Acute Liver Failure in Childhood and Neonates

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Definition

A rare multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in patient with no recognized underlying chronic liver disease…

Bhudari and Vergani

- Biochemical evidence of liver injury
- No history of chronic liver disease
- Hepatic-based coagulopathy (not corrected by vitamin K administration)
  - PT > 15 seconds or INR > 1.5 (with HE)
  - PT > 20 seconds or INR > 2.0 (regardless of HE)
Etiology: PALF Study Group Database

N = 703

- Indeterminant: 47%
- Drug toxicity: 14%
- Autoimmune hepatitis: 10%
- Metabolic disease: 6%
- Viral (HAV, HEV, EBV, etc.): 16%
- Other: 7%

Narkewics et al. J pediatr 2009;155:801-6
Etiology of ALF in Thai Children

N = 35

- Indeterminant (13)
- Wilson disease (2)
- Ischemic hepatitis (2)
- T-cell lymphoma (2)
- Cytomegalovirus (2)
- Hemophagocytic syndrome (1)
- Reye syndrome (1)
- Dengue hemorrhagic fever (12)

Clinical manifestations

- **Neonates**
- **Non specific**: lethargy, poor feeding, vomiting

- **Infants and older children**
  (most patients are previously healthy !!!)
  
  **Prodromic phase**: malaise, myalgia, nausea, vomiting, fever

  **Subsequent jaundice** may be minimal in some causes; toxin, metabolic disease, Reye syndrome
Clinical manifestations (2)

Sign & Symptoms of Liver Dysfunction

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Coagulopathy</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Decreased gluconeogenesis</td>
<td>- Reduction in coagulation</td>
<td>- Inappropriate amounts of</td>
</tr>
<tr>
<td></td>
<td>factor synthesis</td>
<td>neuroregulatory substances</td>
</tr>
<tr>
<td>- Impaired glycogen storage</td>
<td>- Reduction in platelet</td>
<td>- Fail to eliminate</td>
</tr>
<tr>
<td>- Hyperinsulinism</td>
<td>numbers and function</td>
<td>neurotoxins</td>
</tr>
<tr>
<td>- Increased glucose use</td>
<td>- Intravascular coagulation</td>
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Hypoglycemia:
- Decreased gluconeogenesis
- Impaired glycogen storage
- Hyperinsulinism
- Increased glucose use

Coagulopathy:
- Reduction in coagulation factor synthesis
- Reduction in platelet numbers and function
- Intravascular coagulation

Encephalopathy:
- Inappropriate amounts of neuroregulatory substances
- Fail to eliminate neurotoxins
### Stage of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>อาการ</th>
<th>Asterexis/Reflexes</th>
<th>Neurological Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>เริ่มมีการเปลี่ยนแปลง</td>
<td>ไม่พบ / ปกติ</td>
<td>Tremor, ลายมือเปลี่ยนแปลง</td>
</tr>
<tr>
<td></td>
<td>ของพฤติกรรมการนอนหลับ อารมณ์</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>ชิม แต่ปลุกตื่นได้ บันสน</td>
<td>พบ / hyperreflexive</td>
<td>Dysarthria, ataxia</td>
</tr>
<tr>
<td>III</td>
<td>ชิมมากชิ้น ตอบสนองต่อ painful stimuli</td>
<td>พบ / hyperreflexive</td>
<td>muscle rigidity, decerebrate</td>
</tr>
<tr>
<td></td>
<td>ตรวจพบ Barbinski sign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>ไม่รู้สึกตัว ไม่ตอบสนอง</td>
<td>ไม่พบ</td>
<td>decerebrate หรือ decorticate</td>
</tr>
</tbody>
</table>
Diagnosis of ALF

Biochemical of liver injury (elevated transaminase/conjugated hyperbilirubinemia)

Check coagulation

Normal
Abnormal

Vitamin K administration & recheck coagulation in 6 hr.

Normal PT/INR Vitamin K deficiency
Prolonged PT/INR Liver failure confirmed
Do we need to identify cause of ALF?

- Some etiologies have specific treatment
- Different prognosis in different etiology

- **Limitation!!!**...blood volume required for many tests, lack of time interval after presentation, lack of proper tests, etc.
- **Liver biopsy** for histology is not critical and may be harmful
Diagnostic Approach

- Age group
- History
- Physical examination
- Laboratory investigations
<table>
<thead>
<tr>
<th></th>
<th>Neonates and infants</th>
<th>Older children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td><strong>Herpesvirus</strong>, echovirus, adenovirus, HBV</td>
<td><strong>HAV, HEV</strong>, HBV, EBV, dengue, parvovirus, etc.</td>
</tr>
<tr>
<td><strong>Metabolic disease</strong></td>
<td>Galactosemia, tyrosinemia, fructose intolerance, mitochondrial disease</td>
<td>Wilson’s disease, mitochondrial disease</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
<td>Congenital heart disease, severe asphyxia</td>
<td>Shock (ischemic hepatitis)</td>
</tr>
<tr>
<td><strong>Immune disorders</strong></td>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Autoimmune hepatitis, hemophagocytic syndrome (secondary)</td>
</tr>
<tr>
<td><strong>Drugs/ Toxins</strong></td>
<td>Valproate, acetaminophen</td>
<td>Same as infant, <em>Aminita phalloides</em></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Neonatal hemochromatosis (NH), Reye syndrome, malignancy</td>
<td>Reye syndrome, malignancy</td>
</tr>
</tbody>
</table>
History

- History of fetal loss, IUGR, oligohydramnios: **NH**
- History of gram negative (*E. Coli*) septicemia: **galactosemia**
- Recurrent liver failure/ recurrent Reye syndrome, consanguinity, occur after acute illness: **inborn error of metabolism**
- History of neurological manifestations (seizure, hypotonia): **mitochondrial disorder**
- History of viral infection (within 3 weeks) and salicylic acid use: **Reye syndrome**
- History of liver disease in family: **Wilson’s disease**
- Prodrome symptoms: **viral hepatitis**
- Drugs or toxins: **Toxic hepatitis**

**NH**, neonatal hemochromatosis
Physical examination

- Neurologic status and level of encephalopathy
- Sign of chronic liver disease: Wilson’s disease, autoimmune hepatitis
- Liver size:
  - Decreasing liver size with worsen liver functions: fulminant liver failure
  - Hepatomegaly with massive ascites: Budd-Chiari syndrome
- Jaundice: not always present → Reye syndrome, toxin
- Eye examination:
  - Cataract: galactosemia
  - Kayser-Fleischer ring: Wilson’s disease
Warning Signs of Progressive Disease

- Prolonged PT that is unresponsive to vitamin K
- Persistent jaundice (rapid increased of bilirubin, progressive decline of serum aminotransferase)
- Decreasing liver size
- Increasing lethargy or occasional hallucination
- Hemorrhagic diathesis and systemic collapse

Laboratory Investigations

Initial laboratory evaluation

Biochemical tests
- Liver function tests, blood sugar
- Serum electrolytes, BUN, creatinine
- Arterial blood gas, lactate, blood ammonia

Hematological tests
- Complete blood count & peripheral blood smear
- Prothrombin time / INR
- Reticulocyte count

More investigations in neonates
- Herpes simplex virus PCR
- $\alpha$-fetoprotein, serum ferritin
- Urine reducing substance
Laboratory Investigations

Older children

Severe hepatitis + coagulopathy
- Viral hepatitis
- Ischemic hepatitis
- Toxic hepatitis

Moderate hepatitis + coagulopathy
- Normal bilirubin, hypoglycemia

Low ALP, Hemolytic anemia

Viral infection + Salicylate use
- Reye syndrome

High ferritin, cytopenia, hypertriglyceridemia
- Hemophagocytic syndrome

Wilson’s disease
# Disease-specific Investigations

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson’s disease</td>
<td>Serum celuroplasmin</td>
</tr>
<tr>
<td></td>
<td>24-hr urine copper</td>
</tr>
<tr>
<td></td>
<td>Eye examination (Kayser-Fleischer rings)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Autoantibodies (ANA, ASMA, anti-LKM)</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Serum triglyceride, serum ferritin</td>
</tr>
<tr>
<td>(familial &amp; secondary)</td>
<td>Bone marrow examination</td>
</tr>
<tr>
<td>Toxic/drugs</td>
<td>Acetaminophen level</td>
</tr>
<tr>
<td></td>
<td>Urine toxic screening</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Anti-HAV IgM</td>
</tr>
<tr>
<td></td>
<td>HBsAg, HBC IgM, HBC Ag</td>
</tr>
<tr>
<td></td>
<td>Anti-HCV, HCV PCR</td>
</tr>
<tr>
<td></td>
<td>Anti-HEV IgM</td>
</tr>
<tr>
<td></td>
<td>EBV IgM, IgG, CMV IgM, IgG</td>
</tr>
<tr>
<td></td>
<td>PCR for HSV, EBV, CMV, HHV-6, enterovirus, adenovirus, parvovirus</td>
</tr>
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Laboratory Investigations

Neonates

Mild hepatitis + severe coagulopathy

High ferritin
High AFP
Hypersaturation of TIBC

Neonatal hemochromatosis

Mild-moderate hepatitis + severe coagulopathy

Metabolic liver disease

Neonates and infants

Mild hepatitis + severe coagulopathy

Severe hepatitis + coagulopathy

Viral disease
Ischemic hepatitis

AFP, α-fetoprotein
TIBC, total iron binding capacity
Suspected metabolic liver diseases (after exclude infection, toxin)

- Urine reducing substance + (but glucose -)
  - Galactosemia
  - Fructosemia
  - Citrin deficiency

- Urine reducing substance -
  - Urine ketone - while low BS
    - FAOD Mitochondrial dis.
      - FAAOD, fatty acid oxidation defects

- High AFP Severe coagulopathy
  - Tyrosinemia
    - Normal BS, low urea
      - Very high ammonia
        - Respiratory alkalosis
          - Urea cycle defects

- Courtesy: Prof. D Wattanasirichaigoon
## Disease-specific Investigations

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<td>Neonatal hemochromatosis</td>
<td>MRI abdomen or buccal mucosa biopsy (for evidence of extrahepatic siderosis)</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Urine succinyl acetone</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Erythrocyte GALT activity</td>
</tr>
<tr>
<td>Fatty acid oxidation defects</td>
<td>Acylcarnitine profile (dry blood spot)</td>
</tr>
<tr>
<td>Urea cycle defect</td>
<td>Plasma amino acid and urine orotic acid</td>
</tr>
<tr>
<td>Mithochondrial disease</td>
<td>Mitochondrial DNA&lt;br&gt;Blood lactate/pyruvate&lt;br&gt;3-OH-butyrate/acetoacetate&lt;br&gt;muscle and liver biopsy for quantitative respiratory chain enzyme determination</td>
</tr>
</tbody>
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GALT, galactose-1-phosphate uridyltransferase
Critical sample collection if suspected metabolic liver diseases

Caution !!!
blood sample should be collected before blood transfusion /exchange transfusion

✓ 1-2 mL of plasma/serum freeze at -20\(^{\circ}\)C for amino acid analysis, carnitine analysis
✓ 5-30 mL of urine freeze at -20\(^{\circ}\)C for organic acid analysis (include succinylacetone)
✓ Dry blood spot (www.neoscreen.go.th) for acylcarnitine profile analysis
✓ 3-5 mL of EDTA blood at 4\(^{\circ}\)C for DNA testing
So... how can we treat a child with acute liver failure?
Neonatal hemochromatosis

MRI abdomen demonstrates attenuated signal (dark) indicating increased iron storage in pancreas & liver, but typically absent in spleen.

Intra and extrahepatic siderosis