Alpha-1 Antitrypsin Deficiency

Conflicts of Interest:

<table>
<thead>
<tr>
<th>Company</th>
<th>Research</th>
<th>Consultant</th>
<th>Speaker</th>
<th>Education Grant</th>
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<tbody>
<tr>
<td>CSL Behring</td>
<td>x</td>
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<td>Dyax</td>
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<td>Biocryst</td>
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<td>Pharming</td>
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Objectives

- **Recognize** the many ways Alpha-1 Antitrypsin Deficiency (Alpha-1) presents clinically
- **Improve** your understanding of the disease and the genetic background of the disorder
- **Examine** the data supporting augmentation therapy and how to manage these patients
“Chance favors the prepared mind”
Louis Pasteur - 1854

History of AAT

- 1962: Dr. Carl-Bertil Laurell (1919-2001) at the University of Lund, Sweden discovered the absence of the alpha-1 band in 2 serum electrophoresis gels.

- Further investigation by Dr. Sten Eriksson demonstrated 4 more.

- 4 of the 6 patients had emphysema.

Normal AAT Protein

- Normal AAT protein phenotype “M”
- 95% is made in the liver
- Main function is to neutralize/control neutrophil elastase, a potent proteolytic enzyme able to damage the elastin matrix of the lung.
- Autosomal Co-dominant inheritance
Alpha-1-antitrypsin – Z Protein

- PiZ results from a point mutation that encodes a single Amino Acid substitution.
- Z protein misfolds/polymerizes & accumulates in the liver
  - secretion from liver is impaired.
- Low secretion results in “deficient” serum level.
- Z phenotype accounts for 95% of clinical illness.

Carrell and Lomas, 2002

Other Deficient Variants

- S allele:
  - Variant is associated with milder deficiency
  - Not associated with AAT accumulation within hepatocyte
- Null allele – No AAT production
  - Zero serum level
  - Earlier lung but no liver disease
- More than 100 other rare mutations exist

De Serres, 2002 and 2007

Inheritance – Diagnostic Levels

<table>
<thead>
<tr>
<th>Genetic PI Type</th>
<th>Risk of lung disease</th>
<th>Serum level of alpha-antitrypsin in μMol</th>
</tr>
</thead>
<tbody>
<tr>
<td>M M</td>
<td>&quot;normal&quot;</td>
<td>58 mg% – 11 μMol</td>
</tr>
<tr>
<td>M S</td>
<td>low</td>
<td>Above 130 - normal</td>
</tr>
<tr>
<td>S S</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>M Z</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>S Z</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Z Z</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>high</td>
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</table>
Population Screening Studies

- 200,000 neonates screened in Sweden
  - Pi*ZZ in 127, or 1 in 1575
- 20,000 blood donors tested in St. Louis
  - Pi*ZZ : 1 in 2857
- 965 consecutive emphysema patients
  - 1.9% were Pi*ZZ
  - 8.0% were Pi*MZ

Sveger, 1976; Silverman et al, 1989; ATS/ERS AATD Standards, 2003

Prevalence of Alpha-1

- The most prevalent potentially fatal genetic disorder of adult Caucasians in the United States.
  - An estimated 25 million individuals carry deficient genes
  - Over 100,000 Americans have severe Alpha-1 deficiency
  - Less than 10% yet diagnosed

Stoller et al, 2005

Comparison of PI*ZZ Prevalence

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>AAT deficiency (Pi*ZZ)</td>
<td>Over 100,000</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>30,000</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>30,000</td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>186,000</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>128,000</td>
</tr>
<tr>
<td>Testicular Cancer</td>
<td>196,000</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>177,000</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>164,000</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>243,884</td>
</tr>
</tbody>
</table>
Clinical Presentation of Alpha-1

Clinical Pulmonary Presentation

- Results from 2 patient registries regarding prior diagnosis before Alpha-1:
  - 54% had emphysema
    - The mean FEV₁ among 1129 participants in the NHLBI registry was 43% of predicted with a mean age of 45.
  - 72% had respiratory symptoms
  - 42-46% with chronic bronchitis
  - 35% had a diagnosis of asthma.
    - 30% of NHLBI patients had FEV₁ reversibility when tested with spirometry
- Clinical presentation does NOT ID AATD!

NIH-AATD Registry Group, 1998; Silverman and Sandhaus, 2009, Campos et al, 2005

Why do those with Alpha-1 get Lung Disease?

- Uncontrolled proteolytic attack on lung tissue because of low circulating levels of AAT.
- The Z protein is less effective at inhibiting neutrophil elastase than the M protein.
- Cigarette smoke can inactivate the patient’s own AAT in the lungs.
- Normal AAT levels function to suppress inflammatory chemoattraction.
Radiology

- A review of chest radiographs from 165 consecutive ZZ alpha patients:
  - 15% were normal
  - Only 20% showed the "classic" finding of emphysema at the bases
- A review of 102 CTs of ZZ alpha patients
  - 64% showed basal predominance
  - 36% had predominant apical disease
- HRCT often finds bronchiectasis

*Chest x-rays and CT scans can NOT identify AATD.*

Yamashiro et al, 2009

Average Age at Diagnosis

Based on 302 patients with PiZZ out of 26,520 patients tested.
M Brantly, U of Florida
AATD and Survival

- Median survival in smokers = 49 years
- In non-smokers = 69 years
- In non-smokers lung disease often develops after age 50

Seersholm et al, 1995

Missed Clinical Recognition

- Average Alpha-1 patient has symptoms for 7.2 to 8.3 years before diagnosis is made.
- 44% of Alpha-1 patients see at least 3 doctors (PCP or specialist) before a diagnosis is made.

Campos et al, 2009

Alpha-1 Liver Disease
AAT Protein Processing

Synthesis Synthesis

Secretion Secretion

Degradation Degradation

Proteasomal and autophagic degradative pathways may govern hepatic risk

Human ZZ Liver

PAS + intracellular inclusions are polymerized AAT ‘Z’

Highly Variable Hepatic Risk

- Risk of life threatening liver disease in childhood is about 5%
- 2nd most common reason for liver transplant
- Risk of any liver disease or dysfunction in childhood is 15-50% (depends on testing)
- The majority of ZZ infants with problems at birth are well by age 18y.
- Significant, but possibly silent liver disease in older adults likely over 50%

Eriksson, 1985 and 1987
Treatment

- There are no specific treatments to prevent alpha-1 liver damage.
- There are effective treatments used for liver disease in general.
- Liver transplantation: trading one disease for another?
- Augmentation therapy has no effect on liver disease.

Liver Management

- Avoid or limit alcohol: Controversially means less than one drink per day.
- Avoid obesity (fatty liver disease).
- Occasional Tylenol in ordinary doses.
- NSAIDS may have potential to increase hepatic injury. (experimental data)
- Consider hepatitis vaccination

Pearls

- Liver biopsy not required for diagnosis.
- Patients with cirrhosis may remain stable without transplantation for 10y or more.
- The majority of ZZ children will do well with minimal intervention.
- Genetic and environmental disease modifiers are likely important, but poorly understood.
- Typical liver disease supportive care or transplant are the only recommended therapies at this time.
Time to Test

Who Should Be Tested?

- All subjects with COPD or unexplained bronchiectasis regardless of smoking Hx
- All adults with asthma characterized by incompletely reversible airflow
- Subjects with unexplained chronic liver disease
- Necrotizing panniculitis (1 in 1000 ZZ)
- Anti-proteinase 3-positive vasculitis (C-ANCA-positive vasculitis)
  - 5.6 to 17.6% of c-ANCA+ individuals are ZZ

ATS/ERS AATD Standards, 2003

Lab Testing

- Serum blood test that measures the concentration of circulating AAT- “levels”
  - An acute phase reactant
  - Heterozygous/normal overlap but
  - Not between ZZ and normal levels
- "Phenotyping" or Pi-typing of the protein
  - Determine whether the patient is a carrier of the deficiency or homozygous
  - Done by isoelectric focus gel analysis
- Genotyping
  - DNA testing that determines the Pi genes from extracted DNA

Stoller and Brantly, 2013
Testing via Finger Stick

- Testing for AAT levels and genotype via a single finger-stick of blood
- Can be mailed into a central lab

So you found an Alpha.

Now What ?!?!?

Treatment Options

- Standard Therapies in COPD Treatment
  - Smoking cessation
  - Pulmonary Rehab
  - Bronchodilators (rescue/LABA)
  - Inhaled steroids
  - Oxygen
  - Lung transplant
- Management/Evaluation of Liver disease
- Augmentation Therapy
Augmentation Therapy

- Augmentation therapy is used to increase serum and lung epithelial lining fluid (ELF) levels of AAT
- Plasma derived treatment for adults with AATD and emphysema

Augmentation Therapy

- Augmentation therapy was first approved 25 years ago.
- Four approved drugs – Aralast, Glassia, Prolastin, Zemaira
- Original approval based on pharmacokinetic and biochemical data.
- Subsequent approval same criteria.
- None based on therapeutic efficacy.
Why Augmentation Therapy?

Importance of Weekly Dosing

Does Augmentation Clinically Work?
US NHLBI Registry ‘87-95

- Prospective, non-controlled, non-randomized
- Comparison of lung function and mortality in treated versus untreated patients
- Inclusion criteria - AAT level ≤ 11μM
- n : 277 treated vs 650 untreated

NIH-AATD Registry Group, 1998

Mean FEV1 Decline

NHLBI Registry - Mortality
Lung Function

- Number of patients
  - n=295; 97 control, 198 treated

- Main findings
  - Decline in lung function in treated group was lower (FEV1 = 53 vs 75 mL/yr, p = 0.02)
  - Effect best seen with FEV1 = 31 - 65% predicted

Danish Study Group

- Double-blind, randomized, prospective multicenter study (N=56 ex-smokers)
- Comparison of 250 mg/ kg monthly for at least 3 years in patients with Pi*Z.
- Endpoints – PFT and CT densitometry
- No significant difference in decline of lung function expressed in FEV1 per year between both arms

Changes in Lung CT Density

[Graph showing changes in lung CT density over years for Placebo and Active groups]
Canadian Registry 2005

- Patients receiving Alpha-1 vs untreated matched control patients
- N: 21 patients receiving Alpha-1, 42 controls
- Median observation was 5.6 years.
- Median duration of augmentation was 4.4 years.

Chapman et al, 2005

Canadian Registry

Meta Analysis - AATD

- 5 studies with a total of 1509 patients
  - 4 non-randomized trials
  - 1 randomized trial
- Results
  - FEV₁ decline was slower by 23% with augmentation therapy
  - Mainly with FEV₁ 30%-65% of predicted benefited (those with fastest decline)
  - CT densitometry may be a more sensitive measurement of emphysema and its progression.

Chapman et al, 2009
The RAPID Trial – Newly Reported
Presented at the 2013 ATS International Conference

- Placebo controlled – 2 year CT densitometry follow-up
  - Zemaia (60 mg/Kg)
  - Placebo group crossed over to Rx – followed + 2 years.
- Prespecified (in 2003) primary end point of combined CT densitometry score at TLC and FRC was not significantly different (p=0.027) between treated and placebo.
- CT densitometry at TLC was significantly different (p=0.007)
- None of the other secondary endpoints were different between groups (FEV1, exacerbations, quality of life)
- Placebo patients crossed over to treatment and followed for an additional 2 years showed slowing of decline in CT densitometry at TLC
- N.B.: significance is p of 0.025 or better because this was analyzed as a one-sided test

The RAPID Trial
Presented at the 2013 ATS International Conference

Summary

- Alpha-1 Antitrypsin Deficiency is more common than previously taught and still perceived.
- It causes more than just emphysema.
- Testing for Alpha-1 is quick and easy.
- Augmentation therapy is available and effective.
Sometimes “Generic” COPD is actually “Genetic” COPD

Nota Bene

Thank You!

Questions please