VIRAL HEPATITIS IN THE ARCTIC – ON THE EDGE OF EXTINCTION

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Arctic viral hepatitis working group since 2006 with experts from the circumpolar area.

Thanks to
- Brian McMahon, Alaska,
- Anders Koch,
- Vladimir Chulanov, Russia,
- Gerry Minuk, Canada
  - for sharing data and slides

- Nothing to disclose
Viral hepatitis in the Arctic
What matters?

- Hepatitis A and vaccination against hepatitis A
- Hepatitis E
- Hepatitis B
  - Among children
  - Vaccination strategies
  - Risk of cancer
  - Genotypes
- Hepatitis D

The hepatitis viruses

<table>
<thead>
<tr>
<th>Name of Virus</th>
<th>Hepatitis A Virus (HAV)</th>
<th>Hepatitis B Virus (HBV)</th>
<th>Hepatitis C Virus (HCV)</th>
<th>Hepatitis D Virus (HDV)</th>
<th>Hepatitis E Virus (HEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
<td>Picornavirus</td>
<td>Hepadnavirus</td>
<td>Flavivirus</td>
<td>Deltavirus</td>
<td>Hepevirus</td>
</tr>
<tr>
<td>Viral genome</td>
<td>ssRNA</td>
<td>dsDNA</td>
<td>ssRNA</td>
<td>-ssRNA (-ve)</td>
<td>ssRNA</td>
</tr>
<tr>
<td>Transmission</td>
<td>Enteric</td>
<td>Parental</td>
<td>Parental</td>
<td>Parental</td>
<td>Enteric</td>
</tr>
<tr>
<td>Incubation period</td>
<td>15-45 days</td>
<td>45-160 days</td>
<td>15-150 days</td>
<td>30-60 days</td>
<td>15-60 days</td>
</tr>
<tr>
<td>Chronic Hepatitis</td>
<td>No.</td>
<td>Yes. 10% chance</td>
<td>Yes. &gt;50% chance</td>
<td>Yes. &lt;5% of coinfectious</td>
<td>No.</td>
</tr>
<tr>
<td>Cure?</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
<td>Cure rate around 50%</td>
<td>No cure. Treatment: Alpha interferon for 12 months.</td>
<td>No cure. Treatments usually tackle the symptoms</td>
</tr>
</tbody>
</table>
Hepatitis A

- Is endemic with epidemics in the majority of the world
- In the Arctic we saw an epidemic pattern
- In children aged <6 years, 70% of infections are asymptomatic. If illness, < 30% with jaundice
- Among older children and adults, infection is typically symptomatic, with jaundice occurring in >70% of patients.
- Can be prevented by vaccination. Most part of the world a 2-dose schedule after 12 month of age
- Vaccination at a younger age less immunogenic
- Vaccination probably lifelong protection
- Universal HAV vaccination in Alaska, but not in Russia, Greenland and Canada
Hepatitis A (HAV)

- Denmark Incidence 2013: 1.8/100,000 PYRS

Hepatitis A cases in Denmark

HAV epidemics in Greenland

- 1970-74
  - 11/15 districts
  - 4,961 cases (11%) of clinical hepatitis
  - Incidence: 2,606/100,000 persons per year
  - 93% of cases among persons aged 0-25 years
  - Immunity in older persons compatible with 1947-48 epidemic
  - Attack rate Danes: 1/6 AR for Greenlanders
  - Case-fatality rate 0.3%
HAV antibodies at present in Greenland

HAV antibodies
Sisimiut & Ilulissat 1994 (Langer et al).

Hepatitis A in Alaska Natives and Non-Natives in Alaska, by Year
Hepatitis A in Children in Alaska and the Arctic

• All children in Alaska regardless of ethnicity have been given hepatitis A vaccine since 1997 (>8 lower 48)
• Two long-term studies on Alaska Native children vaccinated ages 3-6 years and 6 months-15 months show >90% protection at 20 years and 15 years
• By 2014 the Arctic rated as low risk area by the WHO

Hepatitis E (HEV)

• Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths (Rein, 2012).
• Most cases occur in developing countries
• Hepatitis E case fatality is highest among pregnant women, which can be as high as 20% (3. trimester)

Seroprevalence

• Worldwide 1-50%, (highest South Asia, North Africa)
• Denmark 1983 (31.6%), 2003: (20%), farmers: 51% (Christensen, 2008)
• Greenland: 3% seroprevalence (~rate of false test positivity) (Langer et al, 1994)
Hepatitis B epidemiology

- About 2 million have markers of exposure to HBV (HBcAb+)
- Every year around 4 million new cases of HBV infection
- 4000 million chronic carriers
- Mortality: 1 million/yr
- Can be prevented with vaccination

HBV - Risk of chronic infection by age at infection
Route of HBV transmission

Transmission of HBV Infection
- Sexual Transmission
- Blood Transfusion (Now very low risk in USA as all blood is screened)
- Organs and Tissue Transplantation
- Mother to Baby At Birth
- Contaminated Needles and Syringes (IVDA)
- Child to Child, Early Childhood

Hepatitis B (HBV) in Denmark
- Chronic HBV Denmark (2014): Incidence 4.8/100,000
- Prevalence (2007), total 4,466 persons:
- Age < 25 years: 0.35%, age > 40 years: 0.08%

New Hepatitis B cases in Denmark
Greenland HBV Markers by age 1965-1998

40 – 75% exposed (HBcAb+)
7 – 20% chronically infected (HBsAg+)


Hepatitis B incidence
Greenland

Incidence per 100 person years

(Børresen, 2015)
Hepatitis B in Alaska

- 1972-73: High incidence acute HBV
- 1973-1974: Serosurvey found prevalence of HBsAg in 12 villages in Southwest AK 6.4% (0-20.1%)\(^1\)
  - 1974-1978: Incidence study 1280 seronegative persons: 14.8% HBV\(^2\)
  - 29% infected < 5 years of age became chronic carriers
  - Transmission mainly horizontal from child to child probably through open cuts and scratches
  - HBsAg was found all over environmental surfaces (school lunchroom table tops, homes of carriers)

\(^1\)Schreeder Am J Epidemiol 1983; 118:543-9
\(^2\)McMahon JID 1985; 151:599-603
HBV In Alaska

- From 1983-1987, 52,000 Alaska Native Persons were tested for hepatitis B seromarkers and 40,000 with negative markers were vaccinated
- (3.1% HBsAg pos, 1536 included for follow-up).
  - 657 children < age 20 with chronic hepatitis B virus (HBV) infection were identified
  - All identified persons have been followed prospective since then (median f/u 25 years)
  - All newborns since have received hepatitis B vaccine starting at birth (0,1,12 month)
    - Children of HBsAg-positive mothers also receive HBIG at birth

Incidence Symptomatic HBV in Alaska Native Peoples 1981-2008

CDC/HIS Vaccine Demonstration Program begins in 16 villages of Yukon Kuskokwim Delta
Statewide Program begins-all susceptibles immunized
- pregnant women screened/infants HBvax + HBIG
- begin universal newborns immunization

McMahon et al
HBV In Alaska

Number of HBsAg-positive Alaska Native (AN) Children Under 20 Years of Age: 1988-2008

Prevalence of HBsAg in 20,657 persons <20 years screened 1983-1987 was 3.2%. In 2012, no AN children are known to be HBsAg+.

Hepatitis B Vaccine Coverage
Lifetime Risk of Hepatocellular Carcinoma (HCC)

- Hepatitis B (HBV): lifetime risk of HCC: 1%-25%
- Rates of Hepatocellular carcinoma (HCC) are different within Arctic populations

<table>
<thead>
<tr>
<th>Area</th>
<th>ASR 1969-88</th>
<th>ASR 1989-98</th>
<th>SIR (95% CI) Connecticut</th>
<th>SIR (95% CI) Denmark</th>
<th>SIR (95% CI) Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumpolar</td>
<td>8.0</td>
<td>4.0 (3.0-5.2)</td>
<td>3.1 (2.2-4.3)</td>
<td>4.1 (3.0-5.3)</td>
<td></td>
</tr>
<tr>
<td>Alaska</td>
<td>15.1</td>
<td>7.2 (5.1-9.9)</td>
<td>5.5 (3.9-7.6)</td>
<td>7.7 (5.2-10.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 ♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenland</td>
<td>5.7</td>
<td>2.7 (1.5-4.5)</td>
<td>2.1 (1.2-3.4)</td>
<td>2.8 (1.5-4.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9 ♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1.0</td>
<td>0.4 (0.0-2.2)</td>
<td>0.3 0.0-1.7</td>
<td>0.4 0.0-2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASR Age Standardized rates, SIR Standard Incidence ratios

Based on Friberg, Storm, Rasmussen and McMahon

HCC Inuit
1969-88, 1989-97,
Different incidence of HCC within the Arctic

HBV - Risk of chronic infection and risk of HCC
- Host:
  - Age at infection
  - Area of origin
  - Sex (male)
  - Co-infection with HIV, HDV,
  - Aflatoxin
- Virus:
  - Genotype (A-H)
  - Viral load, HBeAg positivity
  - Mutations

HBV – Genotype (A-H)

Geographic distribution of HBV genotypes
HCC in Alaska Natives <20 years of age

P value for trend = 0.002

Alaska Genotype F

Number of Cases of HCC Occurring in Young Persons by Age and HBV Genotype*

*No cases occurred in persons infected with HBV genotypes B6 or C

McMahon el al, unpublished data
Genotype distribution in the Arctic (%)

<table>
<thead>
<tr>
<th></th>
<th>Alaska</th>
<th>Greenland</th>
<th>Greenland</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=100</td>
<td>N=100</td>
<td>N=52</td>
</tr>
<tr>
<td>A</td>
<td>13</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>15</td>
<td>91</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>56</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1. McMahon et al. 2014
3. Krarup et al. 2004

Questions raised

- HBV genotype distribution different in Alaska and Greenland
  - F frequent in Alaska, not in Greenland
  - B frequent in Greenland, not in Alaska
- Incidence of HCC high in Alaska, low in Greenland
- HBV genotypes related to morbidity in Alaska
  - F related to HCC in young persons
- What is the impact on genotype B on liver disease in the Arctic?
Worldwide - Two major subtypes of Hepatitis B virus genotype B

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
<th>Risk of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bj ('Japan')</td>
<td>B1 Non-recombinant</td>
<td>Less commonly associated with HCC</td>
</tr>
<tr>
<td>Ba ('Asia')</td>
<td>B2 Intergenomic recombination with HBV/C in core promoter/precore/core genome region</td>
<td>Higher risk of HCC development in HBV carriers</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B5</td>
<td></td>
</tr>
</tbody>
</table>

Sakamoto et al. J Gen Virol 2006
Sugachi et al. Gastroenterology 2003
Kao et al. Gastroenterology 2000
Orito et al. Hepatology 2001

Comparative study of HBV B subgenotypes in the Arctic 2007

- 50 HBV carriers
  - Alaska: 31
  - Canada (Baker lake): 8
  - Greenland (Sisimiut): 11
- All native persons
- No HCV or HIV coinfection
- Classification
  - Asymptomatic
  - Chronic liver disease
  - LC or HCC
- 20/50 HBV strains complete genome sequenced
  - 6 Alaska
  - 8 Canada
  - 6 Greenland
- All 50 HBV strains amplified in EnhII/Cp/preC/C regions
- Comparisons with bank HBV sequences from Asia

Phylogenesis based on complete genome sequences

- Asian/Japanese/Arctic HBV strains in 6 distinct clusters
- Asian/Japanese strains in known clusters Bj/B1 + Ba/B2-B5
- All Arctic strains in distinct separate (unclassified) cluster
- Suggested designation B6

Morbidity and HBV B subgenotypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>HBV/B6 (n = 50)</th>
<th>HBV/Bj (n = 50)</th>
<th>HBV/Ba (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td>Matched</td>
</tr>
<tr>
<td>Age, mean ± SD, years</td>
<td>48.1 ± 19.6</td>
<td>48.1 ± 16.9</td>
<td>47.9 ± 13.1</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Hepatitis B e antigen</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA &gt;5 log copies/mL</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical state</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>35 (61)*</td>
<td>22 (44)</td>
<td>15 (30)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>15 (30)</td>
<td>24 (50)</td>
<td>21 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver cirrhosis/hepatocellular carcinoma</td>
<td>0</td>
<td>.4 (6)</td>
<td>14 (26)*</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (% of participants, unless otherwise indicated. HBeAg, hepatitis B e antigen; NS, no significant difference.

* For B6 vs. Ba, P = .0026; for Bj vs. Ba, P = .0143.
* For B6 vs. Bj, P = .0001; for B6 vs. Ba, P = .0006.
* For B6 vs. Bj, P = .0006; for B6 vs. Ba, P = .0541.
* For B6 vs. Bj, P = .0001; for B6 vs. Ba, P = .0214.
Hypothesis: Co-existence of HBV B genotype and Eskimos

- Eskimos migrated from East Asia/Siberia to Alaska 10,000 BC
- Later developed into 3 groups
  - Aleutians (Aleuts, West Alaska)
  - Yupik (West Alaska)
  - Inuit (Point Barrow, Alaska, Canada & Greenland)
- The Inuit spread from Alaska eastwards 1,000 AD
- Subgenotype B6 followed the Eskimos from Asia?
  - Developed from B1?
  - Common forefather of B1/B6?

Hepatitis B – genotype B

- A new HBV/B subgenotype B6 identified
- All 50 Arctic HBV/B strains belonging to that subgenotype
- Related to the non-recombinant Japanese Bj/B1 subgenotype and different from recombinant Asian Ba/B2-B5 subgenotypes
- Non-recombinant B1 & B6 appear less virulent than B2-B5
- Classification of HBV/B into recombinant and non-recombinant forms
- B6 May have followed the Eskimos from Asia
- Larger studies on clinical manifestations of B6 needed
HBV in the Arctic

- HBV vaccination has eliminated new cases of HBV among children in Alaska
- Less long-term consequences than expected in Greenland as compared with Alaska – Different genotypes
- Infection in the 80és in Canada and Alaska among children, and in Greenland in teenage years
- New ‘Arctic’ B₆ sub-genotype identified, related to benign Japanese B₁ sub-genotype

Hepatitis D – delta virus

- Worldwide, 8 genotypes (clades), genotype I most adverse outcomes
- Presence of HBV-DNA and HDV-RNA is associated with a lower HBV remission rate
- Super-infection with HDV has a higher risk of chronicity and worse long term outcome than HDV co-infection
- Hepatitis D is only present in Greenland and Chukotka in Russia in the Arctic
- However different genotypes (I in Greenland, II in Chukotka)
- Does Hepatitis D matter?
Greenland HDV by area

Hepatitis B and D outbreak in Itilleq near Sisimiut in Greenland

Børresen et al., Journal of Viral Hepatitis, 2009,
Severity markers for HBsAg-positive, 2006-2007

<table>
<thead>
<tr>
<th></th>
<th>Children (n=15) (%)</th>
<th>Adults (n=16) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 45 I/U</td>
<td>73</td>
<td>38</td>
</tr>
<tr>
<td>Viral load &gt; 1 mio. IU/mL</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis D (HDV) positive</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>HDV-seroconversion</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

Regression model:
Hepatitis D the strongest predictor for elevated ALT (liver damage)
In 2009, additional 2 children HDV seroconverted

HBV in Itilleq – Conclusions

- High prevalence of chronic HBV infection, especially among children (genotype D)
- Elevated liver enzymes in chronic infected (HBeAg-positive) children
- Super-infection with Hepatitis D most likely, (clade I)
- Ongoing HDV outbreak in Itilleq
Viral hepatitis – On the edge of extinction?

- Hepatitis A By 2014 the Arctic rates as low risk country.
- Vaccination against hepatitis A and B in parts of the Arctic is a real success story.
- Hepatitis B – In Alaska the prevalence of HBsAg in children has been reduced to 0.
- Genotype F in Alaska sucks – but is dying out.
- New ‘Arctic’ B₂ sub-genotype identified, related to benign Japanese B₁ sub-genotype.
- Outbreak of Hepatitis D in Greenland - is HDV a treat?
- Hepatitis B introduced in the universal childhood vaccination programme in Greenland in 2010.

Tak for opmærksomheden