Liver enzyme abnormalities among oil refinery workers

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Keywords
Petroleum industry. Occupational exposure, adverse effects. Risk factors. Transferases, diagnostic use. Case-control studies

Abstract

Objective
Occupational exposure typical of an oil refinery may alter liver function among the workers. Thus, the objective of the study was to identify risk factors for liver enzyme abnormalities among oil refinery workers.

Methods
The workers at an oil refinery in Northeastern Brazil underwent routine annual medical examination from 1982 to 1998. This case-control study investigated all the 150 cases of individuals with simultaneous gamma-glutamyltransferase and alanine aminotransferase abnormalities of at least 10% above reference levels. As controls, 150 workers without any liver enzyme or bilirubin abnormalities since starting to work there were selected. Odds ratios and the respective 95% confidence intervals were calculated from logistic regression models.

Results
In all the production sectors, the risk of liver enzyme abnormalities was significantly higher than in the administrative sector (OR=5.7; 95% CI: 1.7-18.4), even when the effects of alcohol, obesity and medical history of hepatitis were controlled for. During the period from 1992 to 1994, 88 out of the 89 cases occurred among workers from the various production sectors.

Conclusions
Occupational exposure plays an important role in causing liver enzyme abnormalities among oil refinery workers. This is in addition to the specifically biological and/or behavioral risk factors such as obesity and alcohol consumption.

INTRODUCTION

Exposure to chemical substances such as anesthetic agents, tranquilizers, tuberculostatic agents, chemotherapy agents and steroids may lead to acute or chronic liver lesions. Hepatotoxicity due to occupational exposure is a wide-ranging and little explored field.[15] Experiments on animals have shown that one chemical agent can boost the hepatotoxic effects of other chemical agents.[7]

The scientific literature on the occurrence of liver diseases among oil refinery workers is relatively scarce and controversial.[1] There is a need for epidemiological investigations in oil refineries, since it is evident that they present exposure to large numbers of chemical agents. The effects of such agents on human health, especially on the liver, need to be adequately brought into the picture.

In 1986, a cross-sectional study carried out among the workforce of an oil refinery in the Recôncavo region of the state of Bahia revealed high prevalence of abnormalities in the serum levels of the enzyme

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Study performed within the Department of Preventive Medicine of the Universidade Federal da Bahia.
Funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - n. 520812/95-6) and Petrobras (CC 220.3.025.97.9).
Received on 4/4/2005. Reviewed on 10/8/2005. Approved on 29/9/2005.

gamma-glutamyltransferase (GGT), and an association was made with alcohol consumption.* In 1995, it was estimated that 38% of the 1,900 workers at this refinery presented raised GGT levels. The prevalence of raised GGT levels was associated with high consumption of alcohol and with occupational exposure to gases, solvents and chemical products. Among the workers who did not use alcohol, 16% had raised GGT levels. It was also observed among those who did not use alcohol that the prevalence of abnormal GGT levels was clearly associated with occupational exposure to gases (prevalence ratio (PR) in relation to non-exposed individuals =10.9), chemical products (PR=3.5) and specific solvents (PR=1.9).**

The Occupational Health Sector of the refinery built up a databank consisting of 548 workers who, over the period from 1982 to 1998, presented abnormalities in biochemical tests on the liver (GGT, ALT – alanine aminotransferase, AST – aspartate aminotransferase, bilirubin and alkaline phosphatase). The most frequent finding was simultaneous raised levels of GGT + ALT, which occurred in 41.4% of the cases, followed by GGT + ALT + AST, in 30% of the 548 workers. Combined raised levels of the enzymes GGT + ALT is considered to be a sensitive[14] and early indicator of liver abnormalities resulting from occupational exposure to hepatotoxic agents.[9] Among the 548 workers, 26% had no history of obesity, daily or frequent consumption of alcohol, blood transfusion, hepatitis, jaundice or schistosomiasis, thus suggesting occupational etiology for these cases.[2]

From 1994 to 2003, workers with persistently raised levels of liver enzymes were referred for specialized hepatological assessment. Biochemical tests and liver biopsies were performed, with evaluation using electron microscopy.[5] A diagnosis of non-alcoholic steatohepatitis (NASH) was made on 20 patients from the refinery. Nine of these NASH patients were placed on sick leave and, during this period, monthly evaluations of GGT, ALT and AST were made. A second liver biopsy was taken, around 12 months after the first one. A gradual decrease in the enzyme levels was observed, and there was histological improvement in all these cases. The biochemical and histological improvements support the hypothesis that toxic petrochemical substances may have been the etiological agents for NASH. A recent study[6] has reaffirmed the hypothesis that NASH presents particular clinical-epidemiological characteristics among the petrochemical workers in the Recôncavo region of the state of Bahia.

Thus, the present study had the objective of identifying the risk factors for liver enzyme abnormalities among the workers at an oil refinery.

METHODS

The oil refinery studied is located 56 km from Salvador, in the municipality of São Francisco do Conde, state of Bahia. It has been in operation since 1950 and was processing around 140,000 barrels of oil per day in the middle of the 1990s. During that decade, the refinery had around 1,900 directly employed workers. The production workers performed their activities in a variety of environments that might correspond to different levels of exposure to atmospheric pollutants. The administrative personnel worked in buildings that were separated from the production area and relatively protected from the atmospheric effluents. A map of occupational risks produced by the company identified around 400 chemical compounds, some with hepatotoxic potential. From 1991 to 1994, the atmospheric concentrations of benzene, toluene, xylene, n-hexane, phenol, methyl-isobutyl-ketone, biphenyl + phenyl oxide, hydrogen sulfide gas, ammonia and carbon monoxide were determined by the company's occupational hygiene technicians. The levels of these compounds were almost always below the limits recommended by the legislation in force, in the production and administration sectors of the refinery.

All the workers at the refinery underwent annual periodic examination, including evaluation of the levels of the enzymes GGT and ALT, from 1982 to 1998. A databank organized by the medical service of the refinery contained information on all the workers who underwent annual periodic examination and presented levels that were 10% or more above the reference values for GGT, ALT, AST, bilirubin or alkaline phosphatase.

The present study was designed as a case-control type of study. The cases were considered to be all the 150 individuals with simultaneous abnormal values for GGT and ALT (more than 10% above the reference level), diagnosed between 1982 and 1998. The controls were selected from the record cards in the medical archives at the refinery: 150 individuals without any liver enzyme abnormalities since their admission to the company. For each case, a respective control was sought from the medical files, by looking through them in increasing numerical order of registration until identifying the record card of a worker who was in the company during the same period of time as the respective

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Table 1 - Characteristics of the workers in the case group (n=150) and control group (n=150). São Francisco do Conde, Brazil, 1982-1998.

Characteristics	Case	Control	p
Gender			0.06
Male	148 (98.7%)	142 (94.7%)	
Female	2 (1.3%)	8 (5.3%)	
Age in years (mean ± sd)	37.6±6.8	36.6±7.1	0.20
Length of service in the company, in years (mean ± sd)	12.1±5.9	11.8±5.7	0.70
Habitual use of medication, n (%)	23 (18.0%)	30 (20.5%)	0.60
Body mass index (mean ± sd)	27.2±3.3	24.9±3.6	0.001
Obesity, n (%)	26 (17.3%)	9 (6.0%)	0.002
Alcohol consumption, n (%)	120 (85.1%)	104 (67.8%)	0.002
History of hepatitis, n (%)	12 (9.0%)	1 (0.7%)	0.001

sd: standard deviation

case. In addition, it was verified that this control had never presented abnormalities in any liver enzyme tests (GGT, ALT or AST) or in direct or indirect bilirubin tests, during their working lives.

Data on the workers' dates of admission, positions held and work sectors within the company, results from laboratory tests, weight, height, consumption of alcoholic drinks, medical history of hepatitis and use of potentially hepatotoxic medications were collected from each worker's record card. Obesity was defined as body mass index (BMI) of more than 29.9. The data collection process was not done in a blind manner. Supplementary information on positions held and work sectors was obtained from the company's Personnel Administration files for each worker, and was considered together with the medical data as an indicator of occupational exposure.

Odds ratios (OR) and the respective 95% confidence intervals (CI) were calculated and stratified statistical analysis was performed by means of the Statcalc software from Epi Info. Multiple regression analysis was carried out using the SPSS for Windows software, following the procedures recommended by Hosmer & Lemeshow.[12]

The study was approved by the Ethics Committee of the "Professor Edgard Santos" University Hospital of the Universidade Federal da Bahia.

RESULTS

The cases and controls had approximately the same mean ages, lengths of service in the company and habitual use of medications. There were 10 women in the study and just two of them were in the case group. The cases differed significantly from the controls in that their BMI was higher, with a greater proportion of obese individuals, they consumed more alcoholic drinks and they more frequently mentioned a history of hepatitis (Table 1).

The overall chance that the cases with liver enzyme abnormalities would work in production was 7.3 times higher than for the controls, which was a statistically significant result (OR=7.3; 95% CI: 2.4-29.4). Production workers, allocated to the sectors of maintenance, operations, movement-transportation-storage, industrial safety, laboratory and asset security, presented higher odds ratios that did workers in the administrative sector. The risk estimates had little likelihood of being distorted due to sampling errors, for maintenance workers (OR=7.9; 95% CI: 2.4-33.5), operations (OR=7.5; 95% CI: 2.3-31.0) and industrial safety (OR=10.7; 95% CI: 2.2-57.7) (Table 2).

The stratified analysis was partially prejudiced by the small number of individuals in the strata of "obese individuals" and "with a history of hepatitis", especially with regard to individuals from the administrative sector. The calculation of the odds ratios and the respective 95% CI had to be done with the addition of 1 to each cell in the tables. Consequently, the evaluation of the interactions and confounding factors should be regarded with reservations in the stratified analysis. In turn, the logistic regression analysis did not reveal the existence of any interactions in the

Table 2 - Refinery worker cases and controls, according to sector of activity. São Francisco do Conde, Brazil, 1982-1998.

Sector	Cases (N=150)	Controls (N=150)	OR (95% CI)*	p
Administrative support	4	25		
Production	146	125	7.3 (2.4-29.4)	0.0001
Maintenance	51	40	7.9 (2.4-33.5)	0.0001
Operations	71	59	7.5 (2.3-31.0)	0.0001
Movement-transportation-storage	6	12	3.1 (0.5-17.6)	0.11
Industrial safety	12	7	10.7 (2.2-57.7)	0.0004
Laboratory	3	2	9.3 (0.7-133.0)	0.05
Asset security	3	5	3.7 (0.4-29.9)	0.15

*Odds ratios and respective 95% confidence intervals

Table 3 - Stratified analysis of the association between liver enzyme abnormalities and occupational exposure, according to certain covariables among oil refinery workers. São Francisco do Conde, Brazil, 1982-1998.

Covariables	n	OR (95% CI)	Raw OR (95% CI)	Adjusted OR (95% CI)
Alcohol consumption				
Yes	224	6.5 (1.7-36.2)		
No	66	5.0 (0.6-229.9)	6.5 (2.1-26.6)	6.0 (1.9-21.7)
Total	290			
Obesity				
Yes	35	10.3*		
No	265	5.8 (1.9-23.8)	7.3 (2.4-29.4)	6.6 (2.2-25.5)
Total	300			
History of hepatitis				
Yes	13	3.0*		
No	264	7.9 (2.3-41.9)	6.4 (2.1-26.1)	7.5 (2.1-27.2)
Total	277			

*Because of the small numbers of obese individuals in the administrative sector, the calculation of the 95% CI was prejudiced. The results from the Fischer exact test obtained after adding 1 to each cell in the Table were p=0.06, for the covariable of obesity, and p=0.46, for the covariable of history of hepatitis

model investigated. The data in Table 3 show that the odds ratios for the association between occupational exposure and liver enzyme abnormalities remained high (between 6.0 and 7.5) and statistically significant, even after adjustment for alcohol consumption, obesity and history of hepatitis.

At the preselection stage for the logistic model, the variables of gender, habitual use of medication and length of service in the company were excluded from the logistic analysis. After discounting the losses, 273 workers remained for the multiple logistic modeling. The variable "age" was automatically removed from the final model. The interaction terms (occupational exposure and obesity), (occupational exposure and alcohol consumption) and occupational exposure and history of hepatitis) could not be analyzed because their inclusion caused instability in the model.

The logistic regression model confirmed that the liver enzyme abnormalities were significantly associated with occupational exposure (production sector), even after controlling for the effects of the covariables of medical history of hepatitis, consumption of alcoholic drinks and obesity. Each of these covariables had an independent statistical association with the liver enzyme abnormalities. The logistic model produced the estimate that the production sector workers presented a risk of liver abnormalities that was 5.7 times greater than for the administrative sector, which was a significant risk (p = 0.0007) (Table 4).

Table 4 - Results from the final model for the logistic regression analysis, showing risk factors for abnormal levels of the enzymes GGT + ALT, among oil refinery workers. São Francisco do Conde, Brazil, 1982-1998.

Variables	OR (95% CI)*	p
Occupational exposure	5.7 (1.7-18.4)	0.0007
History of hepatitis	17.6 (2.1-146.2)	0.0003
Alcohol consumption	2.2 (1.2-4.3)	0.0098
Obesity	4.1 (1.5-11.0)	0.0021

*Odds ratios and respective 95% confidence intervals, adjusted for the other variables presented in the table. The variables of age, gender, habitual use of medications and length of service in the company were excluded from the model at earlier stages of the analysis. P-values from Chi-square test. Quality of the adjustment =278,696; 268 df; p=0.3139

The results relating to "history of hepatitis" must be interpreted with caution, given that this variable may form part of the causal pathway between exposure and effect. Thus, the workers who mentioned "hepatitis" in reality had a complaint of raised levels of liver enzymes resulting from toxic hepatitis of occupational nature. Adjustment of the final logistic model without this variable resulted in raising the odds ratio for the principal independent variable (occupational exposure) to 6.2 (95% CI: 2.0-18.1).

The Figure shows that the liver abnormalities in the cases occurred between 1982 and 1998, reaching a peak in 1993. During the period 1992-1994, 89 cases were registered, of which 88 came from various production sectors.

DISCUSSION

Many of the odds ratios calculated presented extremely wide confidence intervals, and this may give rise to large imprecision in the results. However, it must be remembered that the study design did not include sampling or randomization, which are fundamental conditions for correct interpretation of the confidence intervals. The absolute values of the odds ratios should be judged in order to correctly interpret them. But what is more important than the amplitude of the confidence intervals is the finding that the odds ratios for liver enzyme abnormalities among workers in each of the six production sectors were higher than the odds ratio for the workers in the administrative sector.

A cross-sectional study[1] carried out in 1997/1998 found that refinery workers presented a prevalence of liver abnormalities that was 3.56 times greater (95%

CI: 1.99-6.38) than the prevalence for the company's office workers, who were located in the urban area of Salvador. This risk was adjusted for other relevant covariables: obesity, practice of physical exercise, smoking and alcoholic drinks. However, that study considered that the cases consisted of simultaneous raising of GGT + ALT above their respective reference levels.

The results from the present study suggest that, in addition to the specifically biological and/or behavioral risk factors, occupational exposure plays an important role in causing liver enzyme abnormalities among oil refinery workers. Obesity, alcohol consumption,[3,8] black race, older age and insulin resistance[3] have been indicated as the principal factors responsible for liver enzyme alterations among petrochemical workers. A study carried out among all the male workers in a company in the USA[3] investigated the levels of the enzymes GGT, ALT and AST in consecutive periodic tests. The BMI and alcohol consumption had associations with enzymatic activity in both tests. BMI remained statistically associated with the levels of each enzyme after controlling for the effects of alcohol consumption, race and age. However, the occupational exposure was not assessed.

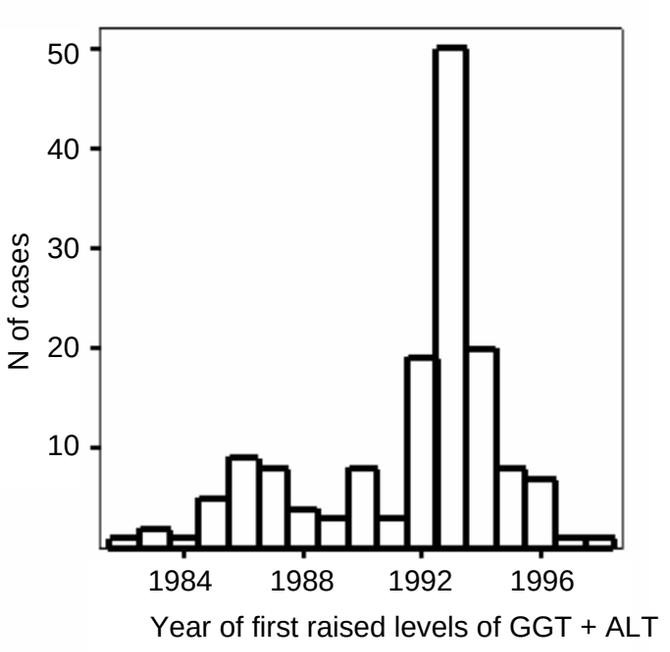

Figure - Cases of liver enzyme abnormalities, according to year when raised levels of GGT + ALT were first observed. São Francisco do Conde, Brazil, 1982-1998.

A variety of studies have reported an association between occupational exposure to organic products and liver enzyme abnormalities. The GGT levels in 141 Italian workers exposed to tetracloroethylene were significantly higher than the levels in 130 non-exposed workers, and they presented cholestatic liver lesions.[9] Other studies[4,11,13] have associated liver enzyme abnormalities with occupational exposure to a variety of solvents.

Ho et al[10] found abnormalities in various liver enzymes in 13 (4.8%) out of 271 workers with occupational exposure to vinyl chloride monomer (VCM). Among these 13 workers, 12 (92.3%) presented liver enzyme abnormalities that were probably induced by exposure to VCM. They also observed that the raising of serum ALT levels was the first enzymatic abnormality to occur, followed by abnormalities in GGT levels. Their study was carried out between 1971 and 1982, a time when the VCM exposure ranged from one to 21 parts per million (ppm). After 1982, when the exposure was reduced to less than 1 ppm, no new cases of liver disorders induced by VCM were identified. Their study demonstrated that concomitant raised levels of the enzymes GGT + ALT could be useful as an early detector of liver abnormalities, before irreversible lesions might develop. Another important aspect of the work by Ho et al[10] was the reduction in enzyme levels observed after the cases had been removed from exposure. Reversal of the condition seen through clinical, laboratory and histological examination was also observed in cases of non-alcoholic steatohepatitis (NASH) resulting from chronic exposure to petrochemical products in Bahia, when the individuals were put on sick leave.[5]

The fact that 88 of the 89 cases that occurred between 1992 and 1994 were in production sector workers can be highlighted. Even though case-control studies are not the most appropriate method for giving evidence of the existence of epidemics, the strong clustering of cases over this period suggests the occurrence of an epidemic of liver enzyme abnormalities in the workforce. The present study was exploratory in nature and was not designed to specifically investigate an epidemic. The causes of high levels of liver enzymes continue not to have adequate identification.

The hepatitis B and C viruses were not investigated systematically at the periodic examinations for all the refinery workers. Neither was these workers' immunological state regarding the B and C viruses. Nonetheless, between 1994 and 2003, all the 69 refinery workers who presented sustained high levels of liver enzymes (GGT + ALT and/or AST), in

at least three determinations over a minimum period of three months, were referred by the refinery for specialized hepatological evaluation. Of these, only six cases of hepatitis C were confirmed by laboratory findings. The clinical assessment usually involved a battery of laboratory tests: hemogram, mean corpuscular volume, platelets, AST, ALT, GGT, alkaline phosphatase, proteins and fractions, prothrombin time, bilirubin, total cholesterol and fractions, triglycerides, glycemia, insulin, anti-HCV (antibody against the hepatitis C virus), HBsAg (surface antigen for the hepatitis B virus), ferritin and transferrin saturation. In selected cases when necessary, the following further investigations were made: auto-antibodies (anti-nucleus, anti-mitochondria, anti-smooth muscle), alpha-1 antitrypsin, serum and urinary copper, ceruloplasmin and ultrasonography of the liver and bile ducts. The occurrence of 89 cases of hepatitis would possibly have been identified by the company's medical service. Therefore, it is improbable that an outbreak of viral hepatitis could have caused the epidemic.

Between 1982 and 1998, the refinery implemented wide-ranging alterations to its diversified production process. However, the professionals of the Industrial Hygiene and Safety and Occupational Medicine sectors and the Internal Accident Prevention Committee were unable to identify which changes in the refinery environment might have been associated with the epidemic of liver enzyme abnormalities observed.

In conclusion, occupational exposure plays an important role in causing liver enzyme abnormalities among oil refinery workers, in addition to the specifically biological and/or behavioral risk factors such as obesity and alcohol consumption.

ACKNOWLEDGEMENTS

To Drs. José Florentino Gidi de Oliveira, Roberto Charles Góes and Helton Rosa, doctors in the Occupational Health Clinic of the oil refinery, for their participation in building up the databank and discussing the results from the study.

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