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原 著

Prevalence of Liver Abnormalities in the General Population of Okinawa, Japan

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Abstract A total of 2,825 Japanese over 20 years of age living in the Yaeyama District of Okinawa, Japan were investigated in 1983 and 1984 to determine the prevalence and risk factors of liver abnormalities. Obesity index, hepatitis B virus markers, hepatitis C virus marker and serum transaminase were measured and the history of alcohol intake was recorded. People with elevated transaminase levels were assumed to have abnormalities of the liver. The overall prevalence of liver abnormalities was 3.6% and was significantly higher in men than in women ($p < 0.001$). Logistic regression analysis showed that the strongest predictors of liver abnormalities were alcohol for the men and obesity for the women. Hepatitis B virus was the second most prevalent risk factor in both sexes.

Key words : alcohol, hepatitis B virus, liver abnormalities, obesity

Introduction

The etiology of liver diseases is linked to virus, alcohol, drugs, malnutrition, metabolic diseases, heart failure, and malignancy¹⁹⁾. The rate of the various etiologies of liver diseases differ ethnically and geographically.

Patients with chronic liver abnormalities, except for those with an acute hepatitis, may be asymptomatic. After being told they have a chronic liver disease, they may complain of fatigue, anorexia, or discomfort in the region of the liver. Clinical parameters are most often normal and it is the biochemical tests which reveal the abnormalities.

We examined the prevalence and risk factors of people with liver abnormalities in the

general population of the Yaeyama District of Okinawa, an area with a high prevalence of hepatitis B virus (HBV). Our findings are reported herein¹¹⁾.

Materials and Methods

We surveyed populations of Japanese people living in several islands in the Yaeyama District of southwestern Okinawa Prefecture, a subtropical area about 1,000 km south of the main islands of Japan. (Yonaguni, Hateruma, Kuroshima, Kohama, Taketomi, and Iriomote Islands)

A total of 2,825 people who came for free health examinations in 1983 and 1984 were checked. These examinations were announced by distributing written notices to each household.

Table 1 Age- and sex-specific estimated population, number and percentage of individuals tested in the Yaeyama District, Okinawa, Japan, in 1983-1984

Age (years)	Men			Women			Total		
	Estimated population	n	%	Estimated population	n	%	Estimated population	n	%
20-29	291	201	69.1	239	194	81.2	530	395	74.5
30-39	343	265	77.3	259	209	80.7	602	474	78.7
40-49	252	191	75.8	231	204	88.3	483	395	81.8
50-59	379	315	83.1	408	376	92.2	787	691	87.8
60-69	272	232	85.3	301	272	90.4	573	504	88.0
70+	190	143	75.3	270	223	82.6	460	366	79.6
Total	1727	1347	78.0	1708	1478	86.5	3435	2825	82.2

The age- and sex-specific estimated population, number, and the percentage of people over the age of 20 tested are shown in table 1. The Taketomi and Yonaguni Town offices estimated the population of this area on the basis of family registers in 1983. The number and percentage of males and females tested were much the same. Approximately 80 per cent of the estimated population was examined.

Physical examinations and blood sample collections were carried out at public halls in each district. All were done by medical doctors. Later, health nurses questioned each person on history of blood transfusion, surgery, and diseases affecting liver function. Health nurses were chosen for this work because they are native to the area, have long been involved with health problems of the general population and know the socio-economic factors related to each household.

Weight (Kg) and height (cm) of all persons were recorded. Using a modified Broca's index, the obesity index (per cent) was calculated by the following formula:

Obesity index = $100 \times (\text{Weight} / \text{Standard weight})$
where standard weight was defined as $0.9 \times (\text{Height} - 100)$.

Blood samples were taken by venipuncture from the forearm while fasting and sera stored at -20°C until tested. Serum levels of aspar-

tate transaminase (AST) and alanine transaminase (ALT) were measured and hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (anti-HCV) were tested. People with a level of over 40 IU/L of AST and/or ALT were classed among those with liver abnormalities. Patients with myocardial infarction or progressive muscular dystrophies who were found to have elevated AST were excluded from this study^{23,14}. All HBsAg positive people were retested for HBsAg after six months. HBsAg-positive people for six months or longer were considered to be HBsAg carriers. The prevalences of HBsAg and anti-HCV were 7.5 per cent and 0.6 per cent.

All people were interviewed by the same physician as regards to alcohol drinking habits, age at start of alcohol drinking, duration of drinking, and average alcohol consumption per day. These interviews were carried out once a year starting in 1977. The answers were recorded on private cards each year. Those who answered negatively for alcohol consumption were considered nondrinkers and all other were considered drinkers.

All drinkers were asked the frequency and amount of alcoholic beverages currently being consumed. They were asked how many days they consumed alcoholic beverages in one week and how much beer, rice wine, Awamori

and other liquor they consumed in one day.

Awamori is a high alcohol content liquor made from rice. The number of grams of alcohol consumed per day was thus calculated.

This information was recorded in standard units (633 ml bottle of beer, 43 ml jigger of other liquor, 180 ml cup of rice wine, and 180 ml cup of Awamori). Using information from the United States Department of Agriculture (USDA) Handbook-456¹⁾ and the work by Ishii¹⁰⁾, we calculated the following ethanol contents: beer, 22.3 g/bottle; other liquor, 15.1 g/jigger; rice wine, 23.8 g/cup; and Awamori, 54.0 g/cup. With these estimates, we computed the total grams of ethanol consumed in one average day.

Reversed passive hemagglutination (RPHA) (Reverscell, Meguroken, Osaka, Japan) was used to test for HBsAg. Anti-HCV (HCV EIA II, Abbott Laboratories, North Chicago, IL, USA)⁷⁾ was examined using enzyme linked immunosorbent assay.

We compared the prevalence of people with liver abnormalities between men and women using the chi-square test. The number of female drinkers was so small that, when we analyzed according to sex, we excluded alcohol from the multiple logistic regression analysis of women. The prevalence of anti-HCV in this district (0.6 percent) was so low that we excluded HCV from multiple logistic regression analysis. To evaluate the influence of various factors such as age, HBV, obesity, and alcohol where the response variable was with or without liver abnormalities and the explanatory variables were the four factors, analysis was by multiple logistic regression to the data. We modeled age (year), obesity (per cent), and alcohol (gram) as a continuous variable in this analysis. To study the influence of HBV on liver abnormalities, we applied the Freeman-

Halton exact probability test⁵⁾.

Results

Table 2 shows that the total prevalence of liver abnormalities was 3.6 percent. The prevalence was significantly higher in men (5.5 per cent) than in women (1.8 per cent) ($p < 0.001$). For each age group, prevalence was higher in men, most markedly in the age groups 30-39 and over 70. The prevalence of liver abnormalities in men was the highest (9.1 per cent) in the 30-39 age group and was about four per cent in other age groups. The prevalence in women over 70 was the lowest (0.4 per cent), with prevalence in the other age groups ranging from 1.0 to 2.9 per cent.

Table 3 shows the results of logistic regression analysis of the liver abnormalities; estimates of the standardized regression coefficients with associated p-values of liver abnormalities. In men, from the standardized coefficients, the influence of alcohol on liver abnormalities was the strongest predictor ($p = \text{near } 0$) followed by HBV and age. Alcohol was the only statistically significant factor. Obesity was not found to be associated with liver abnormalities in men. In women, the influence of obesity on liver abnormalities was the strongest predictor ($p = 0.057$) followed by HBV. Age was not found to be associated with liver abnormalities in women. There were no interactions between alcohol and HBV or between alcohol and age among men, or between HBV and obesity among women.

Table 4 shows the results of Freeman-Halton exact probability. The association between HBV and liver abnormalities among men was of borderline significance ($p = 0.068$). The association between HBV and liver abnormalities among women was nearly identical to that of men, but the association was not statisti-

Table 2 Age- and sex-specific prevalence of liver abnormalities among 2,825 people in the Yaeyama District, Okinawa, Japan, in 1983-1984.

Age (years)	Men		Women		Total	
	No. tested	Prevalence (%)	No. tested	Prevalence (%)	No. tested	Prevalence (%)
20-29	201	4.5	194	1.0	395	2.8
30-39	265	9.1**	209	1.4**	474	5.7
40-49	191	4.7	204	2.0	395	3.3
50-59	315	4.8	376	2.9	691	3.8
60-69	232	4.7	272	2.2	504	3.4
70+	143	4.2*	223	0.4*	366	1.9
Total	1347	5.5**	1478	1.8**	2825	3.6

* : $p < 0.05$, ** : $p < 0.001$. (men vs women)**Table 3** Result of logistic regression analysis of liver abnormalities in people in the Yaeyama District, Okinawa, Japan in 1983-1984.

	Associated factors	Factor value or range	Standardized coefficients	p value
Men	Age	years	-1.0578	0.29
	HBV	positive	1.0482	0.29
	Alcohol	grams	4.1583	near 0
	Obesity	per cent	-0.3080	0.76
Women	Age	years	-0.0612	0.95
	HBV	positive	1.1751	0.24
	Obesity	per cent	1.9034	0.05

Table 4 Results of comparison between people with and without liver abnormalities by HBV and sex in the Yaeyama District, Okinawa, Japan in 1983-1984.

Sex	with liver abnormalities No. tested (%)	without liver abnormalities No. tested (%)	Total No. tested (%)	Exact* probability
Men	74 (16.2)	1273 (9.4)	1347 (9.8)	$p=0.068$
Women	27 (11.1)	1451 (5.4)	1478 (5.5)	$p=0.181$

* : Freeman-Halton exact probability

(%) : prevalence

cally significant ($p=0.181$).

Eight men and four women had received blood transfusions. A history of surgery was noted for 17 men and five women. Among the HBsAg-negative non-obese nondrinkers, five of eight men (62.5 per cent) and two of nine

women (22.2 per cent) with liver abnormalities had histories of blood transfusion.

Discussion

Liver abnormalities occur in patients with chronic viral hepatitis, alcoholic liver diseases,

auto-immune hepatitis, drug induced hepatitis, liver cirrhosis, and hepatoma¹⁹⁾. Many of these patients may be asymptomatic, hence, there are few reports on the prevalence of liver abnormalities in the general population of Japan⁹⁾¹²⁾. We have defined the prevalence and risk factors of those with liver abnormalities in the general population by biochemical examination.

In the present study, the prevalence of liver abnormalities was higher in the men. One reason was that the percentage of alcohol drinkers was larger in men (73.2 per cent) than in women (3.6 per cent). Secondly, in this district, the prevalence of HBsAg carriers was higher in men (9.8 per cent) than in women (5.5 per cent) as was the prevalence of HBeAg, 6.1 per cent in men to 3.7 per cent in women. The results of this study are similar to previously reported data¹¹⁾. These results indicate that alcohol and HBV may have greater influences on liver abnormalities in men than women.

Lieber CS et al. have reported evidence of the direct hepato-toxic affect of alcohol¹⁵⁾¹⁶⁾.

In the present study, alcohol was significantly associated with liver abnormalities and was the strongest predictor of liver abnormalities in men.

We have previously reported a high prevalence of HBsAg in the Yaeyama¹¹⁾. In this study, the lack of statistical significance in the association between HBV and liver abnormalities in both sexes reflects only the small sample size and HBV was shown to be the second most predictive factor. HBV seems to be one of the important risk factors involved in liver abnormalities in both sexes.

We as well as Villa et al. have found that chronic, symptomless HBsAg carriers were at risk for hepatic disorders when drinking an amount of ethanol which seemed to be harm-

less for HBsAg-negative subjects¹⁷⁾²⁰⁾. Both HBV and alcohol seemed to be risk factors for liver abnormalities, but the interaction between HBV and alcohol for liver abnormalities was not considered in this study because there were few HBsAg-positive people.

Zelman et al. have reported that simple obesity in adults was likely to be associated with fat deposition in the liver²¹⁾. The prevalence of a fatty liver was higher in obese than in the non-obese people¹⁸⁾. In the present study, we found no association between obesity and liver abnormalities among men, but a significant association between obesity and liver abnormalities among women, few who were drinkers.

In a previous study, the strongest predictor of liver abnormalities among men was found to be obesity¹²⁾. In the present study, the strongest predictor of liver abnormalities among a different population of men was alcohol. The mean daily alcohol consumption being larger in the Yaeyama District (20.2 g/day) than the mean daily alcohol consumption in Japan (12.4 g/day), excluding Okinawa may explain these differences⁹⁾.

Among HBsAg-negative non-obese non-drinkers, 7 of 17 (41.2 per cent) with liver abnormalities had a history of blood transfusion, hence possibly having had post transfusion hepatitis due to non-A non-B hepatitis virus. The untransfused remainder may be carriers of the non-A non-B hepatitis virus. Recently it has become possible to measure hepatitis C virus (HCV) using anti-HCV⁴⁾⁶⁾¹³⁾. The positive rate of anti-HCV has been reported low in this district and in Japan⁸⁾. Because of this we did not survey for anti-HCV in this study.

In conclusion, our data suggest that the prevalence of liver abnormalities is higher in men than in women, and that the strongest predictors of liver abnormalities are alcohol

for men and obesity for women, followed in importance by HBV in both sexes.

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(和文抄録)

沖縄住民の肝機能障害について

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沖縄県八重山地区の20歳以上の2825名の住民について、肝機能異常のリスクファクターについて、1983年から1984年にかけて、検討を行なった。肥満度・HBVマーカー・HCVマーカー・血清トランスアミナーゼ(GOT, GPT)を測定した。飲酒歴については、問診により記録した。血清トランスアミナーゼ(GOT,

GPT)の高い対象者を、肝機能障害者とした。肝機能障害者の陽性率は、3.6%であった。男性は、女性に比べ有意に高かった。多変量解析では、男性では、飲酒が、女性では、肥満が、第一の危険因子であった。HBVは、男女とも、第二の危険因子であった。