ANTI-HEPATITIS A VIRUS SEROPREVALENCE AMONG CHRONIC VIRAL HEPATITIS B AND C LIVER DISEASE IN HUSM AND ITS ASSOCIATION WITH *CYP3A4*18* POLYMORPHISM

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LIST OF ABBREVIATIONS

ALD	Alcoholic liver disease
ALT	Alanine Transferase
Anti-HCV	HCV antibody
AST	Aspartate Transferase
CLD	Chronic liver disease
CYP	Cytochrome P-450
CYP3A4	Cytochrome P-450 3A4
DNA	Deoxyribonucleic acid
GGTP	Gamma
HAV	Hepatitis A virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCC	Hepatocellular Carcinoma
HBsAg	Hepatitis B surface antigen
HUKM	Hospital Universiti Kebangsaan Malaysia
HUSM	Hospital Universiti Sains Malaysia
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LC	Liver Cirrhosis
PCR	Polymerase chain reaction
RFLP	Restriction fragment length polymorphism

ABSTRAK

PREVALEN ANTIBODI HEPATITIS A DI KALANGAN PESAKIT VIRAL HEPATITIS B DAN C KRONIK DI HOSPITAL UNIVERSITI SAINS MALAYSIA DAN KAITANNYA DENGAN VARIASI GEN *CYP3A4*18*

Latar Belakang dan Objektif

Vaksinasi menentang hepatitis A telah disyorkan untuk pesakit berpenyakit hati kronik untuk mengelakkan kegagalan hati disebabkan jangkitan berganda. *CYP3A4* adalah 'cytochrome' utama pada manusia dan fungsinya berkurangan bagi pesakit hati kronik dan sirosis. Penemuan variasi gen ini mungkin mempunyai impak besar bagi pesakit berpenyakit hati kronik jika mereka mendapat jangkitan berganda hepatitis A. Ini kerana fungsi hati untuk menyahtoksin serta menghapuskan dadah dan ubatan semakin berkurangan. Untuk itu, mereka perlu mendapat vaksinasi hepatitis A. Matlamat utama kajian ini adalah untuk mengkaji prevalen antibodi anti-HAV di kalangan pesakit viral hepatitis B dan C kronik dan kaitannya dengan variasi gen *CYP3A4*18*, juga untuk menentukan keperluan vaksinasi bagi pesakit berpenyakit hati kronik yang menghidap hepatitis A.

Metodologi

Dari Julai ke September 2009, 120 pesakit yang menghadiri Klinik Pakar Gastroenterologi, Universiti Sains Malaysia telah menyertai kajian kes kawalan ini. Seseorang yang mempunyai penanda virus selama 6 bulan atau lebih dianggap sebagai penghidap penyakit hati kronik, manakala diagnosis penyakit hati sirosis adalah berdasarkan profail klinikal, biokimia serta radiologi. Serum milik

pesakit-pesakit akan diuji untuk antibodi terhadap virus hepatitis A dengan menggunakan kit ujian dan darah juga dihantar untuk analisa variasi gen *CYP3A4*.

Keputusan

Secara keseluruhannya, prevalen anti-HAV adalah 88.2%. Penyebab kepada penyakit hati kronik adalah hepatitis B bagi 96 pesakit (80.7%) dan hepatitis C bagi 23 pesakit (19.3%). Purata umur peserta kajian adalah 44.4 ±14. Pesakit-pesakit mengikut pembahagian dekad umur; 24 (20.2%) pesakit di dalam dekad 21-30 tahun, 22(18.5%) pesakit di dalam dekad 31-40 tahun, 31 (26.1%) pesakit di dalam dekad 41-50 tahun, 23 (19.3%) pesakit di dalam dekad 51-60 tahun dan 19 (16.0%) pesakit berumur lebih 60 tahun. Prevalen anti-HAV berdasarkan dekad umur ialah 66.7%, 95.5%, 93.5%, 91.3% dan 94.7% setiap dekad. Terdapat peningkatan prevalen yang ketara selepas umur 30 tahun (p=0.008). 17 pesakit berpenyakit hati sirosis dan prevalen anti-HAV mereka adalah 100% berbanding pesakit bukan sirosis dimana prevalen mereka adalah 86.3% (p=0.216). Variasi gen *CYP3A4*18* dikesan dikalangan 3 pesakit; dengan frekuensi 2.5% dalam populasi kajian pesakit berpenyakit hati kronik. Mutasi *CYP3A4*18* yang dikesan adalah kesemuanya heterozigos.

Kesimpulan

Kajian ini menunjukkan bahawa prevalen keseluruhan anti-HAV adalah 88.2% dan faktor umur adalah paling penting dalam menentukan keputusan positif. Kebanyakan pesakit melebihi umur 30 tahun mempunyai imuniti semulajadi kepada hepatitis A. Tiada kaitan antara mutasi *CYP3A4*18* dan serologi anti-HAV yang dapat ditunjukkan. Saranan untuk vaksinasi mungkin tidak perlu terutamanya untuk pesakit berumur lebih daripada 30 tahun.

ABSTRACT

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Background and Objectives

Vaccination against hepatitis A virus is recommended in patients with chronic liver disease to prevent hepatic decompensation due to superinfection. *CYP3A4* is the major cytochrome in humans and its activity is reduced in chronic liver disease as well as hepatic cirrhosis. Detection of *CYP3A4* polymorphism may predict detrimental effects on patients with chronic viral hepatitis with superimposed Hepatitis A infection due to reduced hepatic activity to eliminate drugs and harmful environmental toxin. Therefore, the need for vaccination is augmented. The aim of this study is to find out the seroprevalence of anti-HAV antibodies in patients with chronic viral hepatitis B and C liver disease and its association with *CYP3A4* polymorphism as well as to justify the need for vaccination against hepatitis A in these patients.

Methodology

From July to September 2009, 120 patients attending the Gastroenterology Clinic, Hospital Universiti Sains Malaysia were enrolled into this case control study. The diagnosis of chronic viral hepatitis B and C liver disease was based on presence of viral markers of more than 6 months and the diagnosis of liver cirrhosis was based on clinical, biochemical, radiological

profiles. Serum from all patients were tested for anti-HAVIgG using a commercially available kit and blood was sent for *CYP3A4* polymorphism analysis.

Results

The overall anti-HAV seroprevalence was 88.2%. The aetiology of chronic viral liver disease was hepatitis B in 96 patients (80.7%) and hepatitis C in 23 patients (19.3%). The mean age was 44.4 ±14. Patients were categorized by decades of age as follows: 24 (20.2%) patients in the 21-30 age group, 22(18.5%) in the 31-40 age group, 31 (26.1%) in the 41-50 age group, 23 (19.3%) in the 51-60 age group and 19 (16.0%) patients aged more than 60 years. The seroprevalence according to age group was 66.7%, 95.5%, 93.5%, 91.3% and 94.7% respectively. There was marked increase of prevalence in age group after 30 years (p=0.008). Seventeen patients were cirrhotics and the anti-HAV seroprevalence was 100% compared to non-cirrhotic group which was only 86.3%(p=0.216). *CYP3A4*18* polymorphism was detected in 3 of our chronic viral liver disease patients, with the frequency of 2.5% . All patients with the *CYP3A4*18* mutations were found to be heterozygous.

Conclusion

Our study demonstrated that the overall seroprevalence was 88.2% and age was the most important factor in determining anti-HAV positivity. Most patient aged more than 30 are likely to have natural immunity towards hepatitis A. There was no significant association between CP3A4*18 mutation and anti-HAV serology. Since the prevalence of anti-HAVIgG is high, the hepatitis A vaccination may not be routinely required in this region especially in individual who are older than 30 years of age.