Arch Iranian Med 2006; 9 (4): 324 – 328

Original Article

Silent Liver Diseases in Autopsies from Forensic Medicine of Tehran

Rasoul Sotoudehmanesh MD•*, Masoud Sotoudeh MD*, Ali Ali-Asgari MD*, Behnoush Abedi-Ardakani MD*, Seyed-Mohammad Tavangar MD*, Ali Khakinejad MD*, Zohreh Sadeghi MD*, Reza Malekzadeh MD*

Background: Histology is the unique method for diagnosis of silent liver diseases; so, we aimed to determine the prevalence of fatty liver and other silent liver diseases among those who passed away for causes other than liver diseases in Tehran.

Methods: Over a two-year period (2002 – 2004) we enrolled autopsies performed at the Forensic Medicine Center in Tehran. Demographic information, history of known acute and chronic liver diseases, and causes of death were determined. Samples from the right and left lobe and one sample from deeper areas of the liver as well as specimens from any grossly visible lesions were obtained in each case. Tissue sections stained by hematoxylin and eosin were evaluated. Reticulin and Masson's trichrome stains were also performed for evaluation of liver architecture and degree of fibrosis when necessary.

Results: Satisfactory tissue samples for histologic evaluation were available in 896 cases (777 males) with a mean age of 43.8 years. Normal histology was found in 467 cases (52.1%). Important findings included: steatosis in 283 (31.6%), steatohepatitis in 19 (2.1%), chronic hepatitis in 23 (2.6%), and cirrhosis in 7 (0.8%) cases. Causes of death were: trauma (35%), acute myocardial infarction (30%), opiate overdose (13%), cerebrovascular accidents (4%), infectious diseases (3%), and others (15%).

Conclusion: Silent diseases of the liver are not uncommon. Steatosis is the most common finding but inflammatory disorders comprise a significant minority.

Archives of Iranian Medicine, Volume 9, Number 4, 2006: 324 – 328.

Keywords: Autopsy • liver disease • steatohepatitis

Introduction

Most of the chronic liver diseases, even in advanced stages, may cause no prominent clinical signs or symptoms. They either go undiagnosed or are found incidentally during general health check-ups, investigations for other diseases, surgery, or autopsy. The underlying causes of chronic liver diseases vary in different geographic areas and are based on various factors such as socioeconomic status, life style, diet, local or regional infections, and other endemic diseases.

In the study of 4908 autopsy cases from Russia, the most frequent hepatic lesions were steatosis and inflammatory disorders.[1] Berry in 1500 autopsies performed in the coronal system in South-East London reported cirrhosis, adenoma, metastatic carcinoma, and hammartoma as the most common findings. Space occupying lesions were found in about 5% of livers in that study.[2] Another study based on analysis of 1839 necropsies in Singapore revealed that unanticipated liver lesions are common. The most important ones were cholelithiasis, cirrhosis, and primary carcinoma of the liver.[3]

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of liver diseases, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. Nonalcoholic steatohepatitis (NASH) represents a stage in the spectrum of NAFLD, characterized by presence of

Authors' affiliation: *Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
•Corresponding author and reprints: Rasoul Sotodehmanesh MD, Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Telefax: +98-21-88012992, E-mail: setoodeh@ams.ac.ir.
Accepted for publication: 5 July 2006

inflammation leading to gradual fibrosis in some of the affected patients. This disease is presently the most common chronic liver problem in western societies.[4, 5] The clinical importance of NAFLD is related to its prevalence and natural history. According to a recent study, the prevalence of NAFLD and NASH in western general population is approximately 20% and 3%, respectively.[5]

There is no published data on the frequency of silent liver diseases, especially NAFLD and NASH, in Iran. This study aimed to determine the prevalence of these diseases in a series of forensic autopsies in Tehran.

Materials and Methods

During a period of two years (May 2002 - May 2004) random autopsies performed at the Forensic Medicine Center in Tehran were studied. Demographic information, causes of death, history of alcohol use, and previous hepatic and nonhepatic chronic diseases such as diabetes mellitus were asked from the first degree relatives of the cases. Gross appearance of the liver was also recorded. Sampling was done by two physicians.

Cases with a history of any liver disease and those with autolyzed liver samples were excluded. Wedge necropsies (2 × 2 × 2 cm) from the right and left lobes and one biopsy of the same size from deeper areas of the liver parenchyma were obtained in each case. Any grossly abnormal area were also sampled.

All the liver specimens were fixed in 10% neutral buffered formalin. The specimens were processed, sectioned, and stained with hematoxylin and eosin after standard procedures. Other sections were stained with reticulin and Masson's trichrome methods for evaluation of liver architecture and fibrosis, when necessary.

Degree of steatosis was graded as:

I. When micro and macrovesicular steatosis affected 5 – 25% of the liver parenchyma;
II. When 26 – 50% of the parenchyma was affected;
III. When 51 – 75% was affected; and
IV. When more than 75% of the parenchyma was involved.

The three pathologists involved in this study agreed on terms, definitions, and the histologic criteria of the pathologic lesions. A second pathologist in the group checked all positive findings again. In addition, one out of each 10 samples was randomly selected and rechecked by another pathologist. In case of any diagnostic discrepancy, the result was reported according to the consensus of a joint slide review session. Histologic findings were recorded in a standard form.

Statistical methods

Categorical variables were presented as percentages, and continuous variables were presented as mean ± standard deviation. Chi-square test was used for categorical and *t* test for continuous variables. Age, sex, history of diabetes, alcohol use, and cause of death were introduced in the stepwise backwards binary logistic regression models to assess their role in steatosis. We used SPSS software, version 11.5.0 for all statistical tests.

Results

During the study period, 945 cases were assessed. Forty-nine cases were excluded because of moderate to severe autolysis in liver tissue or history of known chronic liver disease and 896 cases were enrolled in the study including 777 males and 119 females with a mean age of 43.8 ± 19.7 years.

Causes of death were: trauma (35%), ischemic heart disease (30%), opiate overdose (13%), cerebrovascular accidents (4%), infectious diseases and sepsis (3%), and others (15%). Completely normal liver histology was found in 467 cases (52.1%). Major pathologic findings are shown in Table 1. History of diabetes mellitus was found in 10 cases with steatosis and one case with steatohepatitis. Pathologic findings were not significantly different between patients with and without history of diabetes. Thirteen cases with history of diabetes did not show any evidence of steatosis or steatohepatitis on biopsy. Table 2 shows grading of steatosis with or without steatohepatitis in our patients.

Table 1. Frequency of important lesions observed by histologic evaluation of liver in autopsy series from Tehran.

Pathologic findings	Number (%)
Steatosis	283 (31.6)
Chronic hepatitis	23 (2.6)
Steatohepatitis	19 (2.1)
Cirrhosis	7 (0.8)
Granulomatous hepatitis	2 (0.2)
Focal nodular hyperplasia	2 (0.2)
Hemangioma	1 (0.1)
Hepatocellular carcinoma	1 (0.1)

Age was the only significant factor related to steatosis in the logistic regression analysis (OR: 1.02, 95% CI: 1.01 – 1.03; $P < 0.001$). Other variables including sex, history of diabetes, and causes of death did not show significant correlation.

Discussion

This study showed that steatosis is the most common silent liver disease but inflammatory disorders including NASH comprise a significant minority.

The true incidence and prevalence of NAFLD and NASH are not well known in different populations. This is partly because liver histology is required as the gold standard for precise diagnosis of this condition and the relatively invasive procedure of liver biopsy is still not considered essential for management of NAFLD by many physicians.

Most of the reports about the prevalence rates of this disease are based on ultrasonographic studies and/or the presence of elevated serum levels of aminotransferases in the absence of any other known liver disease or significant alcohol consumption.[5]

The prevalence of NAFLD in patients undergoing liver biopsy for any reason ranges between 15% and 39%.[6 – 8] This wide range is naturally related to the differences in the populations studied. In these studies, the prevalence of NASH ranges between 1.4% and 4.8%.

In clinical practice, diagnostic liver biopsy is only performed for highly selected patients. Therefore, the reported rates which are based on liver biopsies cannot reflect the true prevalence of NAFLD in the general population. Autopsies, performed for those who have passed away for reasons other than liver diseases, are certainly better sources for determination of a more reliable prevalence for NAFLD and NASH.

The particular characteristics of forensic autopsies are the relatively young age of subjects and usually better general health condition before death. Among our cases male gender was predominant, most of the subjects had no history of chronic diseases, and in more than 70% of the cases the cause of death was acute events like car accident, trauma, and cardiovascular problems. Thus, this sample may not be representative of the general population of Tehran.

Table 2. Grading of steatosis in cases with nonalcoholic fatty liver disease in an autopsy series from Tehran.

Grading	Number (%)
I	196 (64.8)
II	52 (17.7)
III	40 (12.9)
IV	14 (4.5)

The results of the present investigation are similar to those reported from a random pathology-based study looking at individuals who died from car accidents. In that study, NAFLD and NASH had a rate of 24% and 2.4%, respectively.[9] Our study showed that 34.9 % of the cases undergoing autopsy for forensic reasons in Tehran had evidence of NAFLD. More than 82.9% of these cases had grade I or II fatty change in the hepatocytes and only 2.1% had NASH. Although the prevalence of NAFLD was slightly more in females (30.9% males, 37.0% females) and NASH was more prevalent in males (2.3% males, 0.9% females), these differences were not significant. The prevalence of NAFLD in this predominantly male population was even higher than the rates reported from the western countries.[9] Malnutrition is very rare in the adult population of Tehran and definitively can not be considered as the cause of NAFLD. The reason for such a high rate of NAFLD in our study is probably due to the life style and the changes in the dietary habits.

Alcohol use was not reported in any of our patients. In contrast to western countries, alcohol trading is forbidden in Iran, though it is available in black market. Thus, the alcohol use is rare but not nil. In the past 30 years, this habit have shown dramatic changes getting more and more similar to industrialized countries.

We were not able to measure the body mass index (BMI) in our cases, are recent studies more than 65% of people living in Tehran are overweight and 15% can be considered obese.[10] One of the most controversial issues related to NAFLD and NASH is how often these conditions lead to liver cirrhosis. Although there is substantial evidence that NASH may lead to cirrhosis in about 20% of cases and is the most common etiology for cryptogenic cirrhosis,[11] well-designed prospective long-term studies for determination of the patients' outcome with NAFLD are lacking.[4, 5]

A few studies describe a number of patients with NASH and serial liver biopsies for determination of histologic progression. Some cases developed significant fibrosis, cirrhosis, and hepatocellular carcinoma on follow-up.[12, 13] We

found NASH in 2.1% and cirrhosis in 0.8% of our subjects; given the fact that viral hepatitis is the most common cause of cirrhosis in Iran,[14] this may emphasize that only a minority of patients with NAFLD may progress to NASH and cirrhosis.

Chronic hepatitis B (2% of the general population are HBsAg carriers) is presently the most common cause of cirrhosis and liver related mortality in Iran. Hepatitis B is reported to be the etiology of at least 60% of cirrhoses in this country.[14, 15] Serologic studies for viral markers were not performed in the present study, but it is most likely that HBV (and probably HCV as the second possibility) has been responsible for the 23 (2.5%) cases of chronic hepatitis and the majority of seven cirrhotics (0.8%) observed. Therefore, NASH can be considered to be as common as HBV carrier state in Iran.[15] In one study, about 25% of cirrhotics were cryptogenic.[15] Many of these cases can be attributed to NASH. Shakoori reviewed the report of histology of 4025 liver specimens during a 5-year period. He found a 6.8% prevalence rate for chronic hepatitis.[16] He did not separate steatohepatitis from chronic hepatitis and this may be the reason for the difference between the prevalence rates in these two studies.

Silent cirrhosis in our study is less than 1%. Bethke and Schubert showed that in a fifty-year autopsy series on 22000 cases, 0.4 – 7.2% of cases had cirrhosis.[17] Our result is lower than similar studies and may indicate a lower prevalence of silent cirrhosis in Iran. In addition, the most common cause of liver cirrhosis in this country is post-necrotic (HBV-related) instead of alcoholic in western countries,[14] and this difference in etiology of cirrhosis may explain the different natural course of being silent or not.

In a study from Italy, the prevalence of hepatocellular carcinoma in cirrhotic patients was 17.6% vs. 0.4% in noncirrhotics.[18] The etiology of hepatocellular carcinoma is different in different geographic areas. Even among Asian countries, the proportion of viral etiology is different. Hepatitis C virus plays a major role in Japan, whereas hepatitis B predominates in other Asian countries.[19, 20] In our study, the prevalence of silent hepatocellular carcinoma was low; one patient (0.1%) without a background of cirrhosis.

Granulomas are frequently encountered in liver biopsies and their existence will capture the attention of clinicians and pathologists.[21, 22] They have been detected in 2 – 10% of liver biopsies in large series.[23] Granulomas are found in virtually all patients with disseminated tuberculosis.[24] In one of our two cases with granulomatous hepatitis (which were compatible with tuberculosis), there were symptoms and signs of tuberculosis and other clues in autopsy were in favor of disseminated tuberculosis. In the other case there were no complaints by history taken from the family of the patient and the cause of death was myocardial infarction.

In our study, two cases had nodular regenerative hyperplasia (0.2%). Both were males without previous disease and their cause of death was trauma. In a study from Japan performed on 577 cases, 2.1% had nodular regenerative hyperplasia and their causes were organic cardiac disease, pulmonary diseases with right-sided heart failure, and systemic amyloidosis.[25] In this study, all patients were adults and there was no significant sex predominance. Wanless proposed that uneven distribution of portal as well as arterial blood flow related to portal venopathy and/or arterial disease within the liver may be important for the occurrence of this disease.[26, 27]

In summary, asymptomatic fatty liver might be the most common silent liver disease among the general population in Tehran. Since NAFLD and NASH are common and may lead to serious clinical consequences, they should seriously be considered as an important threat to the health of the general population. Further studies to assess the etiology and natural history of these lesions are certainly warranted.

Acknowledgment

This study was supported by a grant from Digestive Disease Research Center of Tehran University of Medical Sciences. We also wish to express our gratitude towards the Forensic Medicine Center in Tehran; Seyed-Bardia Hosseini, Hamid-Reza Khalatbari, Nasser Kordani, and Afsaneh Mehrnami (medical students and physicians of Tehran Azad University); and Dr. Zohreh Movahedi, for their collaboration in this study.

References

1 Voinova LV. Etiological and nosological structure of liver diseases (on autopsy data of clinics of I.M. Sechenov Moscow Medical Academy in 1988 – 1997). *Arkh Patol*. 2000; **62:** 45 – 47.

2 Berry CL. Liver lesions in an autopsy population. *Hum Toxicol.* 1987; **6:** 209 – 214.

3 Lee YS. The pattern of liver diseases in Singapore. An autopsy study. *Trop Geogr Med*. 1979; **31:** 69 – 74.

4 Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002; **346:** 1221 – 1231.

5 Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis*. 2001; **21:** 17 – 26.

6 Propst A, Propst T, Judmaier G, Vogel W. Prognosis in nonalcoholic steatohepatitis. *Gastroenterology*. 1995; **108:** 1607.

7 Hultcrantz R, Glaumann H, Lindberg G, Nilsson LH. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. *Scand J Gastroenterol*. 1986; **21:** 109 – 113.

8 Nonomura A, Mizukami Y, Unoura M, Kobayashi K, Takeda Y, Takeda R. Clinicopathologic study of alcohol-like liver disease in nonalcoholics; nonalcoholic steatohepatitis and fibrosis. *Gastroenterol Jpn*. 1992; **27:** 521 – 528.

9 Hilden M, Christoffersen P, Juhl E, Dalgaard JB. Liver histology in a 'normal' population—examinations of 503 consecutive fatal traffic casualties. *Scand J Gastroenterol*. 1977; **12:** 593 – 597.

10 Malekzadeh R, Nasseri-Moghaddam S, Sotoudeh M. Gastroesophageal reflux disease: the new epidemic. *Arch Iranian Med*. 2003; **6:** 127 – 140.

11 Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology*. 1999; **29:** 664 – 669.

12 Ratziu V, Bonyhay L, Di Martino V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology*. 2002; **35:** 1485 – 1493.

13 Kochar N, Lowes J, Teague RH. Nonalcoholic fatty liver disease (NAFLD) in South West England. *Gastroenterology*. 2002; **122:** A-669.

14 Azimi K, Sarafi M, Alavian SM, Alawi M, Mikaeli J, Malekzadeh R. Causes of cirrhosis in cirrhotic patients in Shariati Hospital. *Govaresh*. 2002; **37:** 19 – 26.

15 Merat S, Malekzadeh R, Rezvan H, Khatibian M. Hepatitis B in Iran. *Arch Iranian Med*. 2000; **3:** 192 – 201.

16 Shakoori A. Silent chronic hepatitis in forensic medicine [in Persian]. *Pezeshki Ghanooni*. 1994; **1:** 52 – 58.

17 Bethke BA, Schubert GE. Primary hepatic cancer and liver cirrhosis. *Hepatogastroenterology*. 1984; **31:** 211 – 214.

18 Zotti S, Piccigallo E, Rampinelli L, Romagnoli G, Tufano A, Dagnini G. Primary and metastatic tumors of the liver associated with cirrhosis: a study based on laparoscopy and autopsy. *Gastrointest Endosc*. 1986; **32:** 91 – 95.

19 Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C-viral infection in Japan. *Hepatology*. 1995; **22:** 1027 – 1033.

20 Poovorawn Y, Sripattanawatb R, Theamboonlers A, Chongsrisawat V, Nuchprayoon I. Hepatocellular carcinoma: significance of HBV vertical transmission. *Asian Pac J Allergy Immunol*. 1998; **16:** 93 – 103.

21 Zumla A, James DG. Granulomatous infections: etiology and classification. *Clin Infect Dis*. 1996; **23:** 146 – 158.

22 Ishak KG. Granulomas of the liver. *Adv Pathol Lab Med*. 1995; **8:** 247 – 261.

23 Cunnigham D, Mills PR, Quigley EM, Patrick RS, Watkinson G, MacKenzie JF, et al. Hepatic granulomas: experience over a 10-year period in the West of Scotland. *Q J Med*. 1982; **51:** 162 – 170.

24 Klatskin G. Hepatic granulomata: problems in interpretation. *Mt Sinai J Med*. 1977; **44:** 798 – 812.

25 Nakanuma Y. Nodular regenerative hyperplasia of the liver: restrospective survey in autopsy series. *J Clin Gastroenterol*. 1990; **12:** 460 – 465.

26 Wanless IR. Understanding noncirrhotic portal hypertension. *Hepatology*. 1988; **8:** 192 – 193.

27 Wanless IR. The use of morphometry in the study of nodular regenerative and vascular lesions of the liver. *Anal Quant Cytol Histol*. 1987; **9:** 39 – 41.