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Serum Alanine Aminotransferase Levels in Relation to Hepatitis B and C Virus Infections Among Drug Abusers in an Area Hyperendemic for Hepatitis B

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Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the major agents responsible for hepatitis in Taiwan. The purpose of this study was to assess the serum alanine aminotransferase (ALT) activity in relation to HBV and HCV infection among drug abusers. This survey included 769 male drug abusers aged 14–59 years, from the Kaohsiung Narcotic Abstention Institute and Kaohsiung Prision. The prevalence of HBsAg seropositivity was 21.5%, and anti-HCV seropositivity was 27.2%, respectively. Drug abusers with HBsAg or anti-HCV had higher serum AST and ALT levels than those without HBsAg and anti-HCV. The prevalence of raised ALT and AST (≥45 IU/liter) in the HCV-positive group was more significant than in the negative group, while that of the HBsAg-positive group did not reach statistical significance. Among the HCV-positive group, ALT levels are more closely associated with HCV infection than AST levels. Our results indicated that HCV infection plays an important role in the etiology of raised ALT activity among drug abusers, while HBV infection plays a minor role. ALT screening still remains a simple and valuable method in the early recognition of HCV infection.

KEY WORDS: hepatitis B surface antigen; hepatitis C virus antibody; serum alanine aminotransferase; drug abusers.

Hepatitis C virus (HCV) is the major etiologic agent of posttransfusion hepatitis and sporadic non-A, non-B hepatitis (1). Taiwan is a hyperendemic area for hepatitis B virus (HBV) infection (2). HBV and HCV infections are the major agents responsible for hepatitis in Taiwan (3, 4). Alanine transaminase (ALT) is commonly used as a marker of hepatic inflammation and damage in subjects with acute and chronic hepatitis (5, 6). Elevated ALT and antibody to hepatitis B core antigen have been used as surrogate markers to reduce the incidence of posttransfusion hepatitis (7, 8). Although a considerably higher prevalence of HBV and HCV infections among drug abusers in Taiwan has been reported (9–11), so far few studies have dealt with the association of ALT activity with HBV and HCV infection. The purpose of this study was to assess serum ALT activity in relation to HBV and HCV infections among drug abusers.

MATERIALS AND METHODS

From October 1994 to February 1996, a total of 769 male drug abusers, aged 14–59 years (mean age: 31.5 years), were examined at the Kaohsiung Narcotic Abstention In-

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Table 1. Age-Specific Prevalence of HBsAg and Anti-HCV Status Among Drug Users

	HBsAg/anti-HCV			
Age (yr)	*Neg/Neg*	*Pos/Neg*	*Neg/Pos*	*Pos/Pos*
<20	15 (65.2)	5 (21.7)	3 (13.0)	0 (0.0)
20–29	207 (65.1)	52 (16.4)	49 (15.4)	10 (3.1)
30–39	159 (50.3)	56 (17.7)	84 (26.6)	17 (5.4)
≥40	51 (45.5)	15 (13.4)	36 (32.1)	10 (8.9)
Total	432 (56.2)	128 (16.6)	172 (22.4)	37 (4.8)

stitute and Kaohsiung Prison. Of these, 183 (23.8%) had histories of injecting pentazocine and heroin. In this study, an intravenous drug user (IVDU) is defined as a person who has ever been an intravenous user of illicit drugs, regardless of whether or not he is currently an illicit intravenous drug user. Subjects taking other drugs related to hepatic damage, including sedatives, were excluded.

Anti-HCV testing was done by enzyme immunoassay (Abbott HCV EIA second generation; Abbott Laboratories, Abbott Park, Illinois), using a recombinant antigen of viral genome including putative structural and nonstructural proteins. All samples were stored frozen at −70°C, then were thawed at room temperature and tested according to the manufacturer's instructions. Specimens with absorbance values greater than the cutoff value were considered reactive. The reactive samples were retested and considered positive if both tests were reactive. All serum samples were tested for HBsAg by radioimmunoassay (RIA) using commercially available reagents (Abbott Laboratories). AST and ALT measurements (JSCC method) were performed on a Hitachi 763-40 autoanalyzer using Wako Pure Chemical Industries reagents.

On the day blood samples were taken, copies of a structured questionnaire were distributed among the respondents, and all 769 volunteers answered them. The questionnaires included information about demographic data, blood transfusions, age of starting drug use, and duration of drug use. Duration of drug use among IVDU subjects is defined as the period of time from a participant's reported first injection to his last injection of illicit drugs. Because some IVDU subjects intermittently used illicit drugs intravenously, the duration of drug use was calculated by summing up the time periods of injections. To reduce the risk of underreporting, the participants underwent confidential, face-to-face interviews with a trained family physician in a quiet, private room.

A χ^2 test was used in the assessment of the significance of differences in prevalence rates. Student's t test was used in testing the differences between the means of the two groups. Odds ratio (OR) with 95% confidence intervals (CI) were calculated to estimate the risks of raised ALT activity in relation to HBV and HCV infection. To compare the population-attributable risk for raised ALT levels, the prevalence of anti-HCV and HBsAg in the group with normal ALT was used as the prevalence in the general population. Before analysis, serum AST and ALT were logarithmically transformed because their distributions were found to be positively skewed.

RESULTS

Of the 769 respondents tested, 128 (16.6%) were positive for HBsAg, 172 (22.4%) positive for anti-HCV and 37 (4.8%) positive for HBsAg and anti-HCV. No change in the prevalence of HBsAg positivity was found with increasing age. However, the prevalence of HCV-positive and both-positive markers were found to increase with increasing age (Table 1).

The main clinical and biological features of the four groups are given in Table 2. In the HCV-positive and both-positive groups, the percentage of subjects with histories of intravenous drug use was significantly higher than in the negative group. The HBsAg-positive group had higher AST and ALT levels than the negative group. The HCV-positive and both-positive groups had a higher average age, greater duration of drug use, and more elevated AST and ALT levels than the negative group. The prevalence of higher AST and ALT levels between the HBsAg-positive and -negative groups were not significantly different. The HCV-positive group had more subjects

Table 2. Clinical Characteristics in Relation to HBsAg and Anti-HCV Status Among Drug Users

	HBsAg/anti-HCV			
	Neg/Neg	*Pos/Neg*	*Neg/Pos*	*Pos/Pos*
N	432	128	172	37
Age (yr)*	30.4 ± 7.1	30.9 ± 6.9	33.3 ± 7.1[a]	35.0 ± 7.2[a]
Intravenous drug use (%)	10.2	9.4	59.9[a]	64.9[a]
Duration of drug use (yr)*	1.8 ± 1.7	2.2 ± 2.5	3.0 ± 3.1[a]	3.8 ± 4.4[b]
Blood transfusion (%)	9.0	7.0	11.1	18.9
AST (IU/liter)*	14.8 ± 9.9	18.4 ± 13.3[a]	27.5 ± 32.2[a]	22.0 ± 9.4[a]
ALT (IU/liter)*	16.2 ± 19.3	22.6 ± 27.0[a]	39.7 ± 54.9[a]	27.9 ± 19.2[a]
AST > 45 (IU/liter) (%)	1.9	2.3	7.6	2.7
ALT > 45 (IU/liter) (%)	4.4	6.3	22.1[b]	13.5[c]

*Values are means ± SE.
[a]$P < 0.001$,; [b]$P < 0.01$, [c]$P < 0.05$, as compared to Neg/Neg.

TABLE 3. RISK FACTORS FOR RAISED SERUM ALT LEVELS IN DRUG USERS

	*Serum ALT level** N *(%)*		
HBsAg/anti-HCV	*Raised*	*Normal*	*OR (95% CI)*
Negative/negative	19 (4.4)	413 (95.6)	1.00
Positive/negative	8 (6.3)	120 (93.7)	1.45 (0.62–3.39)
Negative/positive	38 (22.1)	134 (77.9)	6.16 (3.62–10.49)
Positive/positive	5 (13.5)	32 (86.5)	3.40 (1.25–9.20)

*Upper limit of normal: 45 IU/liter.

with AST > 45 IU/liter, ALT > 45 IU/liter than the negative group. In the both-positive groups, the percentage of subjects with ALT > 45 IU/liter was significantly higher than in subjects in the negative group.

Table 3 shows the association between raised ALT levels and the status of HBsAg and anti-HCV in drug abusers. Compared with the negative group, the odds ratio of raised ALT was 6.2 (95% CI: 3.6–10.5) for HCV-positive and 3.4 (95% CI: 1.3–9.2) for both-positive groups, while the prevalence of raised ALT levels in the HBsAg-positive group was not statistically different from the negative group. Multiple logistic regression analysis was performed to adjust the confounding effects of age and intravenous drug use history. The results indicated that anti-HCV positivity was an independent risk factor for raised serum ALT activity.

DISCUSSION

The prevalence of HBsAg positivity among Taiwanese drug abusers (21.5%), regardless of whether or not they were intravenous drug abusers, is similar to that of the general population (12). Most of the HBsAg carriers were perinatally infected with HBV (13, 14). The prevalence of HBsAg positivity was not found to change with increasing age (Table 1), suggesting that HBV infection among drug abusers most likely occurred before drug abuse began. The seropositive rate of HCV infection among drug abusers (27.2%) is higher than the value (1.5%) observed among 20,768 blood donors in Taiwan (15). The prevalence of HCV positivity was found to increase with increasing age (Table 1), and because age is a cumulative factor, it indicated that several routes of transmission related to age may contribute to HCV infection, such as parenteral exposure, tattooing, sexual exposure, and iatrogenic injection.

Table 2 shows that drug abusers with HBsAg or anti-HCV had higher serum AST and ALT levels than those without HBsAg and anti-HCV. For AST and ALT levels, the differences were markedly higher in the HCV-positive group than in the HBsAg-positive group. The prevalence of raised ALT and AST in the HCV-positive group was more significant than in the negative group, while the HBsAg-positive group was not significantly different. Those findings were consistent with other studies (16–19). Van der Poel et al (16) showed that elevated ALT, rather than anti-HBc, was strongly associated with anti-HCV. In a study from Taiwan that compared to HBsAg-positive blood donors, donors with anti-HCV had higher serum ALT levels and were more significantly associated with raised ALT activity (17). Kurosaki et al (19) documented that patients with ALT levels above 100 IU/liter invariably had high levels of HCV-RNA (19).

As shown in Tables 2 and 3, among the HCV-positive group, the ALT levels are more closely associated with HCV infection than AST levels: 20.6% (43/209) of the drug abusers with HCV infections had elevated ALT. In contrast to our finding, a higher prevalence (37.2–39.5%) of subjects with raised ALT level were found (17, 18). In our study, among HCV seropositive subjects, 80.4% had ALT values that were in the normal range. This indicated that an elevated ALT level is neither a sensitive nor a specific marker of HCV infection among drug abusers.

In our cohort study, 43 of 70 (61.4%) drug abusers with raised ALT levels had serological evidence of HCV infection. The estimated population-attributable risk indicated that HCV infection contributed to 48.6% of raised ALT levels in drug abusers. However, a surrogate marker (ALT) undoubtedly has both lower sensitivity and lower specificity in identifying HCV infection than does a specific anti-HCV assay. A study conducted among donors with elevated ALT reported that ~30% of the PCR-positive cases were not detected by the most sensitive immunological assays (21). Thus, HCV RNA is the only available marker that can reliably identify active HCV infection (21, 22). Moreover, the delay in the appearance of antibody response during acute HCV infection, generally preceded by the increase in ALT levels (22), underlines the importance of continuing to screen donors for ALT values. Due to the expense of PCR assays and the high prevalence of drug abusers with liver function abnormalities who tested positive for HCV, we suggest that ALT could be retained as a surrogate marker for HCV infection among drug abusers.

In conclusion, HCV infection is an independent risk factor of raised serum ALT levels among drug

abusers and contributed to 48% of raised ALT levels among drug abusers in Taiwan. This means that HCV infection plays an important role in the etiology of raised ALT activity. However, HBV infection plays a minor role in the etiology of raised ALT activity among drug abusers. Although raised ALT levels are neither a sensitive nor a specific marker of HCV infection among drug abusers, ALT screening remains a simple and valuable method in the early recognition of not only HCV, but also of other as yet unrecognized agents of viral hepatitis.

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