Liver Disease in ADPKD

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Liver Disease in ADPKD

Saturday, June 23rd

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Mayo Clinic College of Medicine

www.pkdcure.org
Outline

• Historical
• Natural History
• How do you get liver cysts
• Symptoms
• Medical management
• Surgical management
• New treatments
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD</td>
<td>PKD1</td>
<td>16p13.3</td>
<td>Polycystin 1</td>
<td>Membrane receptor</td>
</tr>
<tr>
<td></td>
<td>PKD2</td>
<td>4q21-23</td>
<td>Polycystin 2</td>
<td>Calcium channel</td>
</tr>
<tr>
<td>ADPLLD</td>
<td>PLD1</td>
<td>19 p13.2</td>
<td>Glucosidase II</td>
<td>ER protein</td>
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<td></td>
<td>PLD2</td>
<td>6</td>
<td>SEC63</td>
<td>ER protein</td>
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</tbody>
</table>
Cystogenesis in ADPKD/ADPLD

- Normal
- PLD

Intralobular ductule
Interlobular duct
Area duct
Segment duct
Right hepatic duct
Common hepatic duct
Common bile duct

www.pkdcure.org
51yo (59kg) With ADPKD With A 9.1-kg Liver Underwent Liver Transplant

Wall WJ. NEJM 2007
Prevalence of Liver Cysts in ADPKD

General Population

ADPKD

Scintiscanning (n=158)
Ultrasonography (n=483)
Computed tomography (n=83)

www.pkdcure.org

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- Prevalence of liver cysts in early ADPKD
- Is liver cyst volume related to kidney cyst and kidney volume?
- Compared liver and kidney cyst volumes (compared with age, gender)
- Quantitative MRI scans: 3mm slices

Coronal T2-weighted MRI from four different patients with variable severity of hepatic and renal cysts

24yo man liver cysts 6.3ml renal cysts (15.4 ml).

46yo man mild hepatic cyst 9.3 ml severe renal cysts 1940 ml.

44yo man hepatic cysts(318.7 ml) but mild renal cyst burden (37.6 ml).

30yo woman hepatic cysts (2368.8 ml) and renal cysts (1084.5 ml).

Relationship Between Liver Cyst Volume And Age In Women And Men

### Correlation Coefficients Between Liver Cyst Volume And Kidney Cyst Volumes

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Group (Yr)</th>
<th>Renal Volume</th>
<th>Renal Cyst Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Correlation</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>All</td>
<td>0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Men</td>
<td>All</td>
<td>0.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Both</td>
<td>≤24</td>
<td>0.01</td>
<td>0.96</td>
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<tr>
<td></td>
<td>25 to 34</td>
<td>0.10</td>
<td>0.42</td>
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<tr>
<td></td>
<td>≥35</td>
<td>0.03</td>
<td>0.75</td>
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<tr>
<td>Women</td>
<td>≤24</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>25 to 34</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>0.15</td>
<td>0.25</td>
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<tr>
<td>Men</td>
<td>≤24</td>
<td>0.01</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>25 to 34</td>
<td>0.34</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>−0.04</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*aCorrelations were computed using log transformation for all volumes.*
Symptomatic Polycystic Liver Disease (1)

**Mass Effect (by dominant cyst or massive PLD)**

- Abdominal distension/pain
- Early satiety, heartburn, emesis
- Malnutrition, loss of muscle/fat
- Dyspnea, orthopnea
- Change in bowel pattern, hemorrhoids
- Back pain
- Hernias, uterine prolapse, rib fractures
- Venous obstruction (hepatic, IVC, porta)
- Bile duct obstruction
Symptomatic Polycystic Liver Disease

Complications
- Hemorrhage
- Rupture
- Infection

Rare Associations
- Bile duct dilatation
- Congenital hepatic fibrosis
- Cholangiocarcinoma
Liver Cyst Infection

• Risk Factors
  – Recent abdominal surgery
  – Kidney Transplant
  – Chronic dialysis

• Symptoms
  – Fever + new onset RUQ pain
  – Leukocytosis ↑ESR
  – ↑ ALP
  – Bacteremia
  – Cultures of undrained cyst fluid +ve
Liver Cyst Infection

CT- Anatomic resolution
  – Gas bubbles in cysts
  – Changes in cyst walls; nodularity, thickening, indistinct margins, contour enhancement of the cyst wall,
  – calcification
  – dominant cyst showing enlargement on serial exam

MRI- most sensitive

$^{111}$In

PET Scan:

C. Bleeker-Rovers. 41 (6).2003. AJKD.
Symptomatic Polycystic Liver Disease
Nonsurgical Treatment Options

• Avoid estrogens, caffeine
• $H_2$-blocker or $H^+\!/K^+$ ATPase inhibitor
• Long-acting octreotide (?)
Symptomatic Polycystic Liver Disease
Surgical Treatment Options

- Percutaneous aspiration/sclerosis
- Fenestration (laparoscopic or open)
- Hepatic resection/fenestration
- Liver transplantation
Symptomatic Polycystic Liver Disease
Autosomal Dominant Polycystic Liver Disease: Alcohol Sclerosis of Liver Cysts

Success rate
Primary: 69%
Secondary: 23%
Failure: 8%

Complications:
Major: None
Minor: Transient pain
Autosomal Dominant Polycystic Liver Disease
Laparoscopic Fenestration For Polycystic Liver

INTRAOPERATIVE COMPLICATIONS
- Hypothermia
- Hypercapnia

POSTOPERATIVE COMPLICATIONS
- Transient ascites (46%)

SYMPTOMATIC RELIEF
- 85%

RECURRENCE of SYMPTOMS
- 73%
  - Useful for few large cysts

Kabbej Brit J Surgery 83:1697, 1996
Massive Polycystic Liver Disease

- Focal (preserved liver segments in >80% of patients)
- Parenchymal volume constant

Everson et al: Hepatology 8:1627, 1988
Resection-Fenestration for Polycystic Liver Disease
Distribution of Segmental Resection

Segments

%
Massive Polycystic Liver Disease

Combined Resection-Fenestration

- Liver volume
  - Preop: 9,357 mL
  - Postop: 3,567 mL

- Mortality
  - 3%

- Complications
  - Transient pleural effusion: 37%
  - Transient ascites: 23%
  - Hemorrhage: 13%
  - Infection: 7%
  - Transient biliary leak: 7%

- Sustained relief
  - 90%
Massive Polycystic Liver Disease
Combined Resection-Fenestration
Liver transplantation for Massive Polycystic Liver Disease
Model for End-Stage Liver Disease (MELD)

Numerical system that ranks (from 6 to 40) patients waiting for a liver based on three lab test results:

• Bilirubin (how effectively the liver excretes bile)
• INR (prothrombin time, ability to clot blood)
• Creatinine (kidney function)
Symptomatic Polycystic Liver Disease
Alternative Treatment Options

- Hepatic artery embolization
- Endovascular stent
- Transjugular intrahepatic portosystemic shunt (TIPS)
- La Veen shunt
POLYCYSTIC LIVER DISEASE
STENTING for INFERIOR VENA CAVA OBSTRUCTION
Severe Polycystic Liver Disease
Hepatic artery embolization

Ubara. AJKD 43: 733, 2004
Severe Polycystic Liver Disease

Hepatic artery embolization

Pre

Post (2 years)

Ubara. AJKD 43: 733, 2004
Hepatic Venous Outflow Tract Obstruction
Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

- Avoid estrogens, caffeine
- H2-blocker or H+/K+ ATPase inhibitor
- Long-acting octreotide (?)
Long-acting Octreotide Trials

Randomized, placebo-controlled, cross-over design, n=12

Ongoing phase III, placebo-controlled clinical trial, n=66

Ruggenenti, Kidney Int, 68:206, 2005
cAMP in Isolated Bile Duct Units

Masyuk TV. Gastroenterology. 2007.

www.pkdcure.org
Twice a day, daily, at 12 hours interval, intra-peritoneally

**10 mg/kg b.w**

- **Group I**: 4 wks
- **Group II**: 8 wks
- **Group III**: 12 wks
- **Group IV**: 16 wks

**100 mg/kg b.w**

- **H**: 4 wks

PCK rats, n = 12
Age - 3 weeks

PCK rats, n = 48
Age - 3 weeks

Masyuk TV. Gastroenterology. 2007.
Octreotide In PCK Rats: cAMP Levels

Masyuk TV. Gastroenterology. 2007.
Octreotide In PCK Rats: Cyst Volumes

Masyuk TV. Gastroenterology. 2007.
Saline Control

<table>
<thead>
<tr>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
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Octreotide Treated

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<th>16 weeks</th>
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10 mg

Masyuk TV. Gastroenterology. 2007.
Saline Control

Octreotide Treated

<table>
<thead>
<tr>
<th></th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
<th>4 weeks</th>
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<tbody>
<tr>
<td>10μg</td>
<td></td>
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</tbody>
</table>

Masyuk TV. Gastroenterology. 2007.
Octreotide in PCK Rats: Fibrosis

Masyuk TV. Gastroenterology. 2007.
Pilot Study of Long-Acting Octreotide (Octreotide LAR® Depot) in the Treatment of Patients with Severe Polycystic Liver Disease
LONG-ACTING OCTREOTIDE TRIAL
(Mayo Clinic)

Prospective, double blind, placebo controlled (2:1), 42 patients

Octreotide LAR 40 mg IM every 4 weeks

Primary endpoint: % change in liver volume at 12 months (MRI)

Secondary endpoints: % change in kidney and liver/renal cyst volumes

Patient Characteristics
- Age ≥ 18 years
- PLD associated with ADPKD or isolated ADPLD
- Liver volume >4000 mL or symptomatic due to mass effects
- Not a candidate for or declining surgical intervention
- Serum creatinine <3 mg/dL
- No exclusion criteria (pregnancy, major illness, uncontrolled DM)
Symptomatic Polycystic Liver Disease
Nonsurgical Treatment Options

• Avoid estrogens, caffeine
• H₂-blocker or H⁺/K⁺ ATPase inhibitor
• Long-acting octreotidite (?)
• mTor inhibitors (?)
Acknowledgments:

- Vicente Torres MD PhD
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- Octreotide Study:
  - Study Coordinator: page.linda@mayo.edu
  - Novartis
  - Mayo Foundation