Alpha-1 Antitrypsin Deficiency: An Under-Recognized Cause of Chronic Obstructive Pulmonary Disease

Stephen P. Peters, MD, PhD FAAAAI
Wake Forest School of Medicine
Center for Genomics and Personalized Medicine Research

Outline

- **Chronic Obstructive Pulmonary Disease (COPD)**
- **Alpha-1 Antitrypsin (AAT) Deficiency**
  - Definition and Epidemiology of AAT Deficiency
  - Pathophysiology of AAT Deficiency
  - Genetics and Diagnosis of AAT Deficiency
  - Clinical Aspects of AAT Deficiency
  - Treatment of AAT Deficiency
Risk Factors for COPD

- Exposure
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Air pollution
- Host factors
  - Airway hyperresponsiveness
  - Stunted lung development
  - Alpha-1 antitrypsin (AAT) deficiency

Outline

- Chronic Obstructive Pulmonary Disease (COPD)
- Alpha-1 Antitrypsin (AAT) Deficiency
  - Definition and Epidemiology of AAT Deficiency
  - Pathophysiology of AAT Deficiency
  - Genetics and Diagnosis of AAT Deficiency
  - Clinical Aspects of AAT Deficiency
  - Treatment of AAT Deficiency
AAT

- 51 KDa glycoprotein made predominantly in the liver
- Secreted to blood, permeates all tissues
- Circulating serum levels in normal individuals range from 150–350 mg/dL (20–48 µM)
- Protease inhibitor
- Primary target is the white blood cell protease, neutrophil elastase (NE)

AAT Deficiency

- AAT deficiency is an autosomal, codominant, hereditary disorder characterized by low serum and lung levels of AAT
- AAT gene resides at the proteinase inhibitor (Pi) locus on chromosome 14
- The most common mutant AAT allele (Pi*Z) produces an abnormal protein that is polymerized and sequestered in hepatocytes
- AAT deficiency predisposes affected individuals to lung, liver, and other diseases

AAT Alleles

- There are more than 100 distinct AAT alleles, with varying clinical significance
- Deficiency alleles encode abnormal protein that is not secreted normally, resulting in decreased circulating levels of AAT
- Most common alleles
  - Pi*M (normal)
  - Pi*S (moderately deficient)
  - Pi*Z (severely deficient)
- The null allele (rare), which produces no protein, results in the most severe deficiency
Prevalence of AAT Deficiency

- 3.4 million individuals with mutant AAT allele combinations worldwide\(^1\)
  - PI*ZZ = 175,268
  - PI*SZ = 929,014
  - PI*SS = 2,260,801

- Based on direct population screening studies, prevalence of PI*ZZ in the US may be 80,000–100,000\(^2-4\)

- Only approximately 5,000 individuals in the US are currently diagnosed with PI*ZZ
  - 95% undiagnosed

Prevalence in the US vs. Genetic Disorders and Certain Cancers

- **AAT deficiency (PI*ZZ)**: 80,000–100,000\(^1-3\)
- Spina bifida: 70,000\(^4\)
- Huntington’s disease: 30,000\(^5\)
- Cystic fibrosis: 30,000\(^6\)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAT deficiency (PI*ZZ)</td>
<td>80,000–100,000(^1-3)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>70,000(^4)</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>30,000(^5)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>30,000(^6)</td>
</tr>
</tbody>
</table>

Prevalence of AAT Deficiency in Patients With COPD

- Estimated prevalence of severe AAT deficiency in patients with COPD is approximately 2% to 3%\(^7\)

- “…all subjects with COPD or asthma characterized by incompletely reversible airflow obstruction should be tested once for quantitative AAT determination.”

ATS/ERS Standards

\(^{1}\)de Serres FJ. Chest. 2002;122:1818.
\(^{2}\)Colp C. Chest. 1993;103:812;.
\(^{3}\)O’Brien ML. J Pediatr. 1978;92:1006;.
\(^{5}\)www.sbaa.org, www.sbaa.org,
\(^{6}\)www.hdsa.org, www.hdsa.org,
\(^{7}\)www.cff.org, www.cff.org,
Outline

- Chronic Obstructive Pulmonary Disease (COPD)
- Alpha-1 Antitrypsin (AAT) Deficiency
  - Definition and Epidemiology of AAT Deficiency
  - Pathophysiology of AAT Deficiency
  - Genetics and Diagnosis of AAT Deficiency
  - Clinical Aspects of AAT Deficiency
  - Treatment of AAT Deficiency

AAT is Secreted by the Liver

Structure of Mutant AAT Loop-Sheet Polymers

Orphanet Journal of Rare Diseases 2008, 3:16
Mutant AAT is not Secreted Efficiently

Liver

Blood vessel

AAT

To all tissues

Hepatocytes

Blood vessel

Sequestered AAT polymers

Pathogenesis of α-1-AAT Deficiency

Orphanet Journal of Rare Diseases 2008, 3:16

Outline

• Chronic Obstructive Pulmonary Disease (COPD)
• Alpha-1 Antitrypsin (AAT) Deficiency
  – Definition and Epidemiology of AAT Deficiency
  – Pathophysiology of AAT Deficiency
  – Genetics and Diagnosis of AAT Deficiency
  – Clinical Aspects of AAT Deficiency
  – Treatment of AAT Deficiency
Inheritance of AAT Alleles

- MM (25%)
- MZ (50%)
- ZZ (25%)

Range of Serum Levels by Phenotype

- Bottom normal level
AAT Phenotypes

- AAT phenotype refers to the AAT protein type, characterized by position of the protein on isoelectric focusing (IEF)
- Can define the heterozygous or homozygous states
- Phenotype can be confirmed with genotyping (DNA analysis)
- Serum levels of AAT and risk of disease vary by phenotype

Outline

- Chronic Obstructive Pulmonary Disease (COPD)
- Alpha-1 Antitrypsin (AAT) Deficiency
  - Definition and Epidemiology of AAT Deficiency
  - Pathophysiology of AAT Deficiency
  - Genetics and Diagnosis of AAT Deficiency
  - Clinical Aspects of AAT Deficiency
  - Treatment of AAT Deficiency
Lung Disease Associated with AAT Deficiency

• A common manifestation of AAT deficiency
• Defining characteristics\(^1,2\):
  – Panacinar emphysema
  – Early-onset of disease (35–50 years of age) in presence of additional risk factors
  – Airway obstruction not completely reversible with treatment

Spirometry: Normal vs. AAT Deficiency

<table>
<thead>
<tr>
<th></th>
<th>FEV(_1)</th>
<th>FVC</th>
<th>FEV(_1)/FVC</th>
<th>FEV(_1)% Pred</th>
<th>FVC % Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4.150</td>
<td>5.20</td>
<td>80%</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td>COPD</td>
<td>2.350</td>
<td>3.90</td>
<td>60%</td>
<td>82%</td>
<td>72%</td>
</tr>
</tbody>
</table>


Lower Lobe Emphysema in AAT Deficiency

- Lower zone disease
- Higher zone disease


Lower Lobe Emphysema & Compressive Atelectasis in AAT Deficiency

Other Diseases That May Be Associated With AAT Deficiency

- Liver disease is another primary manifestation of AAT deficiency
  - Childhood and adult liver disease
- AAT deficiency is also more rarely associated with:
  - Panniculitis
  - C-ANCA–positive vasculitis
  - Wegener's granulomatosis

Risk Factors of Lung Disease Associated with AAT Deficiency

- AAT deficiency has a highly variable clinical course of disease
- In absence of additional risk factors, individuals with AAT deficiency can have an almost normal life span
- Risk factors:
  - Smoking
  - Passive smoking
  - Occupational/environmental exposures
  - Lung infections
α-1-Antitrypsin Testing Algorithm

Range of Serum Levels and Risk of Disease by AAT Phenotype

Outline

- Chronic Obstructive Pulmonary Disease (COPD)
- Alpha-1 Antitrypsin (AAT) Deficiency
  - Definition and Epidemiology of AAT Deficiency
  - Pathophysiology of AAT Deficiency
  - Genetics and Diagnosis of AAT Deficiency
  - Clinical Aspects of AAT Deficiency
  - Treatment of AAT Deficiency
AAT Deficiency–Specific Therapy for Lung Disease

- IV augmentation therapy
  - Purified human AAT concentrate
  - 60 mg/kg weekly maintains serum AAT levels above protective threshold (11 µM/80 mg/dL)\(^1-3\)
  - Increases AAT levels in lung epithelial lining fluid (ELF)\(^1-3\)
  - Goal is to slow progressive lung tissue destruction

ATS/ERS Recommendations for Use of Augmentation Therapy

- Patients with AAT serum level <11 µM with obstructive lung disease, independent of phenotype
- Patients with FEV\(_1\) 30% to 65% predicted have greatest benefit
  - Benefits for severe or mild airflow obstruction less clear
- Possible benefit in post-lung transplant during respiratory tract inflammation or acute or chronic rejection

Safety of Augmentation Therapy

- Relatively few side effects reported
- Most frequent:
  - Headaches
  - Myalgias
  - Arthralgias
  - Low back pain
- No treatment or occasional analgesic use required
Augmentation Therapy Efficacy Studies

- Two registry studies (Danish and National Heart, Lung and Blood Institute [NHLBI]) demonstrated decreased annual decline in FEV₁ in treated vs. untreated registry patients
  - A mortality benefit was demonstrated with treatment in the NHLBI Registry study
  - A randomized study demonstrated decreased loss of lung tissue in treated vs. untreated patients
  - A longitudinal study demonstrated a slower decline in FEV₁ in patients after vs. before they received augmentation therapy

Study of Efficacy of Augmentation Therapy in NHLBI Registry

Study Design

- Annual decline in FEV₁ of 650 treated patients on registry compared with 277 untreated patients
- Followed 3.5 to 7 years
- Spirometry measured pre- and post-bronchodilator every 6 to 12 months

Study of Efficacy of Augmentation Therapy in NHLBI Registry: FEV₁

- [Graph showing FEV₁ comparison]
Study of Efficacy of Augmentation Therapy in NHLBI Registry: Mortality*

*Surgery with FEV1 <50% predicted


Surgical Treatment for AAT-Associated Lung Disease

- Lung transplantation
  - For patients who do not respond to more conservative therapy or who have extensive lung damage
  - 5% to 10% of lung transplants performed in the US each year are performed due to AAT deficiency
  - 5-year survival is approximately 50%
- Lung volume reduction surgery
  - May improve dyspnea and lung function
  - Not recommended due to lack of evidence


Treatment for AAT-Associated Liver Disease

- No specific treatment
- Avoidance of alcohol
- Hepatitis A and B vaccinations
- Liver transplantation
  - For patients who do not respond to more conservative therapy or who have extensive liver damage

AAT Deficiency Conclusions

- AAT deficiency is under-diagnosed
- Some of your COPD patients have AAT deficiency
  - Early onset of COPD (<50 years of age)
  - Emphysema in the absence of risk factors or with prominent basilar hyperlucency
  - Asthma not completely reversible with treatment
  - Family history of emphysema, bronchiectasis, liver disease, or panniculitis
  - Unexplained liver disease or panniculitis or vasculitis
  - Bronchiectasis

AAT Deficiency Conclusions (continued)

- AAT augmentation therapy can slow the annual decline in FEV₁, decrease mortality, and possibly slow the loss of lung tissue
- If you don’t test, you can’t:
  - Test family members
  - Initiate interventions (smoking prevention or cessation, occupational decisions)
  - Treat with augmentation therapy
  - Affect mortality associated with AAT deficiency