphysema pathogenesis. Clinically, they described an illness that became one of the first examples of personalized medical care with specific targeted therapy to treat a specific abnormality. More than a quarter-century ago, Wewer and colleagues reported that the infusion of purified alpha-1 antitrypsin protein in a dosage of 60 mg per kilogram per week could restore and maintain serum levels to theoretically protective thresholds with infused protein detectable in BAL fluid (2). Later observational studies confirmed that the accelerated decline in lung function associated with the deficiency could be slowed by this treatment and, in those who are most obstructed, loss of life delayed (3, 4). More recently, randomized controlled trials have shown that lung structure, as measured by computed tomographic scan lung density estimates, is preserved by infusions (5). Although the treatment of alpha-1 antitrypsin deficiency liver disease has lagged, there is growing evidence that as well as supportive measures and transplantation, the use of chaperone proteins holds promise for reducing the impact of damage to the liver by the retention of alpha-1 antitrypsin polypeptides.

Despite the long history of alpha-1 antitrypsin deficiency, its characteristic clinical phenotype, and the availability of therapy, the disorder remains underdiagnosed (6). Simple routine testing could remedy this, and the Global Initiative for Chronic Obstructive Lung Disease Strategy, for example, recommends routine testing of all newly diagnosed patients with chronic obstructive pulmonary disease (COPD) (7). However, testing for the disorder is potentially complex. Not all gene variants result in decreased serum levels of alpha-1 antitrypsin protein. Some variants produce measurable but dysfunctional serum proteins, the F variant being the foremost example (8). Thus, the concerned clinician must consider an array of potential testing strategies. Simplest and least expensive remains quantifying serum levels of alpha-1 antitrypsin protein. Costing only a few dollars per test, it is widely available and screens adequately for the most common of alpha-1 antitrypsin deficiency disorders. But serum level measurements are inadequate for carrier detection, may be transiently elevated during acute inflammatory events, and will not detect functionally abnormal variants. If serum levels are low or the clinician's index of suspicion is high, serum protein may be phenotyped, the approach pioneered by Laurell and Eriksson. Although their technology has been updated or replaced, their legacy has included the nonstandard nomenclature for alpha-1 antitrypsin abnormalities reflecting the mobility of proteins in electrophoresis gels. Protein phenotyping has the potential to detect both known and novel variants but may fail to reveal complex abnormalities. Today, protein phenotyping is typically bypassed in favor of genetic testing, usually targeting the most common of deficiency and dysfunction variants Z, S, F, and I. This four-variant PCR panel will characterize the vast majority of important and known alpha-1 antitrypsin abnormalities, but if a novel abnormality is suspected, sequencing becomes necessary. When is a novel abnormality suspected? Such a possibility should be considered when there is a discrepancy between what is measured and what is expected. Such discordance should not be dismissed as random variability in test results until the possibility of a novel variant has been considered.

In this issue of the *Journal*, Matamala and colleagues (pp. 444–451) describe two novel *in cis* variants of the *SERPINA1* gene that modify the properties of the PI*S allele, increasing hepatocellular retention and decreasing secretion into the bloodstream. The result is production of a functional null variant in what by conventional testing appears to be unremarkable S variant findings, typically a mild deficiency variant with little risk of liver disease (9). Their elegant investigation of the problem was sparked by relatively mild discordance among clinical findings, serum alpha-1 antitrypsin quantification and genotype as revealed by targeted gene testing. One man with COPD had a serum alpha-1 antitrypsin level ~20% to 25% lower than expected for what appeared to be SS genotype. Their analysis found one S variant and what they have termed an S+ variant (S+p.Tyr138Cys), a variant associated with null-like activity. This additional *in cis*

Originally Published in Press as DOI: 10.1165/rcmb.2020-0243ED on July 27, 2020

abnormality modulates the otherwise innocuous S variant to produce null-like activity with reduction of serum levels by trapping polypeptides in the hepatocyte. Thus, this patient who might otherwise have been regarded as having tobacco-related COPD with an unrelated mild alpha-1 antitrypsin deficiency variant was more correctly identified as having an intermediate deficiency variant potentially treatable by augmentation therapy. A second patient suffering from liver disease with the same *in cis* variant was initially identified as having MS genotype until further investigation revealed the S+ variant, thereby accounting for lower-than-expected serum levels of alpha-1 antitrypsin and retention of alpha-1 antitrypsin polypeptides in the endoplasmic reticulum of hepatocytes. A third patient with pulmonary involvement but lower-than-expected serum level for genotype MS was found to have type MS+ genotype, the *in cis* variant in this example producing null-like activity differently (S+p.Pro391Thr).

These novel findings have implications for all of us in the field of pulmonary medicine. At the bedside, we must be alert to discordant findings. Although few clinicians could trace out the testing pathways that led to these complex and novel variants, clinicians should recognize when simple serum levels are lower than anticipated. Such findings should not be dismissed without further investigation. Communicating directly with the testing lab may provide further insights and suggestions for testing. As sequencing becomes accessible for clinical purposes, we might expect further rare variants to be described in this way. At the bench, we would do well to emulate the initiatives of Laurell and Eriksson. Even half a century on, the story of alpha-1 antitrypsin deficiency remains incomplete, and one cannot help but wonder how many variations to the story remain untold. ■

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

Kenneth R. Chapman, M.D., M.Sc.
Professor of Medicine
University of Toronto
Toronto, Canada
and
Asthma and Airway Centre
University Health Network
Toronto, Canada

ORCID ID: 0000-0002-2498-9859 (K.R.C.).

References

1. Laurell CB, Eriksson S. The electrophoretic alpha1-globullin pattern of serum in alpha1-antitrypsin deficiency. *Scand J Clin Lab Invest* 1963; 115:132–140.
2. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, *et al*. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. *N Engl J Med* 1987;316:1055–1062.
3. Vreim CE, Wu M, Crystal RG, Buist AS, Burrows B, Cohen AB, *et al*. Survival and FEV1 decline in individuals with severe deficiency of α1-antitrypsin. *Am J Respir Crit Care Med* 1998;158:49–59.
4. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. *COPD* 2009;6:177–184.
5. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, *et al*.; RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:360–368.
6. Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. *CMAJ* 2012;184:1365–1371.
7. Global Initiative for Chronic Obstructive Lung Disease. GOLD COVID-19 Guidance. Fontana, WI: GOLD; 2020 [accessed 2020 Jul 8]. Available from: www.goldcopd.org.
8. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 antitrypsin deficiency. GeneReviews. 1993–2020. PMID: 20301692. Seattle, WA: University of Washington, Seattle; 2006 Oct 27 [updated 2020 May 21; accessed 2020 Jul 8]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1519/.
9. Matamala N, Gomez-Mariano G, Perez JA, Baladrón B, Torres-Durán M, Michel FJ, *et al*. New *cis*-acting variants in PI*S background produce null phenotypes causing alpha-1 antitrypsin deficiency. *Am J Respir Cell Mol Biol* 2020;63:444–451.