HEPATITIS B INFECTION IN GREENLAND

Epidemiology and burden of disease

PHD THESIS

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DANSKE RESUMÉ

Baggrund

På verdensplan medfører smitsom leverbetændelsesvirus type B (Hepatitis B-virus-infektion, HBV) høj sygelighed, primært i form af akut og kronisk leverbetændelse (hepatitis), skrumpelever (cirrose) og kræft i leveren (hepatocellulært karcinom, HCC) [1]. HBV-infektion er hyppig i Grønland. Tidligere tværsnitsundersøgelser har fundet, at ca. 42 % af befolkningen er HBcAb- positive, og 7 % HBsAg-positive som udtryk for henholdsvis tidligere smitte og kronisk infektion [2-4]. I Alaska er HBV-prævalensen ligeledes høj blandt Inuitter, og forekomsten af HCC og cirrose som forventet ud fra fund i andre høj-endemiske områder i verden, tilsvarende høj [5,6,9]. I Grønland derimod, er cirrose og HCC observeret sjældnere end forventeligt i en befolkning med så høj forekomst af HBV, og forekommer ikke hyppigere end i Danmark [7,8]. Disse forhold er usædvanlige og uforklarede. Selvom tekniske faktorer som f. eks færre diagnostiske muligheder og lavere obduktionsfrekvens i Grønland end i Danmark kan medføre lavere observerede rater af HCC og cirrose i Grønland vil dette næppe kunne forklare den store forskel. Biologiske forklaringer på den lavere frekvens af langtids-konsekvenser kan være, at smittemønstret blandt grønlændere er anderledes end i andre høj-endemiske lande; at der findes mere godartede virus-undertyper i Grønland, eller at grønlændere har en særlig genetisk sammensætning, som gør at de reagere anderledes overfor HBV infektion end andre populationer. Det har længe været diskuteret, i hvilket omfang HBV vaccination skulle indføres i børnevaccinationsprogrammet i Grønland, men der har manglet solide data til at underbygge en vaccinationsstrategi. Eneste vaccinationsprogram har været vaccination af børn af kronisk smittede mødre, men det har været uvist, i hvor høj grad dette program har fungeret.

Formål

At redegøre for epidemiologien og de kliniske konsekvenser af HBV-infektion i Grønland

Delformål

Studie I

At undersøge årsagen til udbrud af klinisk HBV og biokemisk leverpåvirkning blandt børn i bygden Itilleq i Sisimiut distrikt.

Studie II

At evaluere effektiviteten af det grønlandske HBV-vaccinationsprogram ved at bestemme graden af vaccinationsdækning af børn født af HBsAg-positive mødre, samt at bestemme niveauet af vaccine-inducerede antistoffer og HBV-status blandt disse børn.

Studie III

På baggrund af longitudinel information om HBV-status i en populationsbaseret kohorte fulgt fra 1987 at beskrive epidemiologien af HBV-infektion i Grønland ved aldersspecifikke forekomster og nye tilfælde af HBV infektion og HBsAg seroclearance (dvs. tab af HBsAg i en kronisk smittet person)

Studie IV

At beskrive de kliniske konsekvenser af HBV-infektion i Grønland i form af sygelighed og dødelighed i en populationsbaseret kohorte for kronisk HBV-smittede grønlændere sammenlignet med HBV-immune og HBV-negative personer.

Konklusioner

I) Den primære årsag til forhøjet ALAT blandt børn i bygden Itilleq synes at være et verserende hepatitis D (HDV) udbrud blandt HBV kronisk smittede børn.

II) Den nuværende HBV-vaccinationsstrategi er ineffektiv; færre end 2/3 af børn født af HBsAg-positive mødre fik 3+ vaccinationer. Desuden er det vaccine-inducerede antistofniveau overraskende lavt, tydende på et ineffektivt vaccinationsrespons blandt vaccinerede børn.

III) Hyppigheden af nye HBV tilfælde (incidencen) var 5 per 100 personår (PY) i alderen 15-24 år, hvorimod incidencen var <1 per 100 PY i alderen 5-14 år. Dette indikerer at det primære smittetidspunkt i Grønland er i sen ungdom og voksenalderen. Desuden medfører HBV infektion blandt voksne i Grønland en høj andel af kronisk smittede, en andel højere end hvad der er set i andre befolkninger. Tab af HBsAg blandt kronisk smittede (HBsAg seroclearance) var i samme størrelsesorden som set i andre longitudinelle studier og synes ikke at forklare den høje forekomst af kronisk HBV infektion blandt grønlændere.

IV) Kronisk HBV-smittede personer har højere risiko for HCC og cirrose end immune og negative personer, men den aldersstandardiseret rate af HCC og cirrose blandt kronisk smittede i Grønland var lavere end blandt kronisk smittede i andre populationer.

Folkesundhedsmæssige implikationer

Afdækningen af HDV-udbruddet i Itilleq har været en medvirkende årsag til, at HBV-vaccination indføres i børnevaccinationsprogrammet pr.1. september 2010. Der vil blive givet 4 vaccinationer ved 0, 3, 5 og 12 månedersalderen. Vaccination mod HBV vil yderligere forebygge Hepatitis D infektion (HDV er et inkomplet virus, som er afhængig af HBV for at komme ind i levercellerne). Screening af gravide vil fortsætte, og børn af HBsAg positive mødre vil fortsat gives immunoglobulin ved fødslen.

SUMMARY IN ENGLISH

Background

Worldwide, Hepatitis B (HBV) infection causes a high degree of morbidity mainly in the form of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma, HCC [1]. HBV is highly prevalent in Greenland. In earlier cross-sectional studies approximately 40% and 7% of the population were HBcAb positive and HBsAg-positive, reflecting previous infection and chronic infection, respectively [2-4]. Similar high rates of HBV infection have been found in other Inuit populations in Alaska, where rates of HCC and liver cirrhosis are consequently high [5,6].

Despite the high prevalence of HBV, liver cirrhosis and liver cancer are seen much less frequently than expected in Greenland, and the incidence rates of liver cirrhosis are not higher in Greenland than in Denmark [7,8]. This lack of sequels is unexpected. Although technical factors (e.g. diagnostic tools used and frequencies of autopsies) may contribute to the differences, they are unlikely to explain the difference. Biological explanations for the lower frequencies of long-term consequences may include factors such as age at primary time of infection, less virulent HBV genotypes, or a particular genetic constitution among Greenlanders.

Although debated for decades, HBV vaccination is not included in the childhood vaccination programme in Greenland. Only since 1992 have all pregnant women been screened for HBsAg, and infants of HBsAg-positive mothers vaccinated postnatally. However, the effectiveness of this targeted vaccination programme is unknown.

Objectives

The overall aim of this PhD thesis was to describe the epidemiology and the clinical burden in prospective studies and the effect of the installed protective measures organised against HBV in Greenland.

Specific aims

Study I

To describe an outbreak of clinical hepatitis and elevated liver enzymes among children in a settlement, Itilleq, and identify explanatory factors for the outbreak.

Study II

To determine the coverage of the nationwide HBV vaccination programme for at-risk children of HBsAg-positive mothers and to estimate the effectiveness of the HBV vaccination.

Study III

In a population-based cohort setting based on longitudinal information on HBV status to describe the epidemiology of HBV infection in Greenland by investigating the age-specific incidence and HBsAg seroclearance (e.g. loss of HBsAg in a chronically infected person) as well as the proportion of chronic carriers.

Study IV

In a population-based longitudinal setting to describe the clinical burden of HBV disease in Greenland by investigating the morbidity and mortality by HBV status

Conclusions

I) An ongoing hepatitis D (HDV) outbreak among chronically HBV-infected children in the settlement Itilleq seems to cause elevated liver enzymes.

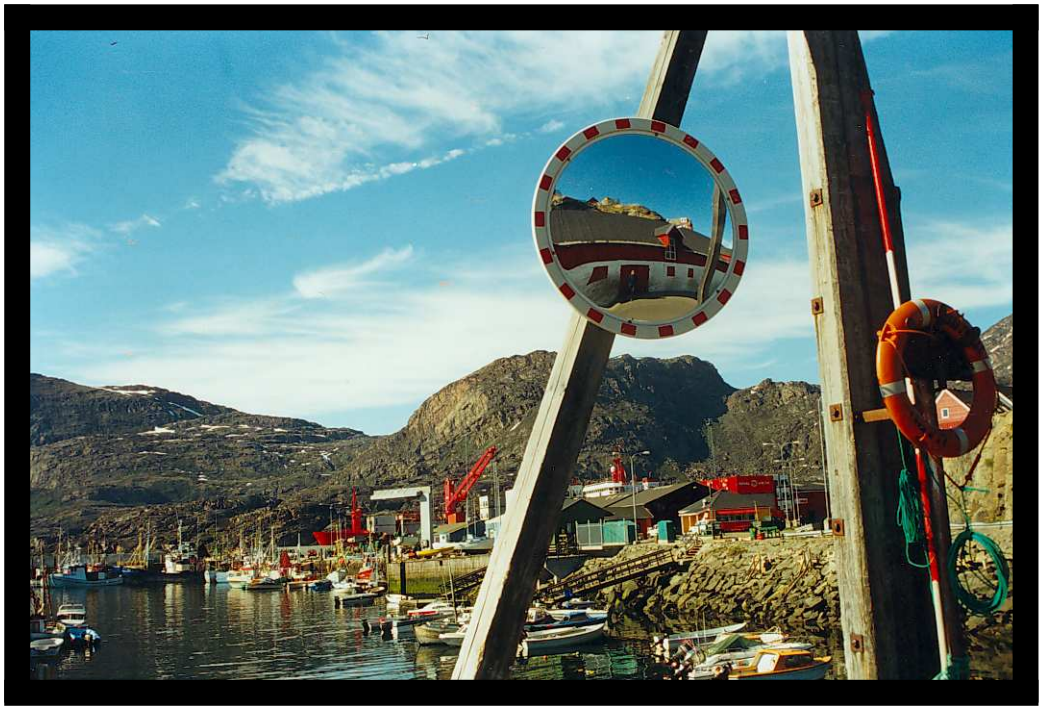
II) The current HBV vaccination strategy in Greenland is ineffective. Less than 2/3 of at-risk children born to HBsAg-positive mothers received three or more HBV vaccinations and the HBsAb levels of vaccinated children were surprisingly low even in supposedly vaccinated children, indicating ineffective vaccine response.

III) The incidence of HBV infection in the age group 15-24 years of age was 5 per 100 person years (PY) whereas the incidence among 5-14 year-olds was <1 per 100 PY indicating that HBV transmission among Inuit in Greenland appears mainly to be transmitted in adolescence and adulthood. Furthermore, HBV infection among adults seems to lead to a much higher proportion of chronic carriers than seen elsewhere. The incidence of HBsAg seroclearance among chronic carriers was of same magnitude as in other longitudinal studies and does not seem explain the high prevalence of chronic infection among Greenlanders.

IV) We found an increased incidence rate ratio in first time hospitalisations of overall liver-related diseases, non-alcoholic cirrhosis and HCC for HBV chronic carriers vs. HBV-negative persons, but the age-standardised incidence rates for the diseases among chronic carriers in Greenland were low compared with other populations of chronically HBV infected persons.

Public health implications

The characterisation of the HDV outbreak in Itilleq has been an important factor in the decision to include the HBV vaccination in the childhood vaccination programme September 1. 2010, with a schedule of four vaccinations at age 0, 3, 5 and 12 months of age. HBV vaccination will also protect against HDV, an incomplete virus dependent on HBV to entrance the hepatocytes. Pregnant women will still be offered a screening during pregnancy to give infants of HBsAg-positive mothers hepatitis B specific Immunoglobulin after birth.



NAALISARNERA (grønlandsk resumé)

Tunuliaqutit

Tunillannartumik tingullunneq type B (HBV) Nunarsuatsinni tamarmi annertuumik napparsimalissutaasarpoq, nappaatit makku kingunerisinnaagamigit; sakkorttumik katsorsarneqarsinaanngitsumillu tingukkut aseruuttoorneq (hepatitis), tinguup eqinnera (cirrose) aamma tingukkut kræfteqalerneq (hepatocellulært karcinom, HCC) [1].

Tunillannartumik tingullunneq HBV Kalaallit Nunaanni atugaaqaaq. Siusinnerusukkut misissuisoqartarnerani paasinarsivoq innuttat 42 % - iisa missingi tunillatsereersimasut 7 % -llu missingi tunillatseqqammersut. [2-4].

Tunillannartumik tingullunneq aamma Alaskami naggueqatigiit inuit akornanni atugaasorujussuuvoq, taamaattumik tingup eqinneranik nappateqalersartut aamma tingummikkut kræfteqalersartut amerlapput, nunarsuatsinnimi sumiiffinni allani tunillaassorfiusuni najugallit aamma taamaapput [5,6,9].

Kisianni Kalaallit Nunaanni paasisat allaanerussuteqarput, tassami tunillannartumik tingulluttut taamak amerlatigigaluartut tingup eqittoorneranik nappaatillit aamma tingummikkut kræfteqalersartut ilimagisamit ikinnerupput, Danmarkimi pissutsit assigiinnarpaat. [7,8]. Tamanna paasiuminaallunilu nassuiaruminaappoq. Kalaallit Nunaanni nappaatip suuneranik aamma suup toqqutaasimaneranik misissuisarnerit Danmarkimiit appasinneruneralluunniit eqqarsaatigigaluaraanni tamanna assigiinngissutsimut nassuiaataasinnaanngillaq. Kalaallit Nunaanni tingullunnerup piffissaq sivisunerusoq isigalugu kingunipilorisinnaasaasa ilimagisamit annikinnerunerinut nassuiaataasinnaasutut makku ilimagineqarsinnaapput; kalaallit akornanni tunillaassuunneq nunani allani nappaatinik taamaattunik atuiffiusuni tunilaassuuttarnernit allaaneruneri, kalaallit arlaannik iluaqutaasinnaasunik virusseqarneri, imaluunniit kalaallit kingornuttakkamik sananeqaatsimikkut allaanerussuteqarnertik pissutigalugu tingullunnermut iluaquteqartut.

Kalaallit Nunaanni naalungiarsuit tingullunnermut illersuummik kapitittalernissaat sivisuumik oqallisigineqartareerpoq, ilisimasalli tutsuinartut aallartinnissaanut amigaataasimapput. Manna tikillugu taamaallaat anaanat tingullunnermik katsorsarneqarsinnaanngitsumik tunillatsissimasut meeraat kisimik illersuutissamik kapitinneqartussaapput, tamarmilli ilumut kapitittarnersut ilisimaneqanngilaq.

Siunertaq

Kalaallit Nunaanni tingullunnerup katsorsarneqarsinnaanngitsup tunillaassornera tamatumalu kingunerisinnaasai pillugit nassuiaateqarnissaq.

Anguniakkat ilaat

Misissuineq I

Tingullunnerup katsorsarneqarsinnaanngitsup tunillaassuuneranut patsisit misissornissaat, aamma Sisimiut eqqaanni Itillimi meeqqat tinguinik misissuinermi paasisat.

Misissuineq II

Kalaallit Nunaanni tingullunnermut BHV-mut illersuutissamik meeqqat kapitittarnissaannik pilersaarusiap qanoq malinneqarsimatigineranik naliliineq, tamanna pissaaq anaanat tunillatsissimagaluarlutik ajorunnaarlutik tunillatseqqissinnaajunnaarsimasut meerai tamarmik illersuutissamik kapineqartarsimanersut paasiniarlugu misissuinikkut, aamma meeqqat kapitissimasut qanoq akiuussutissaqartiginerisa misissorneqarnerisigut kiisalu tinguisa qanoq innerinik misissuinikkut.

Misissuineq III

Tingullunneq HBV pillugu 1987-mi inunnik misissuineq aallaavigalugu Kalaallit Nunaanni ullumikkut nappaatip taassuma qanoq siaruaassimatiginerata aamma qassinik ukiullit tunillatsittarnerisa allaaserinissaa, taakkununnga ilanngullugit tunillatsisimasut nutaat aamma tunillatsissimagaluarlutik ajorunnaarlutik tunillatseqqissinnaajunnaarsimasut qanoq amerlatigineri.

Misissuineq IV

Kalaallit Nunaanni tingullunnerup HBV-ip kingunerisaasa allaaserinissaat. Tassa nappaalanernut qanoq pissutaatigisarnersoq aamma qanoq toqqutaatigisarnersoq paasiniarlugu, aamma tunillatsissimagaluarlutik ajorunnaarlutik tunillatseqqissinnaajunnaartunut tunillatsissimanngitsunullu naleqqiullugu qanoq innersoq.

Naalisakkat

I) Itillimi meeqqat tingullunnerisa taamak qaffasitsiginerinut patsisaanerpaagunarpoq meeqqat tingullunnermik katsorsarneqarsinnaanngitsumik HBV-mik tunillatsissimasut aamma tingullunnermik allamik, tassa hepatitis D-mik (HDV-mik taaneqartartumik) nappaateqalersimanerat. Tingulluutip D-p tingulluummik B-mik nappaateqareersut napparsimanerulersissinnaavai.

II) Meeqqat tingullunnermut B-mut illersuutissamik kapineqartarnerat ingerlalluanngilaq; anaanat tunillatsinnerminnik qaangiisimasut meeraat tamarmik illersuutissamik kapineqartarsimanngillat 2/3-liinnaat pingasoriarlutik kapitittarsimapput. Aammattaaq kapitissimasut akornanni iluaqutissap annertussusaa timimiittoq tupinnaannartumik appasippoq, tamatumalu ersersippaa meeqqat kapitissimasut illersuutissamik iluamik sunnerneqarsimanngitsut.
III) Qassinik ukiullit tunillatsissimanerinik misissuinermi erserpoq amerlanersaat 15-24–nik ukioqarlutik tunillatsissimasut. Tassa inuusuttuunermi inersimasuunermilu tunillatsittartut amerlanerupput. Nunanili allani tamanna allaanneruvoq meeqqat tunillatsissimasut amerlanerusarmata. Kalaallilli tunillatsittut amerlanersaat ajorunnaarnatik katsorsarneqarsinnaanngitsumik tinguluttunngortarput, nunanili allani inersimasut tunillanneqarsinnaajunnaarlutik ajorunnaartartut amerlanerullutik. Pissutsit taamaannerat Kalaallit Nunaanni tingulunnerup tunillaassuunnerujussuannut nassuiaataasinnaavoq.
IV) Tingullunnermik katsorsarneqarsinnaanngitsumik tunillatsissimasut tunillatsissimanngitsunit tingummikkut kræfteqalernissamut aamma tingumminnik eqittoornissamut qaninnerupput. Misissuinerilli ersersippaat kalaallit tunillatsissimasut tingummik eqittoortut kræfteqalersullu nunani allamiunut tunillatsissimasunut naleqqiullutik ikinnerusut. Taamaasilluni kalaallit tingulullersimasut oqinnerusumik atugassaqarsinnaanerat ilimanarsivoq.

Peqqissutsimut sunniutit

Itillermi tingullunnerup HDV-p nappaatigineqalersimanerata paasineqarnera pissutaaqataavoq naalungiarsuit tingullunnermut HBV- mut illersuutissamik 1. septemper 2010 aallarnerfigalugu kapitinneqartalernerannut. Naalungiarsuit sisamariarlutik kapitittassapput; inoorlaajunerminni, pingasunik aamma tallimanik qaammateqalernerminni kiisalu ataatsimik ukioqalernerminni. Tingullunneq HBV-mut illersuutissamik kapitinneq aamma tingullunneq HDV – mut illersuutaavoq (HDV virusiuvoq namminneersinnaanngitsoq aatsaat HBV-mik tingulluttoqarnerani tingup sananeqaataanut pisinnaasoq). Arnat tunillatsinnikuugaluarlutik ajorunnaarlutik tunillatseqqissinnaajunnaarsimasut naartuleraangamik misissorneqartarnerat ingerlaannassaaq, meerartaavisalu inunngorneranni akiuussutissamik kapineqartarnerat aammattaaq ingerlaannassaaq.

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