Viral hepatitis in the Arctic

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ABSTRACT

Objectives. Summarize research on viral hepatitis in indigenous populations in the Arctic. Study Design. Literature review. Methods. Medline search from 1966-2003. Results. High prevalence rates of total hepatitis A antibody of >50% and of hepatitis B of between 22% in Alaska and 42% in Greenland for total infection and between 3% in Canada and 12% in Siberia for chronic infection have been reported. Universal childhood vaccination with hepatitis A vaccine beginning at age 2 have stopped epidemics of HAV in Alaska and newborn hepatitis B immunization programs in Alaska and Canada have reduced new infections. However, in all Arctic countries several thousand persons chronically infected with HBV remain at risk for the development of cirrhosis and hepatocellular carcinoma. Prevalence rates of hepatitis C (HCV) reported are <1.4% in the Arctic. Hepatitis D virus, which co-infects with HBV, has been found in 40% of persons with HBV in Greenland. Conclusions. High rates of viral hepatitis A, B, C, and D are found in the Arctic. Effective vaccines against HAV, HBV and HDV can prevent transmission of these viruses. In addition, new antiviral therapies for HBV and HCV can be used effectively to treat many chronically infected patients.

Keywords: Viral Hepatitis, Arctic, Indigenous Peoples

INTRODUCTION

Of the five types of viral hepatitis that have been identified in the world, four are found in the Arctic Region: hepatitis A, B, C and D. The molecular characteristics of these five viruses and the areas where they are found in the Arctic are displayed in Table I. These viruses to a great extent effect the indigenous populations of the circumpolar area. In this paper I will review the epidemiology of viral hepatitis in the Arctic region, discuss the chronic sequelae that three of these viral infections can cause, review measures that have been put into place to prevent the spread of some of these viruses and discuss programs that have been established in the region to manage the complications of these infections, primarily chronic liver disease and hepatocellular carcinoma (HCC). Finally, I will discuss control measures that could be introduced and suggest areas for research to delineate the impact of these viral diseases.

Hepatitis A Virus

Hepatitis A is an RNA virus that is transmitted via the fecal-oral route primarily by close personal contact with an infected person (1). Most young children under 5 years of age are asymptomatic, but are a source of transmission for older individuals, whereas up to 70% of older children and adults develop icteric illness. Recovery from hepatitis A confers lifelong immunity. High prevalence rates of exposure to hepatitis A are found throughout the Arctic region in all indigenous groups that have been studied thus far. In the 1970s large epidemics of hepatitis A were reported in Greenland (2) and in 1994, a serosurvey do-
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The prevalence of total hepatitis A antibody (anti-HAV), the marker for past infection, was revealed in two communities in West Greenland to be 54% in Inuit individuals (3). This serosurvey demonstrated that the prevalence of hepatitis A increased from 9% to 50% between the second and third decades of life. A serosurvey in two Inuit communities in Canada conducted in 1980 found the prevalence of anti-HAV to be 71%, with a steep rise in prevalence from 40% to 80% between ages 10 to 20 years (4). These two studies imply that childhood immunization could be an effective means of controlling HAV in Greenland and the Canadian North, as routine vaccination of children and adolescents should interrupt transmission and may prevent future epidemics. Two studies in the Russian literature abstracted in English have been reported. One survey of 100 persons from the Purov region of the Tumen district in 1995 found that all persons tested had evidence of past hepatitis A (5). In another report published in 1994, hepatitis A was found to be the leading cause of acute hepatitis in Khabarovsk (6). Obviously, more serosurveys are needed from Siberia to determine the prevalence of HAV in the region. In Alaska, large epidemics of hepatitis A occurred in the past every 7 to 10 years. The highest attack rate occurred among children ages 5 to 15 years (7). Previous attempts to control these epidemics with immune globulin were unsuccessful, merely slowing the pace of transmission temporarily. These epidemics tied up public health nurses and other workers and had the effect of temporarily disrupting the public health delivery system in rural Alaska, including the on-time delivery of routine childhood immunizations. In 1992 a study was conducted to attempt to stop an epidemic by administering one dose of hepatitis A vaccine to over 5,000 susceptible young people from 25 villages. This measure was successful in halting the epidemic within 4 to 6 weeks in each community as long as at least 70% of susceptible persons had been immunized (8). After the success of this vaccination study and the licensure of hepatitis A vaccine in the US, the State of Alaska implemented the routine administration of hepatitis A vaccine to all children beginning at age 2 years and in 2002, required hepatitis A vaccination be complete before school entry was allowed. This has resulted in a marked drop in the number of new cases and no new epidemics have occurred for the past 10 years.

While the availability of a highly immunogenic vaccine that is effective against hepatitis A is a major tool in preventing this disease, several important issues need to be addressed in the future. First, the vaccine is not licensed in the US for children under 2 years of age. While this vaccine is safe in infants, maternal antibody interferes with the response when it is present. A randomized study of hepatitis A vaccine recently conducted in Alaska Native infants should answer the question of when is the best time to administer this vaccine. Secondly, studies are needed to de-

Table I. Types of Viral Hepatitis: Genomic Structure, Route of Transmission and Locations Identified in the Arctic.

| Type           | Genome | Route     | Geographic Location                  |
|----------------|--------|-----------|--------------------------------------|
| Hepatitis A (HAV) | RNA    | Fecal/Oral| All Arctic Regions                   |
| Hepatitis B (HBV)  | DNA    | Parenteral| Western Alaska, Northern Canada, Greenland, Siberia |
| Hepatitis C (HCV)  | RNA    | Parenteral| Alaska, Siberia                      |
| Hepatitis D (HDV)  | RNA    | Parenteral| Greenland                            |
| Hepatitis E        | RNA    | Fecal/Oral| Not Found in Arctic                  |

Table II. Age-adjusted rates of Hepatocellular Carcinoma in the Inuit (Eskimo) Populations of the Arctic: 1969-1988. Adapted from Storm(39).

| Area     | ASR* | SIR** (95% CI) | SIR** (95% CI) | SIR** (95% CI) |
|----------|------|----------------|----------------|----------------|
|          |      | Connecticut    | Denmark        | Canada         |
| Circumpolar | 8.0  | 4.0 (3.0-5.2)  | 3.1 (2.2-4.3)  | 4.1 (3.0-5.3)  |
| Alaska    | 15.1 | 7.2 (5.1-9.9)  | 5.5 (3.9-7.6)  | 7.7 (5.2-10.2) |
| Greenland | 5.7  | 2.7 (1.5-4.5)  | 2.1 (1.2-3.4)  | 2.8 (1.5-4.5)  |
| Canada    | 1.0  | 0.4 (0.0-2.2)  | 0.3 0.0-1.7   | 0.4 0.0-2.1    |

* ASR: Age Standardized Rate World
** SIR: Standard Incidence Ratios
termine how long protection will last. Preliminary studies suggest protection in adults will last 20 to 30 years and the vaccine is protective for at least 5 years in older children (9). However, long-term studies in infants and children are needed and these studies are now being conducted in Alaska Natives. In the Arctic, hepatitis A vaccine could not only be used to stop epidemics in indigenous populations, but if cost effective, could be given routinely to children as is done in Alaska to prevent future epidemics. It is conceivable that only one dose of this vaccine could provide long-term protection, but this needs to be studied.

Hepatitis B Virus
Hepatitis B virus (HBV) is a DNA virus that can cause chronic infection that can result in chronic liver disease leading to cirrhosis or hepatocellular carcinoma (HCC) (10). Approximately 2 billion of the world’s 6 billion people have been infected by the hepatitis B virus (HBV). Children who are infected through perinatal transmission at birth or through horizontal transmission under the age of 5 years, have a 90% and 30% risk, respectively, of becoming chronically infected. Over 350 million people worldwide are chronically infected with HBV. The areas that have been found to have the highest rate of HBV infection are in East Asia, the South Pacific region, sub-Saharan Africa, the Amazon Delta and the indigenous populations of the Arctic. Seven distinct genotypes of HBV have been identified, A-G. Preliminary studies suggest that certain of these genotypes, particularly genotypes C and D, may be associated more frequently with the development of chronic liver disease (10). Three serosurveys have been performed in Greenland. The first, conducted from 1965 to 1972 in six communities in three geographic areas of Greenland, east, northwest and southwest, demonstrated a prevalence of hepatitis B surface antigen (HBsAg), the marker for chronic infection, of 16.6% and of antibody to hepatitis B core antigen (anti-HBc), the marker of exposure to HBV of 62.5% (2,11). This compares to prevalence rates of HBsAg of < 0.5% and anti-HBs of 8% in the US and northern Europe. In 1989, another survey was performed in an area of west Greenland not surveyed in the first study, and the prevalence of HBsAg was found to be 11.5% with 75% of the population over 25 years having anti-HBc in their sera (12). At the same time a high rate of acute hepatitis B was reported of 185/100,000. In 1997, a serosurvey in two villages in west Greenland in the area surveyed in 1989, found the prevalence of HBsAg to be 7% with 42% of persons anti-HBc-positive (3). In the latter survey, the prevalence of anti-HBc increased from 11% in 10-to-19-year-olds to 57% in 40-to-49-year-olds. In these two villages, genotype D was found in 83% of HBsAg positive persons and A in 17%. Genotype D has been identified in the Mediterranean region of Europe and genotype A in northern Europe. Genotype D has been associated with a more aggressive form of chronic hepatitis B in the Mediterranean region (10).

In Canada, high rates of acute hepatitis B were reported in the mid-1980s from the Yukon and Northwest Territories, 16.77/100,000 and 15.7/100,000 respectively (13). In Northern Canada a serosurvey was performed in the early 1980s in two communities in Nunavut, and HBsAg was found in 4% of the population and anti-HBc in 27% (4,14). Based on these findings it was decided to offer HBV testing to residents in 42 communities in this area and vaccine to those who were seronegative. HBsAg was found in 3% of persons overall and ranged from 2.3% to 6.9% and anti-HBc in 35.7% (range 22% to 36%) (15). A separate serosurvey in communities in Labrador found HBsAg in 3.2% and total seropositivity in 14.7% (16). Hepatitis B immunizations beginning at birth are administered throughout Canada.

Several serosurveys have been published from Siberia. In a serosurvey of 348 Siberian Natives from the Kamchatka Peninsula, HBsAg was found in 41 (11.8%) and the prevalence of HBsAg or antibody to hepatitis B surface antigen
(anti-HBs) was 48% (17). A serosurvey of 231 indigenous persons from a village in the Republic of Altai in southwest Siberia demonstrated a prevalence of HBsAg of 13.4% and 53% had anti-HBc (18). A survey of 5 different groups from Novosibirsk in western Siberia found the prevalence of HBsAg to range from 1.1% in blood donors to 3.5% in medical students (19). From 1992 to 1999, the incidence of acute hepatitis B in Russia rose from 18.1 to 43.4 cases/100,000 population and the incidence was over 50/100,000 in Eastern Siberia (20). In urban areas in Russia such as Moscow and St. Petersburg, sexual transmission and injecting drug use appears to play a major role in HBV transmission (20,21). Thus, HBV infection is a significant problem in all of Russia and especially in Siberia. Russia has a policy of universal infant immunization for hepatitis B since 2001 and immunization programs are currently being implemented including school-based catch up programs in some areas.

The first surveys in Alaska were conducted in the early 1970s and found high rates of HBV in Alaska Natives residing in southwest Alaska (22). A prospective observational cohort study of 1,200 seronegative persons followed over 4 years conducted shortly thereafter found that transmission was primarily horizontal, with the highest attack rate found in young children (23). Of those infected under the age of 5 years, 28% developed chronic infection. Between 1983 and 1987, 53,000 persons were screened and hepatitis B vaccine was given to 42,000 of those who were seronegative (24). Hepatitis B vaccine was also introduced as a routine vaccination in all newborns. As a result, the rate of acute hepatitis B has fallen dramatically in Southwest Alaska from over 200/100,000 in 1981 to < 5/100,000 in 2002. In addition, a serosurvey conducted 10 years after the initiation of universal hepatitis B vaccination demonstrated that the rate of chronic HBV infection had fallen dramatically, as no child <10 years of age was HBsAg-positive compared to 16% of those ages 11-30, indicating that a generation of children was free of chronic HBV (25). The success of hepatitis B vaccination programs have also been demonstrated in Taiwan and American Samoa (26,27), and in Taiwan, universal infant vaccination has shown a significant reduction in HCC rates in children. This demonstrates that hepatitis B vaccine is the first vaccine developed that prevents cancer (27).

**Hepatitis C Virus**

Hepatitis C virus is an RNA virus that is transmitted via contaminated blood or direct needle inoculation (28). In the US, the prevalence of antibody to hepatitis C virus (anti-HCV) was found to be 1.8%, and injecting drug use has been found to be the major risk factor in the majority of cases (29). Chronic infection develops in 70% to 85% of persons infected, and chronic infection leads to cirrhosis and/or HCC in up to 25% of those persons. HCV is a rapidly mutating virus and development of a vaccine has been unsuccessful thus far. Treatment is only effective in less than 50% of patients, has significant toxicity, is very costly and has to be administered for 6 months to a year. Several serosurveys of hepatitis C virus have been reported from the Arctic. A study in two communities in west Greenland reported in 1997, found the prevalence of anti-HCV to be only 0.5% (3). A survey conducted in seven villages in southwest Alaska found that antibody to hepatitis C virus was found in only 1 in 600 persons. However, in urban Alaska HCV infection is more frequent and a study in Alaska Natives has found over 1,000 persons who are anti-HCV-positive (30). In Siberia, three serosurveys have been reported. In the serosurvey from Siberian Natives in Kamchatka, anti-HCV was found in 5 (1.4%) of 348 persons (17). A survey conducted in the Purov region of the Tumen district in 1995 found a prevalence of anti-HCV of 0.93% (18). The prevalence of anti-HCV in both of these two studies from Siberia is similar to the 1.8% found in the US. However, in a study of five population groups from Novosibirsk, the prevalence of anti-HCV ranged from 2.1% in blood donors to 6.4% in medical uni-
versity students (19). Furthermore, HCV seems to be a problem in urban areas such as St. Petersburg, where injecting drug use may substantially contribute to transmission (21,31). More data regarding the impact of HCV in the Siberian Arctic are needed.

**Hepatitis D Virus**

Hepatitis D virus (HDV) is a defective RNA virus which requires a helper virus, HBV, in order to be infective (32). Two patterns of HDV infection have been found in man. A person can become infected acutely with both HDV and HBV by acquiring these viruses from contact with a person who has a dual infection, referred to as an acute HBV/HDV co-infection. Also, a person who is chronically infected with HBV could acquire HDV infection, referred to as an HDV superinfection. HDV co-infection has a high mortality rate, up to 15%, but most persons who recover clear both of these viruses and have lifelong immunity. In contrast, HDV superinfection not only results in a high mortality rate acutely, also about 15%, but usually leads to chronic infection from both viruses that can increase the risk of developing cirrhosis. Three serosurveys for HDV have been conducted in the Arctic. In southwest Alaska, HDV was not found in any HBV carriers (25), but in Greenland 40% of HBsAg-positive persons in the most recent survey also had HDV (3). One survey of 186 persons of Inuit and native Indian descent from Newfoundland and Labrador conducted in the mid-1980s did not find any individuals positive for HDV (33).

**Hepatitis E Virus**

Hepatitis E virus (HEV) is an RNA virus that like hepatitis A, is transmitted by the fecal oral route (34). It is found in tropical and subtropical areas, and in many countries is the leading cause of icteric viral hepatitis. The tests for HEV, IgM and total antibody to hepatitis E have about a 2% false-positive rate. Two serosurveys of HEV have been conducted in the Arctic, one in southwest Alaska and one in Greenland (3). The prevalence of total anti-HEV was about 2% in both of these studies and would be consistent with the false positive rate of the test (35). Furthermore, reports of acute cases of HEV in the Arctic have not been published. Thus, there is currently no evidence that HEV causes hepatitis in the Arctic.

**Viral Hepatitis and Hepatocellular Carcinoma**

Both HBV and HCV can cause hepatocellular carcinoma (HCC) (36). Initial reports from Greenland did not find high rates of HCC, and Greenland was the only region endemic for HBV in the world that did not report high rates of HCC (37,38). However, a more recent report of the incidence of HCC in a 30-year period from 1969-1988 in the Inuit populations of the North found that the rate of HCC was high in this indigenous group, and furthermore, the rates were high in Greenland when compared to age-adjusted rates in Connecticut, Denmark and Canada (Table II) (39). Rates in Canadian Inuit were low, possibly due to the smaller number of HBsAg carriers. Alaska Natives with chronic HBV have been found to have a high annual incidence of HCC, 1.9/1,000 (40). In Alaska, a program to screen HBsAg carriers with alpha-fetoprotein has shown that 70% of these tumors can be detected at a size small enough for potential surgical cure and the 5- and 10-year survival rates in HBsAg carriers were significantly better since this program was instituted in 1982, when compared to historical controls diagnosed prior to the screening program (41).

**CONCLUSION**

High rates of viral hepatitis A and B have been found in all Arctic regions. Both of these viral infections can be prevented by vaccination. Introduction of hepatitis A vaccine for children over age 2 years has been shown to successfully halt epidemics of hepatitis A in Alaska. Careful cost benefit analysis of utilizing hepatitis A vaccine in Canada, Greenland and Arctic Russia should be done to determine if hepatitis A vaccine should be introduced to prevent epidemics.
and endemic transmission. Hepatitis B vaccine is already routinely utilized in newborns or being introduced into newborns and children in Alaska, Canada and Siberia. Careful consideration should be given to the utilization of this vaccine in Greenland, where the prevalence of HBV is high, hepatitis D co-infection is present in 40% of those with chronic HBV and recent studies have shown a high incidence of HCC. Hepatitis B vaccine is not utilized routinely in the Arctic areas of Scandinavia and data are needed to determine the prevalence of HBV in this region. In addition, prospective studies of persons chronically infected with HBV should be considered in Canada and Greenland to determine the prevalence of liver disease due to HBV in those chronically infected as well as the incidence of HCC. Effective treatment that has been shown to decrease the risk of cirrhosis in persons with chronic active hepatitis B is now available and is recommended for use in these circumstances by evidenced-based practice guidelines developed by liver disease societies in the US, Canada, Europe and Asia (10,42-44). Several oral antiviral medications active against hepatitis B with minimal side effects are now licensed in most countries, and these medications can readily be administered to persons living in remote locations. All persons with chronic HBV in the Arctic should be periodically evaluated to determine whether they would benefit from antiviral therapy. Rates of hepatitis C are variable in the Arctic and more epidemiologic data are needed to determine the impact of this virus on the health of Northern peoples. Hepatitis D appears to be a problem in Greenland, but not in Alaska, but data on Canada and Siberia are incomplete. There is no evidence that cases of hepatitis E have been found in the Arctic and if they were, they would likely be found in persons who traveled to endemic areas in the Tropics and sub-Tropics.

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