Viral hepatitis; a global health problem

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Virally caused liver inflammations are a global health threat and affects billions of individuals in the human population as well as animals such as pigs and monkeys. 130 million people are infected with hepatitis C virus (HCV). The number is even higher for hepatitis B virus (HBV) infection where 2000 million people are carriers of the virus, out of which 350 million people have developed chronic HBV infection. Regions with high prevalence of these viruses suffer from extremely negative socioeconomic problems because of high infection rate, it takes weeks to months to recover from an infection and return to daily life such as work and school. Commonly identified with the viruses is also the negative impact on food establishment and local productivity, primarily in developing countries. At present day there is no cure once infected for any of the viruses, however antiviral drug therapies and preventive vaccinations for hepatitis A virus and hepatitis B virus have exhibited a positive response, and the number of newly infected individuals has declined in countries where these vaccination are given, such as the United States and a number of European countries.

Viral hepatitis and the liver

Viral hepatitis is the main cause of liver inflammations in the human population worldwide. Even though many virus families can cause viral hepatitis, five main viruses have been identified as the major cause of infections. These viruses are named hepatitis A, B, C, D and E virus. The viruses are divided into two groups depending on transmission rout. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are waterborne and transmission occurs through the fecal-oral or the enteral rout through ingestion of contaminated water or food while hepatitis B, C and D virus are transmitted parentally, which is transmission through sexual intercourse, from mother to child at berth, contaminated blood transfusion, sharing of contaminated injection needles or syringes and direct contact with contaminated blood. Access to clean water in most developing countries is a major problem, which increases the prevalence of these viruses, especially those transmitted via the fecal-oral rout in those countries.

The liver is a vital organ with manifold and essential functions such as energy production, detoxification of the blood and extraction of nutrients from the blood coming directly from the intestine. It is also the center for protein synthesis, for example the plasma proteins and proteins that control blood coagulation. It is also a blood depot thereby important component of the immune defense system. Additionally it functions as glucose storage as glycogen, lipid and proteins. Another essential function of the liver is controlling the blood glucose-level where it releases glucose in response to regulatory hormones such as insulin. Being the first organ that encounters microbes such as bacteria and virus ingested with food, the liver has a central role in both the innate and adaptive immune response activation.

Hepatitis viruses: chronic hepatitis, hepatocellular cancer and liver cirrhosis

A generally accepted definition of a virus is an obligate intracellular parasite that requires host energy source and replicates by assembly of preformed intermediates. This means viruses are entirely dependent on proliferating (energetically active/dividing) host cells for energy production to compensate their lack of biochemical and genetic potential to generate the

energy necessary to drive biological processes. Hepatitis viruses infect the liver cells known as hepatocytes and replicates in the cytoplasm or the nucleus of these cells. HBV, HDV and HCV replicates in the nucleus while HAV and HEV replicate in the cytoplasm. The general life cycle of the abovementioned viruses begins with viral surface proteins bind to the surface of hepatocytes. Cell entry occurs via receptor-mediated endocytosis meaning engulfment of the virus by the cell or membrane fusion where the virus membrane fuses with hepatocyte membrane and the genetic material of the virus is released into the cells. Cells use endocytosis to efficiently (without energy cost) take up and concentrate extracellular macromolecules such as proteins from the outside environment and viruses hijack this system to be eternalized into cells. Most DNA viruses including HBV are enveloped which means the viral membrane is derived from cellular membrane. These viruses enter the cell through membrane fusion or/and endocytosis due high similarity between the viral envelope and the cells membrane; nevertheless initiation of membrane fusion requires the presence of viral produced fusion proteins that require receptor proteins on the surfaces of hepatocytes. Suggested such receptors for HBV for example are proteins that are highly involved in controlling blood coagulation, inflammation and important processes that lead to immune activation and elimination of microbes and damages cells. However the exact molecular interaction that takes place between HBV and the host is yet to be identified. Complex enveloped virus such as the hepatitis C virus (HCV) produces own fusion proteins. In this case HCV produce proteins called E1 and E2 that target receptors on the surfaces of hepatocytes.

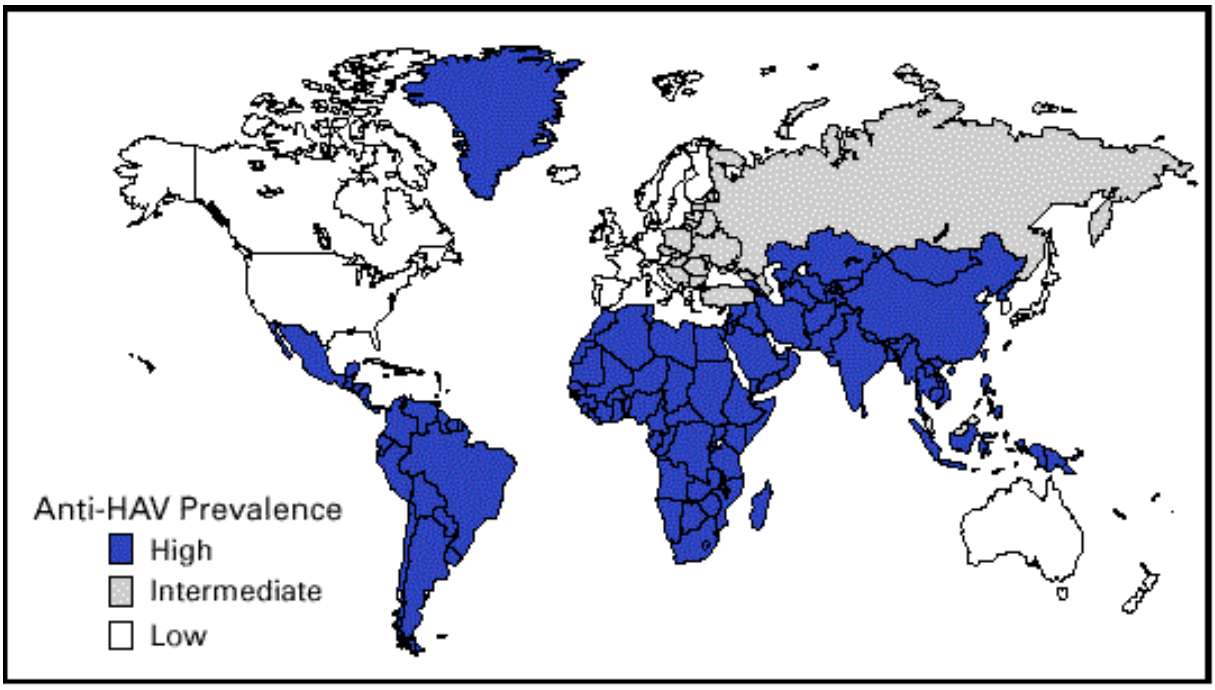

Figure 1. The prevalence of anti-HAV meaning the presence of human and animal produced antigens against the virus in the environment such as water have be shown to have a direct reflection on morbidity and mortality due to hepatitis A infections.

What happens in the liver?

The consequences of viral infections of the liver can vary from mild and transient to severe and prolonged. That is why any liver inflammation caused by hepatitis A-E viruses can be chronic or acute, which is dependent on the duration or persistence of infection but also the nature of the viral genome. Hepatitis A and E virus infections cause acute insult that resolute rapidly upon elimination of virus and normal liver architecture and function can be restored.

However there are cases where insults of the same viruses cause sever liver derangements where the outcome is deadly. An infected individuals ability to clear these infection depend on age, the immune status of the patient, nutrition, other factors such as pregnancy and co-infection with immune suppressing diseases such as HIV/AIDS. Other examples are infection with HEV during pregnancy. The death rate is twenty percent higher for pregnant women including higher risk of giving birth to premature infants. Hepatitis B, C and D lead to severe liver injuries that persist for very long period which many times exceed to cirrhosis, the hallmark of chronic liver injury. Cirrhosis is most often followed by fibrosis and the end stage of this development is hepatocellular carcinoma (HCC). Lipocytes, another class of liver cells that normally function as fat storage cells in the liver are activated by massive hepatocyte cell death and start uncontrollable production of collagen fibers usually found in the extracellular matrix and result in liver fibrosis. HCC is the most common tumor disease and a primary cause of cancer-related death worldwide. It is widely spread and is an immense problem in developing countries but also a growing problem in many European countries, China and the US. The estimation is approximately 80% HCC is caused by HBV. The definition of cancer is uncontrolled division of cells and synthesis of biomolecules. DNA synthesis in hepatocytes is indeed increased in cirrhotic liver in comparison with healthy liver cells. In cirrhotic nodules formed after persistent infection, molecular features of clonal cell expansion meaning cancer cell development are observed where the nodules are abundant. These nodules form scars in the liver making areas of the liver none-functional.

The future: Prevention, vaccination and antiviral therapies

Understanding the various mechanisms behind hepatitis virus infections is an important tool for the development of vaccines, antiviral therapies and treatments. So far scientist have over come major milestones giving insight into the molecular mechanisms of infection, the host ability to clear infection as well as the mechanisms responsible for the host's failure to control viral replication, for example infection with hepatitis C virus cause persistent liver injury in two-third of infected population while one-third of the population establish successful immune response that clears infection. Nonetheless a limited therapy option that often consists of drugs such as pegylated interferon-α and ribavirin treatment, which are highly associated with toxicity, resistance development and do not work for treating certain share of infected individuals. The drugs do not cure the disease but reduce the viral load in infected individuals meaning ultimately most part of these individuals will develop chronic liver injuries that result in cirrhosis, fibrosis or hepatocellular carcinoma.

Few of the explanations for the global distribution of theses viruses are lack of preventive vaccination; lack of implementation of immunization programs for those viruses we do have vaccination against are also factors that indirectly have directed a global distribution of the viruses. However prevention of spread can be achieved simply by understanding the mode of transmission e.g. improving access to clean water. Suitable hygienic precautions are also associated with access to clean water. If one washes his or her hand or raw food such as fruits and vegetables with contaminated water, the risk of spreading viruses increase tremendously. Inaccessibility of clean water and lack of good sanitation program is the hallmark of many developing countries making it difficult to prevent spread. However with increasing globalization and high numbers of travellers a global spread of disease causing viruses is now evident and need the public's attention.

Effective vaccine for HBV has been available for approximately two decades. Ten years later the World Health Organization recommended the implementation of mass immunization programs, which has reduced HBV infection drastically in infants, children and adolescents in

several countries. However as it is in many cases of vaccination programs many developing countries has not implemented the recommendations and remains having large numbers of the population infected with HBV. Nevertheless in recent years many effective antiviral drugs has been developed, which in countries where used as treatment has shown decreasing numbers of morbidity and mortality. The first antiviral drugs developed was interferon-α and lamivudine, interferon-α has displays decent result producing a durable response in moderate proportion of patients. The backside of these drugs is the imminent side effects and only work for a portion of infected individuals. Many new promising treatments are emerging which includes adefovir, ribavirin, pegylated interferon-α2 which has shown to produce response in modest proportion of individuals with chronic HBV infection. The problem with treating with antiviral drugs besides the highly negative side-effects is that they requires prolonged treatment to prevent relapses and there have been many cases where patients relapse and develop cirrhosis and primary liver cancer.

When it comes to vaccination against HAV countries, such as the United States and few European countries have implemented vaccination as routine in childhood vaccination. However large-scale immunization programs show to be more effective in small countries or in areas where outbreaks affect low numbers of individuals. This evidence supports vaccination in itself is not enough and it should be supplemented by health education to improve sanitation and hygiene practice.

Recommended literature

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Figure

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