“Vertically acquired hepatitis C virus infection: correlates of transmission and disease progression”

Dr. Silvia GARAZZINO
Paediatric Dept, Infectious Diseases Unit
Regina Margherita Children’s Hospital, Turin (IT)
European Paediatric HCV Network
Evolution of vertically acquired HCV-infection
Evolution of vertically acquired HCV-infection

- Currently, mother-to-infant transmission of HCV is the most common cause of HCV infection amongst children in developed Countries

- Estimates of the risk of mother-to-child transmission of HCV range from 3% - 7%

Tovo PA, WJG 2016
Diagnosis of HCV infection in children born to seropositive mothers

- Persistence of HCV antibodies beyond 18 months of age
- Serum HCV-RNA in at least two separate determinations

Primary HCV infection

At birth and in the first weeks of life:

- no jaundice
- no HCV-associated signs $\rightarrow$ no clinical diagnosis of infection
- a substantial proportion of children has normal or mildly increased ALT levels $\rightarrow$ ALT activity is a poor surrogate marker of infection
Sensitivity and specificity of HCV-PCR in 547 children born to seropositive mothers

<table>
<thead>
<tr>
<th>Age</th>
<th>Nº PCR</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>199</td>
<td>28 %</td>
<td>98 %</td>
</tr>
<tr>
<td>1 month</td>
<td>188</td>
<td>79 %</td>
<td>98 %</td>
</tr>
<tr>
<td>3 months</td>
<td>326</td>
<td>75 %</td>
<td>98 %</td>
</tr>
<tr>
<td>6 months</td>
<td>306</td>
<td>85 %</td>
<td>98 %</td>
</tr>
<tr>
<td>9 months</td>
<td>183</td>
<td>70 %</td>
<td>98 %</td>
</tr>
</tbody>
</table>

EPHN - J Med Virol 2006; 78: 305-10
Evolution of viraemia in infected children

- Large fluctuations over time
- Non-viraemic children may have increased ALT values and vice versa
- Possible spontaneous viral clearance
  - Negative HCV-PCR at the last 2 or 3 consecutive tests at least 12 weeks apart
Spontaneous viral clearance in vertically infected children

<table>
<thead>
<tr>
<th>Study</th>
<th>N° children</th>
<th>HCV RNA -</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHN Clin Infect Dis 2005</td>
<td>238</td>
<td>20 %</td>
</tr>
<tr>
<td>Yeung LT J Viral Hepat 2007</td>
<td>34</td>
<td>25 %</td>
</tr>
<tr>
<td>Moriné-Borjoan E AIDS 2007</td>
<td>12</td>
<td>25 %</td>
</tr>
<tr>
<td>Garazzino S Eur J Ped</td>
<td>45</td>
<td>27 %</td>
</tr>
<tr>
<td>Bortolotti F Gastroenterology 2008</td>
<td>240</td>
<td>11 - 16 %</td>
</tr>
<tr>
<td>Abdel-Hady M J Viral Hepat 2011</td>
<td>65</td>
<td>9 %</td>
</tr>
</tbody>
</table>
- SVC is associated with biochemical remission of hepatitis

- SVC usually occurs by 7 years of age (Ref: [Yeung LT, Farmand S, Garazzino S])
  → “conventional” antiviral therapy should be postponed beyond the preschool age, apart from selected cases

**Turin cohort:**
907 children born to HCV-infected mothers followed from birth

48 children diagnosed to be HCV-infected
45 HCV+ children enrolled
Median age at last visit: **12 years**

Genotype-3 infection is an independent predictor of SVC
Spontaneous resolution of viremia – host factors

- Positive IFN-γ responses against structural and nonstructural recombinant HCV-antigens (El-Kamary SS, 2013)
- Altered NK cells number and phenotypes (Indolfi G, 2016)
- Presence of the rs 12979860 single-nucleotide C/C of the interleukin 28B gene, particularly with genotype 1 infection (Indolfi G, 2014)

→ It is noteworthy that IL-28B elicits the transcription of IFN-stimulated genes that are responsible for antiviral activity
Children with SVC have higher ALT levels in the first two years of life when compared to those with persistent infection [Resti M 2003; Garazzino S 2014].

ALT levels are highest in the first two years of life then decline. They are poorly predictive of the underlying liver damage.

Fig. 2 Mean ALT levels over time in group 1 children (with sustained viral clearance) and group 2 children (with persistent viremia)
Overall increase in ALT levels is less frequent and enhanced than in adults.
Chronic HCV infection (I)

- Different clinical course in children as compared to adults.
- In children HCV progression is minimal or mild, generally asymptomatic.
- HIV co-infection accelerates progression.
- Other influencing factors: ethnicity, obesity, toxins, co-morbidities (hemolytic anemias, chemotherapy, immunosuppression) and genetic factors such as IL-28B genotype.

Tovo PA, WJG 2016
Chronic HCV infection (II)

- 30-40% of children → chronic active infection
  - = persistent viraemia, abnormal ALT values and sometimes hepatomegaly (1/4 in the first decade of life)

- severe hepatic damage is rare but liver transplantation may be required

- Hepatocellular carcinoma is extremely rare
Chronic HCV infection (III)

- Children grow regularly without variations from normal height and weight ranges.
- A wide spectrum of histopathological alterations has been found in the liver.
- The grade of disease varies from minimal to moderate - pictures of overt cirrhosis are rare.
- Liver biopsy is not a routine procedure but still the gold standard to quantify liver damage; transient elastography may help monitoring the evolution of liver fibrosis over time.
- New biomarkers of liver injury (ITIH4, C4a, arginase 1) have been shown to reflect liver fibrosis and steatosis.
Transient elastography

32/45 patients

- Stiffness 4 - 5 kPa: 7 HCV RNA-negative
  14 HCV RNA-positive

- Stiffness 5.1 - 6.7 kPa: 9 HCV RNA-positive

- Stiffness of 8.1 and 8.6 kPa in 2 viremic children respectively
Humoral immunity

Virtually all vertically infected children develop specific antibodies against HCV. Some pts with SVC can seroconvert after many years.

A few HCV RNA-positive, antibody-negative asymptomatic children have been described.

Tovo PA, WJG 2016
Extrahepatic manifestations

Mixed cryoglobulinemia is the most frequent HCV-related extrahepatic manifestation in adults

→ uncontrolled clonal expansion of B-lymphocyte with membranoproliferative glomerulonephritis, purpura, arthralgia, peripheral neuropathy and ultimately non-Hodgkin’s lymphoma

Mixed cryoglobulinemia had not been previously described in children.

<table>
<thead>
<tr>
<th></th>
<th>Cryoglobulins</th>
<th>Other extrahepatic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=12)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Positive (n=33)</td>
<td>13</td>
<td>Renal impairment (2) diabetes mellitus (1)</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

median age 6.6 years

Garazzino S, Eur J Ped 2014
## Non-organ specific autoantibodies (NOSAs)

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° of children</td>
<td>47</td>
<td>51</td>
<td>40</td>
<td>37</td>
<td>39</td>
<td>80*</td>
</tr>
<tr>
<td>NOSAs +</td>
<td>34%</td>
<td>65%</td>
<td>32.5%</td>
<td>16%</td>
<td>8%</td>
<td>40%</td>
</tr>
<tr>
<td>Anti-smooth muscle</td>
<td>17%</td>
<td>51%</td>
<td>17.5%</td>
<td>3%</td>
<td>5%</td>
<td>40%</td>
</tr>
<tr>
<td>Anti-LKM1</td>
<td>15%</td>
<td>8%</td>
<td>10%</td>
<td>5.5%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>ANA</td>
<td>9%</td>
<td>10%</td>
<td>7.5%</td>
<td>5.5%</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

a: Muratori P Clin Infect Dis 2003; 37:1320-6  
e: Gehring S Word J Gastroenterol 2006;12:5787-92  
f: Hamed ME Saudi J Gastroenterol 2013;19:262-70

*only genotype 4

LKM-1 positivity, even if not the most common, was the most peculiar autoimmune feature of children with chronic hepatitis C (not found in controls)
Table 1 Genotype and HCV-related phenomena according to virological status

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Genotype</th>
<th>NOSAs</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1  2  3  4  NA</td>
<td>ANA  SMA  ANA + SMA  LKM</td>
<td></td>
</tr>
<tr>
<td>Negative (n=12)</td>
<td>3  0  6  0  3</td>
<td>0  5  2  0</td>
<td></td>
</tr>
<tr>
<td>Positive (n=33)</td>
<td>21  3  6  3  0</td>
<td>4  8  3  2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24  3 12  3  3</td>
<td>4 13  5  2</td>
<td></td>
</tr>
</tbody>
</table>

Age distribution at first detection of NOSAs

Autoantibodies do not predict liver fibrosis progression!

Garazzino S, Eur J Ped 2014
Vertically-acquired HCV infection is characterized by a high chronicity rate, but mild liver injury for most

This subclinical evolution does not rule out long-term negative outcome

NOSAs and cryoglobulins may be an occasional finding in children with chronic infection, independently from viremia, but autoimmune diseases or HCV-associated extrahepatic manifestations are rare

In the era of DAAs, optimal timing for treatment in children should be defined

Treatment of HCV-infected women in childbearing age (or earlier?) is crucial to prevent vertical infection
Thank you for your attention