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Hepatitis B among Inuit: A review with focus on Greenland Inuit

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Abstract

Hepatitis B virus (HBV) infection is a disease with a highly variable course. Chronic HBV infection may cause end-stage liver disease including cirrhosis and hepatocellular carcinoma, which is the 3rd most common cause of cancer related death due to the poor prognosis. The prevalence of HBV infection is low in many countries. Still, it remains important due to the potential consequences of the disease. HBV is endemic in the Arctic with serologic markers of chronic HBV infection in up to 29% of the population in some areas in Greenland. Interestingly, Inuit populations rarely show signs of liver disease despite the fact that around half of all Inuit has been exposed to HBV and around 8% of Inuit are chronically infected with HBV. These findings have been consistent in surveys conducted for more than four decades among Arctic Inuit. We thus review HBV infection in the Arctic with focus on Greenland Inuit and compared with Inuit in Canada, Alaska and Siberia. The aspects described include epidemiology and monitoring of the disease, as well as treatment and the risk of liver cancer.

Key words: Hepatitis B; Hepatitis D; Monitoring disease; Prevention; Liver cancer; Inuit; Greenland; Arctic

Core tip: Hepatitis B virus (HBV) is endemic in the Arctic with serologic markers of chronic HBV infection in up to 29% of the population in some areas in Greenland. Interestingly, Inuit populations in Greenland and Canada rarely show signs of liver disease as opposed to Alaskan Inuit where hepatocellular carcinoma was common before introduction of vaccination. Wheather this is related to a special favorable genotype or other host or environmental factors remains to be clarified. This paper is a review of present status.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is recognized as a disease with several stages ranging from immune tolerant and an inactive carrier state to cirrhosis with end-stage liver disease and liver cancer. The course of the disease is influenced by a number of factors such as hepatitis B e-antigen (HBeAg) seroconversion, HBV-DNA level, HBV genotype, pre-core (pre-C) and core promoter mutations, reactivation with flares, co-infections, *etc*. Also, age at infection, disease duration, environmental and genetic factors, ethnicity and gender influences the disease[1]. Still, HBV causes a potentially lethal infection and a number of aspects of the disease remain unknown with lessons to be learned from populations with endemic disease occurrence.

More than 350 million people are chronically infected with HBV globally and HBV will continue to pose a health problem for decades[2,3]. In general, the risk of chronic disease is 90% in children vertically infected, while the risk is approximately 30% in horizontally infected children under the age of five and less than 10% in adults[3,4]. Chronic HBV infection relates to end-stage liver disease, including cirrhosis and hepatocellular carcinoma (HCC), and it causes 1 million deaths per year[2]. Hence, HCC is now the 6th most common cause of cancer in the world, and the third most common cause of cancer death due to the poor prognosis[5].

Earlier studies in the circumpolar region have shown HBV infection to be endemic in the various indigenous populations with the highest prevalence among Arctic Inuit[6-9].

This paper will address HBV epidemiology, monitoring, treatment and consequences of chronic HBV infection among Inuit. The focus is on Greenland Inuit, which is a major Inuit population, and the perspective is based on comparisons with Inuit in Canada, Alaska and Russia.

EPIDEMIOLOGY

Greenland Inuit

The population in Greenland is around 57000 people and most are of Inuit descent. Around 7000 are born outside Greenland, most in Denmark, and around 18000 persons in Denmark are of Greenlandic descent[10,11].

Greenland has for many years been recognized as a high-risk area for hepatitis B[12]. Markers of present or previous HBV infection have been found to vary from 42% to 88% in studies of different age groups and from different areas in Greenland[8,9,13-15].

Studies have shown a prevalence of hepatitis B surface antigen (HBsAg) ranging from 12% to 29% among Inuit in East Greenland, 6.2% to 17% in Northwest Greenland and between 1.2% and 7.3% among Inuit in Southwest Greenland (Table 1)[9,12,13]. A comprehensive study among a population aged 12 years and above in Greenland's second largest town showed that 75% of population had signs of present or previous HBV infection at the age of 25 and a rise in HBV markers of 40% was seen between the ages of 15 and 25 years[8]. The highest incidence of acute HBV infection was observed in that same age interval. This suggested that sexual transmission is an important mode of transmission[8] in addition to other modes of horizontal spread. Also, extensive horizontal transmission between the ages of 5 and 20 years rather than from mother to child has been reported among Inuit in Greenland[13,15-17].

In a later study among individuals aged 7 through 79 years Langer found 7% (n = 35) HBsAg positive (Table 1). HBeAg was positive in 6% of these and 94% were anti-HBe positive. HBV-DNA could be measured in 49% and genotype could be determined in 11 persons of which 9 had genotype D and 2 had genotype A[15].

In a more recent study among individuals aged 50 through 69 years, HBsAg was positive in 20% (n = 86). This study found a difference with geography as HBsAg was positive in 28.9% in East Greenland and 2.7% in West Greenland[9]. HBeAg was positive in 1%, five percent were both HBeAg and anti-HBe positive, and 94% were anti-HBe positive only. HBV-DNA could be measured in 71% of HBsAg positive individuals. The dominating genotype B was found in 47 individuals, 4 had genotype D and 1 had both B and D. Genotype B was subtyped to be genotype B6[9].

In a comprehensive study covering all age groups in most of West Greenland, Børresen *et al*[18] describes in her thesis 650 (7.3%) HBsAg positive subjects out of a total of 8879 participants.

Based on this study and other population based studies it can be estimated that there are between 3000 to 4000 carriers of HBsAg in Greenland, and that only 17% of the Inuit population in Greenland has never been exposed to HBV[9].

Greenland Inuit in Denmark

As described above Denmark hosts a greater part of Inuit migrants from Greenland and their descendants. This provides an opportunity to gain insight into some aspects of the influence of migration on the prevalence and consequences of hosting an HBV infection. Rex *et al*[19] showed that the occurrence of markers of HBV infection was similar among Inuit in Denmark and in Greenland. Accordingly, 54.5% of this group aged 40 through 69 years had serological signs of HBV exposure. Present HBV infection was found in 4% of individuals (Table 1) and all were anti-HBe positive[20]. Thus, there was no difference between Inuit in Denmark and in Greenland even though a major group of those migrated had lived in Denmark for decades. These data suggest that migration does not influence the prevalence of HBV infection.

Table 1 Studies of hepatitis B virus markers among Inuit populations

Country	Ref.	HBsAg %	Anti-HBs %	Anti-HBc %	HBeAg %	Anti-HBe %	Participants Inuit/*n*	Year
Greenland								
	Skinhoj *et al*[12]	7.1					2904/2904	1974
	Skinhoj *et al*[13]	16.6[1]	45.8[1]	41.6[1]	6[2]	30[3]	1450/1450	1977
	Skinhøj *et al*[16]	16.7	23.6		0.0	2.6	191/254	1979
	Melby *et al*[17]	0-20[4]	0-35[4]				193/371	1984
	Olsen *et al*[8]	11.5[5]					NA/1893	1989
	Langer *et al*[15]	7.0		42.0	0.4		503/503	1997
	Krarup *et al*[9]	20					434/434	2008
	Børresen *et al*[14]	18.9		62.6	4.3		185/185	2010
	Børresen *et al*[18]	7.8		37.4			NA/8879	2011
	Rex *et al*[20]	4.4			0.0		136/136	2012
Canada								
	Minuk *et al*[21]	4.0[5]			0.0	3.8[3]	671/720	1982
	Larke *et al*[7]	3.9	24.5		8.8[2]		8282/14198	1987
	Baikie *et al*[22]	6.9		26.4	0.0[2]		766/2156	1989
Alaska								
	Schreeder *et al*[23]	6.4	17.8				3053/3053	1983
Russia								
	Ohba *et al*[24]	11.8[5]	35.9[5]				NA/348	1999

[1]Calculated from randomly selected samples; [2]Among all HBsAg positive tested for HBeAg; [3]Among all HBsAg positive tested for anti-HBe; [4]Age specific prevalences; [5]Among all studied. HBeAg: Hepatitis B e-antigen; HBsAg: Hepatitis B surface antigen; Anti-HBc: Hepatitis B core antibody; Anti-HBs: Hepatitis B surface antibody; Anti-HBe: Hepatitis B e antibody; NA: Not analyzed.

Inuit in Canada, Alaska and Russia

A survey in 1980 that included 720 people (93% Canadian Inuit) found serologic markers of HBV infection in 27%, an increase with age, and an overall prevalence rate of HBsAg of 4% in Nunavut[21]. The 29 HBsAg carriers were adults who were anti-HBe positive[21]. A comprehensive study in the Northwest Territories in Canada in the early 1980-ties included 51% (*n* = 8282) of the Inuit population[7]. Among Inuit, they found a prevalence of 3.9% (*n* = 309) for HBsAg and 24.5% (*n* = 2031) for anti-HBs. Among the 14198 participants 428 were HBsAg positive and 37 HBeAg positive[7]. Baikie *et al*[22] reported HBsAg carrier rate among Inuit in seven northern Labrador communities to be 6.9% (Table 1) and none were HBeAg positive. Furthermore, they found that 85% had a marker of HBV exposure. These reports suggest a similar pattern of HBV exposure and infection among Canadian Inuit compared to Greenland Inuit.

Studies in Alaska have found HBsAg in 6.4% of 3053 residents of 12 Inuit villages (Table 1)[23]. Evidence of HBV exposure as defined by either positive HBsAg or anti-HBs was suggested in 5% to 70% of those surveyed. The occurrence differed between villages and age groups with a rise with age[23].

Data on hepatitis from the Russian Arctic are sparse. However, Ohba *et al*[24] reported the prevalence of HBV infection in 348 Siberian natives who lived in the Kamchatka Peninsula of Russia. HBsAg was found in 41 of 348 (12%) and anti-HBs was found in 125 of 348 (36%)[24]. Though the data are limited the occurrence may be comparable to that seen among the Inuit in Alaska, Canada and Greenland.

CO-INFECTION WITH HBV AND HDV, HCV OR HUMAN IMMUNODEFICIENCY VIRUS

A limited number of studies have focused on co-infection of HBV with HDV, HCV or human immunodeficiency virus (HIV) among Inuit. Nevertheless, co-infection with HDV could become a problem in Greenland as superinfection in chronic carriers of HBV has caused severe liver disease even in children. An outbreak of hepatitis D infection was reported in one settlement in West Greenland[14] but also sporadic cases have been identified from the remaining parts of the west coast (Krarup, personal communication). Still, HDV was rare in a systematic testing of adults aged 50 through 70 years in East or West Greenland[20]. However, there is limited data available for Greenland Inuit.

Olsen *et al*[8] found no HIV positive in their study among Greenlanders.

Spradling *et al*[25] found that co-infection with HIV or HCV was uncommon and HIV was found in only 3 of 300 HBV infected Alaska natives with defined risk factors for HIV[25]. Also HDV co-infection prevalence was stated to be low[25].

There are very limited data published on HBV co-infections among Inuit in Canada and the Russian Arctic. In Canada co-infection with HDV was rare in a study of several ethnic groups[26] but the number of Inuit was not specified.

The high number of Inuit with HBV infection in Greenland and the other Arctic countries poses a risk to the Inuit societies. Should HDV spread in the population as a super infection it is a threat as it has been related

to more severe accelerated fulminant acute hepatitis, chronic active hepatitis, cirrhosis and HCC in other populations[27,28] as well as in a single outbreak in Greenland[14].

VACCINATION AND MONITORING OF HBV

Greenland

All health care services are publicly funded in Greenland. This includes free vaccination, treatment and all visits to health care providers. Such free services support high coverage of health care and reliability of programs to monitor populations.

Screening for hepatitis B has been carried out among pregnant women in Greenland since 1992[18]. Universal hepatitis B vaccination of newborns was introduced in 2010 as part of the childhood immunization program[18]. Also, the Greenlandic Hepatitis B database (HB database) has operated since 1992. It records the results of HBV testing in Greenland, performed at Queen Ingrid's Hospital, Nuuk[18]. Thus, recording of HBV among Greenland Inuit is ongoing.

Legislation enforces reporting of acute and chronic hepatitis, and HBV infections are notifiable to the Chief Medical Officer in Greenland. Laboratory findings of persons tested positive for hepatitis are reported to the Chief Medical Officer. Cases of viral hepatitis are also identified through the mandatory screening of blood donors, pregnant women and through the diagnostic workup of patients undergoing routine clinical investigations. Besides, screening for HBV infection is recommended in Greenland in all patients referred for chemotherapy and immunosuppressive treatment, including tumor necrosis factor-inhibitors and patient on corticosteroid for more than one month, in patients with HIV and in those who have elevated alanine aminotransferases. Despite these case finding measures, hepatitis B infection is still likely to be underdiagnosed and underreported in Greenland.

The National Board of Health in Greenland collects surveillance data using the unique 10-digit civil registration number assigned to all individuals in Greenland. Data on several infectious diseases, including HBV, and data on childhood vaccination can be retrieved through the national electronic patient record systems.

A new childhood vaccination program against hepatitis B was introduced in Greenland 2010. This includes four vaccinations in all, at birth and at 1, 2 and 12 mo. Also, children born before the initiation of the program are offered three vaccinations after the age of twelve. Recording of vaccinations changed from being based on pen and paper to electronic reporting. This was believed to improve the quality of the data reported. However, the records were incomplete in 2010 and 2011, and it has not been possible to estimate vaccination coverage for these years. Thus, results are available for 2012 only[11].

Based on the electronic registration it seems that fewer children were vaccinated than previously. However, data may be lacking.

Data from 2012 showed that the universal hepatitis B vaccination at birth covers 55%, and that 38.5% receives the fourth hepatitis vaccination. The vaccination at the age of 12 mo is only given to children who have had the first three HBV vaccinations.

Unlike Alaska, Greenland has no systematic follow-up on patients with chronic HBV infection despite knowledge on HBV status. There are intentions to initiate such a program but as yet this has not been established. Furthermore, there are no national guidelines for diagnostic work-up and follow-up of HBV infection in Greenland. Treatment is in accordance with international guidelines. Both recording of vaccination and follow-up on chronic carriers may be optimised as a new nation-wide electronic patient record system is scheduled for implementation.

HDV infection is not a notifiable disease in Greenland as is the case in most of the countries in the Arctic. Hence, limited information on hepatitis D infection is available.

Canada, Alaska and Russia

Canada has a universal vaccination program against hepatitis B. However, the vaccination schedules are reported to differ between provinces and the children and adolescents may not be vaccinated if they move between provinces at certain ages[29,30]. As a result a nation-wide HBV vaccination programme for newborns and children does not provide full coverage[31,32] and it may be calculated that among adult Canadians approximately 39.7% are immunized[33].

A surveillance system of hepatitis B has been operating in Canada since 1998, including The Northwest Territories from 2009. This surveillance system provides clinical and laboratory data of new cases of acute and chronic hepatitis B[34]. Also, follow-up of newborns occurs in all regions of the North[30].

Alaska has been the lead in childhood vaccination against hepatitis B. Alaska natives received universal HBV vaccination since 1984, and since 1994 The State of Alaska has had a policy of universal hepatitis B vaccination of all newborns[34]. This included all children up to age of 18 years from 1997 and was free of charge. The universal hepatitis B vaccination program coverage in Alaska is at the moment approximately 59.4% for newborns and 92.1% for 24 mo old children[35]. Surveillance of HBV is a State responsibility in Alaska, and laboratories and health care providers are required by law to report cases of acute hepatitis B[4]. In 2003 there were 1300 Alaska Natives followed for chronic hepatitis B[4].

In Russia HBV vaccination of newborns and 13-year-old children was introduced in 1998[30]. Universal infant immunization was added from 2001, which included school-based catch up programs[4]. The childhood vaccination programs in Russia have an average coverage

rate of over 95%[36,37].

A surveillance program for infection with HBV operating in Russia includes acute and chronic HBV infection as well as the carrier state[30,34].

TREATMENT

Vaccination and immunoglobulin treatment of newborns has been shown to have a huge impact on the incidence of chronic hepatitis among the circumpolar populations as documented also in other areas[38]. This supports the benefit of vaccination. However, a unique characteristic among Greenland Inuit has been the lack of apparent disease among those infected with HBV. Hence, there has been little attention to the need for treatment of HBV infection. Still, a few patients have been identified with signs of moderate fibrosis on liver biopsy (Krarup, personal communication). These patients were initially treated with lamivudine and since 2009 with tenofovir. Furthermore, patients co-infected with hepatitis D have been treated with interferon-alpha, and in recent years this has been as pegylated interferon. Still, systematic follow-up on these patients has not been undertaken yet.

The Greenlandic guidelines on treatment of chronic hepatitis are similar to the Danish guidelines[39]. All hepatitis B infected Greenlanders in need of diagnostic work-up or treatment are consulted by one central unit in Greenland. The consultants at the Department of Internal Medicine at Queen Ingrid's Hospital in Nuuk are further in close consultancy with hepatitis experts in Denmark. This structure supports an updated treatment in Greenland.

Even though subpopulations in Canada host HBV infections with endemic prevalence there are no data regarding the effects of anti-viral therapy in Canadian circumpolar populations infected with viral hepatitis[40]. Treatment of HBV infection in Alaska is in accordance with the AASLD guidelines[41].

LIVER CANCER

The long term clinical outcome of hepatitis B infection is variable. HCC has in general demonstrated a low occurrence among Inuit in Greenland compared to what would be expected based on the prevalence of HBsAg. Similar findings are available for other populations in the Arctic region, specifically in Canada. In 1978 Skinhøj *et al*[42] reported an occurrence of HCC in Greenland Inuit similar to that seen in Northern European populations. This report was based on official mortality statistics and biopsies and necropsies, and it covered the time period from 1951 through 1975. They recognised that death statistics were not comprehensive. In addition, the greater part of this time span was prior to westernisation and the referral to hospital and travel from the small settlements scattered along the vast coastline of the world's largest island was likely limited. This probably hampered the diagnosis of HCC.

Similar limitations account for the study by Melbye *et al*[17] using the same methods. They identified 12 cases in the same area between 1960 and 1981 with a 15 year overlap between the two studies. Thus, the diagnosis of HCC was probably not comprehensive in this study either.

Nielsen and Storm reported a total of 3255 incident cancers diagnosed from 1969 to 1988 in 85000-110000 individuals among circumpolar Inuit in Greenland, Canada, Alaska and Russia. Among these inhabitants of the circumpolar region primary liver cancer was reported in 53 men with 37 from Alaska, 15 from Greenland, and 1 from Canada[43]. There were 16 cases among women with 6 from Alaska, 7 from Greenland, and 3 from Canada. They also reported an increasing incidence in Greenland Inuit and a decreasing incidence among Alaska Inuit. This coincided with the introduction of the vaccination program in Alaska. Indirect standardization showed excess risk of cancer of the liver and stomach compared to populations in the lower states in United States, in Canada and in Denmark[43]. The study by Nielsen was more comprehensive than previous studies in Greenland, and a gradual improvement of the validity of the registries may be anticipated.

Friborg *et al*[44] retrieved information of liver cancer cases among a total of 72331 individuals born in Greenland and alive from 1973 to 1997. These individuals were tracked in the Danish Cancer Registry by the use of their Civil Registration Number. Cancers among Inuit living in Denmark at the time of diagnosis were included. Standardized incidence ratio for liver cancers in Greenlandic men was 1.9 (95%CI: 1.0-3.5) compared with Denmark from 1988 to 1997[44]. This conforms to the notion that liver cancer was not a prominent disease in Greenland at least up until 15 years ago.

A more recent study on the occurrence of liver related disease among Greenland Inuit was based on more valid hospital statistics. The study was conducted as a follow-up in 2007 on studies performed in 1987 and 1998[18]. A main finding was a lower frequency of hospitalization due to liver disease than what would be expected even when compared to areas with a low HBV prevalence[18]. Also, the authors identified 15 cases of HCC. This may still not cover all cases of HCC in Greenland due to logistics, patient choice and the aggressive nature of HCC. However, the number is low, and the data suggest that HBV infection in Greenland may be associated with a lower risk of liver cancer and liver disease than in other parts of the world[18]. Further investigations based on this finding are of interest as new aspects of the infection may present themselves and contribute to an understanding of what causes a benign or non-benign outcome of the disease.

The overall low incidence HCC in chronically HBV-infected Inuit has suggested a more benign course in Greenland than in other parts of the world[9,18,43]. This finding is not restricted to Greenland Inuit. HCC is also uncommon in Canadian Inuit[45]. The incidence is only

marginally higher in Inuit compared to Danes who have a low occurrence of HBV. Among Alaskan Native people infected with HBV, genotypes F and C associate with a higher incidence of HCC. This outcome may be associated with the genomic variability of the predominant HBV genotype in each country[46].

Hepatitis B vaccination programs and especially universal infant vaccinations have demonstrated success in reducing both incidence of disease and chronic carriers but indeed also in reducing HCC occurrence in children[38,47,48]. Even though the incidence is low in Inuit the vaccination programmes in the Arctic should prevent the few cases that may be anticipated.

FUTURE ASSESSMENT

Health care workers, health care providers and the population of Greenland and other Arctic countries must be advised on the burden of hepatitis. A nation-wide approach that acts according to international guidelines on the monitoring of hepatitis should be implemented. For economical, educational, feasibility and technical reasons monitoring should be performed through readily available IT-programs to reduce technical problems among health-care staff in a geographical area with huge infrastructural challenges due to sparse populations in vast areas. Also, patients should be given the opportunity to have blood samples drawn whenever they come to a town. Patients with clinical and/or biochemical abnormalities should go through the usual clinical work-up through contact to physicians at the medical department at the local hospital.

CONCLUSION

Infection with HBV is endemic in Greenland Inuit as in other Inuit populations across the Arctic. Still, studies seem to confirm a benign course of the disease among Inuit both in Greenland and Canada, but not in Alaska. This has contributed to a late initiation of a universal HBV vaccination program in Greenland in contrast to Alaskan, Canadian and Russian Arctic. Thus, a monitoring program for viral hepatitis in Greenland is relevant and the inclusion in an electronic patient file system covering all of Greenland is warranted and scheduled.

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