Intrahepatic Gallstones

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Intrahepatic Stones – Hepatolithiasis
Definitions

Located proximal to the confluence of the right and left hepatic ducts,
(irrespective of the co-existence of stones in the common bile duct and/or the gallbladder)

- **Secondary** intrahepatic stones: retrograde migration from the gallbladder or the common bile duct (CBD)

- **Primary** intrahepatic stones: formed de novo in intrahepatic ducts
Hepatolithiasis
Relative Prevalence
(% of patients with gallstones)

• Western countries: 1% (few reports)

• Asia:
  – Up to 50% in China
  – 5% in Japan
  – but decreasing:
    • 1970-77: 4.1%
    • 1985-88: 2.2%
    • 1993-95: 1.7% in Japan
      (Mori et al, Best Pract Res Clin Gastroenterol 2006)
    • westernization of the diet?
## Hepatolithiasis - Classification

### 2 types

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol Stones</th>
<th>Brown Pigment Stones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main component</strong></td>
<td>Cholesterol</td>
<td>Calcium bilirubinate</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td>Yellowish to white</td>
<td>Brown to orange</td>
</tr>
<tr>
<td><strong>Main Area</strong></td>
<td>West</td>
<td>East</td>
</tr>
<tr>
<td><strong>Sex Ratio</strong></td>
<td>3♀ / 1♂</td>
<td>♀ = ♂</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Usually Small</td>
<td>Usually Large</td>
</tr>
<tr>
<td><strong>Abnormal bile ducts</strong></td>
<td>Usually NO</td>
<td>YES (dilatation +/- stricture)</td>
</tr>
</tbody>
</table>
Cholesterol Stones: Intrahepatic vs Gallbladder Specificities
Low Bile Phospholipid [C]

(Jacquemin, Sem Liv Dis 2001)
ABCB4 Gene $\Rightarrow$ MDR3 Protein
Brown Pigment Stones - Pathogenesis

Formation of unconjugated bilirubin precipitating as calcium bilirubinate:

Main identified factors:

Bile stasis and infection
(either singly or in combination)

- Bacterial infection: $\uparrow$ $\beta$–glucuronidase activity
- Stasis:
  - Congenital dilatation (Caroli syndrome in the West)
  - Strictures of any cause (post-operative, primary or secondary sclerosing cholangitis, tumors...)
  - Left lobe (acute angle CBD-left hepatic duct) ?
Brown Pigment Stones
Intrahepatic vs CBD Specificities

- **Cholesterol-rich** pigment stones (more cholesterol than in pigment stones located in extra-hepatic ducts):
  - cholesterol-supersaturated bile
  - ↓ biliary secretion of phospholipids (↓ MDR3 expression but no clear association with ABCB4 mutations)  
    
    (Shoda et al, Front Biosci 2006)

- Additional factors:
  - Parasitic infections (*Clonorchis sinensis, Ascaris lumbricoides*): incidental rather than causative
  - Diet: low protein and fat diet → ↓ β–glucuronidase inhibitor
Clinical Features and Management

- Hepatolithiasis without biliary tract abnormalities (cholesterol stones): LPAC syndrome

- Hepatolithiasis with biliary tract abnormalities (pigment or mixed stones)
Description of the LPAC syndrome
(Low phospholipid associated cholelithiasis)

- Age at the onset of biliary symptoms lower than 40 years* (Sex ratio: 3♀/ 1♂).
- Recurrence of the biliary symptoms despite cholecystectomy*.
- Intrahepatic hyperechoic foci with or without intrahepatic sludge or microlithiasis*.
- Association with cholecystitis, cholangitis or acute pancreatitis.
- Familial history of biliary disease.
- Onset of biliary symptoms at the end or after pregnancy.
- Major therapeutic and prophylactic effects of ursodeoxycholic acid (UDCA) on the biliary symptoms and recurrences.
US Findings in LPAC Patients

Comet tail
(experienced radiologist)

Acoustic shadow
LPAC phenotype

ABCB4 genotype

56% with point mutation

44% without point mutation

(heterozygoty ++++, false-sens ++)

Genomic large rearrangements (Exons, introns)
Variants in the promoter region (PPARα, FXR)
Other genes (BCB11, ABCG5/G8, ABCC2…)

(Rosmorduc et al, Gastroenterology 2003)

n = 32
UDCA

Cholesterol solubilization

(Marschall et al, Gastroenterology 2006)
Localized intrahepatic non cystic bile duct dilatations filled with cholesterol gallstones associated with ABCB4 gene mutations

((Poupon et al, Gastroenterol Clin Biol 2010))
Hepatolithiasis with Biliary Tract Abnormalities (Pigment Stones)

• Bouts of biliary pain, fever, jaundice (acute cholangitis, « recurrent pyogenic cholangitis »), septic complications (liver abscess, shock…)

• In the long term: secondary sclerosing cholangitis, portal thrombosis, liver atrophy, cholangiocarcinoma (5 -15 %)

• Asymptomatic patients (up to 39%)

  (Kusano et al, J Clin Gastroenterol 2001)

• Course highly variable
Diagnostic Tools

• Goals:
  – Not only presence of intrahepatic stones
  – But also exact location, *stricture* of bile ducts (cause ?), concurrent cholangiocarcinoma, parenchymal aspect, blood flow…

• Non-invasive modalities:
  – US
  – CT
  – MRCP +++ (accuracy vs PTC : 98% for stones, 97% for bile strictures) ⇒ mapping of the biliary tree
    \( (Park \ et \ al, \ Endoscopy \ 2004) \)

• Invasive modalities: gold standard but significant morbidity
  – ERCP
  – PTC

*Main role: therapeutic procedures*
MRCP in Hepatolithiasis

Quality in Endoscopy: ERCP, Munich 2011
Hepatolithiasis Classification Systems

Severity of hepatolithiasis graded as proposed by the Hepatolithiasis Research Group, Japan

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>No symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>III</td>
<td>Transient jaundice or cholangitis</td>
</tr>
<tr>
<td>IV</td>
<td>Continuous jaundice, sepsis or cholangiocarcinoma</td>
</tr>
</tbody>
</table>

Severity of hepatolithiasis graded according to the Tsunoda classification

<table>
<thead>
<tr>
<th>Tsunoda class</th>
<th>Findings</th>
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<tbody>
<tr>
<td>I</td>
<td>No marked dilatation or strictures of intrahepatic ducts</td>
</tr>
<tr>
<td>II</td>
<td>Diffuse dilatation of intrahepatic ducts without strictures</td>
</tr>
<tr>
<td>III</td>
<td>Unilateral Solitary or multiple cystic dilatation of intrahepatic ducts with strictures</td>
</tr>
<tr>
<td>IV</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

(Sakpal et al, HBP 2009)
Treatment (in Symptomatic Patients)

- **Primary aims:**
  - To eliminate attacks of cholangitis
  - To prevent recurrence, progression and complications
  
  ⇒ Clearance of stones and elimination of bile stasis

- **Tools:**
  - Endoscopic approach (+/- lithotrypsy)
  - Percutaneous approach (+/- lithotrypsy)
  - Surgery
    - (+/- subcutaneous jejunal loop for interventional access)
  - UDCA

- **No definitive treatment**
Multidisciplinary Approach
(fashioned on individual basis)

Clearance of stones:
- PTC *
- Surgical resection
- +/- Endoscopy *

Elimination of bile stasis:
- PTC *
- Surgical resection
- +/- Endoscopy *

(*: multiple sessions)

Surgical resection favored in case of:
- Unilobar HL (left +++)
- Liver atrophy and abscesses
- Suspicion of cholangiocarcinoma
- Failure of other therapies
UDCA

• Cholesterol-rich pigment stones and low bile phospholipid concentration

• “Ursodeoxycholic acid treatment of primary hepatolithiasis in Caroli's syndrome”
  – 12 patients with hepatolithiasis and Caroli syndrome
  – UDCA (10-20 mg/kg/d)
  – Follow-up: 48 months
    → Clinical remission
    → Stone dissolution in all (9 partial, 3 complete)

(Ros et al, Lancet 1993)
Conclusions

2 main types of Hepatolithiasis:

– « New » Hepatolithiasis (cholesterol stones)
  ⇒ LPAC syndrome:
    • Genetic testing (ABCB4)
    • UDCA therapy

– « Traditional » Hepatolithiasis (pigment/mixed stones)
  • Genetic testing (ABCB4)? (in the absence of obvious cause)
  • Mapping of the biliary tree (MRCP)
  • Multidisciplinary approach (endoscopic, percutaneous, surgical)