Liver flukes and Human Fascioliasis

Lecture 2

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Etiology

Global zoonotic disease

### Diseases Caused by Flukes in the Bile Duct

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Clonorchiasis</th>
<th>Opisthorchiasis</th>
<th>Fascioliasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other mammalian hosts</td>
<td>Dogs, cats, pigs</td>
<td>Dogs, cats, foxes, pigs</td>
<td>Sheep, cattle</td>
</tr>
<tr>
<td>Mode of spread</td>
<td>Ova in faeces, water</td>
<td>As for <em>C. sinensis</em></td>
<td>Ova in faeces on to wet pasture</td>
</tr>
<tr>
<td>1st intermed host</td>
<td>Snails</td>
<td>Snails</td>
<td>Snails</td>
</tr>
<tr>
<td>2nd intermed host</td>
<td>Freshwater fish</td>
<td>Freshwater fish</td>
<td>Encysts on vegetation</td>
</tr>
<tr>
<td>Geographical distribution</td>
<td>Far East, especially South China</td>
<td>Far East, especially North-east Thailand</td>
<td>Cosmopolitan, including UK</td>
</tr>
<tr>
<td>Pathology</td>
<td><em>E. coli</em> cholangitis, abscesses, biliary carcinoma</td>
<td>As for <em>C. sinensis</em></td>
<td>Toxaemia, cholangitis, eosinophilia</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Often symptom-free, recurrent jaundice</td>
<td>As for <em>C. sinensis</em></td>
<td>Unexplained fever, tender liver, may be ectopic, e.g. subcutaneous fluke</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Ova in stool or duodenal aspirate</td>
<td>As for <em>C. sinensis</em></td>
<td>As for <em>C. sinensis</em>, also serology</td>
</tr>
<tr>
<td>Prevention</td>
<td>Cook fish</td>
<td>Cook fish</td>
<td>Avoid contaminated watercress</td>
</tr>
<tr>
<td>Treatment</td>
<td>Praziquantel 25 mg/kg 8-hourly for 2 days</td>
<td>As for <em>C. sinensis</em> but for 1 day only</td>
<td>Triclabendazole 10 mg/kg single dose; repeat treatment may be required</td>
</tr>
</tbody>
</table>
Most of the areas with high endemicity of human fascioliasis involve *F. hepatica*. In Africa *F. gigantica* predominates. In Asia / Egypt: *F. hepatica / F. gigantica* overlaps & difficult to identify the particular species involved, so referred to as *Fasciola* species.

**Human Fascioliasis : Clinical Concept and Epidemiological Concept**

*Clinical conception*

*Fasciola* species inhabits the hepatobiliary system causing considerable human morbidity dependent on the number of worms & stage of infection.

The course of infection passes through three phases:
- The acute phase
- The chronic phase
- The obstructive phase

Pathology / clinical manifestations are related to the phase

The acute phase:
- Coincides with migration of the immature flukes through the peritoneal cavity, penetrating liver capsule then through liver parenchyma till they reach the bile ducts.
- It persists for several weeks to months (3-4 months).
- Severe pathology results from parasite migration/ destruction of parenchymal tissue, causing toxic and allergic reactions.
Symptoms:
- Acute symptoms
- Asymptomatic (unusual)
- Severe illness (prostration & jaundice) (unusual)

- The chronic phase, coincides with the presence of the flukes in the bile ducts
- The life span of the parasite is 10-13 years
- Pathology tends to be mild

Symptoms:
- Asymptomatic
- OR
- Few gastrointestinal symptoms
- Intermittent fever with persistent prominent eosinophilia
- Recurrences of the acute signs & symptoms
- Recurrent cholangitis

Obstructive phase
(heavy / prolonged infection)
Coincides with epithelial changes in the bile ducts due to irritation of the epithelium by the spines & the activity of proline.

Severe pathology occur in the form of epithelial hyperplasia & proliferation, peri-ductal inflammation then fibrosis & even calcification leading to partial obstruction

Symptoms
- Recurrent cholangitis & cholecystitis (calculous or acalculous)
**Ectopic fascioliasis** may occur during any of the three phases of the disease but is most common during the acute phase.

1. Juveniles that migrate out of the intestine but do not locate in the liver so they form ectopic lesions in many abdominal tissues
   2. Juveniles that enter the portal circulation, so distributed throughout the body.
      - Manifested as masses, abscesses, migration tracks or haemorrhage.
      - These are often misdiagnosed as malignant ulcers or tumours.
      - Exploratory abdominal surgery may be needed to make the diagnosis

**Interesting ectopic sites & lesions**
- Gastric fascioliasis
- Fascioliasis of the head of pancreas
- A mass in the right iliac fossa
- The peritoneal cavity massive ascitis
- Mitral insufficiency secondary to myocardial fibrosis
- Intraocular bleeding
- Hydrocele due to epididymitis
- Effusion of the knee joint
- Ectopic Fasciola worms in the ankle joint
- Cervical / generalized lymphadenopathy
- Abdominal subcutaneous nodules
- Pleural effusion associated with/without pulmonary infiltrates, pyopneumothorax & pleurisy.

**Complications**
1. Liver abscess & haematoma (subcapsular) (acute stage)
2. Biliary cirrhosis: due to the peri-ductal fibrosis
3. Obstructive jaundice: Obstruction of the common bile duct by *Fasciola adults* +.
4. Biliary sludge / stones: in gall bladder & biliary tree may be formed in chronic patients, which remains unchanged after therapy may predispose to recurrent cholecystitis, cholangitis or biliary stone
5. Bleeding: Bleeding may occur due to ulcerations in the common bile duct (haemobilia)
6. Death: rare, major causes of death are biliary bleeding & biliary cirrhosis
Diagnosis
1. Clinical + the haematological / biochemical findings
2. Parasitological diagnosis
3. Immuno-diagnosis
4. Imaging procedures
5. Liver biopsy

1. Clinical + the haematological / biochemical
Not reliable because:
- The clinical manifestations are not markedly different from hepatobiliary disease of other origins. so hepatomegaly, fever, anaemia, marked eosinophilia are only highly suggestive of the disease
- Ectopic localization of the parasite may cause a confusing clinical presentation

2. Parasitological diagnosis:
- Eggs are not excreted during the invasive stage of infection when many patients present with severe symptoms
- Sometimes eggs are undetectable during the chronic phase.
- Differentiation of eggs of F. hepatica, F. gigantica, echinostomes & Fasciolopsis is difficult

3. Immuno-diagnosis:
The advantage over parasitological techniques is:
Can detect early, prepatent infections as well as chronic stage with little or no egg output.
Tests have been developed for
- Detection of Fasciola antigens (Circulating, Coproantigens)
- Detection of the circulating antibodies (IgM, IgG, IgG4)
- Detection of the circulating immune complexes.

Sources of antigens
1. Adult (crude, purified...)
   Whole somatic extract of adult
   Tegumental extract of the surface tegument
   Excretory-secretory products (ES) contain several enzymes such as cysteine proteinase and cathepsin-L proteinases.

2. Metacercarial antigen and juvenile somatic antigen

3. Miracidial antigen
Numerous assays for immunodiagnosis:

- ELISA
- Indirect haemagglutination test (IHA)
- Counter immuno electrophoresis (CIEP)
- Indirect fluorescent antibody test (IFA)

Problems with cross-reactivity with other trematode infections are avoided by using purified specific antigens, or specific antibody subclasses (IgG4).

Many techniques revealed 100% sensitivity & specificity e.g. IgG4 ELISA (recombinant CL-1) & cystatin capture ELISA (cysteine proteinase)

4. Imaging

Various imaging techniques proved useful to diagnose human fascioliasis:

1. Ultrasonography (US)
2. Computed Axial Tomography (CAT)
3. Magnetic Resonance Imaging (MRI)
4. Endoscopic Retrograde Cholangio-Pancreatography (E.R.C.P.)
5. Percutaneous transhepatic cholangiography (P.T.C)

Valuable in the diagnosis of...

- The migratory tracks of the juvenile flukes seen as peripherally located branching or tortuous lesions
- Pathological lesions secondary to migration e.g. abscesses & parenchymal hemorrhages

- Vermiform flukes moving within the gall bladder

- Hepatomegaly & periportal fibrosis
- Bile aspiration from the gall bladder for verification in cases suspicious to be metastatic liver disease (US, E.R.C.P)
5. Liver biopsy may demonstrate:
   • Microabscesses
   • Tunnels of parenchymal necrosis
   • Eggs & adult worms

Treatment

Curative treatment is essential in human fascioliasis to control symptoms & to avoid the hepatobiliary complications

• Several drugs have been used & efficacy was often variable
• Chemotherapeutic agents in common use in human fascioliasis:
  ➢ Effective with no or little side effects: Triclabendazole, bithionol, Mirazid
  ➢ Effective with side effects: severe (dehydroemetine), or moderate (Metronidazole)
  ➢ Controversial therapeutic results (Praziquantel)

Triclabendazole TCZ appears to be the drug of choice for acute & chronic human fascioliasis, recently registered for human use against fascioliasis (WHO, 1998):
  ➢ Effective against juveniles / adults
  ➢ Excellent tolerance & efficacy in adults & children
  ➢ Ease of administration (single oral dose)
  ➢ Several reports documented its efficacy in the treatment of the disease since 1988.
  ➢ The criteria for cure:
    1) Amelioration of symptoms & achievement of clinical wellbeing (Clinical cure)
    2) Normalization of haematological & biochemical data: declining then returning to normal values
    3) Absence of ova (parasitologic cure) in repeated stool examinations in chronic cases
    4) Decreasing antigenaemia / antibody levels
    5) Disappearance or improvement of imaging findings

Treatment efficacy

• The detection of circulating Fasciola antigen & coproantigen is an efficient immuno-diagnostic tool to assess the effect of therapy in fascioliasis, as antigenaemia in the host reflects an active infection
• Role of antibody detection to assess treatment efficacy is controversial.

Some claim that none of the Fasciola isotypes change after treatment, even after 6 months,
others documented the drop of antibodies rapidly after successful treatment

Individuals who do not respond to oral drug therapy can be treated successfully by biliary drainage & the take out of worms or by flushing of the biliary system with povidone iodide

**Epidemiological conception**

The epidemiological picture of the disease has changed in recent years.

- The expected correlation between animal & human fascioliasis was found to occur only at a basic level.
- A high prevalence in humans does not seem to correlate with areas where fascioliasis is a major veterinary problem

**Prevalence /distribution**

- The number of humans infected with *Fasciola species* has increased significantly since 1980 & several geographical areas have been described as endemic for the disease in humans, with prevalence & intensity ranging from low to very high.
- Reports from Turkey & Iran.
- The disease is worldwide in distribution but endemic in South & Central America, Puerto Rico, the Caribbean region, many parts of Africa, Asia, the Middle East, Australia, China.
- There have been a number of focal outbreaks reported from Europe, including southern France & the Mediterranean region

There is a significant positive association between human fascioliasis & schistosomiasis

- Prevention and control
  1. Periodic examination / treatment of livestock
  2. Control of the snail vectors
  3. Health education.
  4. People must be aware of how infection might occur.