The Effect of Genotype/Subgenotype of Hepatitis B Virus on HBeAg Expression and Perinatal Transmission

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The clinical implications of hepatitis B virus genotypes and HBeAg in pediatrics

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HBeAg

Genome: partially double stranded DNA
Capsid: HBeAg
Polymerase

L-HBsAg
S-HBsAg
M-HBsAg

Envelo

X protein
HBeAg
Non-particulate proteins

Relative levels
HBV DNA
ALT

Time (years)
0
10
20
30

Liver activity
Mild or no necroinflammation
Moderate to severe necroinflammation
Necro-inflammation
Absent

Phase
High replicative/low inflammatory
Immune clearance
HBeAg-negative Chronic Hepatitis
Non-replicative

Anti-HBc
HBeAg
HBsAg
Anti-HBs
Anti-HBe
**Function of HBeAg**

- Not required for viral assembly or replication but is important for natural infection *in vivo*.
- Clinically
  - Index of viral replication
  - Infectivity
  - Severity of disease
  - Response to antiviral treatment

**Immunoregulatory protein**
- Immunogen
- Tolerogen
- ↓ Innate IR

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https://classconnection.s3.amazonaws.com/129/flashcards/475129/gif/vasa_previa1352911684347.gif
HBeAg Expression and Mother-to-Child Transmission

HBeAg+ve vs HBeAg-ve 9.26% vs. 0.23%, p <0.001

HBeAg and Anti-HBe Detection by Radioimmunoassay: Correlation With Vertical Transmission of Hepatitis B Virus in Taiwan

Cladd E. Stevens, Robert A. Neurath, R. Palmer Beasley, and Wolf Szmuness
HBV Viral Load
HBeAg-ve versus HBeAg+ve

A
HBeAg (-) mothers
n = 222
2.7 ± 1.4 log_{10} copies/ml

B
HBeAg (+) mothers
n = 81
7.4 ± 1.9 log_{10} copies/ml

Wen et al, J Hepatol 2013; 59:24 -30
Predictive Rates of HBV Infection versus Maternal VL

![Graph showing predictive rates of HBV infection versus maternal viral load](image)

*Wen et al, J Hepatol 2013; 59:24-30*
Regional Differences in HBeAg-positivity

- Sub-Saharan Africa
  - HBeAg+ve
  - HBeAg-ve

- South East Asia
  - HBeAg+ve
  - HBeAg-ve


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HBeAg-positivity and Genetic Factors?

Perinatal transmission of hepatitis B virus in high-incidence countries

Y. Ghendon

*World Health Organization, Geneva, Switzerland*

(Accepted 27 March 1987)

Genetic factors in perinatal transmission of HBV

The expression of HBeAg seems to be determined genetically: most Chinese carrier women but rather fewer African carrier women are HBeAg-positive and throughout children born to Chinese carrier mothers, 40–70% become carriers; to African mothers about 30%; to Asian mothers about 6–8% and to European mothers almost none (Derso et al., 1978; Stevens et al., 1975; Wong et al., 1980).
The Genotypes of HBV

Kramvis & Kew J Viral Hepat 1998; 5:357-367
Kramvis et al Vaccine 2005;23:2409-2423
Kramvis Intervirology 2014;57:141-150
Expression of HBeAg

HBV DNA

Precore/core

Precore mRNA

Precursor

N-terminal cleavage

C-terminal cleavage

HBeAg

G1896A Mutation in Genotype D

DNA

transcription

TA\textsuperscript{A}

Precore/core gene

A\textsubscript{1762T}/G\textsubscript{1764A}

RNA

translation

U\textsubscript{AA}

G1896A

precursor

G1896A Mutation in Genotype D

- DNA transcription
- RNA translation

A1762T/G1764A

Precursor

Bar graph: C, F, E, D, C, B, A
Subgenotype A2
Subgenotype A1
The Effect of Genotype/Subgenotype on HBeAg Expression
Geographic Distribution of Genotype A

Subgenotype A1
Subgenotype A2
The Slave Trade

9th to 19th Century A.D.
Slave trade

To Europe

Triangular Trade
SAINTAGO

To N. America

To W. Indies

To Brazil

Slave coast
SAO TOME

Luanda
Benquela

Mombasa

ZANZIBAR

Mogadishu

To Arabian & Indian Subcontinents

From E. Indies

Slave Entrepot

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Kramvis & Paraskevis Antiviral Ther 2013; 18:513
North Africa: The Other Side of Europe's Migrant Crisis

October 7, 2016 | 09:16 GMT
Changing HBV Genotype Distribution


First Epidemiological and Phylogenetic Analysis of Hepatitis B Virus Infection in Migrants From Mali

American Journal of Epidemiology
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DOI: 10.1093/aje/kwx064

Takano et al J Gastroenterol 2017; DOI:10.1007/s00535-017-1315-4

Original Contribution

Characteristics of US-Born Versus Foreign-Born Americans of African Descent With Chronic Hepatitis B

J Gastroenterol
DOI 10.1007/s00535-017-1315-4

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Natural history of chronic hepatitis B virus infection in children in Japan: a comparison of mother-to-child transmission with horizontal transmission

Hassan et al Am J Epidemiol 2017; DOI:10.1093/aje/kwx064
Takano et al J Gastroenterol 2017; DOI:10.1007/s00535-017-1315-4
### Comparison of US versus Foreign Born African Americans with Chronic Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>USAA</th>
<th>FBAA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>47 years</td>
<td>40 years</td>
</tr>
<tr>
<td><strong>Sexual transmission</strong></td>
<td>59%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>HBeAg-positivity</strong></td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td>CH</td>
<td>IC</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>A2</td>
<td>A1/E</td>
</tr>
</tbody>
</table>

#### Diagrams:

- **A)** USA: 84%, Other: 16%
- **B)** East Africa: 78%, Other: 19%
- **C)** West Africa: 67%, Other: 4%
- **D)** Other: 82%, Other: 2%

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Hassan et al Am J Epidemiol 2017; DOI:10.1093/aje/kwx064
Comparison of MTCT *versus* Horizontal in Japanese Children

<table>
<thead>
<tr>
<th></th>
<th>MTCT</th>
<th>Horizontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype*</td>
<td>C</td>
<td>A or B</td>
</tr>
<tr>
<td>HBeAg-negativity at 15 years of age*</td>
<td>33%</td>
<td>45%</td>
</tr>
<tr>
<td>Hepatitis &lt; 4 years*</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>HCC at 30 years</td>
<td>6%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Take Home Message

One size does not fit all!

We need tailor-made strategies for the prevention of perinatal transmission and genotypes/subgenotypes may need to be taken into account!
BWTS Programme “Bilateral (International) scientific and technological cooperation (BSTC)”