Current Management of Biliary Atresia

Janeen Jordan, MD
PGY5
Surgery Grand Rounds
November 19, 2007
Overview

- Etiology and diagnosis
- Work-up and management
- History of Kasai
- Portoenterostomy
  - Studies
  - Advances
  - Recommendations
- Transplant
- Summary
Biliary Atresia (BA)

- John Thompson in 1891
- Holmes (Johns Hopkins) in early 1900s
- Morio Kasai 1955 pioneered HPE

Type 1
Type 2
Type 3
Biliary Atresia

2 Subtypes
- Embryonic – associated with other anomalies
- Perinatal
  - 80-90%
  - Acquired
    - CMV, Reovirus, Rotavirus

Incidence
- 1/5000-18,000 births (~300 per year)
- 2/3 female predominance
- Asian and African descent
**Laboratory evaluation:**
- Cultures: Blood, viral
- Metabolic Screening (e.g., LFTs, T4, TSH, cortisol, iron, cholesterol, triglycerides, fasting glucose, lactate, amino acids)
- Urine profile (e.g., cultures, reducing substances, amino acids, organic acids)
- α-1 anti-trypsin, galactose-1-phosphate UDT
- Sweat chloride
- TORCH serology

Further laboratory evaluation:
- Neonatal hepatitis
- Medical management
- Possible liver biopsy

**Excretion**
- Bile duct proliferation ± Bile plugs ± portal fibrosis
  - PCC
  - Operative cholangiogram, Surgery

**No excretion**
- Liver biopsy
  - Giant cell hepatitis
  - Acholic stools

- Neonatal hepatitis
- Medical management
Neonatal jaundice
Conjugated hyperbilirubinemia

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**Diagnostic---Treat**

**Nondiagnostic**

**Abdominal ultrasound**

**Hepatobiliary Scintigraphy**

**Excretion**

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Medical management
Management

- Goal to diagnose prior to 60-90 days
- >100 days or cirrhosis then transplant
  - Most die within 2 yrs from ESLD
- Initial Management is surgical
  - Kasai Portoenterostomy
    - Excise obliterated biliary tree
    - Roux loop from proximal jejunum anastomosed to porta hepatis
Kasai Portoenterostomy

- Factors that influence success
  - Age at surgery
  - Histology
  - Surgical Expertise

- Complications
  - Bile leak
  - Ascending cholangitis
  - Malabsorption
  - Progressive cirrhosis
NIH: Biliary Atresia Research Consortium

- September 2006
- 2day meeting
- >25 world-wide experts
- Discussion points
  - Etiology
  - Epidemiology
  - Diagnosis
  - Surgical and Medical Management
  - Screening
  - Future Research Goals
## Contemporary Outcome of Biliary Atresia Following Kasai Hepatoportoenterostomy (HPE) and Liver Transplantation

<table>
<thead>
<tr>
<th>Country, Year, and Number of Centers</th>
<th>Number of Patients</th>
<th>Age at HPE</th>
<th>Survival with Native Liver</th>
<th>Survival After Liver Transplantation</th>
<th>Overall Survival of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan, 1989-1999, 93 centers</td>
<td>1381</td>
<td>Median of 61-70 days</td>
<td>5 years: 59.7% (actuarial)</td>
<td>-</td>
<td>5 years: 75.5% (actual)</td>
</tr>
<tr>
<td>United Kingdom and Ireland, 1993-1995, 15 centers</td>
<td>93</td>
<td>Median of 54 days</td>
<td>5 years: 30.1% (actuarial)</td>
<td>2.4 years: 89% (actual)</td>
<td>5 years: 85% (actuarial)</td>
</tr>
<tr>
<td>United States, 1997-2000, 9 centers</td>
<td>104</td>
<td>Mean of 61 days</td>
<td>2 years: 55.8% (actual)</td>
<td>2 years: 88% (actual)</td>
<td>2 years: 91.3% (actual)</td>
</tr>
<tr>
<td>France, 1997-2002, 22 centers</td>
<td>271</td>
<td>Median of 57 days</td>
<td>4 years: 42.7% (actuarial)</td>
<td>4 years: 88.8% (actuarial)</td>
<td>4 years: 87.1% (actuarial)</td>
</tr>
<tr>
<td>England and Wales, 1999-2002, 3 centers</td>
<td>148</td>
<td>Median of 54 days</td>
<td>4 years: 51% (actuarial)</td>
<td>2 years: 89% (actuarial)</td>
<td>4 years: 89% (actuarial)</td>
</tr>
</tbody>
</table>

Japan

- JBAR 1989 – 1999
- 93 centers
- 1381 patients (863 girls, 507 boys)
- 84.1% Type III
- 19% associated anomalies (Polysplenia)
- HPE 61 day
- Survival with Native Liver
  - 5-yr: 59.7%
  - 10-yr: 52.8%

US

Cholangitis

- 47% no cholangitis
- 31% in the first year (15% at 18-24 mos)
- NOT associated with decreased survival

Ascites

- 24% of patients in the first year

Esophageal varices

- 8% only 3 were bleeding

US cont
What’s New

- **Corticosteroids**
  - RCT UK 2007 Hepatology
    - Type III only given oral prednisolone (2mg/kg/d)
    - Lower at 1 month, no diff at 6 or 12 months.
    - Reduced need for transplant at 12 months.

- **Laparoscopy**
  - Retrospective Brazil 2005 Sem in Ped Surg
    - 41 patients

- **Robotics**
So what’s the debate

- The disease is progressive
- Most children will develop
  - portal fibrosis,
  - cirrhosis
  - portal hypertension

- WHY NOT JUST TRANSPLANT
Liver Transplantation

- 70-76% of patients have progressive disease
- Transplant improves overall survival
- Indications
  - Failed HPE
  - age >100-120 days at diagnosis
  - Progressive cholestasis
  - Development of cirrhosis
  - Portal hypertension unresponsive to medical management
Liver Transplantation

- 90% survival at 10yrs
- Complications
  - Death (25-30%/20yr)
  - HAT (20%)
  - PVT (10%)
  - Biliary complications (12-20%)
  - Rejection (50%)
  - Infectious (25%)
  - Sensorineuronal hearing loss
  - Decreased nutrition, bone density, growth

Recommendations

- **Canada**
  - 7% HPE <30d
  - 52% survival with native liver 17yrs
  - 21% survival if 90d or greater

- **Earlier screening**
  - Include a direct bilirubin on serum measurements
  - Visit within 2-4wks
  - Stool color cards

3. Find x.

Here it is
Summary

- BA 100% fatal w/i 2yrs without intervention
- Goal to diagnose and treat w/i 30days
- Kasai HPE is effective and can delay OLT
  - 5yrs in 60% of patients
  - 10yrs in 50% of patients
  - 20yrs in 25% of patients
- Improved steroids
- Minimally Invasive techniques are available
- Delay transplant
“The primacy and value of the Kasai operation in biliary atresia should now be unquestioned…”

Mark Davenport, ChM
<table>
<thead>
<tr>
<th>Author/s</th>
<th>Year</th>
<th>n</th>
<th>Successful Bile Drainage</th>
<th>10-Year Native Liver Survival (%)</th>
<th>10-Year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valayer et al.</td>
<td>1996</td>
<td>27</td>
<td>NA</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Davenport</td>
<td>1997</td>
<td>33</td>
<td>NA</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>van Heurn et al.</td>
<td>2003</td>
<td>77</td>
<td>64%</td>
<td>68</td>
<td>88</td>
</tr>
</tbody>
</table>
Table 4. Candidate Genes and Biliary Phenotype in Mice with Gene Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Intrahepatic Bile Ducts</th>
<th>Extrahepatic Bile Duct</th>
<th>Gallbladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inversin</td>
<td>Normal</td>
<td>Obstruction</td>
<td>Normal</td>
</tr>
<tr>
<td>Jagged-notch circuit</td>
<td>Abnormal</td>
<td>Unaffected</td>
<td>Unaffected</td>
</tr>
<tr>
<td>Hairy and enhancer of split 1 (Hes 1)</td>
<td>Unaffected</td>
<td>Hypoplasia</td>
<td>Agenesis</td>
</tr>
<tr>
<td>Hepatocyte nuclear factor 6</td>
<td>Ductal plate malformation</td>
<td>Abnormal</td>
<td>Agenesis</td>
</tr>
<tr>
<td></td>
<td>Intrahepatic biliary cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte nuclear factor 1</td>
<td>Paucity of small intrahepatic bile ducts</td>
<td>?</td>
<td>Abnormal epithelium</td>
</tr>
<tr>
<td></td>
<td>Dysplasia of larger intrahepatic bile ducts</td>
<td>Dilated cystic duct</td>
<td></td>
</tr>
<tr>
<td>Forkhead box F1</td>
<td>Normal</td>
<td>?</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No epithelial cells</td>
</tr>
<tr>
<td>Forkhead box M1b</td>
<td>Agenesis</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Adapted from HEPATOLOGY 2005;42:222-235.
Presentation
A 5 week old male who presented with jaundice and hepatomegaly. Total bilirubin = 8.0 (direct = 4.9), alkaline phosphatase = 567, AST = 174, ALT = 116. Abdominal U/S showed no evidence of a gallbladder.

Imaging Findings
Initial dynamic images performed over one hour show uptake of tracer into the hepatic parenchyma. There is no visualization of the biliary tree, nor is tracer seen in the small bowel during the initial hour of imaging. Enhanced renal excretion and urinary bladder collection of tracer is seen. Delayed static images performed at 4.5 and 24 hours show no evidence of tracer excretion into the small bowel.

Diagnosis
Suggestive but not diagnostic of biliary atresia. Discussion
Scintigraphic evaluation of biliary atresia is most commonly performed with (-IDA) agents. DISIDA, which has greater hepatic uptake than HIDA is used at Children's Hospital of Boston. Initial dynamic images are taken over 1 hour centered on the abdomen. Delayed imaging is performed at 4 hours and 24 hours. Early diagnosis of biliary atresia is important because the results of surgical intervention are most successful during the first 2 months of life. The key finding is lack of tracer excretion into the bowel by 24 hours of imaging. There are various other etiologies that could result in a "non-draining" scan, but the most common is neonatal hepatitis.

In a study of 86 patients less than four months of age with documented conjugated hyperbilirubinemia, Gilmour et al found that 53 had "non-draining" scans and 33 had "draining" scans. Of the 53 non-draining scans, 40 (75%) were subsequently found to have biliary atresia. Of the 33 draining scans, 24(75%) were subsequently found to have neonatal hepatitis. A key finding was that no patient with extrahepatic biliary atresia had a draining hepatobiliary scan. However, 25% of patients with neonatal hepatitis had “non-draining” scans.

The patient in these images underwent an intraoperative cholangiogram which demonstrated the patency of the distal common bile duct into the duodenum with no proximal ducts. Further exploration demonstrated a very atretic common hepatic duct going up to the portal plate. A Kasai procedure was successfully performed and the patient was discharged seven days later.

Conclusions:
Hepatobiliary scintigraphy can rule out biliary atresia when it demonstrates passage of radiotracer into the bowel.
If passage of tracer is not seen, a suspected diagnosis of biliary atresia is supported but not established.
Biliary Atresia: Diagnosis

- Full term infant
- Persisting jaundice from day 2
- Pale stool, dark urine, FTT, hepato/splenomegaly
- Other anomalies
  - Polysplenism, interrupted IVC, malrotation, situs inversus
- Lab abnormalities
  - Conjugated hyperbilirubinemia
    - >20% of total bili (2mg/dL)
    - Mildly elevated LFTs, Alk Phos (500-100 IU/L)
- Late Findings
  - Coagulopathy
  - Malabsorption
  - Fat Sol Vit Deficiency
polysplenia