**Alpha 1 Antitrypsin Deficiency**

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**What is the physiology of emphysema?**

Two basic functional changes:

1. Loss of elastic recoil
2. Loss of membrane surface area

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**Pulmonary Emphysema**

- Permanent enlargement of airspaces distal to the terminal respiratory bronchioles which involves destructive changes in alveolar walls
- Affects as many as 5-10% of adults in U.S.
Elastic Recoil Important for Airway Patency

Normal Airway

Emphysematous Airway

Normal

Emphysema

Spirometry

<table>
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<tr>
<th>Volume Liters</th>
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<tr>
<td>0</td>
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FEV1

FVC

Restriction

Obstruction

Doubles Tennis Court

Alveolar Capillary Membrane

Alveolar capillary membrane

Red blood cell
Alveolar Capillary Membrane

Emphysema

Symptomatic at minimal exertion

Emphysema

How Does It Happen?

Lessons from alpha 1-antitrypsin deficiency

Smoking Effects on Lung Function

A1AT Genetic Defect

**Z Mutation for Alpha 1-Antitrypsin**

Glu342 (GAG) → Lys342 (AAG)

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<th>Ⅲ</th>
<th>Ⅳ</th>
<th>Ⅴ</th>
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5’ → 3’

Alpha 1-Antitrypsin Gene

**Serum Protein Electrophoresis**

- Albumin
- Alpha-1
- Beta
- Alpha-2
- M-spike
- Gamma

**Alpha 1 and Emphysema**

- 5 patients found to have deficient alpha 1 peaks on their serum protein electrophoresis
- 3 of the 5 had severe emphysema

How does this defect cause disease?

**Protease/Antiprotease Hypothesis**

  - 3/5 cases had emphysema
  - “Some connection between degenerative pulmonary disease and α1-antitrypsin deficiency is suggested.”

  - Papain into silicotic rats
  - Induced emphysema

**Protease-Antiprotease Imbalance Hypothesis**

- Infection
- Smoking
- Dust
- A1AT
- Inherited Type

**A Few Case Histories: Patients with A1AT Deficiency**


- FEV1 as % of L1 at 20
- Disability

- Non-smoker
- Smoker (controls)
Alpha₁ a Rare Disease?

1972-1974 All newborns in Sweden screened finding 127 of 200,000 with Pi ZZ.

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency</th>
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<tr>
<td>1 in 1600</td>
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<tr>
<td>Oregon</td>
<td>1 in 5097</td>
</tr>
<tr>
<td>St. Louis</td>
<td>1 in 2857</td>
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<tr>
<td>New York</td>
<td>1 in 3694</td>
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</table>

~ 1 in 3000 in US

AATD: Recommendations from the AAT Deficiency Task Force

- Genetic testing is recommended for
  - Absent alpha-1 peak on SPEP
  - Early onset pulmonary emphysema (regardless of smoking history)
  - Family members of known AATD patients
  - Dyspnea and cough occurring in multiple family members in same or different generations

AATD Individuals Identified

< 5000 Identified

95,000 Unidentified

AATD: Recommendations from the AAT Deficiency Task Force

- Genetic testing is recommended for
  - Liver disease of unknown cause
  - All subjects with COPD
  - Adults with bronchiectasis without evident etiology
  - Patients with asthma whose spirometry fails to return to normal with therapy
  - Unexplained panniculitis and anti-proteinase 3 vasculitis

AATD, alpha-1 antitrypsin deficiency.

[References]
- Sveger, Pediatrics 1978; 62:22
- O'Brien J Pediat 1978; 92:1006
- Silverman ARRD 1989; 140:961
- C Chest 1993; 103:812
Clinical Manifestations

- Panacinar Emphysema
  - Early onset
  - Most common in current or past smokers
- Bronchiectasis
  - Atypical Mycobacterial Disease
- Hepatic insufficiency
  - Both Infant and after age 50 predominant

Clinical Manifestations

- Panniculitis
- Association with Anti-proteinase 3 vasculitis
- Association with Connective Tissue Diseases
- Poorly responsive HIV
- Association with Lung Cancer
AAT Is Normally Secreted by the Liver

Liver
Hepatocytes
Blood vessel

Alpha-1 Registry Respondents Reporting Liver Disease

Age (y)
Respondents (n)

Other/Unknown
PiSZ
PiMZ
Pi*ZZ

Alpha-1 Liver Disease

139 Liver Affected

30 Diagnosed before Age 18
15 Transplants

109 Adults

84 Non-transplant
More Alcohol Use
And Viral Hepatitis

25 Transplant
More Obesity
What are the treatment options?

Protease-Antiprotease Imbalance Hypothesis

- Infection
- Smoking
- Dust

Protease-Antiprotease Imbalance Hypothesis

- A1AT
- Inherited type

First Infusions of Alpha 1-antitrypsin

  - 5 patients for 4 weeks

  - 21 patients for 6 months
A1AT Infusion Therapy

A1AT Trough Levels Over 6 Months of Therapy

Protease-Antiprotease Imbalance Hypothesis

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Protease-Antiprotease Imbalance Hypothesis

- Smoking
  - Infection
  - Dust

Treatment Options

- Smoking cessation
- Avoid dusty occupational exposures and passive smoking
- Preventive measures: handwashing; vaccines for influenza and pneumonia
- Treat infections early
- Augmentation therapy with alpha 1 antitrypsin ($$$)

Smoking Cessation and FEV1 in A1AT Deficiency

Future Hopes for Therapy

- Genetic manipulation to remove the PiZZ gene from hepatocytes and replace with functioning PiMM gene
- Enhanced antitobacco legislation to help prevent institution of tobacco habit
Some of the Not For Profit Faces

- **Alpha-1 Association**
  - Member-based organization:
    - Support and Education Advocacy
  - Genetic Counselling Center

- **Alpha-1 Foundation**
  - Research-focused organization:
    - Increase research
    - Improve health
    - Worldwide detection
    - Cure for Alpha-1
  - Registry DNA and Tissue Bank

- **AlphaNet**
  - Health management organization:
    - Health maintenance and disease prevention
    - Outcome studies
  - Clinical research
  - Health Management Coordinators
  - Not-for-Profit but revenue generating

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**Registry Newsletter**

**LETTER FROM THE MEDICAL DIRECTION**

β-SECRETASE MUTATIONS HAVE BEEN IDENTIFIED AS THE AATD FOUNDATION

**Regulatory Council**

The regulatory council oversees the clinical trials to ensure the safety and efficacy of the treatments for AATD.

**Update**

**Why should we detect individuals with AATD?**

- Assist in smoking cessation
- Assist in occupational decisions
- Meaningful genetic data to family members
- Disease specific support
- Allow therapy specific for AATD

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**Alpha-1 Registry Participants (N=2021)**

- Blue = 1 participant
- Purple = 2 participants
- Yellow = 3 participants
- Red = 4 participants