Alpha-1 Antitrypsin Deficiency: 50th Anniversary of a Disease

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Challenges in Pulmonary & Critical Care: 2013

Faculty Disclosures

• **Advisory committee:**
  Grifols, CSL Behring

• **Protocol writing:**
  Kamada
Objectives

• Discuss the etiology of alpha-1 antitrypsin (AATD)

• Explain the treatments for AATD

• Address how to change your office flow to incorporate testing for AATD

• Utilization of ancillary staff and the Pulmonary function lab

On a scale of 1 to 5:
Please rate how confident you would be treating a patient with Alpha-1 Antitrypsin Deficiency:

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2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test Question 2

Which statement is true about patients with alpha-1 antitrypsin deficiency (Alpha-1)?

1. People with Alpha-1 always develop emphysema or COPD
2. Emphysema in Alpha-1 involves the lung bases exclusively
3. People with Alpha-1 get quickly diagnosed once they present to their physicians
4. Lung disease in Alpha-1 is difficult to distinguish from usual COPD

Pre-Test Question 3

All of these statements about alpha-1 antitrypsin (AAT) are true except:

1. It is a neutrophil elastase inhibitor
2. It is secreted mostly in the lungs
3. Its deficiency can result in COPD
4. Mutations in the AAT gene can result in liver damage
Pre-Test Question 4

Who should be tested for alpha-1 antitrypsin deficiency (Alpha-1)?

1. All adults with non-reversible airway obstruction
2. Only patients with COPD who are less than 50 years old
3. Only patients with panacinar emphysema (based on CXR or CT scan)
4. Only patients with COPD who have never smoked, regardless of age

Pre-Test Question 5

In the management of those diagnosed with Alpha-1, what is the most important first step?

1. Initiation of inhaled corticosteroid therapy
2. Referral to lung transplantation program
3. Smoking cessation counseling
4. Initiation of augmentation therapy
A Single Slide Introduction to Alpha-1 Antitrypsin (AAT) Deficiency

- Single gene mutation characterized by decreased plasma levels of AAT
- AAT gene (serpina1) on the long arm of chromosome 14 in Pi locus
- AAT is an anti-proteolytic, anti-inflammatory, anti-apoptotic protein synthesized primarily in liver
- In the most commonly identified mutation (Z), decreased circulating levels result from intrahepatocyte polymerization and accumulation
- Heterozygote deficient individuals have an increased risk of destructive lung disease, liver failure, and other conditions

SERPINA1

>200 genetic variants have been identified to date; not all variants are associated with the disease:
The two most frequent deficient alleles are Pi S and Pi Z.
Inheritance of two deficient alleles results in severe deficiency of AAT.

ATS/ERS Standards: Am J Respir Crit Care Med 2003;168:818–900
Gooptu B: J Exp Med 2008; 205:1529
Alpha-1: 1963 to 1973

- Jacobsson describes ability of proteins in the alpha, band of SPEP to inhibit trypsin
- Gross describes animal model of emphysema using papain
- Sharp finds liver disease in newborns is related to AAT deficiency
- Protease pathogenesis model of pulmonary emphysema

1963
- Ericksson & Laurell observe loss of alpha, band and potential association with familial emphysema. Name it AAT deficiency
- Janoff describes Human Neutrophil Elastase (HNE)
- Multiple investigators show 1) HNE can cause emphysema in animals, 2) AAT blocks HNE, 3) cigarette smoke destroys function of AAT

1973

Alpha-1: 1973 to now

- NIH Registry
- Alpha-1 Association
- Alpha-1 Foundation
- AlphaNet
- AAT Polymerization
- Trials in patients with 4PBA, gene therapy, disease management as well as multiple studies to document augmentation therapy efficacy

1979
- NIH begins studies infusing AAT derived from normal plasma to Alpha-1 patients

1980
- NIH Registry

1985
- NIH Registry

1987
- Lung and blood levels of AAT are effectively raised by augmentation therapy
- FDA approves Prolastin

1990s
- Additional augmentation therapies approved: Aralast, Zemaira, and Glassia

2000s

2013
The "Good" M Phenotype

The "Bad" Z Phenotype
The Genome and Alpha-1

~ 14,000 base pairs

394 amino acids

Co-dominant allelic expression

Disease Associated with Alpha-1

Liver

Childhood and adult liver disease
- Fulminant liver failure
- Cirrhosis

Lung

Lung disease – “AAT-COPD”
- Emphysema
- Bronchiectasis
Disease Associated with Alpha-1

- Others
  - Necrotizing panniculitis
  - Vasculitis (especially Wegener’s Granulomatosis)
  - Hepatocellular carcinoma
  - Susceptibility to atypical TB
  - Susceptibility to chronic active hepatitis
  - Pancreatitis
  - Arterial aneurysm

FEV₁ in Swedish PI ZZ Nonsmokers

*Figure 1: FEV₁ (% predicted) versus age in PI ZZ men (n=107) and women (n=118) who had never smoked.*

Pitulainen et al., Thorax 1997; 52:244
Disease Mechanisms

- Lung disease
  - Lack of protease inhibitor
  - Pro-inflammatory state
- Liver disease
  - Excess of protease inhibitor
  - Polymerization of Alpha-1
    - Decreases inhibitory activity
    - Pro-inflammatory?
Who should be tested?

• All individuals with COPD
• Asthma with incomplete reversibility on maximal therapy
• Bronchiectasis without other risk factors
• Siblings of AAT deficient individual
• Fam Hx of AAT deficiency or early onset COPD
• Cirrhosis without apparent risk factors

Making the Diagnosis

• Simple to diagnosis
  – Tube of blood
  – Finger stick
  – Buccal swab
  – Level
  – Phenotyping
  – Genotyping

• Alpha-1 is a laboratory diagnosis, not a clinical diagnosis
• Problems
  – Differences between the various testing methods difficult to appreciate
• ACT Study
Making the Diagnosis

• Issues related to testing in the office
  – Free test kits
    • Highly accurate and, did I mention, free -- BUT
      – Finger stick
      – Drying and mailing
      – Getting the results into the AHR
  – Local lab
    • Accuracy sometimes suspect (not at your institution, of course)
    • Ordering confusing both to orderer and orderee
      – E.g.: order an alpha-1 test and get an alpha-fetoprotein result

Making the Diagnosis

• Fix the testing problems
  – Commit a staff person to test all COPD patients who have not been tested before
  – Flag the record of those who have been tested
  – Empower respiratory therapists/pulmonary function technicians
    • Teach to identify those with COPD (or unexplained liver disease)
    • Ask if patient has been tested for Alpha-1 before
    • If not, ask permission to test for Alpha-1
    • Stick that finger
Alpha-1 COPD is Treatable!

Reduce Risk → Education → Smoking cessation
Reduce Symptoms → Education → Bronchodilators
Reduce Complications → Education → Treat exacerbations
Reduce Lung Destruction → Education → Augmentation therapy

Augmentation Therapy

- Human plasma derived, purified alpha-1 proteinase inhibitor (a.k.a. alpha-1 antitrypsin or AAT or API)
- Administered intravenously, on a weekly basis and dosed based on body weight (60 mg/kg/week)
- Given to those with severe AAT deficiency with documented emphysema
- Aside from smoking cessation, perhaps the only mechanism-based treatment for COPD
- 6 products:
  - Prolastin-C, Aralast NP, Zemaira, Glassia in U.S. and some of Europe
  - Trypsone, French API in some of Europe
  - Individual approvals in other parts of the world
The Studies

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<td>CT Densitometry</td>
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- CSL Behring – personal communication and presentation at ATS 2013

The Results

- **Studies with FEV₁ endpoints**
  - Subjects with FEV₁ <60-65% and >30-35% on therapy showed a reduction in rate of decline
  - Subjects with faster initial rate of decline (rapid decliners) showed greater effect of therapy
- **NIH Registry also showed improved survival**
The RAPID Trial

Problems

- Each case control study has potential bias
  - Not randomized
  - Reasons for some with lung disease to be off therapy
- RCTs
  - First two were under-powered to detect primary endpoint
  - RAPID study possibly chose a poor primary statistical endpoint
    (combined TLC and FRC CT data)
Alpha-1 Disease Management and Prevention Program

ADMAPP is . . .
Nurse training and testing
Coordinator training and testing
Patient and Professional Education
Treatment planning and review
Patient Worksheets
AlphaNet Coordinator Follow-up
Outcome measurement
Disease Management Advisory Committee (DMAC)

Distant horizon:
- Stem cell gene correction
- Other gene correction modalities

Liver Directed:
- Liver cell transplant
- Gene silencing
- Gene therapy
- Stem cells
- Depolymerization Strategies

Lung directed:
- Improved lung transplants
- Stem cells
- Small elastase inhibitors
- Lung regrowth
Thank You

Sten Eriksson
Carl-Bertil Laurell
Harvey Sharp
Aaron Janoff
Gerry Turino
Alan Cohen
Jim Travis
Gordon Snider
Bob Fallat
Ron Crystal
Jim Gedek
Mark Wewers
Richard Hubbard
Mark Brantly
Franck Rahaghi
Jim Stocks
Rob Stockley
David Lomas
Robin Carrell
Gerry McEvany

George Weinbaum
Phil Kimbel
Charles Mittman
Fred Kueppers
Ed Silverman
Jamie Stoller
Asger Dirksen
Jan Stoik
Maurizio Luissetti
Mark Miravitlles
Eva Pitaluainen
Ken Chapman
Claus Vogelmeier
Ed Edin
Charlie Strange
Michael Campos
Adam Wanner
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Alan Barker
Bruce Trappell

Ed Campbell
Jack Lieberman
Bob Senior
Kjel Ohlsson
Jerry Kleinerman
Jack Pierce
Paul Gross
Inez Mandl
Chick Kuhn
Barry Starcher
David Parr
Magne Fagerhol
Tomas Sveger
Marion Wencker
Nick Konietzko
David Perlmutter
Neels Seersholm
Terry Flotte
John W. Walsh
Sonia Buiste
And many others . . .
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Which of the statements below describes your approach to diagnosing and treating patients with Alpha-1 Antitrypsin Deficiency?

1. I do not manage patients with Alpha-1 Antitrypsin Deficiency, nor do I plan to this year.
2. I did not manage patients with Alpha-1 Antitrypsin Deficiency before this course, but as a result of attending this course I’m thinking of managing it now.
3. I do manage patients with Alpha-1 Antitrypsin Deficiency and this course helped me change my treatment methods.
4. I do manage patients with Alpha-1 Antitrypsin Deficiency and this course confirmed that I don’t need to change my treatment methods.
Discussion and Questions