Alpha-1 Antitrypsin Deficiency and Hepatic Transplantation

Kunskap är vår medicin

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A1AT and hepatic Tx

• what do we know?
• what don’t know?
• what can we know more?
• what can we do more?
50 years ago…

• Laurell C-B, Eriksson S
  "The electrophoretic alpha-1 globulin pattern of serum in alpha-1 antitrypsin deficiency”

• Starzl TE et al
  "Homotransplantation of the liver in humans”
  Surg Gynecol Obstet 1963;117:659-676
Liver transplantation in A1AT patients - results

- 1% of all adult liver transplants
- 4% of pediatric liver transplants
- Patient survival: 1 yr 3 yr 5 yr 10yr
  90% 88% 85% 78%
Alpha-1 Antitrypsin deficiency

✓ rare indication for liver TX (1%)
✓ neonatal hepatitis/cholestasis in 10% of ZZ (2-3% cirrhosis); jaundice
✓ in adults; 30-40% of ZZ develop cirrhosis usually in their 50’s; portal hypertension and lung disease
✓ risk of liver cancer increased x20
✓ liver transplantation normalize A1AT levels
More Knowledge needed

• we need to better study lung function before and after liver transplantation to find answers on what a normalized level of A1AT means for lung function in A1AT ZZ patients

• hepatic transplantation before cirrhosis or combine lungs/liver Tx needed?
# A1AT phenotypes

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<tr>
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<th>Pi MM</th>
<th>Pi MZ</th>
<th>Pi SS</th>
<th>Pi SZ</th>
<th>Pi ZZ</th>
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<tr>
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<td>Values</td>
<td>20-48</td>
<td>17-33</td>
<td>15-33</td>
<td>8-16</td>
<td>2,5-7</td>
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<td>150-350</td>
<td>90-210</td>
<td>100-200</td>
<td>75-120</td>
<td>20-45</td>
<td>0 mg/dl</td>
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## Etiology of Cirrhosis in Patients With Splenic Artery Aneurysm Rupture

<table>
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<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Percent of Total</th>
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<tbody>
<tr>
<td>Alpha-1 AT deficiency</td>
<td>7</td>
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<tr>
<td>Cholestatic liver disease (PBC/PSC)</td>
<td>4</td>
<td>24</td>
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<td>ETOH cirrhosis</td>
<td>2</td>
<td>11</td>
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<td>Autoimmune hepatitis</td>
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<td>Cryptogenic</td>
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<td>HCV</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Hemochromatosis</td>
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</tbody>
</table>

Splenic artery aneurysm

65 % mortality risk after rupture

Treatment:
- Expectation
- Embolization
- Ligation
- Splenectomy

No consensus
Liver transplantation for A1AT at Karolinska University Hospital

• 17 patients transplanted between
  – 7 children with AAT
    Sex 4M/3F, mean age 6.7±6.5, median 5.0 (range 0.65 – 17)
  – 6 adults with AAT
    Sex 3M/3F, mean age 45.1±19.2, median 49.3 (range 20.7 – 66.7)
  – 4 adults with incidental AAT diagnosis: sex 3M/1F, mean age 48.8±20.0, median 56.7 (range 19.4 – 62.5)
    • indications for Ltx: Alcoholic cirrhosis (1)
      NASH (1)
      HCV (1)
      AIH (1)
Outcome of Liver transplantation for α1–anti trypsin deficiency. A Nordic multicenter study.

More knowledge we get more effective medicine we have!

• we need to study lung function before and after liver transplantation to find answers on what a normalized level of A1AT means for lung function in A1AT ZZ patients

• liver transplantation before cirrhosis?
Alpha-1 Antitrypsin deficiency

✓ lung function/FEV1 after LTx: -45% - +77% (all patients are followed?)
✓ even if pulmonary functions decline, progression to end-stage lung disease is rare
✓ pulmonary function before and after LTx should be assessed by appropriate phenotyping rather than deficiency characterization
✓ development of lung cancer / smoking
Preoperative evaluation (1)

- demographic information on the recipient: sex, age, BMI, date of A1AT diagnosis, date of Tx, comorbidity (patients identification)
- donor characteristic: age, BMI, CIT,
- liver function tests: bilirubin, PK INR, GT, AST/ALT
  - only standard liver tests (*Pfermenges DC, 2013*) and A1AT levels (*Carey EJ, 2013*) are prognostic for liver disease due to A1AT
- presence of HCC
- MELD/PELD
Preoperative evaluation(2)

- pulmonary function tests/spirometry: TLC, FVC, FEV1, DLCO; and levels of A1AT
- incidence of splenic artery aneurysm; preTx DT angio?
- exclude combine lung-liver Tx
- information about lifestyle? smoking, alcohol, others?
- recipient phenotype MZ, SZ, ZZ
Postoperative evaluation (1)

- spirometry? how many do we have? should we call in all the patients now for new evaluation? use the last available?
- levels of A1AT, all available? last one or new evaluation right now?
- any use of lung rtg/CT
- need for control group?
Postoperative evaluation (2)

- patient/graft survival
- immunosuppression
- episodes of rejection/treatment and chronic kidney disease
- yearly liver blood tests or the last available?
statistics

✓ descriptive analyses: means/SD
✓ continuous variables: t-test
✓ categorical variables: chi-square test and Fisher’s exact test
✓ survival after LTx: Kaplan-Meyer analyses
Incidental A1AT liver graft

- heterozygous
- posttransplant cryptogen hepatit
- liver tests abnormality 6yrs after LTx
- 10 years liver biopsi with characteristic cytoplasmic inclusions
- should all patients with chronic hepatitis be tested?

Lee SM et al; 2012
additional groups?

• do we have heterozygous donors? outcome?
  (Stkhlm 3 donors to recipients with HCV, PSC, HCV/HCC); if "0" biopsy with suspicions of A1AT, should we genotype the donor? what information should we give to the recipient? should we check A1AT? recommendations t.ex. don’t smoke, etc?

• screening for noncirrhotic HCC?

• incidental A1AT with other indications (Stkhlm 4 pat.); have they been genotyped? should they? check A1AT levels?
Time schedule

2014
• end of Nov: protocol for discussion send to Helena, Allan, Gustaf and Tim

2015
• end of Jan: final protocol and participants / PhD student
• end of March: data collection
• end of June: results in abstract form
• October/next NTLG meeting: presentation of results and submission of results in manuscript form + Nordic recomendations
On-going research

✓ immunomodulation
✓ role of A1AT in acute liver failure
✓ role of hepatocytes Tx
✓ ....
Prevalence of the PiMZ heterozygous state in patients with chronic liver diseases

From: Does the Heterozygous State of Alpha-1 Antitrypsin Deficiency Have a Role in Chronic Liver Diseases? Interim Results of a Large Case-Control Study. Regev A, et al. Manuscript
Hepatocytes Tx in A1AT

- non-cirrhotic patients
- in lung Tx patients (already on immunosuppression; anti-inflammatory effect/levels LTR-B4, IL-8)
- waiting list
- procedure: low risk, full postsurgical monitoring, repeated
- referral system / internal costs
Liver Cell Transplantation
Minimally Invasive Therapy for potentially Life-Threatening Diseases

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A1AT and hepatic Tx

- what do we know?

Liver transplantation is well accepted treatment for patients with cirrhosis; with good patient survival and restoration of A1AT levels.
A1AT and hepatic Tx

• what don’t know?

What is the effect of liver transplantation on lung function?
A1AT and hepatic Tx

• what can we know more?
Check incidence of
  1’ vascular complications
  2’ coexisting A1AT with other types of hepatitis.
A1AT and hepatic Tx

• what can we do more?

Hepatocytes Tx is an alternative to LTx in noncirrhotic patients.