JAMA Diagnostic Test Interpretation

Serum α_1-Antitrypsin Concentration in the Diagnosis of α_1-Antitrypsin Deficiency

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A 64-year-old man who was a nonsmoker with a history of asthma was referred to pulmonary clinic with a 25-year history of dyspnea on exertion and multiple episodes of pneumonia. He reported that his father and paternal uncle had early-onset lung disease. An abdominal computed tomographic scan (**Figure**) performed for abdominal pain and weight loss revealed emphysema in the lung bases. Measurement of the patient's serum α_1-antitrypsin (AAT) showed a concentration of 14 mg/dL (reference range, 102-254 mg/dL [to convert to μM, multiply by 0.184]).

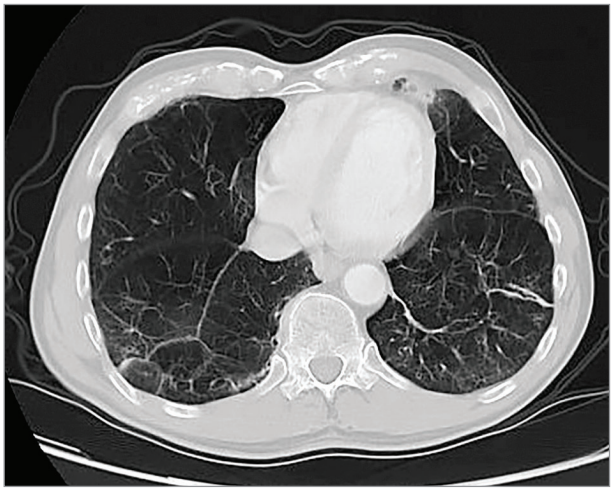

Figure. Computed tomographic image, taken from the superior slices of an abdominal scan performed for abdominal pain, showing panacinar emphysema in the lung bases.

HOW DO YOU INTERPRET THIS TEST RESULT?

A. The AAT level indicates a diagnosis of heterozygous protease inhibitor (Pi) MZ phenotype.

B. The AAT level indicates a diagnosis of AAT deficiency with homozygous PiZZ phenotype.

C. The AAT level indicates a deficiency consistent with compound heterozygous phenotype PiSZ.

D. The AAT level suggests an AAT deficiency that requires further testing.

Answer

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Test Characteristics

AAT protein normally functions as an antiprotease, protecting the lungs from elastases such as neutrophil elastase. AAT deficiency, the most frequent genetic disorder causing pulmonary emphysema, is caused by mutations in the *SERPINA1* gene leading to an abnormal AAT protein, which accumulates in the endoplasmic reticulum of cells and results in low levels of AAT in the serum and alveolar lining fluid. Deficiency of AAT, together with cigarette smoking or other environmental exposures, can lead to pulmonary emphysema. AAT deficiency is also associated with neonatal jaundice, acute hepatitis, cirrhosis, hepatocellular carcinoma, bronchiectasis, granulomatosis with polyangiitis, and necrotizing panniculitis of the skin. The serum AAT concentration does not distinguish between normal and abnormal protein, but the abnormal protein can be identified using Pi phenotyping with an isoelectric gel.

The most common SERPINA1 alleles are the M allele (normal), the S allele, and the Z allele; the S and Z alleles account for 95% of mutations in individuals with AAT deficiency.[1] Individuals who are homozygous for the S allele have 60% of normal AAT abundance, and those who are homozygous for the Z allele have 15% of normal AAT abundance[2,3] (**Table**). The prevalence of AAT deficiency, type PiZZ (ie, protease inhibitor deficiency resulting from homozygous Z mutation), is estimated to be between 1:2000 and 1:10 000 in Europe and the United States, but there is significant underdiagnosis.[3] Recent guidelines recommend testing for AAT deficiency in all patients with chronic obstructive pulmonary disease (COPD), bronchiectasis, or unexplained chronic liver disease regardless of age or ethnicity.[4]

Using a cutoff of 85 mg/dL or less, the serum AAT level identifies individuals with a PiZZ phenotype with a sensitivity of 99.5% and a specificity of 96.5%, but the sensitivity of this threshold to identify other phenotypes, such as PiSZ, is only 85.9%.[2] A normal- or intermediate-range serum AAT indicates a normal phenotype with no added risk of lung or liver disease. However, this situation may occur in individuals with a heterozygous phenotype (such as PiMZ), who are at risk of developing lung disease after smoke exposure[5] and can pass the mutant Z allele to their children. In addition, AAT is an acute-phase protein that increases during infection and inflammatory states, which could lead to a missed diagnosis.[4] Therefore, current guidelines recommend genotyping at-risk individuals for the most

Table. Commonly Identified Pi Phenotypes With the Corresponding Range of Serum α_1-Antitrypsin Concentration in mg/dL (and μM), Predicted Prevalence in the United States, and Disease Association

Phenotype	Range of Serum AAT Concentration, mg/dL (μM)[a]	US Predicted Prevalence[b]	Disease Association
PiMM	102-254 (19-47)	NA	None
PiMS	86-218 (16-40)	1:17	No proven association
PiMZ	62-151 (11-28)	1:48	Lung disease
PiSS	43-154 (8-28)	1:922	Lung disease
PiSZ	38-108 (7-20)	1:1299	Lung and liver disease
PiZZ	≤29-52 (≤5-10)	1:6211	Lung and liver disease

Abbreviation: AAT, α_1-antitrypsin.
[a] From Bornhorst et al 2013.[2]
[b] From de Serres et al 2014.[3]

common clinically important mutations, the Z and S alleles.[4] If the genotype results are inconclusive or inconsistent with the patient's clinical presentation, such as severe emphysema or liver disease, further testing with serum concentration of AAT can confirm AAT deficiency. Pi phenotyping can directly identify the abnormal serum protein, and full gene sequencing can characterize rare mutations.[4] After a proband has been identified, genetic testing among first-degree family members is recommended. The Medicare midpoint reimbursements for serum concentration of AAT is $16.59 and for the *SERPINA1* genotype is and $53.89.[6]

Application of Test Results to This Patient

The patient's presentation after years of asthma misdiagnosis is common in AAT deficiency. The low serum AAT concentration is consistent with either ZZ genotype or a compound heterozygote such as a single Z allele plus a rare null mutation. The serum level alone cannot determine the genotype because the range of serum AAT levels for each genotype is overlapping. Further testing, such as genotyping for the Z and S alleles or serum Pi phenotyping, is required to confirm the diagnosis and clarify the genotype present.

Alternative Testing

In contrast to US guidelines,[4] which recommend genotyping in all patients with COPD, a recent European Respiratory Society statement recommends first measuring plasma AAT concentration with subsequent genetic testing or Pi phenotyping when AAT values are low.[7]

Patient Outcome

Serum Pi phenotyping demonstrated PiZZ phenotype. Pulmonary function testing showed moderate airflow obstruction, air trapping, and reduced diffusion capacity, consistent with emphysema. Results of serum liver function tests and hepatic ultrasound were normal. Weekly infusions of AAT augmentation therapy were initiated, and the patient has had no significant clinical progression in 2 years.

Clinical Bottom Line

- Current guidelines recommend that all patients with COPD, unexplained bronchiectasis, or chronic unexplained liver disease, regardless of age or ethnicity, should be tested for AAT deficiency. In patients with AAT deficiency, smoking cessation improves outcomes. AAT augmentation therapy can also be considered.
- To test patients for AAT deficiency, US guidelines recommend genotyping for the most common genetic mutations (the Z and S alleles) because the serum concentration alone may miss some patients with AAT deficiency. If necessary, further testing should include either serum level of AAT, Pi phenotyping, or gene sequencing.
- Family screening after a proband has been identified should be carried out using a genetic test.

ARTICLE INFORMATION

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