Göteborg, 2018

Epidemiology, molecular characterization of hepatitis viruses in Rwanda and implication on liver disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Mikrobiologen föreläsningssal, vån 3, Guldhedsgatan 10A, Göteborg fredag den 7 september 2018, klockan 13.00

av **Theogene Twagirumugabe**

Fakultetsopponent:

Daniel Lavanchy, professor

World Health Organisation (WHO)

Geneva, Switzerland

Avhandlingen baseras på följande delarbeten

I. **Twagirumugabe T**, Swaibu G, Walker TD, Lindh M, Gahutu JB, Bergström T, Norder H: Hepatitis B virus strains from Rwandan blood donors are genetically similar and form one clade within subgenotype A1. *BMC Infect Dis 2017; 17:32*

II. **Twagirumugabe T**, Swaibu G, Walker TD, Bergström, T Gahutu JB, Norder H: Low prevalence of hepatitis C virus RNA in blood donors with anti-hepatitis C virus reactivity in Rwanda. *Transfusion 2017; 57:2420-2432*

III. **Twagirumugabe T**, Mukabatsinda C, Habarurema S, Seruyange E, Bergström T, Gahutu JB, Walker TD, Norder H: Hepatitis C virus infection is common among females and hepatitis B virus infection among males with liver disease in Rwanda. *Manuscript submitted to BMC Infect Dis*

IV. **Twagirumugabe T**, Saguti F, Habarurema S, Gahutu JB, Bergström T, Norder H: Hepatitis A and E virus infections are common in Rwanda but with different epidemiological patterns. *Manuscript submitted to Int J Infect Dis*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICINE

GÖTEBORGS UNIVERSITET

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Epidemiology, molecular characterization of hepatitis viruses in Rwanda and implication on liver disease

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ABSTRACT

Hepatitis viruses cause major health problems worldwide and, according to WHO, is the seventh leading cause of death globally. It is primarily hepatitis B and C virus that causes chronic hepatitis, liver damage and fibrosis, and long-term risk of cirrhosis and liver cancer. These viruses have different spread globally and shown to cause the majority of deaths in liver diseases, especially in Asia and sub-Saharan Africa. In Rwanda, liver diseases are common and cause 1.5% of annual deaths. As little is known if these liver diseases were caused by viruses or had other etiology, we investigated the presence of serologic markers for HBV, HCV, HDV, HEV and HAV in blood donors and liver disease patients and their matched controls. The persons originated from all five regions of Rwanda and demographic data on the patients and their controls were collected at the same time as they were sampled. The samples were collected between 2014 and 2016. All blood donor samples had been analyzed for HBV and HCV at the National Center for Blood and Transfusion in Kigali, Rwanda.

HBV infection in the form of detectable HBsAg was in samples from 4.1% of the donors, in 3.7% in the controls, and in 31.3% of the liver disease patients. Anti-HBe was more common than HBeAg and was detected in about 70% of HBsAg positive samples. More than 60% of them had detectable HBV DNA. HBV DNA in the samples was sequenced in the structural gene, and family trees were constructed which showed that all HBV strains belonged to subgenotype A1 and 93% of them formed their own branch of the tree, indicating that it is a unique HBV strain spread in Rwanda. No one was shown to have hepatitis delta infection.

For HCV, the picture was different. Primarily, 16% of blood donors' samples had anti-HCV, but 67% of these had false reactivity, so only 5% remained true anti-HCV reactive. Among the controls, 13.4% had anti-HCV compared with 44.3% of the liver disease patients. HCV RNA was detected in 17% of blood donor samples, in 56% of samples from the controls and in 84% of samples from liver disease patients. The virus strains were sequenced and family trees were constructed which showed that the majority of the strains (98.3%) were of genotype 4 and the remainder were genotype 3. The subtypes 4k, 4r, 4q and untyped genotype 4 dominated in samples from all patient groups.

When examining for HEV and HAV markers, 11.7% of all patients had HEV markers. The highest prevalence was found in people from the western and southern provinces where there is a high density of pig breeding. No age-dependent anti-HEV pattern could be identified as opposed to anti-HAV, which increased with age, with fewer anti-HAV positive in persons younger than 25 years compared to the elder group ($p < 0.0001$).

We found in these studies that both HBV and HCV are endemic in Rwanda and caused 74% of the liver diseases, where HCV was more common in patients with liver cirrhosis and liver cancer than HBV. Increased age and female sex were independent risk factors for HCV infection. For HBV, the risk factors were young age, multiple sex partners and male gender. These differences can explain why there were more controls than blood donors that were HCV infected. A risk factor for both HBV and HCV was the presence of people with liver disease in the same household. HEV and HAV were also shown to be endemic, but a decrease in exposure to HAV at younger ages was noted and HEV epidemiology reflected that in countries with possible spread from pigs

Key words: hepatitis viruses**,** cirrhosis, genotypes, prevalence, Rwanda

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