What are the risk-factors with an impact on fatality rate in fulminant hepatitis A?

Daniel Shouval
Liver Unit
Hadassah-Hebrew University
Jerusalem, Israel
Hepatitis in Chimpanzees inoculated with HAV

*Adopted from Nainan et al. Clinical Microbiology Reviews 2006;19;63*
Cumulative Experience

- Acute HAV infection resolves spontaneously in > 99% of infected individuals.
- Fulminant hepatitis is rare with a wide range of estimated rates, up to 1:10,000 or more in immuno-competent individuals.
- Patients with chronic liver disease are at an increased risk for developing severe or fulminant hepatitis.
- Mortality in fulminant hepatitis is rare and linked to hepatitis A in older age > 50 y.
## Patients Survival in Fulminant Viral Hepatitis Without OLT*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>66%</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>50%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>39%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>20%</td>
</tr>
<tr>
<td>Halothane</td>
<td>13%</td>
</tr>
</tbody>
</table>

*O’Grady et al, Gastroenterology 1988; 94: 1186.*
# Age-specific Mortality Due to Hepatitis A

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Case-Fatality (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3.0</td>
</tr>
<tr>
<td>5-14</td>
<td>1.6</td>
</tr>
<tr>
<td>15-29</td>
<td>1.6</td>
</tr>
<tr>
<td>30-49</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;49</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4.1</strong></td>
</tr>
</tbody>
</table>

Source: US Viral Hepatitis Surveillance Program, 1983-1989

Similar data CDC Hepatitis surveillance report No 58, 2003 p 1
Fulminant Hepatitis A in children

Number of reports is rising?
- Turkey  4 cases (6/04-11/06)
- UK      9 cases (1991-2000)
- Argentina 128 cases (5/82-9/02)
- Argentina 41 cases (9/03-1/06)
- Brazil  13 cases (1998-2007)

Reports are retrospective and released by individual centers

Rising Incidence of Fulminant Hepatitis A irrespective of age*

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>0</td>
</tr>
<tr>
<td>2004</td>
<td>3.4</td>
</tr>
<tr>
<td>2005</td>
<td>3.2</td>
</tr>
<tr>
<td>2006</td>
<td>6.0</td>
</tr>
<tr>
<td>2007</td>
<td>7.7</td>
</tr>
<tr>
<td>2008</td>
<td>13.0</td>
</tr>
</tbody>
</table>

- 35/568 HAV patients had fulminant hepatitis (KCH)
- Spontaneous survival 20/35 (57.1%)
- Transplanted 13/35 (37.1%)
- Died 5/35 (14.3%)

Total survival 85.7%

*Kim JM et al. Korean J Hepatol 2008;14:474
Etiology of Acute Liver Failure in Adults

Etiology of Acute Liver Failure in 3-18y olds

*Acute Liver Failure (US)/ Hepatology 2008;47:1401
Trends in the incidence of hepatitis A virus related acute liver failure in the United States.

The incidence of patients undergoing liver transplantation for HAV related ALF in the UNOS database significantly declined between 1988 and 2005 (P<.001). Similarly, the frequency of HAV patients enrolled in the ALFSG significantly declined between 1998 and 2005 (P=.007).

*Taylor RM et al. Hepatology 2006;44:1589
Outcomes of patients with HAV listed for liver transplantation in the UNOS database. All patients were listed between 1/98 and 9/15/05

*Taylor RM et al. Hepatology 2006;44:1589*
Outcomes of patients with HAV enrolled in the Acute Liver Failure Study Group* All patients were enrolled between 1/98 and 9/15/05 and followed for 3 weeks after enrollment

*Taylor RM et al. Hepatology 2006;44:1589
Outcomes of patients with HAV enrolled in the Acute Liver Failure Study Group*
All patients were enrolled between 1/98 and 9/15/05 and followed for 3 weeks after enrollment

Results
- 16 HAV patients recovered spontaneously (55%)
- 13 HAV patients were transplanted or died (45%)
Factors with an impact on fatality rate in fulminant hepatitis A

• Host
  ▪ Age
  ▪ co-infection with hepatotrophic viruses
  ▪ immune response?

• Virus
  ▪ genomic variations
  ▪ virulence

• Treatment for liver failure
  ▪ improved intensive care
  ▪ liver transplantation
Risk factors associated with fulminant hepatitis A and liver failure

• Age of infection
• Chronic liver disease and co-infection with other hepatotrophic viruses (HBV, HCV)
• Intake of paracetamol
• Viral factors?

• Pregnancy???
Increased severity of HAV infection

- In the elderly: hospitalization rates rose from 3% in 40-49y olds to 42% <age of 70y (Brown&Persley Southern Med J 2002;95:826)

- In HCV, HBV and HIV co-infection (Laurence JC Am J Med 2005;118:75)


*34/79458 acute hepatitis
13/34 Acute HAV 'with premature contractions, placenta separation, membrane rupture
Fulminant hepatitis associated with hepatitis A virus super-infection in patients with chronic hepatitis C

• In a prospective study, 27/595 adults with chronic liver disease (HBV, n=163) and chronic HCV, n=432) developed acute hepatitis A

• 17/27 patients who developed acute HAV had chronic HCV infection

• 7/10 patients with chronic HCV developed fulminant hepatitis A Vs 0/10 HBV patients

Vento S et al. NEJM 1998;338:286
Increased incidence of fulminant hepatitis A in previously unrecognized HBsAg carriers with acute hepatitis*

- Incidence of liver failure - 3.2% in patients hospitalized for acute hepatitis, irrespective of etiology (5/157)
- Incidence of liver failure in HBsAg+ subjects – 20.3% (36/177); P<0.001

**Conclusion**: HBsAg carriers were at 9 Fold increased risk of fulminant hepatitis A than non-carriers

*Chu CM, Liaw YF. Infection 2005;33:136
Search for host and viral factors associated with an increased risk for development of fulminant hepatitis A

• In spite of the unique single HAV serotype, some genetic diversity has been evident from the sequencing data obtained from a large number of HAV isolates
• Based on sequence variations at the VP1/2A junction, genotypes and subgenotypes have been defined
• So far - no confirmed correlation was found between defined HAV sequences and increased risk for developing fulminant hepatitis A. However the issue remains open.
Viral Risk factors associated with fulminant HAV*

- 19/76 subjects with acute ALF and encephalopathy were significantly older, had higher bilirubin levels, and were more likely to be females. (older age was not confirmed by multivariate analysis)

- 40/76 patients reported intake of medications of whom 19 took acetaminophen (<3.0gr/day) for less than 3 days

- 36/50 patients with available serum were HAV-RNA positive (>100 copies/ml)

- Phylogenetic analysis revealed 18 patients with genotype 1A, 12 patients 1B and 4 patients with genotype 3

- 9/19 patients with fulminant hepatitis A and encephalopathy had undetectable HAV-RNA (VP1/2A PCR), compared to 5/31 controls without ALF (P<.02)

- 8/19 patients recovered spontaneously and 10 were transplanted

- High bilirubin levels and low viremia were significantly related to risk of death or transplantation by mutivariate analysis

*Rezende G et al. Hepatology 2003;38:613
### Selected day 1 clinical features of patients with FH - ALFSG*

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous survival</th>
<th>Transplanted/Died</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>69</td>
<td>23</td>
<td>.008</td>
</tr>
<tr>
<td>MELD score</td>
<td>29</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (u) at admis..03</td>
<td>3362</td>
<td>1675</td>
<td>.03</td>
</tr>
<tr>
<td>Alk. Phosphat.</td>
<td>179</td>
<td>118</td>
<td>.02</td>
</tr>
<tr>
<td>Creatinine &gt;2md/dl</td>
<td>13%</td>
<td>54%</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3-4 encephalopathy</td>
<td>38%</td>
<td>69%</td>
<td>NS</td>
</tr>
<tr>
<td>Pressors</td>
<td>0%</td>
<td>46%</td>
<td>.0004</td>
</tr>
<tr>
<td>Intubation</td>
<td>25%</td>
<td>85%</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Taylor RM et al. Hepatology 2006;44:1589*
Models to Predict Transplant/Death in 29 Patients With Hepatitis A Enrolled in the Acute Liver Failure Study Group

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AURO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALFSG index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 Factor</td>
<td>20</td>
<td>100%</td>
<td>56%</td>
<td>65%</td>
<td>100%</td>
<td>.781</td>
</tr>
<tr>
<td>&gt;2 Factors</td>
<td>14</td>
<td>92%</td>
<td>88%</td>
<td>86%</td>
<td>93%</td>
<td>.899</td>
</tr>
<tr>
<td>&gt;3 Factors</td>
<td>9</td>
<td>62%</td>
<td>94%</td>
<td>89%</td>
<td>75%</td>
<td>.766</td>
</tr>
<tr>
<td>4 Factors</td>
<td>1</td>
<td>8%</td>
<td>100%</td>
<td>100%</td>
<td>57%</td>
<td>.538</td>
</tr>
<tr>
<td><strong>Other models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD ≥35</td>
<td>9</td>
<td>54%</td>
<td>88%</td>
<td>78%</td>
<td>70%</td>
<td>.707</td>
</tr>
<tr>
<td>King's College</td>
<td>5</td>
<td>31%</td>
<td>94%</td>
<td>80%</td>
<td>62%</td>
<td>.623</td>
</tr>
</tbody>
</table>

*Taylor RM et al. Hepatology 2006;44:1589*
Phylogenetic analysis of HAV in sera of Japanese patients with fulminant hepatitis

- Association between severity of hepatitis and genomic variations
- Mutations at the 5’ NCR corresponding to the internal ribosome entry site may increase severity of liver disease in HAV (N=27 patients)
- Full length genome study in 3 patients suggests that these changes are not related to genotype
- Similar changes were also found in HAV adopted for growth in tissue culture

**Investigators conclusion**: Genetic organization of HAV may influence replication and virulence

Fujiwara K et al. J Hepatol 200135:112
Fujiwara K et al. Liver Int 2005;25:194
Fujiwara K et al. Liver Int 2008, Epub
Molecular characterization of HAV in children with fulminant hepatic failure in Argentina: 9/2003-1/2006*

- N=41 children, age M 6.8y (1-15y), 22F/19M
- HAV-RNA analyzed through probes of the 5’ non-coding and VP1/2A regions
- 18/41 HAV cases positive for the 5’ NCR (39%) and 18/41 HAV cases for the VP1/2A region (39%)
- FHF variants had some minor differences in nucleotide or amino acid sequences as compared to self limited acute HAV cases with no common pattern of substitution, temporal and geographic parameters

*Munne MS et al. Liver Int  2008*
Putative Host Factors
(Familial Clustering)*

• 3 siblings developed fulminant hepatitis A in a family in Israel
• Cloning and sequencing of HAV in progress

Conclusions

- The incidence of fulminant hepatitis A is low but there seems to be an increase in reports in children.
- Improved intensive care and liver transplantation have markedly changed the fatality rates from fulminant hepatitis A.
- Major risk factors include age, underlying liver disease and intake of paracetamol.
- Conflicting and yet unconfirmed data have been reported on minor genetic substitutions of viral sequences with a putative impact on viral replication and cytopathic effect.
Thank You

The Hadassah-Hebrew University Campus – Jerusalem, Israel