2012 Arctic Viral Hep Meeting

August 3, 2012
Alaska Native Tribal Health Consortium
Anchorage, AK USA

Welcome and Opening Remarks- ANTHC and Tribal Leadership

REGIONAL EPIDEMIOLOGY UPDATES:

Alaska/Tribal Perspective – Drs. Brian McMahon and Stephen Livingston

Continued observations of a significant decrease in chronic and symptomatic Hepatitis B infection.

However, large increases in Hepatitis C infection continue to be observed.

Dr. McMahon provided an overview of automated bi-annual follow-up system for chronic viral hepatitis infection within the Alaska Tribal Health System (ATHS);

1. Registries have proven to be highly effective in providing:
    - Background clinical information
    - Recommendations for vaccination – vaccination records
    - Cost-effectiveness analysis over time
2. The ATHS system implements a greater stringency on AFP cut off (10ng/mL) to better detect potentially cancer diagnosis within remote communities. If AFP is elevated – there is referral for ultrasound and further testing for recommendations for anti-viral therapy or follow-up for cancer screening and care.
3. Long distance, bi-annual follow-up includes treatment of Active Phase of chronic HBV - including HBV DNA and liver function tests
4. Cost of chronic hepatitis B treatment is approximately US$ 70,000 / year . Treatment follow-up includes 3 month evaluations monitoring HBV Viral Load, if Viral Load is negative – than can move follow-up to every 6 months.
5. Due to more stringent AFP criteria, 89% of hepatocellular carcinoma (HCC) cases are detected at early, curable stages
6. If AFP < 10, 99% chance the individual does not have cancer
7. The Alaska program wants to increase Ultrasound more frequently for screening – when available, with these clinical groups prioritized -
    - Genotype C over 40 years of age
    - All Females over 50 years of age
    - Genotype F at any age
    - All Males over 40 years of age
8. HEPATITIS C REGISTRY – Stephen Livingston MD

- 1082/1340 identified anti-HCV+ cases are Chronic Hepatitis C infection
- 53:47 Female-Male ratio
- Of all chronic hepatitis C carriers: 66% Genotype 1, 19% Genotype 2, 14% Genotype 3
- Few chronic HCV carriers are (n=18) HIV-coinfected
- 57% IDU, 20% Blood Transfusion
- 163 treated so far
- 35% BMI>30
- 1994-2005 Outcome Study for Chronic Hepatitis C (Livingston et al 2007)
    - 121/431 End Stage Liver Disease (ESLD)
    - 40/431 has HCC
    - 266/431 deceased (66 Liver-Related Death)
- IL-28 Genotype Analysis:
    - n=70 tested so far
    - 38% CC, 53 % CT, 9% TT genotypes
- Vitamin D (n=377) testing so far:
    - 27% >30, 73%<30

LiverConnect – The ANTHC Liver Disease and Hepatitis Program Telemedicine Initiative for providers across Alaska. This program also includes a resource website that providers provider and patient education materials.

<u>State of Alaska – Hepatitis Update – Ginger Provo RN</u>

One Viral Hepatitis Coordinator Assigned to each state in the U.S. by the CDC Division of Viral Hepatitis.

The State of Alaska Viral Hepatitis Program provides:

1. webpage and resource guides for provider and patient training onsite and webinars
2. Immunization initiative – 4,000 doses of adult HBV – 55 venues, 20+ locations
3. Will be using the oral rapid HCV test
4. Automated online database for Hepatitis cases
5. Dramatically decreased Hepatitis A in Alaska – previous universal coverage in 1996, since 2001 all children attending child care facilities and schools are required to receive HAV vaccine.
-HepA vaccination usually is delayed until school age (decision by parents)
6. HepB in Alaska also dramatically has dropped thanks to vaccination – universal vaccination requires an initial birth dose within 12 hours of delivery.
7. Historically no chronic hepB database
8. Alaska demographics – Asian/Pacific Islander population is growing and has the highest rate of hepatitis B.
9. State reports given by Economic regions

10. Perinatal Hepatitis B Program
    --Following HBsAg+ mothers
11. Since 1996, HCV is a reportable disease in Alaska, however no funding yet to support enhanced surveillance for HCV
    -Hep C and HepB in Alaska follow age trends as the rest of the U.S.
    -Most reports of Hepatitis C come from laboratories and no race or other information is included.

12. Linkage to Care

Greenland Update – Anders Koch MD PHD MPH

High high rates of Hepatitis B historically 7-10% and remains unchanged
Not documenting degree of severity as observed in Canada and Alaska

HBV most concerning – little concern re: HAV and HCV

Previous Research:
-HDV outbreak in west Greenlandic settlement
-HBV vaccine coverage of pregnant women
-B6 genotype
-Cohort Study – Malene (Age specific HBV incidence, Morbidity and Mortality in HBV infected persons).
-Mutation rates of genotypes B, D and F

Ongoing Projects :
1. HBV Status and Markers for clinical outcome – Greenland Cohort Study (n=1200).
2. HBV mutations in vaccinated, but chronically infected children (presented later today)
3. Phylogenesis of HBV and HDV isolates
    130 HBV and 40 HDV isolates from Greenland settlement (presented later today)
4. Relation between levels of PCBs/POPs and HBV and Di-Te vaccination responses
    Do environmental pollutants influence vaccination response through immune modulatory mechanisms?
    Children born to chronically infected mothers

5. HBV status and genotypes in HCC cases
    stored pathology samples of HCC – Why so little liver cancer in Greenland?
    Stain tissue for HBsAg and PCR for HBV and HDV

6. Re-sampling 2008 of elders with determination of HBV status

Canada Update – Gerald Minuk MD

1. Long term follow-up of Occult HBV infection (OBI) in Northern First Nations populations
   -document the prevalence of OBI in Northern Canadian First Nations communities
   -describe and compare demographics of individuals with and without OBI in these communities
   document serologic profile and HBV-DNA features
   -document clinical outcomes

   HBsAg prevalence: 11-12%
   Assess viral sequence of HBsAg+ samples
   OBI prevalence 1.3% (9/706)
   >50% females had OBI
   No difference in age or frequency of Anti-HBs positivity
   The majority of OBI were DNA negative 17 years later
   All OBI had lower APRI scores, all way below 1.0

   OBI not associated with long term adverse clinical outcomes

2. Longterm follow-up of Canadian Inuit – Chronic HBsAg+ HBV
   -document over time clinical data, mortality morbidities, etc.
   -Study Demographics:
      61% Male (no difference between carriers and controls)
      mean 38 years (no difference)
      Age and gender matched control cohort
   N=114 HBsAg+ individuals
   No difference between carriers and control in liver biochemistry

   Liver morbidity (hospitalizations) – HBsAG carriers seen more at hospitals presenting with liver-related morbidities

   Mortality rates similar

   Survivors vs. Non-Survivors
   Non survivors had higher percentage of precore mutation (nt 1896)

   Predictors of Outcome in HBsAg Positive Carriers

<u>Russia Update – Vladmir Chulanov PhD</u>
Russian Arctic –
Russia overall 10% indigenous population
Yakutia and Chukchi region – higher percentage >50% indigenous population

Incidence of Hepatitis A 1989-2011
Dramatic decrease from 1990 (200 per 100,000) – currently 4 per 100,000

The majority of Russian territories < 4 per 100,000
Select areas incidence higher at 11-20 per 100,000

Increasing percentages of Hepatitis A – in those >30 years and older
Introduced from Asian countries

Incidence of Hepatitis B 1998-2011
43 per 100,000 to 1.7 per 100,000
Total of 108 cases reported from Arctic Regions in 2011 (acute/symptomatic)
Arctic Chronic HBV 21 per 100,000 as compared to all of Russia 13 per 100,000

143 million vaccinated (close to 100% vaccination efficiency)
Genotype D is the most prevalenct
Some Genotype A and C

Genotype D1, D2 and D3
D3 is dominant in Chuckchi (least to most West to East in Russia)
D3 is highest amongst indigenous population

HDV infection – higher rates of HDV (anti-HDV+) in Eastern regions, Chuckchi regions

Most HDV coinfections in Chuckchi found within indigenous populations
Most coinfected were genotype D, most were genotype D3

Most prevalent HDV genotypes Gentoype 1

Only in Yukutia is found Genotype 2 HDV (found in Japan, but different than strain identified in Yakutia).

Incidence of Chronic Hepatitis C in Russia 1999-2011
40 cases per 100,000 in Russia in Arctic is 56 per 100,000
Higher incidence in Northern regions – some as high as 144 cases per 100,000
Anti-HCV 4% Positivity in Moscow
The majority between ages 20-40

Northern territories – HCV genotype of 1b is much higher - Chuckchi indigenous – only genotype 1b

IL-28b genotype distribution
Western Russia – greater percentage of CT and TT
Larger percentages of CC Genotype in Yakutia and Chukchi
CC seems to be higher in the indigenous population

Questions / Discussions

Bryce Larke MD (Alberta, CANADA):
Role of Alcohol in Disease progression – how does this relate to control groups? Can you match? What does it influence?

Brian McMahon MD (Alaska, USA):
Recent Livingston Study on Hepatitis C and influence of Alcohol

Do not have much data on Hepatitis B – since do not see these patients are regularly

Julia Rempel PhD (U Manitoba, CANADA):
Heavy influence of alcohol need more recent data

VIRAL HEPATITIS PREVENTION AND CARE

Michael Bruce MD MPH – Longitudinal Hepatitis B Vaccine Cohort
30 years post-vaccination in Yup'ik Eskimos

Hep B Vaccine was first used in Alaska in 1981. This was a plasma derived vaccine, current vaccines are a recombinant vaccine. Studies of immunogenicity began at that time.

Long Term Immunogenicity –
No booster given in first 15 years

Those that had detectable anti-HB antibody levels >10mIU/mL following the 3 dose vaccination series:

5 years 81%
7 years 74%
15 years 66%

16 breakthrough infections during the first 15 years– no new breakthroughs since 15-year follow-up

At 22 years 60% of participants still indicated an anti-HB titer >10mIU/mL

VaxDemo 22 Results:
Boosted with Recombivax 10mcg given to those with anti-HBs <10mIU/mL
Combined, 93% of the entire cohort had immunity prior or with boosting

VaxDemo 30

Primary Objectives;
Look at proportion that had existing anti-HBs>10mIU/mL
Immune response to booster of those with <10mIU/mL
Characteristics of these groups

Inclusion Criteria
3 doses of plasma vaccine
Excluded those who had received a booster dose, unless from VaxDemo 22 study.

Visit 1
Blood draw assess antibody levels

Visit 2
Booster if needed

Visit 3
Blood draw on those boosted

51% of the overall cohort had existing anti-HB antibody >10mIU/mL

3 main statistical groups:

1. persons receiving booster at 22 years (n=63)
   14% had >10mIU/mL
   Not boosted
2. persons drawn at 22 years not boosted (n=129)
   66% had >10mIU/mL
   boosted
3. not drawn at 22 years (n=241)
   51% had >10mIU/mL -- boosted

Group 2: 44% that had originally <10mIU/mL – data so far indicates 94% respond to booster

Group 3: 49% had <10mIU/mL – data so far indicates 88% responses to booster

Preliminary conclusion: protection by plasma vaccine lasts 30 years

<u>Greenland Vaccination Updates – Malene Borresen MD PHD</u>

Hepatitis B Vaccination Regiment – 4 doses 0,3,5, 12 months implementation

HBsAg testing of women >98% screening rate

Catch up on 12 year olds with MFR and HPV

Enrollment of electronic registry/database

Evaluation of vaccination program (targeted) – only children born to HBsAg+ mothers were targeted for vaccination

132 children born to sAg+ mothes

Prevalence of break-through infections
Levels of protective antibodies

20% of at-risk children did not receive vaccination
Only 30% received 3 or 4 vaccination doses

6% had breakthrough infections (most occurring in children with at least 3 doses)
59% of HBcAb-negative children with 3+ vaccinations had antibody <10mIU/mL
73% of all included children had HBsAB <10mIU/mL

Why vaccine low response?
Quality of vaccine?
Escape mutations?
Infection despite vaccination? Poor responders?

Quality Control Found no reasons to question vaccine integrity

Escape mutants in HBV strains in Greenland- in collaboration with Osiowy in Canada
-no mutations associated with immune escape
But specific mutations with stop mutation in the pre-s and post-s region of HBV

6 persons HBV DNA positive – do these persons have the same special stop mutation?

Relationship between host factors and the HBV vaccination response
-Th1 or Th2 response plays a role for the antibody response when vaccinated
-5-10% of newborns are non-responders

Organic Pollutants can reduce vaccine response and are immune modlators
Can be exposed through exposure to mother's milk

Granjean et al indicated a correlation between PFCs and antibody levels

PCF and POPs (Organic pollutants) are high in the Greenlandic population due to intake of fish and whale

Aim: relationship between organic pollutants and HBV vaccination response, as well as tetanus and diphtheria antibodies – have a cohort of 69 children so far

Comparing HBsAB and tetanus AB – a negative cluster found between non-responders to tetanus or HBV

Tetanus antibodies by Age – still fairly low after 5 years of age boost

Same negative cluster of non-responders comparing diphtheria and HBs AB
Diphtheria AB very low despite post-booster age

Next Step: Antibody levels compared with organic pollutants

MOLECULAR STUDIES IN VIRAL HEPATITIS

Julia Rempel PHD–Hepatitis C infection in Indigenous People of Canada

Liver Disease is the leading cause of death for indigenous peoples of North America

Prevalences amongst indigenous populations:
Canada ~0.8%
US ~1.8%

65-85% become chronically infected

Community surveys of chronic hepatitis C prevalence :
Manitoba: 2.2%, Minuk et.al. 2003

Clinical Surveys 8-24% Neumeister et al 2007, Scott et al, 2008

High Risk Populations
60-70%, prevalence, which is similar to non-indigenous populations.

Incidence studies – newly diagnosed
Canada – 6 health regions

18.9/100,000 Aboriginal
2.8/100,000 non-Aboriginal

U.S.:
6 fold greater for AI/AN in 2001
2009 , 2-4 X greater compared to non-indigenous

Observation:
Certain aboriginal populations seem to clear acute HCV more effectively

Manitoba and Nunavut communities

British Columbia Study:
Self-identified as aboriginals indicated higher rates of HCV clearance – Dawood et al 2006

Greenland this may also be occurring, but not in Nebraska or Alaska based on studies

Differences in immunity could contribute to the more effective clearance of HCV infection in certain Aboriginal populations

Proinflammatory vs. Anti-inflammatory in Immune Response

Proinflammatory: associated with spontaneous clerance of HCV infection
Anti-inflammatory: Promotes chronic HCV infection

First nation/Metis appear to have a higher proinflammatory response than Caucasian population in Canada

Assessing KIR (Killer-cell Immunoglobulin-like Receptor) activation of Natural Killer (NK) cells, and IL-10 secretion

Proinflammatory also can be associated with Type2 Diabetes

HCV Treatment:

Similar rates of successes between Aboriginal and non-aboriginal
Potential data suggests aboriginal population may have lower rates of relapse Cooper et al 2008

Uhanova et al
Progression of Chronic Hep C – Longitudinal Data
Progression rate seems similar, but greater decrease in life expectancy (12 years less) in aboriginal compared to non.

Potentially higher risk factors / co-morbidities
Diabetes, alcohol abuse

Potentially even higher risk for aboriginal IDU than non-aboriginal IDUs (?)

Increasingly female, younger, sex trade associations Wu et al 2007, PHAC 2006

CO-infection with HIV
IDU populations:
~60-70% HCV infected

~10% HIV infected

Of the HIV infected individualsalmost all 98% coinfected with HCV Pilon et al 2011

HIV/HCV Co-infection can be up to 7 times higher in Aboriginal IDU than non-aboriginal counterparts

38% IDU attended residential schools
71% had a parent or grandparent that attended residential school (boarding schools)

Projected cost of HCV in direct costs
Canada: $2.9 billion
US: $10.7 billion

Yury Khudyakov PHD - Molecular Epi of HepB Virus among Alaska Native people

Centers for Disease Control and Prevnetion – Division of Viral Hepatitis (USA)
Yury Khudyakov

Looking at HBV on an individual quasispecies-basis

End-Point Limiting Dilution Real-Time PCR for Whole Genome of Intra-Host HBV Variants

Limiting Dilution DNA concentrations –

PLoS One 2011 Ramachandran et al
Technique works well amongst different genotypes

Nature Communications
Thai et al 2012
Works well amongst different drug resistant variants

6 subjects
Genotype D
5/6 Male - all from same region
Had to have detectable HBV DNA for being able to detect DNA
Follow-up 16-26 years
Age at time of infection 2-32

Viral Load over time: Several clinical Groups:
1. Rapid decline

2. Slower decline
3. Little decline 10-15 years than rapid decline

Rapid Decline:
2 separate patients had fairly identical viral genetic trees, along the same timeline of evolution

9. possibly infected with D2 and D3 – but D3 not detected until 16/19 years follow-up
10. quasispecies dominance fluctuates, changes over time
11. phylogeny does not reflect temporal pattern of

**viral load and seroconversion associated with intra-host HBV heterogeneity

**research group discovered patterns of common source of infection

Convergence of pre-core mutations
Population expansion (quasispecies)
D2 and D3 subpopulations can both be present in one patient during infection

Major Conclusions:

Convergence of important genetic and phenotypic traits

Founder population is complex – not just one quasispecies

Variation in density of subpopulations combined with differential capacity of subpopulations to converegence may effective anti-viral therapy and vaccination

Convergence of directionality make intra-host HBV evolution tractable, facilitating prediction of drug resistance and vaccine escape.

QUESTIONS/DISCUSSION:
Masashi Mizokami MD (Tokyo, JAPAN):
High rates of recombination of sub-genotypes? How was this accounted for?

Did not measure any recombination?

Yasuhito Tanaka MD (Nagoya, JAPAN): - Genotype F in Alaska Molecular Analysis

Assessing viral mutation in genotype F HCC cases (Alaska specimens) :

HCC = 20 patients

Controls = 20 patients age/sex matched

Controls-2= age/sex matched with longer follow-up

Genomic mutations detected
Sugiyama et al Hepatology 2006 (methods)

Method 2 – detect HBV replication by Southern Blot

Alaska genotype F phylogeny – Alaska Genotype F – very conserved within each patient.

Young HCC patients 44% cirrhotic
Older HCC 60+% cirrhotic

Discovered several mutations:

BCP/PC mutations

C1938/2051

HCC patient group: All patients begin with no mutation at baseline and develop mutations

HCC patients baseline v. follow-up
-significant loss in HBeAg in patient group
-significant accumulation of BCP/PC mutations and core

Inactive Carriers
-indicate baseline mutations already present (BCP/PC), less frequency of wild type virus
-no significant difference in E antigen conversion either

Young inactive carriers begin with wild type at baseline, then have developed BCP/PC mutations over time – perhaps predicting development of HCC in the future

HCC:
Wild Type → Mutant variant

Inactive Carrier:
Mutant variant → Maintain mutant variant

Creating HBV/F clones from this subject group
Remaining Questions:
1. BCP, PC and 1938 mutations could enhance HBV replication (?)

2. Endoplasmic Reticulum Stress associated with infection (?)

12. markers of ER can measure cellular stress (Grp78)

cellular stress in Huh7 cells assessed – found to be highest in genotype F and C infection

Discovered 2 new mutations in core region C1938 and C2051 – both contained within or flanking T/ B cell epitopes

Cellular stress elevated in genotype F may be link to high incidence of HCC amongst genotype F in Alaska.

<u>Dr. Masashi Mizokami – HepB and Host Genetics by GWAS and HBV disease</u>

Genotype F – behaves differently in Alaska vs. its origins in Argentina (Argentina is a low incidence country, predominantly genotype F HBV).

Same viral genotype in different geographic region can have different clinical outcomes – this implies host factors are involved

Genotype B6

Little TJ Nat Med 2012

Relationship between Host and Pathogen – some diseases fall on the line that divides – some can be attributed 100% to the pathogen/illness and some attributed to 100% of host.

Suggesting that HCV is mostly Pathogen, whereas HBV is mostly Host.

SNPs- why so important?
1. Phenotype
2. Different responses to disease
3. Different responses to drug treatment

Testing HBV sensitive SNPs by GWAS

Comparing infected and non-infected (chronic)

**HLA-DP was one gene factor

**HLA genes are highly polymorphic

**Linkage Disequilibrium amongst HLAs

**HLA-DP variants are clustered on exon 2 – in the antigen binding region of the receptor

Non HBV vs. HBV
Differences in HLA-DP
Rs17401966 strongly associated with Chinese patients with HCC
Zhang et al Nat Genet 2010
But not found in Japanese or Korean populations.

Possibly because of different HBV genotypes and host HLA-DP genetics

<u>Malene Borressen – Molecular Studies in Greenlan of HBV</u>

2 cohorts with sera studies

1. Over 6,000 participants, 6 districts in South/Southwest Greenland aged 15-70 years
2. 2800 from Sisimiut, West Greenland

1,472 consented participants for both the vaccination and outbreak studies

366 HBsAg chronic carrier specimens
130 have been sequenced with enough HBV DNA to do viral genotyping
201 had no DNA detected, but perhaps able to be amplified

West Greenland 74% Genotype D
Southern Greenland 69% Genotype B6

Overall 20% carriers are HDV+

HDV infection will 'override' HBV infection in viral replication

HDV sequence phylogenetic analysis:

8 main clades of HDV
All Greenlandic genotypes are clustered within Clade 1

Different regions/communities cluster together – Sisimiut vs. Itilleq

Observed specific deletion within HDV of 84 bases in most of the isolates/samples 13. True Deletion? Primers/Technical Issue?

Future Questions?
-New/separate Greenlandic Genotype D?
-Viral Load by genotype and HDV status
-Genotypes and Clinical Outcomes to Correlate

QUESTIONS/DISCUSSION
Brian McMahon MD: See further complications of HDV as population ages?? Including liver pathology and elevated LFTs? Suggest using non-invasive methods such as APRI score or FIB 4? Rather than biopsy.

Henrik Krarup MD:
Observed High ALT and HDV Viral Load in Itilleq group – so prognosis not looking good.

Masashi Mizokami MD: Specific SNPs associated with fibrosis of liver

Malene Borresen MD PHD- HDV is causing disease – perhaps why HBV is more devastating in Greenland as compared to Dr. Minuk's data in Canada.

Gerald Minuk MD: Why do more males develop to Chronic Hep B? Genetic?
Masahi Mizokami MD: the sex hormones are known to offer protection to the liver, as evidence - after menopause women increase their risk of HCC. HLA –DP would not be the genetic link between male and female differences in chronic HBV development.

Julia Rempel PhD: Females also protected during Chronic Hepatitis C

<u>Carla Osiowy PHD --Arctic Genotype B6</u>

-B6 is the only genotype found within Canadian Inuit
-B6 clusters with Bj (Japan) – and varies from all other Genotype B subtypes (2-5)
-B6 not a recombination with others 'a pure genotype'
-B6 seems to have a faster evolutionary rate
-B6 displays a higher nucleotide distance between B6 isolates as compared to Genotype D and F.

Intra-host B6 quasispecies: -

B6 quasispecies population within an individual is more dynamic than that observed in HBV/D and HBV/F.

Majority of B6 are E Antigen Negative
Majority of sequences have Pre/core mutation that leads to loss of E Antigen

Reduction (often 0) liver cirrhosis and HCC in B6-infected patients

Remaining Research Questions:
1. Persistent B6 mutation/variation yet decreased viral load and lack of adverse clinical outcomes?
    a. Is increased genetic diversity an inherent characteristic of the strain?
    b. Is there a host pathogen balance between B6 and Inuit host?

2. Is B6 in other areas? Ever going to find it anywhere else?

3. Where did B6 originate?

Appears split in B6 first occurs between Greenland and Alaska/Canada, then splits between Alaska and Canada

→Which would mean that the Greenland sequences would be the 'older' variant

Analysis requires more sequences from Greenland (other than Western) – and more Alaskan sequences

B6 is more prevalent in Eastern Greenland – so would be very useful to have those sequences from this territory

QUESTIONS/DISCUSSION

Brian McMahon MD: B6 in Alaska has only been found in Yu'pik Eskimo population which is SouthWest Alaska – and not the Alaskan Inupiat Eskimo population located in the North (similar to Canadian Inuit).

How did B6 travel from Canada all the way around to Southwest Alaska?

Alaska potentially has EAg+ B6 patients

Migration data indicates pass through Beringia/Alaska was quick, following the whale migration to Greenland quickly, within 100-200 years. Yu'pik are known to have split from Inuit early on.

Julia Rempel PhD:
B6 associated with benign outcome –
Rempel laboratory

Core from B6, D and F – transfected into hepato cell line – is B6 less or more immunogenic

Core from genotype F seems to inhibit NK cell responses much more than Core from B6

Genotype F also not associated with cirrhosis prior to HCC not necessarily – so different mechanism of damage and HCC.

Julia Rempel PhD: Genotype B6 – induces a different immune response that allows for more viral diversity

Masashi Mizokami MD: The more sub-genotypes indicating an older overall genotype – better for virus to find balance with host than to eliminate host.

Brian McMahon MD: Genotype B6 more associated with mild reactivations between inactive and active phase

B6 may still lead to HCC – just much later in life (>80 years) – and at the older age- when will complications or death be attributed to 80 years of age.

Greenland, Alaska, Canada much younger populations than other chronic HepB cohorts.

POTENTIAL COLLABORATION DISCUSSION

Discussing what the Arctic Viral Hepatitis Working Group should focus on in the next year:

Genotype Fs –in contrast to B6
-Expression of X protein/gene associated with disease

Gerry Minuk: Carcinoma stem cell: genotype F more readily infects liver stem cells

CIHR = NIH in Canada

Genotype B6 as treatment – mimicking the ideal immune response

Brian McMahon: Proposing Diagnostic Protocol for care in the Arctic

-Recent study on Chronic HBV and Diabetes indicated no influence of HBV on DM or visa versa

Using APRI scores for screening in rural communities
-APRI >1.5 or 2.0 excludes advanced fibrosis/cirrhosis

-APRI 0.5-1.0 excludes cirrhosis
--examination of APRI over time in patients with serial biopsies and serial APRI measurements

APRI (AST/AST ULNX100)/PLATELET COUNT (10^9)

FIB4 (AGE X AST)/(PLATELET X ALT)

Question Re: Platelet for blood draw (do you have to take 2 tubes?) Answer: No

Question: HCV treatment evaluation – focus on indigenous populations

Stephen Livingston - will be presenting HCV outcome data in Fairbanks next week at ICCH 15.

Question Re: Disproportionate rate of females dropping out of treatment? Due to mental health issues?

Stephen Livingston MD: In Alaska - no difference

ACTION ITEMS

<u>Carla's B6 Molecular Clock Studies</u>
-Alaska – how many E Antigen Positive B6 samples – what sera is available?

---would need Viral Load to be completed on Alaska Specimens
---would need to complete DNA extractions for HBV Viral DNA
---Need general inclusion criteria for those samples included

-Denmark/Greenland – sending samples

<u>Brian – Genotype C between Siberia and Alaska – similarities??</u>

<u>Mizokami – potential new funding on large host-virus studies</u>
May have financial support to pursue collaboration with Arctic Partners including GWAS studies.

<u>Brenna rewrite proposal with Genotype B6 and F??</u>

<u>Using BCP mutations to follow-up on Genotype F patients</u>?
Dr. Mizokami – may be able to provide this service? Lippa??

<u>Bryce Lark – 10mIU/mL a true cut off??</u>
Observes increasing percentage of women with lost antibody titers

What about platforms? What about testing kits?
Changing Vaccine Policy?
Natural Boosting in EAg+

Brenna and Anders update List Serve for e-mail contacts
Arctic Viral Hep Discussion Forum (security?)

Brenna will compile presentations from today and send out to group in PDF format

Circumpolar Meeting 2013 – tentative dates week of 9/23-26
@ New Facilities Staten Serum Institut

Malene and Anders and Gerry Minuk, Dana Bruden/Mike Bruce