Alpha-1 Antitrypsin Deficiency

Irish Thoracic Society

Alpha-1 antitrypsin

- 52kDa glycosylated protein
- Synthesized (>95%) primarily in the liver
- Also produced by some immune cells such as macrophages, monocytes,
- Archetypal serine protease inhibitor (SERPIN)
- Key anti-inflammatory and immunomodulatory protein
- Regulates the effects of numerous inflammatory cytokines, including IL-8 and TNF-α

Alpha-1 antitrypsin deficiency

- Autosomal co-dominant genetic disease
- In most cases, pathology is due to protein misfolding, rather than insufficient protein production
- Misfolded protein fails to escape the endoplasmic reticulum of hepatocytes, polymerizes and accumulates in the liver, leading to a gain-of-function inflammatory burden
- Since the AAT produced by the liver does not reach the circulation, this also results in a loss-of-function absence of the AAT protective screen at the lung
- Although any misfolded AAT that manages to escape the liver does retain some antiprotease and anti-inflammatory properties, it is generally less effective than correctly-folded protein

Genetics

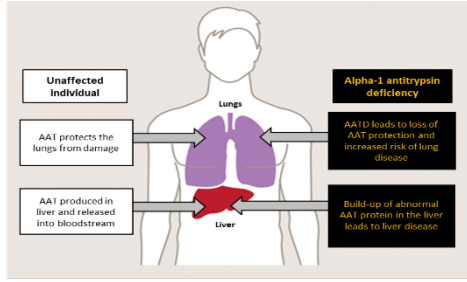
- *SERPINA1* gene on chromosome 14 encodes AAT
- Individuals with two copies of the wild-type M allele (Pi*MM, or simply "MM") have normal circulating levels of the protein
- Key pathological mutation is a single amino acid substitution (Glu342Lys) in *SERPINA1*, which leads to production of misfolded Z-type AAT
- Over 95% of severe AATD (both in terms of circulating AAT levels and severity of disease) is due to homozygosity for the Z allele (Pi*ZZ, or "ZZ")
- Approximately 1 in 25 people of European descent carry a Z allele
- AATD is an autosomal co-dominant disorder, meaning that each allele contributes to the phenotype
- Numerous other *SERPINA1* mutations exist (S, F, I, Pittsburgh, Bolton, etc) which are generally less severe clinically than Z
- Persons with one Z allele and one M allele (Pi*MZ) have an intermediate deficiency of the protein
  - This is the most common form of AATD in Europe
- Those who have a Z allele combined with a less severe mutated allele are known as compound heterozygotes
- Mutations that lead to a complete absence of AAT protein are termed "null" mutations

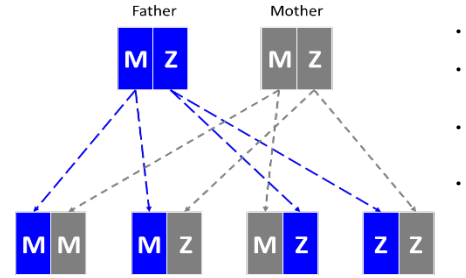
Clinical presentation

- Classic presentation in children is neonatal jaundice
  - AATD is one of the most common indications for neonatal liver transplant, which is essentially curative
- Typical presentation in adults involves early onset bilateral panacinar emphysema with a basal predominance in an individual with a modest smoking history and a family history of COPD
- However, these factors are not always present, and in many cases AATD-associated emphysema may be radiologically indistinguishable from nonhereditary emphysema
- Spirometry shows obstructive pattern, decreased DLCO
- Extrapulmonary manifestations include cirrhosis, HCC, panniculitis, and serositis
- Also associated with AAA, gallstones, and, in Pi*MZs, NAFLD and ANCA-positive vasculitis

Protease-antiprotease hypothesis

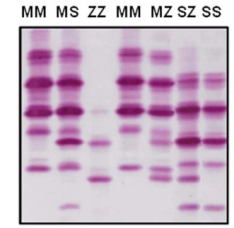
- In broad terms, inspiration is an active process (muscles do work), whereas expiration is a passive process, governed by the elastic recoil of the lungs and chest wall
- Elastin gives the lungs their elastic quality
- Elastin is broken down and degraded by NE, an omnivorous protease released by activated or disintegrating neutrophils in response to pulmonary infection or acute airway inflammation
- AAT serves as the regulator of NE
- In AATD, airway NE activity goes unchecked, with subsequent loss of lung tissue and development of early-onset emphysema
- This risk is amplified in smokers, since cigarette smoke inactivates AAT via oxidation of methionine residues
- Pathogenesis of AATD-associated COPD not fully explained by protease-antiprotease theory however – there are substantial contributions from inflammation and recurrent exacerbations





Who should be tested for AATD?

- Despite being the only recognised genetic cause of COPD, AATD is habitually underdiagnosed
- Average time from first presentation to diagnosis in the absence of targeted screening programmes is 7 years
- WHO recommends targeted screening in any patient with:
  - COPD
  - Non-responsive asthma
  - Cryptogenic liver disease
  - First degree relative with AATD
  - Panniculitis



Screening and diagnosis

- Serum AAT level can be a useful screening test for Pi*ZZ
  - However, this approach is less sensitive for milder forms of AATD
  - Furthermore, since AAT is an acute-phase protein, it s production will increase during infection, illness or physiological stress
  - Therefore, AAT levels should only be sent for patients who are at clinical baseline
- Diagnosis is by immunofixation of serum glycoforms via isoelectric focusing gel electrophoresis (phenotyping, see above) or by genotyping
- In cases where AAT protein phenotyping provides an equivocal result, or where a rare mutation is suspected, confirmatory genotyping should be sought.

Risk of developing COPD

- Pi*ZZ patients at significantly increased risk of developing severe lung disease as early as the 4th and 5th decades of life
  - This risk is much higher in smokers
- Risk of lung disease is 5-10 times higher in Pi*MZ patients who smoke compared to Pi*MM patients who smoke
  - *No increased risk of lung disease in Pi*MZs who don't smoke* N.B.
- Similarly, Pi*SZ patients who don't smoke, or who quit smoking before they develop obstructive spirometry, are not at increased risk

Management

- Most effective and important intervention is smoking cessation
- For AATD patients with lung disease, pharmacological management and indication for vaccinations is the same as for Pi*MM COPD
- In those requiring transplant, particular attention to liver status, and vigilance for post-operative serositis, is recommended
- Only disease-specific treatment is augmentation therapy with AAT purified from the plasma of Pi*MM donors
  - Typically given IV once per week at a dose of 60mg/kg
  - Shown to slow progression of emphysema as measured by CT lung density
  - Group most likely to benefit have FEV1 30-49% pred
  - Definitive effect on mortality not yet shown

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