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Prevalence and Risk Factors of Chronic Liver Disease among Oil Refinery Workers

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Abstract: Prevalence and Risk Factors of Chronic Liver Disease among Oil Refinery Workers: Hon-Ke SIA, *et al.* Department of Internal Medicine, Chang-Hua Christian Hospital—Objectives: The objective of this study was to determine the prevalence and major risk factors of chronic liver diseases among workers in an oil refinery and research factory with ultrasonography as an assessment tool. Methods: After a walk-through survey in the factory, workers were classified into exposed and non-exposed groups. Regular health screening data for the past four years were collected and all 700 workers were asked to fill out a questionnaire about their life style. A total of 345 workers voluntarily participated in the study, and 326 of them had abdominal ultrasonography. Results: Fatty liver disease (FLD) was found to be the most common problem (27.9%), followed by hepatitis virus infection (HBsAg positive rate: 18.0%, anti-HCV positive rate: 2.6%). The major causes of persistent alanine aminotransferase (ALT) increase were FLD and hepatitis virus infection. Obesity was the most important determinant of FLD and hepatitis virus infection was that of parenchymal liver disease (PLD). Modeling by multiple logistic regression model demonstrated that exposure to petroleum distillates or other chemicals in this factory was not associated with FLD, PLD or persistent ALT increase even in workers employed for more than twenty years. Obesity and virus infection did not show a synergistic hepatotoxic effect on solvent exposure probably due to a low level of exposure. Conclusions: Fatty liver and chronic hepatitis B infection were the major chronic liver diseases in oil-refinery workers in Taiwan, where exposure to hepatotoxic solvents was low.
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Acute liver injury due to some organic solvents such as halogenated hydrocarbons, dimethylformamide (DMF) are well known[1, 2], but the chronic effects on liver of long-term occupational exposure to low levels of organic solvents remain undetermined. Many cases of liver cirrhosis without known etiology raise the suspicion that some may be of occupational origin[3]. A recent small case-control study also showed that occupational exposure to organic solvents might play a role in the development of fatty liver disease (FLD)[4].

Associated epidemiological studies in this field were difficult for several reasons, which included: (1) the approach to chronic liver damage among workers was unsuccessful due to vague symptoms and signs and the lack of specificity and sensitivity of conventional liver enzyme tests; (2) the cause of chronic liver damage might lie in a number of factors rather than in isolated occupational exposure[3]. The limitations are further highlighted by the studies among workers exposed to mixed solvents of aromatic and aliphatic hydrocarbon that have failed to detect any abnormality in these serum enzyme tests[5].

The combination effect of occupational and non-occupational factors including alcohol consumption, hepatitis virus B (HBV) or C (HCV) infection, medications and obesity may also be important[6]. Some studies raised the concern that these factors may potentiate the effects of hepatotoxin exposure[7–10]. The causes of an increase in liver transaminase detected in routine screening therefore usually need further diagnostic workup, in which noninvasive ultrasonography (US) may provide additional information.

The major objectives of this cross-sectional study are to determine the prevalence of CLD among workers in

an oil refinery factory. We also identify the major determinants of CLD and investigate whether these factors have a synergistic hepatotoxic effect on solvent exposure. We control for non-occupational factors and apply abdominal US in this study.

Methods

The oil refinery factory produces petroleum distillates containing aliphatic and aromatic hydrocarbons except benzene, toluene and xylene. The general production process of this factory includes distillation, refining, extraction, blending and n-hexane hydrotreating. Many employees who also work in the laboratory of research and development might be occasionally exposed to halogenated hydrocarbons such as chloroform, carbon tetrachloride and trichloroethane.

Subjects and data collection

The study subjects were recruited from workers in an oil refinery factory with 700 employees during the time period from December 1999 to March 2000. All workers had a complete physical examination including serum alanine aminotransferase (ALT), total cholesterol, triglyceride and serological tests for HBV and HCV. All of them were also invited to fill out a questionnaire and have abdominal ultrasonography. Three hundred and forty-five of the 700 employees responded and participated in the study. The questionnaire asked about medical history, occupation (job title, chemical compounds used, duration of employment), alcohol consumption (average drinks per week and duration of drinking) and medications taken. All questionnaires were reviewed by an occupational physician to verify the data and assure data quality. We also collected the health data from regular annual physical examinations in the past four years that were conducted by the staff of St. Martins Hospital, which is a general hospital with 600 beds and has been accredited as a teaching hospital by the Department of Health of Taiwan since 1997. The serum ALT examination was done with an auto-analyzer Integra 700 (U.S.A.). Its cutoff value was provided by the clinical laboratory of this hospital. All workers who had an increase above the normal range twice or more during the last four years of annual screening were regarded as having a persistent ALT increase. In this study, we measured the serum ALT, total cholesterol and triglyceride with a Hitachi 7150 auto-analyzer (Tokyo, Japan). We used enzyme immunoassay (Murex Co., USA) to perform hepatitis B surface antigen (HBsAg) and anti-HCV antibody tests (anti-HCV III, Murex Co., USA).

Ultrasonography was performed and interpreted by two skilled board-certified gastroenterologists. A real-time machine, Panasonic PANAVISTA-LSCI (Panasonic Co. Ltd., Tokyo, Japan) equipped with a linear-type 3.5 MHz transducer, was used. In general, the two major histological features in diffuse parenchymal liver disease are steatosis and fibrosis[11], which can be largely differentiated by US[12, 13]. Briefly, the main indicator of steatosis was an increase in the echogenicity of the liver in comparison with the cortex of the right kidney. We also applied additional parameters including masking the walls of portal vein branches in the right lobe, masking the gallbladder wall, and far gain attenuation of the liver. In contrast, a nodular surface of the liver, coarse or heterogenous echotexture compared with the spleen and irregular narrowing of the hepatic vein suggested a diagnosis of hepatic fibrosis. In our study, the term 'fatty liver disease' (FLD) meant steatosis of the liver whereas 'parenchymal liver disease' (PLD) indicated various diffuse parenchymal liver disease other than fatty liver and implied hepatic fibrosis.

Workplace evaluation

We conducted a comprehensive walk-through survey for every single unit of operation. After identifying all the potential hazards, we classified workers into the following four exposure zones: (1) manufacture: direct exposure to petroleum distillates; (2) utility: intermittent exposure to petroleum distillates; (3) laboratory: occasional exposure to halogenated hydrocarbons; (4) administration: no or very low exposure. Workers in the first three groups were further categorized as the exposed and the last one was the non-exposed.

Data analysis

We used multiple logistic regression to determine the association between risk factors and CLD. The following risk factors were included: age, gender, body mass index (BMI), duration of employment, occupational exposure zone, alcohol consumption, potentially hepatotoxic drugs taken, history of diabetes mellitus (DM), total cholesterol, triglyceride, HBsAg and anti-HCV. BMI was calculated as weight in kilograms divided by squared height in meters. A value greater than 27 was considered obese. Workers who drank 140 grams of ethanol weekly for at least 5 yr were defined as drinkers. Odds ratio with 95% confidence intervals (95% CI) were calculated. All of the statistical analyses were conducted with SPSS/PC 9.0® software on a personal computer[14].

For further evaluation of the relationship between specific solvent exposure and CLD, we also used the Mantel-Haenszel summary procedure and the Mantel-extension for the test of trends[15, 16].

Results

More than three-fourths of all workers were male and the average age was 48 yr. There was a low turnover rate in the factory and the average duration of employment was about 23 yr. Table 1 summarized the demographic characteristics of respondents and non-respondents for

Table 1. Comparison of demographic and health characteristics of respondents and non-respondents in the refinery company

Items	Respondents (N=345)	Non-respondents (N=372)
Male Gender	74.5%	81.7%†
Age (yr)	47.5 ± 6.8*	48.4 ± 7.5
Duration of employment (yr)	22.9 ± 8.4	22.7 ± 9.9
HBsAg positive rate	18.0%	14.9%
Anti-HCV positive rate	2.6%	5.5%
Body mass index (kg/m^2)	24.3 ± 2.9	24.4 ± 3.1
Serum total cholesterol (mg/d*l*)	207.5 ± 36.1	204.7 ± 35.3
Serum triglyceride (mg/d*l*)	127.2 ± 76.4	134.4 ± 108.3
Serum ALT (U/L)	32.7 ± 46.0	31.2 ± 25.0

*Mean ± SD. †$p<0.05$.

Table 2. Frequencies of various liver diseases, stratified by the presence of persistent ALT increase or not

	Persistent ALT increase		Total
	Yes	No	
Hepatitis marker			
Study subjects	66	279	345
Positive HBsAg	17	45	62
Positive Anti-HCV	5	4	9
Abdominal ultrasonography			
Study subjects	56	270	326
Fatty liver disease	32	59	91
Parenchymal liver disease	5	18	23
Hepatocellular carcinoma	0	1	1
Metastatic liver tumor	1	0	1

comparison. The prevalence of HBsAg carriers in respondents was 18.0% which was slightly higher than that in the non-respondents and close to the average nationwide prevalence of 14–20%[17]. The prevalence of anti-HCV was 2.6%, which was also within the range of the general population in Taiwan (about 1–4%)[18, 19]. There were no significant differences between the respondents and non-respondents in the factory except the sex ratio. Three hundred and twenty-six of 345 (94.5%) respondents had successful abdominal ultrasonography.

Table 2 shows the prevalence rates of various liver diseases stratified by persistent ALT increase. We used abdominal ultrasonography, HBsAg, anti-HCV and serum ALT values in the past four years as our diagnostic basis. We also found 39 patients with hepatic cysts, 6 patients with hepatic hemangioma, 11 patients with gallbladder stones and 22 patients with gallbladder polyps but they were not included as CLD in our study. FLD was found to be the most common problem (27.9%), followed by chronic HBV infection (18.0%). Although FLD, HBsAg and anti-HCV carriers were found to be associated with persistent ALT increase, more than two-thirds of them did not show persistent ALT abnormalities.

The effects of various non-occupational and occupational factors on FLD, PLD and persistent ALT increase are summarized in Table 3. It shows that workers who had a BMI greater than 25, total cholesterol greater than 200 mg/d*l* or triglyceride greater than 200 mg/d*l* were associated with increased risk for FLD. Positive HBsAg increased and total cholesterol between 200 and 240 mg/d*l* reduced the risk for PLD. Factors related to persistent ALT increase were male gender, age younger than 45 yr, positive anti-HCV, BMI greater than 25 and a history of DM. Obesity, defined as the BMI index, appeared to be an important contributor to both FLD and persistent ALT increase, and the associations showed a dose-response relationship. HCV infection was

Table 3. Effects of various potential confounders and of solvent exposure on odds ratios (OR, with 95 % confidence interval abbreviated as CI) of persistent alanine aminotransferase (ALT) increase, fatty liver disease and parenchymal liver disease, analyzed by multiple logistic regression (NS: statistically non-significant)

Dependent variable	Independent Variable	Persistent ALT increase	Fatty liver disease	Parenchymal liver disease
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Gender	Male: 1 Female: 0	4.5 (1.4, 14.1)	NS	NS
Age	> 45 y/o: 1 ≦45 y/o: 0	0.4 (0.2, 0.9)	NS	NS
HBsAg	Positive: 1 Negative: 0	NS	NS	15.8 (5.4, 46.6)
Anti-HCV	Positive: 1 Negative: 0	6.6 (1.3, 33.0)	NS	NS
Alcohol consumption	≧140 g/wk: 1 < 140 g/wk: 0	NS	NS	NS
Medications taken	Yes: 1 No: 0	NS	NS	NS
Body mass index (kg/m^2)	25≦BMI<27 vs. BMI<25 BMI≧27 vs. BMI<25	2.6 (1.2, 5.5) 6.3 (2.9, 13.5)	4.5 (2.3, 9.1) 15.7 (7.2, 34.2)	NS NS
History of DM	Yes: 1 No: 0	5.3 (1.5, 18.2)	NS	NS
Total cholesterol (mg/d*l*)	200≦Chol<240 vs. Chol<200 Chol≧240 vs. Chol<200	NS NS	2.0 (1.0, 3.8) 2.4 (1.0, 5.9)	0.3 (0.1, 0.9) NS
Triglyceride (mg/d*l*)	TG≧200:1 TG<200:0	NS	2.9 (1.2, 7.2)	NS
Solvent exposure	Exposed: 1 Non-exposed: 0	NS	NS	NS
Duration of employment	> 20 yr: 1 ≦20 yr: 0	NS	NS	NS

associated with persistent ALT increase (OR 6.6; 95% CI 1.3, 33.0). But HBV infection did not show a similar association, because a large proportion of them were so-called healthy carriers. Nonetheless, HBV infection did play a major role in the formation of PLD (OR 15.8; 95 %CI 5.4, 46.6). Because there were only 10 workers who fulfilled the definition of alcohol drinker, our data did not show a significant effect of alcohol.

We tried several ways to define and analyze occupational exposures in the oil refinery factory. Neither employment for more than 20 years, exposure to various kinds of solvents, nor working in different exposure zones resulted in a statistically significant difference between the exposed and the non-exposed workers for FLD, PLD and persistent ALT increase after adjusting for other potential confounders. There was also no synergistic effect of hepatitis virus infection and solvent exposure on the development of FLD, PLD and persistent ALT increase (data not shown here).

Discussion

The study showed that present exposure to petroleum distillates in the factory or hepatotoxic solvents used in the laboratory was not significantly associated with increased risk of FLD, PLD or persistent ALT increase. Because this is a cross-sectional study and we assume a

present exposure zone for the previous long-term effect, it does not necessarily indicate that there was relatively little risk of CLD with the present exposure level, but the following observations seemed to corroborate the above conclusion. Firstly, petroleum distillates including aliphatic and aromatic solvents were thought to be less hepatotoxic in past studies with the exception of heavy exposure during a short period[7, 20–22]. Secondly, modern oil-refinery factories, like this one, are fully automated and enclosed. There was relatively little chemical exposure, which was demonstrated by the regular air sampling data showing below one-tenth of TLV (threshold limit value) recommended by the ACGIH (American Conference of Governmental Industrial Hygienists)[23]. From our field investigation and discussion with the safety specialist, the major exposure occurred mainly in maintenance operations and unscheduled events such as a leak or spillage. Although laboratory workers are occasionally exposed to well-known hepatotoxic agents, they are protected with adequate equipment especially local exhaust ventilation. Thirdly, HBsAg carriers may be more likely to develop liver damage caused by alcohol and other hepatotoxic agents such as DMF[24, 25], but there were no significant synergistic effects due to various occupational exposures and HBV infection on liver damage in our study. A similar concern was also postulated for obesity and hepatotoxic exposure[8]. But our multi-variate modeling did not find such an effect either on laboratory workers exposed to halogenated hydrocarbons or other workers exposed to petroleum distillates. Although we could not completely rule out the effect of random misclassification or the healthy worker effect on a cross-sectional study design[26], we might still conclude the that non-occupational factors rather than occupational factors play the main role in the occurrence of FLD, PLD and persistent ALT increase in our study subjects.

In general, conventional liver enzyme tests such as ALT reflect acute cytotoxicity and are proposed to be an effective screening marker for acute liver injury[27]. It has been adopted for regular medical surveillance of workers potentially exposed to hepatotoxic or even organic chemicals in many developed countries such as the United States, Germany and Japan, etc.[28]. But, as a result of improved industrial hygiene, acute liver injury seems to have decreased in recent years, even in Taiwan. Current concerns are related to the prolonged, low-level exposure that causes chronic liver damage including chronic inflammation, hepatic fibrosis, steatosis, vascular injury and malignancy, as seen in our study. In this circumstance, ALT provides limited sensitivity and specificity[27]. It might be improved in two ways: firstly, by obtaining serial follow-up ALT data rather than only one single ALT value. If ALTs show persistent abnormalities, chronic liver inflammation should be considered. This is the reason why we used ALT values for four years as a potential indicator of CLD. Secondly, use image study, especially abdominal ultrasonography. For mild liver disease with structural change but no persistent biochemical abnormality, ultrasonic study could provide additional information in assessing either focal or diffuse parenchymal liver disease[29]. The drawback to ultrasonic study is its dependence on the subjective judgement of the operators and it is less feasible to be performed on a large number of exposed individuals as serum biochemical tests. In our study, the ultrasonic studies were performed by two operators with the same training background and reviewed by a third physician according to the diagnostic criteria but without knowing the degree of exposure[12]. Therefore, the bias between operators could be reduced to a minimal. As current ultrasonograph equipment is usually portable, very accurate and non-invasive, we recommend that it be used for screening of chronic liver damage to supplement serial liver enzyme tests, especially for workers with potential hepatotoxin exposure or risk factors of CLD.

We found a low prevalence of alcohol drinking among oil-refiners. This could be partially attributed to the higher prevalence of allele $ALDH2^2$ and $ADH2^2$ in the Taiwanese population[30, 31] compared with western countries. Subjects with these genetypes would experience more intense reaction to alcohol than those without them. Moreover, because workers in this oil-refinery factory were considered to be governmental employees, they were forbidden to drink alcohol in public bars and thus less likely to develop such a habit. Therefore, there might be some healthy selection effect and a tendency to underestimate the prevalence of CLD.

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References

1) Rosenberg J, Cone JE, Katz EA. Solvents In: LaDou J, eds. Occupational and environmental medicine. 2nd ed. Connecticut: Appleton & Lange; 1997: 483–513.
2) Warnes TW, Jain SK, Smith A. Hepatotoxic effects of workplace exposures In: Baxter PJ, Adams PH, Aw TC, Cockcroft A, Harrington JM, eds. Hunter's diseases of occupations. 9th ed. London: Arnold; 2000: 881–900.
3) Dossing M, Skinjob P. Occupational liver injury. Int Arch Occup Environ Health 1985; 56: 1–21.
4) Lundqvist G, Flodin U, Axelson O. A case-control study of fatty liver disease and organic solvent exposure. Am J Ind Med 1999; 35: 132–136.
5) Neghab M, Stacey NH. Serum bile acids as a sensitive biological marker for evaluating hepatic effects of organic solvents. Biomarkers 2000; 5 (2): 81–107.
6) Chen JD, Wang JD, Tsai SY, Chao WI. Effects of

occupational and non-occupational factors on liver function tests in workers exposed to organic solvent mixtures. Arch Environ Health 1997; 52: 270–274.
7) Rees D. Solvent exposure, alcohol consumption and liver injury in workers manufacturing paint. Scand J Work Environ Health 1993; 19: 236–244.
8) Hodgson MJ, Van Thiel DH, Lauschus K, Karpf M. Liver injury tests in hazardous waste workers: the role of obesity. J Occup Med 1989; 31: 238–242.
9) Hodgson M, Van Thiel DH, Goodman-Klein B. Obesity and hepatoxins as risk factors for fatty liver disease. Br J Ind Med 1991; 48: 690–695.
10) Chen JD, Wang JD, Jang JP, Chen YY. Exposure to mixtures of organic solvents among paint workers and biochemical alterations of liver function. Br J Ind Med 1991; 48: 696–701.
11) Editorial: Ultrasound in the assessment of diffuse parenchymal liver disease. Clinical radiol 1991; 44: 219–221.
12) Yang PM, Huang GT, Lin JT, et al. Ultrasonography in diagnosis of benign diffuse parenchymal liver disease: a prospective study. J Formos Med Assoc 1988; 187 (10): 966–977.
13) Joseph AEA, Saverymuttu SU, Al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991; 43: 26–31.
14) SPSS. SPSS for windows, Release 9.0.0 standard version. Chicago, IL: SPSS Inc., 1998.
15) Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719–748.
16) Mantel N. Chi-square tests with one degree of freedom: extension of Mantel- Haenszel procedure. J Am Stat Assoc 1963; 58: 690–700.
17) Sung JL, Chen DS, Lai MY, et al. Epidemiological study on hepatitis B virus infection in Taiwan. Chinese J Gastroenterol 1984; 1: 1–9.
18) Chen DS, Kuo GC, Sung JL, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic disease: the Taiwan experience. J infect Dis 1990; 162: 817–822.
19) Wang JT. Hepatitis C virus infection in Taiwan. Gastroenterol J Taiwan 1995; 12: 66.
20) Ukai H, Takada S, Inui S, et al. Occupational exposure to solvent mixtures: effects on health and metabolism. Occup Environ Med 1994; 51: 523–529.
21) Rasmussen K, Brogren CH, Sabroe S. Subclinical affection of liver and kidney function and solvent exposure. Occup Environ Health 1993; 64: 445–448.
22) Lundberg I, Nise G, Hedenborg G, Hogberg M, Vesterberg O. Liver function tests and urinary albumin in house painters with previous heavy exposure to organic solvents. Occup Environ Med 1994; 51: 347–353.
23) 1999 TLVs and BEIs: threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 1999.
24) Villa E, Rubbiani L, Barchi T, et al. Susceptibility of chronic symptomless HBsAg carriers to ethanol-induced hepatic damage. Lancet 1982; 2: 1243–1244.
25) Wang JD, Lai MY, Chen JS, et al. Dimethylformamide-induced liver damage among synthetic leather workers. Arch Environ Health 1991; 46: 161–166.
26) Wang JD, Miettinen OS. Occupational mortality studies: principles of validity. Scand J Work Environ Health 1982; 8: 153–158.
27) Tamburro CH, Garry ML. Tests for hepatotoxicity: usefulness in screening workers. J Occup Med 1986; 28: 1034–1044.
28) Yang KY. The study of worker's medical examination and occupational health management in different countries. Taipei: Institute of Occupational Safety and Health; 2000; 180–194.
29) Brodkin CA, Daniell W, Checkoway H, et al. Hepatic ultrasonic changes in workers exposed to perchloroethylene. Occup Environ Med 1995; 52 (10): 679–685.
30) Thomasson HR, Edenberg HJ, Crabb DW, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese man. Am J Human Genetics 1991; 48: 677–681.
31) Goedde HW, Agarwal DP, Fritze G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. Human Genetics 1992; 88: 344–346.