Elevated transaminases-
What does it mean?

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Case - 1

- An eight year old boy presents to your office
- Reason: routine check up
- History: diarrhea, mild fever two weeks ago
- Examination: weight 95%, height 25%, edge of liver palpable
- Labs: WBC 3.5, ALT 85, AST 65 – rest normal
Transaminase elevation - Possible Etiology

- An acute illness
- Recovery from an acute hepatitis
- An existing chronic liver dysfunction
- Unrelated to a primary liver disorder
Case – 2

- An eight year old boy presents to your office
- Reason: Yellow eyes, abdominal pain
- History: Diarrhea, mild fever 2 weeks ago
  A trip to Mexico
- Exam: Weight 40%, height 35%, jaundice, hepatosplenomegaly
- Labs: ALT 385, AST 265, TB 7, INR 1.6, A/G 0.7
Transaminase Elevation - Possible Etiology

- An acute liver disease
- An exacerbation of a chronic liver dysfunction
- Secondary to an acute infection
Liver Function Tests

- Metabolic diseases: Acidosis, hypoglycemia
- Tumors: Alpha fetoprotein, LDH
- Chronic dysfunction: Fasting bile acids, platelets
Liver Function tests

• Hepatocellular: Liver injury
  – AST, ALT, LDH

• Excretory: Impaired bile flow, cholestasis
  – Bilirubin, GGT, Alk. Phosphatase, Bile salt

• Synthetic: Defective production
  – PT/PTT, Albumin, Ammonia, cholesterol
Transaminases

• AST - in liver, muscle, kidney, red cell, pancreas, macro AST
• Elevated in any injury- trauma, ischemia, drugs, infection, hemolysis
• ALT- mostly in liver, less in muscle
Transaminases – high and low

- **Very high ALT ( > 1000 IU )**
  - Drugs, anoxia, acute viral infections
- **Moderate elevations ( 200-300 IU)**
  - Chronic hepatitis, autoimmune, NASH
- **AST > ALT:** Hemolysis, muscle pathology, macro AST
  - Fibrosis/cirrhosis, Wilson’s
- **ALT elevation alone:** Celiac Disease and NASH
- **ALT low:** Cell death, B6 deficiency, uremia
Hepatitis B in Children

- 90% children -- asymptomatic
- Risk of chronic HBV decreases with age
- Chronic HBV in:
  - 90% of infants infected at birth
  - 20-50% if infected at 1-5 yrs.
  - 2-6% if infected later
HBV Modes of Transmission

- Parenteral
- Perinatal
- Sexual
HBV- Serologic Markers

- HBsAg: Infection-acute or chronic
- HBsAb: Clinical recovery, immunity
- HBcAb: Presence of infection- acute, chronic
- HBeAg: Active viral replication, infectivity
- HBeAb: Resolution of active infection
- HBV DNA: Measure of viral replication
- ALT: Normal or mild elevation
Acute Hepatitis B Virus Infection with Recovery

- Symptoms
- HBeAg
- anti-HBe
- Total anti-HBc
- HBsAg
- IgM anti-HBc
- anti-HBs

Weeks after Exposure

Titer

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What we know about course of HBV - then & now

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Course of HBV infection

Acute Hepatitis

1-5%

Fulminant hepatitis

Death/OLT

Persistent infection

Immunity

5%
70%
95%

Carrier

Chronic HBV

Cirrhosis/HCC
Progression to Chronic Hepatitis B Virus Infection

![Graph showing progression of hepatitis B virus infection](image-url)
HBV- Prevention

- HBIG- for temporary, post exposure
  - *Perinatal, Needle stick, sexual*
- Vaccinate all children 0-18 yrs
- Dose (0, 1-2, 6 mo.)
- Engerix-B, Recombivax HB
- ? Re-vaccination: test if high risk

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Post Vaccine testing

• Immuno compromised patients
• Vaccine in the buttocks
• Infants born to HBsAg + mothers
• Health care workers in contact with infected blood
• Sex partners of HBV infected persons
HCV - Background

Hepatitis C antibody in the US population, 1988-1994, NHANES III data:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>%</th>
<th>Estimated No</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.8</td>
<td>3.9 million</td>
</tr>
<tr>
<td>6-11 years</td>
<td>0.2</td>
<td>0.4 million</td>
</tr>
<tr>
<td>12-19 years</td>
<td>0.4</td>
<td>0.8 million</td>
</tr>
</tbody>
</table>
Natural History of HCV Infection

100 People
- Resolve (15) 15%
- Chronic (85) 85%
  - Stable (68) 80%
  - Cirrhosis (17) 20%
    - Stable (13) 75%
    - Mortality (4) 25%

Time
HCV- screening

- History of drug use
- Children born to HCV positive mother
- Transfusion/ solid organ Tx before 1992
- Recipient of clotting factors before 1992
- Chronic hemodialysis
- After known parenteral exposure
- Persistently high ALT
Serologic Pattern of Acute HCV Infection with Recovery

- HCV RNA
- ALT
- Symptoms +/-
- HCV antibody

Time after Exposure

Years

Months

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Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

<table>
<thead>
<tr>
<th>Symptoms +/-</th>
<th>HCV antibody</th>
</tr>
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<td>HCV RNA</td>
<td>ALT</td>
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Titer

Months

Years

Time after Exposure

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Children’s HCV Study (1996-2001)

- Transfusion look-back and referrals
- Perinatal (13%), transfusion (68%), both (7%) in 60 children, 7 adoptees
- Duration of infection about 13 years
- Mostly asymptomatic, mild liver disease
- Bridging fibrosis in 12%
- Severe liver disease in 3 children - perinatal

The most common nutritional disorder in the US...

*Obesity*
NAFLD

- Prevalence of obesity 22% over 20 years
- Prevalence of NAFLD in children 7-10%
- Steatosis in 60%; steatohepatitis in 20% of obese people
- Association with Type 2 diabetes and hyperlipidemia, insulin resistance
- Higher prevalence in Hispanic children and African American-22%
- Other genetic/metabolic liver diseases excluded
NAFLD - pathogenesis

- Hyperinsulinemia, insulin resistance - most essential component
- Increased free fatty acids in plasma and liver
- Inhibition of free fatty acid oxidation by insulin
- Hepatocellular oxidant stress, changes in mitochondria and peroxisomes
Progression of NAFLD

- Adipose
- Liver
- FFA
- Hepatocyte Free Fatty Acids
- Hepatocyte TNFα production
- Adiponectin activity
- Steatosis, Insulin resistance
- FIBROSIS
- ROS
- Oxidant stress
- Hepatocyte death, poor repair

Diehl et al

1st hit

2nd hit

www.dechildrens.com
Acanthosis nigricans- metabolic syndrome

Acanthosis nigricans-hyperplasia of cells with insulin receptors- indicates insulin resistance
Diagnosis of NAFLD

• Serum ALT: ( > AST)
  – Screening Tool
  – Poor sensitivity, no cut off value
• Ultrasonography:
  – Low cost, no radiation
  – Increased ECHO texture and vascular blurring
• MRI/MR Spectroscopy
  – Ideal- direct measurement/distribution of fat
• Liver biopsy: *controversial*
Wilson’s Disease

Think “Wilson’s” in anyone over 3 years with unexplained, elevated transaminases
Wilson’s Disease

- Genetic disorder- systemic copper accumulation
- Chromosome 13
- Mutation of ATP7B gene
- Hepatitis, liver failure, cirrhosis
- Extra-pyramidal lesions
- Psychiatric disorders
- Hemolysis, renal disease
Wilson’s Disease- Diagnosis

- Ceruloplasmin < 20 mg/dl
- Liver copper > 250 mcg/dl
- 24 hour urine copper > 100 mcg
- Liver biopsy and measurement of copper
- Mitochondrial changes on EM
- Genetic studies
Alpha-1-antitrypsin deficiency

- Autosomal recessive
- Presentation
  - Asymptomatic: elevated AST, ALT
  - Liver disease, portal HTN
  - Emphysema
- Diagnosis
  - Low serum levels
  - Pi phenotyping: PiZZ
  - Histology
Autoimmune hepatitis - Overview

- Interface hepatitis
- Autoantibodies, high IgG
- Propensity for cirrhosis
- 5.9 % of Liver Tx
- Female preponderance
Autoimmune Hepatitis

• Type I:
  Predominantly in women
  Acne, amenorrhea
  ANA, ASMA, High IgG

• Type II:
  Mainly in children - Europe
  More aggressive course
  Anti LKM antibody

Type III: Similar to Type I
  Soluble Liver Antigen
Drugs and Hepatitis

- Hepatitis-Cholestasis: Erythromycin
- Zonal necrosis: Acetaminophen
- Bland Cholestasis: Cyclosporin
- Steatosis: Valproate
- Adenoma: Estrogens
- Allergic: Phenytoin
- Malignancy: Anabolic steroids
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Asymptomatic patient-High liver enzymes

• Sub clinical HBV or HCV
• Sub clinical Auto-immune Hepatitis
• A-1 AT deficiency
• Wilson’s Disease
• NAFLD/NASH
• Myopathy, celiac
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“Yellow and sick” – high transaminases

- Acute hepatitis: Hepatitis A
- An exacerbation of chronic hepatitis:
  - Hepatitis B/C
  - Autoimmune
  - Metabolic: Wilson’s
- Drugs
  - INH, bactrim
Management

- Medical
- Liver transplantation
Treatment of chronic hepatitis

• Hepatitis B & C - Interferons, oral antiviral agents
• Drug toxicity - stop offending drug
• Wilson’s Disease - chelation
• A1 AT deficiency - liver transplant
• Autoimmune - steroids, immunosuppressant, ursodiol
• Steatohepatitis - weight loss, bariatric surgery