Challenge of α_1-antitrypsin deficiency diagnosis in primary care

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The genetic disorder α_1-antitrypsin deficiency (AATD) contributes to the development of chronic obstructive pulmonary disease (COPD), bronchiectasis, liver cirrhosis, and panniculitis,[1] and affects 1 in 3000 to 5000 individuals in the United States.[2] The exact prevalence of AATD in patients diagnosed with COPD is unknown, but small studies have suggested estimates of 1% to 5%.[3] As many of the symptoms of AATD are nonspecific and might overlap with more common conditions, such as asthma and non-AATD COPD, many patients experience misdiagnoses or substantial delay in diagnosis. It has been estimated that only 4% to 5% of those with AATD have been identified[4] and there is an average of 5.6 years from the onset of symptoms to diagnosis of AATD.[1] This report aims to emphasize both the challenge and the importance of timely diagnosis of AATD in primary care.

Case

A 41-year-old man presented to his family physician with a history of difficulty breathing that was aggravated by only modest levels of physical activity during the preceding 5 to 6 years. He was a recent immigrant from Portugal, but despite several visits with physicians in Portugal his diagnosis remained unclear.

The patient smoked 1 pack of cigarettes per day for 15 years. He had quit smoking in the past year, but continued to be exposed to cigarette smoke at work. He was a carpenter by trade. He denied any illicit drug use or alcohol consumption. He also denied any family or personal history of asthma or atopy.

The findings of the physical examination were unremarkable, with the exception of decreased air entry to the lungs bilaterally and low oxygen saturation (92% at rest on room air). A chest radiograph revealed hyperinflated lungs with flattening of the hemidiaphragms. The anterior-posterior diameter of the chest wall was increased.

His pretreatment spirometry results (**Table 1**) indicated severe airflow obstruction with a postbronchodilator forced expiratory volume in the first second of expiration (FEV_1) of 32% of the predicted normal value and an FEV_1–forced vital capacity (FVC) ratio of only 0.28. Reversibility was observed after bronchodilator challenge in both FEV_1 and FVC, with increases of 32% and 36%, respectively. These findings highlight the challenge of distinguishing AATD from asthma and COPD, as these spirometry data meet the criteria for a diagnosis of either asthma (an increase of at least 12%, or an absolute increase of at least 200 mL, in FEV_1) or COPD (a reduction of the FEV_1-FVC ratio below 0.70 or the lower limit of normal). These findings could also be in keeping with the overlap syndrome consisting of both asthma and COPD.[5] This individual was treated with both oral and inhaled corticosteroids (50 mg of prednisone daily for 10 days) as well as dual long-acting bronchodilator therapy.

One month later, the patient reported no subjective improvement and there was no change in his lung function (**Table 2**). Given his young age, clinical history of dyspnea dating back more than 5 years, few risk factors for asthma, and very advanced airflow obstruction that appeared unresponsive to therapy, screening for α_1-antitrypsin (AAT) was carried out, revealing a very low AAT level of less than 1.84 µmol/L. α_1-Antitrypsin protein phenotyping (protease inhibitor [Pi] typing) was subsequently done and showed his Pi type to be null-rare. For financial reasons, the patient declined testing for genotyping.

EDITOR'S KEY POINTS

- This case highlights the challenge of distinguishing α_1-antitrypsin deficiency (AATD) from asthma and chronic obstructive pulmonary disease (COPD), as the spirometry results of AATD meet the criteria for a diagnosis of either asthma or COPD. Findings could also be in keeping with the overlap syndrome consisting of both asthma and COPD.
- Screening for AATD should be carried out if patients have early onset COPD, disabling emphysema in their 40s or 50s, family history of AATD, fewer than 20 pack-years of smoking history, or asthma that responded poorly to therapy if they were previously thought to have asthma.

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Table 1. Patient spirometry results before treatment: *The FEV_1-FVC ratios were 0.29 before bronchodilation and 0.28 after bronchodilation.*

SPIROMETRY MEASUREMENT	BEFORE BRONCHODILATOR		AFTER BRONCHODILATOR		
	BEST RESULT, L	% OF PREDICTED VALUE	BEST RESULT, L	% OF PREDICTED VALUE	% CHANGE
FVC	3.43	67	4.68	91	36
FEV_1	1.01	24	1.33	32	32

FEV_1—forced expiratory volume in the first second of expiration, FVC—forced vital capacity.

Table 2. Patient spirometry results 1 month after treatment: *The FEV_1-FVC ratios were 0.29 before bronchodilation and 0.29 after bronchodilation.*

SPIROMETRY MEASUREMENT	BEFORE BRONCHODILATOR		AFTER BRONCHODILATOR		
	BEST RESULT, L	% OF PREDICTED VALUE	BEST RESULT, L	% OF PREDICTED VALUE	% CHANGE
FVC	3.27	64	4.86	95	49
FEV_1	0.94	23	1.43	34	51

FEV_1—forced expiratory volume in the first second of expiration, FVC—forced vital capacity.

Discussion

α_1-Antitrypsin is a glycoprotein synthesized mainly in the liver and secreted into the plasma, where its main function is to protect tissues against neutrophil elastase. Severe deficiency of AAT predisposes smokers to the development of disabling panlobular emphysema at a relatively young age (about 40 years), with few of those presenting with pulmonary symptoms surviving to 60 years.[6]

α_1-Antitrypsin deficiency is inherited in an autosomal codominant fashion. The disease occurs as a result of inheritance of 2 copies of deficiency alleles on the Pi locus on chromosome arm 14q. The wild-type allele is *PiM* and the 2 most common deficiency alleles are *PiZ* and *PiS*, with *PiS* being milder than *PiZ*. Those who are heterozygotes with only 1 deficiency allele are not considered at substantial risk of developing severe COPD. The presence of 2 deficiency alleles, most commonly *PiZZ*, results in severely diminished serum AAT levels and is associated with markedly heightened risk of developing panlobular emphysema and liver disease. Other AAT allelic variants include null alleles (which produce no AAT protein) and dysfunctional alleles (normal protein levels, but abnormal protein function). Most clinical disease comes from deficiency and null alleles. The Pi locus of the patient in this case has a copy of the null allele and another copy of a rare disease–causing allele, giving rise to his extremely severe serum deficiency of AAT.[3]

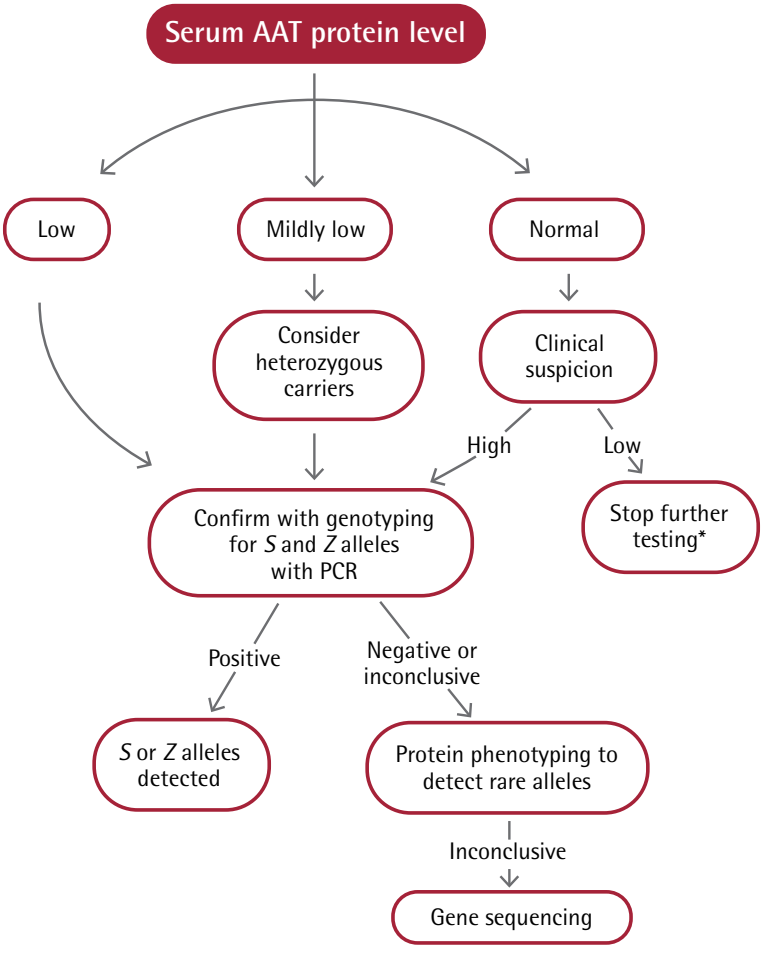
The classic presentation of AATD is similar to that of COPD, although it often occurs at a younger age or with less smoke exposure. Lung function test results also show features typical of COPD such as airflow obstruction and increased lung volumes. In addition, it is not unusual to observe reversibility (>12% in FEV_1) after treatment with bronchodilators, which might lead to a misdiagnosis of asthma. Normal lung function might also be seen, most often in asymptomatic individuals. Smoke exposure is considered the most important determinant of lung function. Among those with *PiZZ*, smokers have a much greater risk of developing abnormalities in lung function and more rapid decline than non-smokers.[1]

There is no universally accepted laboratory algorithm for AATD diagnosis.[7] Quantifying serum AAT levels is a reasonable initial screening test; levels below 11 µmol/L are considered pathophysiologically important.[3] Genotyping via polymerase chain reaction is then performed on blood samples to detect *S* and *Z* alleles. Genotyping is limited in its detection of rare alleles. If serum AAT level measurement and genotyping are inconclusive, phenotyping is the next test of choice. Gene sequencing is currently reserved for cases of low serum AAT levels that cannot be explained fully by genotyping and phenotyping (**Figure 1**).[8]

In the past decade, there have been increased efforts to heighten awareness and to overcome barriers to AATD testing. The American Thoracic Society and the European Respiratory Society recommend genetic screening in all COPD patients regardless of smoking history, in all adults and adolescents with nonresponsive asthma, and in all individuals with unexplained liver disease.[8] The Canadian Thoracic Society guidelines suggest more selective AATD screening, targeting individuals with COPD diagnosed before age 65 or with a smoking history of fewer than 20 pack-years (weak recommendation).[3]

Current treatment of AATD is, for the most part, management of COPD, emphysema, and coexisting lung problems. The goal is to prevent or slow the progression of lung disease. Quitting smoking has by far the greatest effect on survival in patients with emphysema.[9] Augmentation therapy with exogenous AAT is an alternative treatment. The Canadian Thoracic Society recommends AAT augmentation therapy in non-smoking or ex-smoking patients with COPD (FEV_1 25% to 80% of predicted value) and AAT levels equal to or less than 11 µmol/L.[3] Finally, vaccination against hepatitis A and B viruses is advised to decrease the risk of liver

Figure 1. Flow chart for AATD diagnosis



AAT—α_1-antitrypsin, AATD—α_1-antitrypsin deficiency, PCR—polymerase chain reaction.
*AAT protein is an acute-phase reactant and its level in serum can be increased by infection, inflammation, cancer, and thyroid disorders.[8]

disease.[9] Pneumococci and influenza vaccines help lower the exacerbation frequency in patients with AATD.[8]

Conclusion

Primary care physicians are often the first point of contact for patients presenting with symptoms of thoracic disease. Screening for AATD should be carried out if patients have early onset COPD, disabling emphysema in their 40s or 50s, family history of AATD, fewer than 20 pack-years of smoking history, or asthma that responded poorly to therapy if they were previously thought to have asthma.

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Competing interests
None declared

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