Rational approach for diagnosis of liver disease

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Diagnostic algorithm

• History taking
  • Physical examination
  • Standard laboratory parameters
  • Special laboratory parameters (Identification of etiology)
  • Ultrasound/endoscopy/radiology
  • Biopsy (percutaneous vs. laparoscopic)
Patients’ history

- Family history, occupation, social aspects
- Jaundice, fatigue, nausea, prolonged bleeding episodes, edema
- Ethanol consumption, use of drugs or herbals
- Hospital stays, blood transfusions, sexual behavior, i.v. drug use …

May lead to diagnosis or identification of important risk factors
## Adverse drug reactions

<table>
<thead>
<tr>
<th>Mimicked liver disease</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>Isoniazide, Rifampicine, Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Methotrexate, Azathioprine, Cyclosporine A</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>Acetaminophen, Halothane</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>Tetracycline, Methotrexate</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Sexual hormones (Estrogen, androgen, progesterone), tolbutamide</td>
</tr>
<tr>
<td>Chron. hepatitis/Cirrhosis</td>
<td>Valproic acid, Methotrexate, Methyl dopa</td>
</tr>
<tr>
<td>Budd-Chiari-Syndrome</td>
<td>anabolic steroids, contraceptiva</td>
</tr>
</tbody>
</table>
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Physical examination

- Limited value in early phases of liver disease
- Key physical signs at later stages of liver disease (ascites, jaundice, palmar erythema, spider nevi, leukonychia etc.)
- Specific signs may be present
  - Wilson’s disease: Kayser-Fleischer rings
  - Hemochromatosis: bronzed skin
  - PBC: Xanthelasmas
Diagnostic algorithm

- History taking
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- **Standard laboratory parameters**
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Routine laboratory parameters

- **Markers of parenchymal liver injury**
  - Aspartate aminotransferase (AST)
  - Glutamate-pyruvate aminotr. (ALT)

- **Markers of cholestasis**
  - Alkaline phosphatase (AP)
  - Gamma glutamyl transferase (GGT)

- **Markers of liver function**
  - Serum bilirubin
  - Prothrombin time
  - Albumin
Routine laboratory parameters - key messages -

- Parenchymal injury
  - AST/ALT >> AP/GGT

- Cholestatic injury
  - AP/GGT >> GOT/GPT

- Advanced liver disease
  - Abnormal liver function tests
Diagnostic algorithm

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<table>
<thead>
<tr>
<th>Virus</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>anti-HAV</td>
</tr>
<tr>
<td>HBV</td>
<td>HBsAg, anti-HBc, anti-HBs</td>
</tr>
<tr>
<td>HCV</td>
<td>anti-HCV</td>
</tr>
<tr>
<td>HDV</td>
<td>anti-HDAg</td>
</tr>
<tr>
<td>HEV</td>
<td>anti-HEV IgM</td>
</tr>
</tbody>
</table>
## Specific parameters for viral hepatitis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>HBeAg, anti-HBe, HBV-DNA, (HBV genotype)</td>
</tr>
<tr>
<td>HCV</td>
<td>HCV-RNA, HCV genotype,</td>
</tr>
<tr>
<td>HDV</td>
<td>anti-HDAg IgM, HDV-RNA</td>
</tr>
</tbody>
</table>
**Prevalence of genetic liver diseases**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Homozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochromatosis</td>
<td>1:400</td>
</tr>
<tr>
<td>Alpha 1-AT-deficiency</td>
<td>1:1.600</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1:2.500</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>1:30.000</td>
</tr>
</tbody>
</table>
Hemochromatosis

Biochemical parameters
- Transferrin saturation >50%
- Serum ferritin ↑↑↑

HFE genotype
- Homozygous C282Y-mutation
- Compound heterozygosity (H63D/ C282Y)

Liver biopsy with quantification of iron
- Iron concentration (>20 mg/g)
- Liver iron index >1,9

„The three AAA's“
- Asthenia (chronic)
- Arthralgia (fluctuating)
- Aminotransferases (mildly elevated)
Alpha 1-antitrypsin-deficiency

• autosomal recessive inheritance (14q32.1)
• numerous carriers of mutations do not develop symptoms
• phenotypes (electrophoresis): PI MM, PI MZ and PI ZZ, very rare PI 00
• retention of polymers of unnormally folded A1-AT in periportal hepatocytes
• A1-AT-deficiency may present at any stage of life
Wilson's disease

Biochemical parameters
- Serum ceruloplasmin decreased (< 20 mg/dl)
- Serum copper decreased
- 24-h copper (urine) increased
- Coombs-negative hemolytic anemia

Liver biopsy
- Hepatic copper (> 250µg/g dry weight)
Non-alcoholic steatohepatitis (NASH)

- No specific laboratory parameters
- Liver biopsy is diagnostic!
Frequency of NASH

Nach Angulo P, NEJM 2002
Autoimmune liver diseases

- Autoimmune hepatitis (AIH)
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Overlap syndromes
Autoimmune hepatitis (AIH)

- Incidence 1:5000 bis 1:10000
- 75% of patients are female
- Many patients are diagnosed at late stages!
- Diagnostic criteria:
  - Autoantibodies (ANA, SMA, LKM, SLA)
  - Selective IgG increase
  - Histology of chronic Hepatitis
  - No sign of viral hepatitis
Primary biliary cirrhosis (PBC)

- Markers of cholestatic liver injury
- Anti-mitochondrial antibodies (AMA-M2)
- Histology
- Elevation of immunoglobulin M
- 90% female
- Xanthelasmas and xanthomas in chronic cholestasis
Primary sclerosing cholangitis (PSC)

- Cholestasis for more than 6 months
- Typical findings at ERC
- Chronic inflammatory bowel disease
- Histology
  - (pANCA)
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Diagnostic algorithm in patients with jaundice

**Ultrasound**
- Bile ducts dilated?
  - yes
    - ERC
      - Neoplasia
      - No Neoplasia
        - Histology, Staging
          - Operation
          - Endoscopic therapy
  - no
    - Direct hyperbilirubinemia
      - Special laboratory parameters, Liver histology
    - Indirect hyperbilirubinemia
      - Other causes (e.g. hemolysis, Gilbert syndrome)
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Liver biopsy

- percutaneous (Menghini)
- transjugular
- laparoscopic
Liver histology for primary diagnosis

- NASH/NAFLD
- Alcoholic hepatitis
- Drug-induced liver disease
- Autoimmune hepatitis without autoantibodies
- AMA negative PBC
- Genetic liver diseases (Cu, Fe)
Liver histology for follow-up

- Information: Inflammation (Grading)
  Fibrosis (Staging)

- Indication: Follow-up
  Indication for therapy
  Evaluation of therapeutic success
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Summary

**Parechymal injury:**
- HBsAg, anti-HBc, anti-HCV
- ANA, SMA
- Coeruloplasmin
- Protein electrophoresis
- Ferritin

(consider biopsy for NASH and duodenal biopsy for celiac disease)

**Cholestatic injury:**
- AMA, (pANCA)
- Ultrasound
- ERC