Alpha-1-antitrypsin deficiency and liver disease
Pediatric aspects

Antal Németh
Frösundavik, 141108
Disposition

- Why just Sweden?
- Alarming reports
- Facts about Z-protein
- Theories about pathogenesis of liver disease
- Therapeutic options
- Own experience
- Examples of varying course
- Conclusions
Why Sweden?
Why just report from Sweden?

- Scandinavian mutation
- Swedish original finding
- Swedish health care organisation

→ The whole spectrum visible
## Frequency of PiZ allele around the Baltic Sea

<table>
<thead>
<tr>
<th>Country</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>0.030-0.032</td>
</tr>
<tr>
<td>Lithuania</td>
<td>0.008-0.012</td>
</tr>
<tr>
<td>Latvia</td>
<td>0.035-0.045</td>
</tr>
<tr>
<td>Estonia</td>
<td>0.021-0.025</td>
</tr>
<tr>
<td>Finns</td>
<td>0.000 (?)</td>
</tr>
<tr>
<td>Russians</td>
<td>0.004</td>
</tr>
<tr>
<td>Poles</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Beckman, Hum Hered 1999;49:52-5
Citation classics


Sveger, 1976

- **# screened: 200,000**
- # Pi ZZ: 120
- # Pi SZ: 48
- # Pi Z-: 2
- # Pi S-: 1

- Neonatal cholestasis: 10% of PiZZ
Alarming reports
# of patients: 98

Follow-up time: 1 mo – 27 yrs (mean 5.3 yrs)

Age at diagnosis: 5 days – 16 yrs
Ibarguen, 1990

**Symptoms and signs:**
- Cholestasis
- Hepatomegaly
- Splenomegaly
- Failure to thrive
- G.I. bleeding
- Ascites
- Vomiting
- Lethargy/irritability
- Diarrhoea
Ibarguen, 1990

Renal involvement: 15/98

Pulmonary involvement: 16/98
Larsson C, 1978

- 246 PiZZ persons > 20 y.o.a
  - 184 COPD
  - 29 cirrhosis (1/29 "neonatal hepatitis")
    - 27/29 > 50 y.o.a.
    - 3/29 ethanol abusers
    - 8/29 HCC

However: 208/246 persons recruited among hospital patients
Eriksson S et al, NEJM, 1986

- AATD-dead adults in Malmö (1963-82): 19
- Post-mortem: 17
- Cirrhosis: 8/17
- Age at death: 59.2
- HCC: 5/17
Facts about Z-protein
Z-protein

- Single amino-acid substitution (glu → lys)
- Loop-sheath polymerisation
- Sequestration in hepatocytes
- Multiple tissues express AAT (in transgenic mice)
- *Lomas et al, Cambridge → London*
Z-protein

- Is cleared intracellularly by autophagy and proteosomal activity
- Stimulates apoptosis $\rightarrow$ # of ATZ +ve cells diminishes during life
- *Perlmutter, San Louise $\rightarrow$ Pittsburgh*
Starvation signal → Induction → Formation → Docking and fusion → Autophagosome → Breakdown and recycling → Autophagic body → Vacuole

Plasma membrane

Kliensky, 2000
Theories about pathogenesis
Theory # 1

• Liver disease: "gain of function"

• Pulmonary disease: "loss of function"
Theory # 2

- One particular SNP as genetic modifier

Theory # 3

- Infantile type
- Childhood type
- Adolescent type
- Adult-onset type
- > 50% develop liver disease during lifetime

Silverman et al, J Pediatrics, 2013
Therapeutic possibilities
Therapeutic options

- Enhanced ATZ clearance
  
  CBZ, phenotiazines, 4-phenylbutyric acid

- Prevention of polymerisation

- Antisense Rx (mRNA-inhibition)

- Gene Rx

- Hepatocellular Tx

Primary end-point: # of ATZ-cells (?)
• All 89 PiZZ + 40 PiSZ had normal but higher LFT than the controls

• AST even higher (but normal) in PiZZ women on contraceptives, compared to controls
Long-term course of the "Sveger-kids" (PiZ only)

- Dead: 5/127

- 16 yrs: abnormal ALAT 15/81, GT: 7/77

- 18 yrs: abnormal ALAT: 10/82, GT: 7/77

- 30 yrs: abnormal ALAT: 0/89, GT: 0/89
The Stockholm experience
35 years of pediatric AATD at Karolinska- Huddinge

154
(98 boys)

ZZ: 137
86 boys

SZ: 15
10 boys

FZ: 2
2 boys
PiZZ at Karolinska-Huddinge

ZZ
137

Neonatal C.S.: 51
   Alive & well 37
   Cirrhosis 14
   Cirrhosis 3

Other symptoms 34
   Alive & well 31

Accidental / kinship 52
   Alive & well 52
AATD at Huddinge Hospital

SZ: 15

Neonatal: 1
C.S.

Healthy: 14

Alive and well: 15

FZ: 2

Alive and well: 2
AATD at Karolinska University Hospital-Huddinge

17 infants/children with cirrhosis

Onset of symptoms: < 1 yr: 17/17
Evident neonatal cholestasis: 14/17
Age at evident cirrhosis: 3.2 yrs (0.3-14)
BA-like course and cirrhosis: 5/17
(BA-like course, totally: 6 → 1 healthy/5 cirrhosis)

Outcome: - 8 dead without OLT
(0.75-18 yrs, mean 4.2, median 3)
- 9 OLT
3/9 dead after OLT
<table>
<thead>
<tr>
<th>AATD &amp; OLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted: 9</td>
</tr>
<tr>
<td>On waiting list: 0</td>
</tr>
<tr>
<td>Neonatal cholestasis: 9/9</td>
</tr>
<tr>
<td>Age at decision: 7 months – 23 yrs</td>
</tr>
<tr>
<td>Dead after OLT: 3</td>
</tr>
<tr>
<td>Cause of death: aortic rupture, sudden death (2)</td>
</tr>
</tbody>
</table>
Unexpected OLT-related complications

2 intraoperative sudden deaths (cardiac arrest)

2 postoperative aortic ruptures (1 lethal)
# AATD and other diseases

- **CMV / ECHO**: 4  →  1 cirrhosis *
- **Diabetes**: 1  →  0 cirrhosis
- **Ulcerative colitits**: 1  →  0 cirrhosis
- **Pancreatitis**: 1  →  0 cirrhosis
- **Celiac disease**: 1  →  0 cirrhosis
- **Trisomy 21**: 1  →  0 cirrhosis
Varying clinical course
Family XY

MZ Healthy

ZZ

ZZ

ZZ

ZZ Dead, HCC
Index pt: Jessica

- 8 m.o.a: Celiac ? → PiZZ + cirrhosis
- (0-8 m: failure to thrive: covert cholestasis ?)
- 1.5 y.o.a: liver failure → death
Sarah, 12 y.o.a.

- Healthy, PiZZ
- Platelets: 100
- Histology: fibrosis ++/4
- → portal hypertension ??
Sarah, 42 y.o.a.

- Healthy
- LFT normal
- Platelet count normal
- 3 healthy heterozygous children
Yasmin, 10 y.o.a

- Healthy
- LFT: normal
- Liver histology normal
- Untreated, undiagnosed CD!
- Enterocytes: PiZ-sequesters *
- Glutenfree: 10-17 y.o.a., 25 →

See: Carlson J, 1978
Yasmin, 40 y.o.a.

- LFT normal
- Early COPD (non-smoker)
- Glutenfree diet
- 2 healthy heterozygous children
Family P.

- **Robert P:** BA-like course, dead at 9 m.o.a

- **Jenny P:** 0-6 m.o.a: pale stools
  2 y.o.a.: cirrhosis
  2-23 y.o.a: compensated cirrhosis
  polycystic ovary syndrome
  23 y.o.a : OLT (PiMM)
  40 y.o.a: healthy mother of 1 child
Jenny B

- 0-4 y.o.a: follow-up because of neonatal ch.st
- 4 y.o.a: ”healthy”
- 14 y.o.a: acute hepatitis ? → decompensated cirrhosis
- 14-21: compensated cirrhosis + anorhexia
- 21: OLT (Pi MM)
- 22: aortic rupture
- 40: healthy mother of 2
Renal function before and after OLT in one girl with AATD

Time from OLT, years

OLT
Jenny, GFR post-OLT

- + 2 yrs (post OLT): 40
- + 3 yrs: 25
- + 4 yrs (pregnant): 55
- + 10 yrs: 65
- + 20 yrs: 39

→ Avoid CNI!
<table>
<thead>
<tr>
<th>Neonatal cholestasis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>• Congenital CMV</td>
<td>• Congenital CMV</td>
</tr>
<tr>
<td>• 4 y.o.a: fibrosis $\frac{3}{4}$</td>
<td>• 2 y.o.a: cirrhosis</td>
</tr>
<tr>
<td>• Platelet count: 100</td>
<td>• 2-16: compensated</td>
</tr>
<tr>
<td>• 22 y.o.a: healthy (smoker)</td>
<td>• 16: OLT (PiMM)</td>
</tr>
<tr>
<td></td>
<td>• 24: healthy</td>
</tr>
</tbody>
</table>
Leo & Isak, monozygous twins

- Neonatal cholestasis
- Pale but bilous stool
- 6 m: cirrhosis
- 8 mo: failure
- 8.5 mo: OLT (PiMZ)
- 4 yoa: healthy

- Neonatal cholestasis
- Pale but bilous stool
- 6mo: cirrhosis
- 10 mo: failure
- 11 mo: OLT (PiMM)
- 4 yoa: healthy
Conclusions
Conclusions # 1

In the biased group of our tertiary referral ct:

- 35% of all PiZ had neonatal cholestasis
- 30 % of these developed cirrhosis
- 12% of all Pi Z developed cirrhosis
- All had cirrhosis at 4 y.o.a.
Conclusions - 2

• The early figures of Sveger are still holding
• Early clinical development is decisive for the long-range prognosis
• Late-onset cases are probably unrecognised early-onset ones
• Other possible risk-factors do not necessarily influence the natural course
• The phenotypic modifiers are not yet found
Conclusions - 3

• At the age of 4 years it is possible to give a very accurate prognosis
• Careful and frequent F/U during the first 4 years gives reliable prognosis → saves QOL and even money
• Risk of renal involvement has been overestimated
Conclusions - 4

• Only big multicenter studies with careful inclusion of children > 1 y.o.a can give reliable answers on therapeutic trials
• The problem of adult-onset liver disease in AATD might be overestimated
• Pediatric course does not predict risk of malignancy
  ( ? ATZ +ve vs ATZ – ve hepatocytes ? )
• No proper primary end-points have been found for therapeutic trials
Which is the bad guy?
Good or bad guy?
Dutch famine catastrophe

- Nov 1944 - 9 maj 1945
- 25% av landets befolkning
- Jan – maj < 1000 kcal/d per vuxen
- Prospektiv uppföljning av alla som var -0.75 → + 2-3 år gamla under svälten
- Google: 18 100 000 miljoner träffar (130906)
Personalized medicine = the future!

- Personalized medicine is:
- New generation sequencing
- Epigenetics
- "The art of medicine"
Epigenetics is:

- **DNA methylation** *(methylome)*
  - methylation hot-spots at CpG islands
  - the more methylation, the less mRNA *(transcriptome)*
- **Histone modification**
- **miRNA**
Something completely different!

- Liver-cell tx of AATD ZZ patients after Lung-Tx ???