

Minutes: Viral Hepatitis Working Group Meeting **September 21, 2010, Copenhagen, Denmark**

Participants

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Meeting opening

Greeting by Karin Ladefoged and Anders Koch. Wellcome to all. Thanks to sponsors. Round table introduction.

Alex Vorsters. Viral hepatitis Prevention Board (VHPB).

VHPB was established in 1992. First actions related to hepatitis B European organization. Every year the group focuses on the viral hepatitis situation in an European country. In 2010, Portugal and in 2011 Bulgaria. Supported by unrestricted grants from the industry.

Journal: Viral hepatitis

Web site: www.vhpb.org

Session 1. The year in the Arctic HBV research

Chairpersons: Gert Mulvad and Malene Børresen

Yasuhito Tanaka. Department of Virology and liver unit. Nagoya City University Graduate School of Medical science. Japan.

Molecular epidemiology and clinical manifestations of HBV genotype D worldwide.

- Distinct geographic distribution of subgenotypes
- D1 Central Asia, Middle East, Europe
- D2 Japan, Alaska,
- D3 Alaska, Canada, Europe, Russia
- D5 India. D5 being the oldest subgenotype
- D6 Greenland

A study from Saudi Arabia suggests that D1 is the most pathogen subtype.

The importance of core and precore mutations for viral replication associated with hepatocellular carcinoma (HCC) was discussed. Core promoter mutation combinations by genotypes were presented.

CP1: G1757/T1762/A1764

CP2: A1757/T1761/A1766

CP3: T1773/G1775

CP1 and CP2 have been found in genotype F and Bj and increase the risk of HCC.

Brenna Simons. Alaska Native Tribal Health Consortium.

HBV inactive carrier phase and clinical significance

In a cohort of 1500 HBV infected patients were 777 inactive HBsAg pos. anti-HBe carriers with normal ALAT and HBV-DNA < 2000 iu/ml. Among them 92 were identified who could be followed through eight years.

Changes of viral load followed different patterns:

- Steady but low
- Fluctuating
- Elite (undetectable viral load)
- Increasing
- Decreasing

Most seroconverters belonged to the elite group

It was discussed whether the inactive phase followed an evolution from fluctuating to steady low and further to the elite phase or whether the inactive phase could evolve in different directions: Steady, fluctuating or elite phase

Brian McMahon. Alaska Native Tribal Health Consortium.

Update in chronic HBV and predictors for reactivation of HBeAg lost carriers.

- HBV vaccination was introduced in Alaska 1981. Since then there has been 23 breakthrough infections with HBcAb but no case of chronic HBV infection and the incidence of HCC has declined from 2.8 to 0.3 per 100.000 in Alaska.
- Although all children lose HBV antibodies after 15 years there is no need for boosters.
- Grade 1 evidence for treating compensated HBV cirrhosis which may lead to reversal of fibrosis and better outcome. No indication for treating immunotolerant or inactive carriers (Lok and McMahon, Hepatology 2007).
- HBsAg level may predict liver disease (Brunetto, Gastroenterology 2010).
- Alfa-foetoprotein (AFP). Good prognostic marker. Levels above 10ng/ml has a high PPV for HCC.
- Clearance of HBsAg amounts to 0.7% per year. Hereafter no case of cirrhosis has developed but 6 patients had developed HCC median 7.3 years after clearance (McMahon, Hepatology 2010)
- Risk factors for chronic complications:
 - Men
 - BMI, inverse correlation
 - Genotype C as compared to A2, D2/D3 and F
 - Viral load > 20.000iu/ml
 - HBV mutations
 - HBsAg and HBeAg levels
 - Fibrosis markers
 - AFP

Malene Børresen, Statens Serum Institut, Copenhagen.

HBV Research in Greenland.

- Among population based cohorts comprising 8879 persons, 650 was HBsAg positive, 3069 HBcAb positive, but HBsAg negative, 5160 HBcAb negative
- Incidence was highest in the age group 10-25 years
- Chronic carriers amounted to 20% of infected.
- HBsAg clearance was 0.86% per year
- SIR for HCC was 38.5 per 100.000. For cirrhosis it was 24. The SIR for HCC and cirrhosis are lower than in other populations
- Compared to non-infected HBV carriers had x4 increased risk for cirrhosis and x11 increased risk for HCC
- 15% of the population had HDV antibodies. The low heterogeneity of HDV pointed at a recent introduction.

Jeff Potts, Community of Acquired Infections Division, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada.

HBV research in Canada

Jeff Potts presented two ongoing studies:

- Comparison of HCV/HBV clearance rate among the viremic First Nations and Caucasians; evaluation of the possible impact of different genotypes. Epidemiological studies have indicated that North American indigenous people can clear HCV more efficiently than Caucasians. Immunological studies support that. So the working hypothesis is that FN people clear HCV/HBV virus better than Caucasians.
- Study of the association between hepatitis B virus longitudinal genetic variability and clinical outcome in circumpolar indigenous populations. Three populations were studied: Greenland (genotype D), Canada (genotype B6), USA (genotype F).

Vladimir Chulanov. Reference Center for Viral Hepatitis Monitoring. Central Research institute of Epidemiology. Russia

HBV Research in Russia

- HBV vaccination since 1007. &4 mill. Vaccinated. 4.8 x decrease of carrier state.
- Prevalence of chronic infected: 25 per 100.000 in Arctic Russia
- Studies from the Chukchi region revealed a prevalence of HBsAg of 11.2% among indigenous people, 1.4% among non-indigenous. The corresponding prevalences of HCV were 2.3% and 5.4%. 72% of HBV were genotype D, subtypes D3 in 66%, D2 in 28% D2 and D1 in 6%. 29% of HBV were genotype C.
- Subtypes were geographically clustered in Chukchi. HDV was 5 x more frequent among indigenous people and mainly associated with HBV genotype D3.
- The low heterogeneity of HDV pointed at a recent introduction.

Session 2.

Chairpersons: Chong Gee and Flemming Stenz

Flemming Stenz. Chief Medical office, Nuuk, Greenland.

Introduction of hepatitis B vaccination in Greenland – the political process and considerations.

Good news. It has finally been politically decided to include HBV vaccination in the vaccination program for children per September 1, 2010 together with vaccination against Streptococcus pneumonia. All newborn children will be vaccinated and there will be a catch up vaccination of the 12 years old children.

Stephen Linvingstone, Alaska Native Tribal Health Consortium.

HCV in Alaskan natives.

- In the period 1994-2005 a total of 2054 anti HCV patients were identified. 1234 persons were enrolled in an outcome cohort. Among them 78.4% were HCV-RNA positive, 65% genotype 1, 21% genotype 2, 14% genotype 3. Most patients were diagnosed at age 40-60 years. 54% were women.
- High alcohol intake was associated with end stage liver disease and liver related mortality. I
- Intention to treat response rates were 19% in genotype 1, 68% in genotype 2 and 53% in genotype 3. Among those who completed treatment response rate was 44% for genotype 1, 85% for genotype 2 and 80% for genotype 3. In total 39% discontinued treatment.
- Immunological studies were mentioned as were virological investigations. It had been demonstrated that increased non-synonymous mutations were associated with mild disease and few viral variants with severe disease.
- Genetic polymorphism in genotype 1 is associated with variation in response rate (Tanaka, Nature Genetics 2009). This polymorphism shows wide variation in distribution in different populations.

Peer Brehm Christensen. The Department of Infectious Diseases, Odense University Hospital
Hepatitis E from a Danish perspective

The history of hepatitis E was discussed. In 1990 the hepatitis E genome was cloned. In 2007 hepatitis E vaccine was introduced, Since 2008 cases of chronic hepatitis E have been described. Recovery following treatment with ribavirin was mentioned in 2010. Four genotypes have been detected: genotype 1 in India, 3 in Western Europe, 4 in China. In univariate analysis was found association with pig farming

Chong-Gee Teo. CDC Division of Viral Hepatitis, Atlanta.

Evaluating performances of anti-HEV IgM and IgG assays.

- Prerequisite to hepatitis E surveillance are IgM anti HEV, IgG, anti-HEV, animal anti-HEV, HEV-RNA, HEV genotype.
- IgM anti-HEV is mainly used for diagnosis and surveillance of incident HEV infection
- Two in-house and four commercial assays of IgM anti-HEV were compared. Sensitivity ranged from 72% to 98% and specificity from 78% to 96%.
- Persistence of IgG anti-HEV may not be long-term

ICCH15 in Fairbanks was introduced by **Mike Bruce.**

Anders Koch introduced the **Working Group Website: www.arcticinfdis.com.**

Session 3.

Chairpersons: Jeff Potts and Tom Hennessy

Roundtable discussion – HBV preparedness and awareness

The following aspects were discussed

- Do representative countries have a clear sense of hepatitis B and hepatitis C disease burden (i.e., current prevalence and incidence rates) and molecular epidemiology in their jurisdictions?
- Are transmission risk factors common across the region?
- Are prevention policies and programs in place and have they been evaluated for effectiveness?
- Are screening, diagnostics and treatment protocols in place that could be easily inventoried and analysed for comparative purposes?
- Are research and surveillance efforts and investments across the region inclusive of focus on behaviour, psycho-social sciences and social determinants?

Lack of surveillance in Arctic regions, problems with establishing databases enabling data sharing as well public health implications were considered

Brian McMahon and Vladimir Chulanov.

Presentation of HBV database. Element for future international comparisons and analyses.

- Elements of the database were introduced.
- Brian will submit a revised list of database elements for hepatitis B to group members as a template. The list will include definitions.
- Stephen Livingstone will submit the hepatitis C database.
- Deadline 3 months
- Vladimir Chulanov pointed out that establishment of databases may be difficult in Russia since all EDB databases must be licensed from 2011

Session 4: Joint projects.

Chairpersons: Brian McMahon and Vladimir Chulanov.

Yasuhito Tanaka.

The Alaskan genotype F data.

- Genomic changes in HBV genotype that results in HCC were compared with genomic changes in inactive carriers. The patients were retrospectively followed through 12 years.
- BCP core mutations were predictive for HCC and present 6-8 years before the HCC
- At baseline more Pre-HCC patients were HBeAg positive than inactive carriers, but viral load did not differ.
- At follow-up there was no difference with regard to HBeAg, viral load or mutations between carriers and HCC patients.

Suggestions for future studies:

Malene Børresen: Genome-wide association with HCC, inactive carriers. Chronic carriers vs. immune etc.

Yasuhito Tanaka: Comparison of vaccine failure patients and responders

Malene Børresen and Brenna Simons would look into either GWAS possibilities or microarray possibilities.

Brian McMahon: Establishment of mutation rates and phylogenetic relations for genotype A2.

Malene Børresen will coordinate the collection of samples from the circumpolar countries.

Malene Børresen: Molecular clock for genotype B6. To estimate the molecular clock 3 samples from the same person separated with as long distance as possible would be needed. App. 3-5 samples from each country would be sufficient. The best way would be that we sequence the samples ourselves and send the sequences to Yasuhito Tanaka. Malene Børresen will coordinate the collection of samples.

Next meeting: Copenhagen 2011. Chairpersons nominated: Anders Koch, Nina Weis, Brian McMahon

October 6, 2010

Karin Ladefoged