Clinical features and risk factors of patients with fatty liver in Guangzhou area

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INTRODUCTION
Fatty liver is a condition of hepatic steatosis caused by many risk factors and may progress to liver fibrosis and cirrhosis. Generally, the diagnosis of fatty liver should be based on the history, clinical manifestation, laboratory investigation and medical imaging. Liver biopsy should be taken if necessary. After to know the possible related risk factors of fatty liver existed in the history, the abnormal degree of the biochemical and imaging features can provide a clue for early diagnosis. Although the related risk factors and laboratory features have already been reported, there is still no well-accepted conclusion[1-3]. The large-scale clinical studies have not carried yet in Guangzhou area, southern China[4].

Retrospective case-control study was used to analyze fatty liver. The age, gender, obesity, type 2 diabetes mellitus, hyperlipidemia, alcohol abuse, smoking, and history of drugs or toxins and so on were recorded to evaluate the effects of these variables on fatty liver and investigate the related risk factors. The liver function and other serum biochemical levels were compared to find out the difference of laboratory abnormalities, so that they could provide a scientific foundation for the diagnosis, prevention and treatment of fatty liver.

MATERIALS AND METHODS

Clinical data
The data of 413 cases of fatty liver in this hospital from January 1998 to May 2002 were collected. Fatty liver was diagnosed according as the standard by Chinese Association of Medicine and Sherlock[5-7] The 200 cases without fatty liver during the same period were selected randomly as control. Age, gender, serum lipids, fasting plasma glucose (FPG), obesity (body mass index, BMI ≥25), alcohol abuse, smoking, type 2 diabetes mellitus, history of drugs and toxins, hepatitis virus infection (HCV and HBV), pregnancy, jejuno-ileal bypass surgery and total parenteral nutrition were recorded in fatty liver group and non fatty liver group respectively.

The laboratory data of serum triglyceride (TG), cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein AI (Apo AI), apolipoprotein B (Apo B), uric acid (UA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), the ratio of AST/ALT, albumin (ALB), globin (GLB), ratio of A/G, gamma-glutamyltransferease (GGT) and total bilirubin were collected in two groups respectively. The serum biochemical indexes were examined by an autoanalyzer based on a standard protocol.

Statistical analysis
All data analysis was performed with EXCEL 97 and SPSS 10.0/PC statistical package. A P value less than 0.05 (2-tailed) was considered to be statistically significant. The frequency was compared using Chi-squared ($\chi^2$) test. The univariate and multivariate stepwise logistic regression was used to select the independent variables. Data with normal distribution were expressed as mean±SD. The differences between groups were analyzed for statistical significance using Student’s t test. Data

CONCLUSION: Obesity, alcohol abuse, type 2 diabetes mellitus and hyperlipidemia may be independent risk factors of fatty liver. The mildly abnormal hepatic functions can be found in patients with fatty liver. More obvious damages of liver function with AST/ALT usually more than 2 were noted in patients with AFL.

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with abnormal distribution were expressed as median and interquartile range.

RESULTS

General condition
Among 413 fatty liver cases, the gender ratio (M/F) was 1.02:1. The age ranged from 8 to 83 years. The median age was 57 years. No significant differences in age and gender were found between the fatty liver group and non-fatty liver group. The possible causes of fatty liver are shown in Table 1.

Table 1 Possible causes of fatty liver and its comparison with non-fatty liver group (%)

| Factors                        | Fatty liver group (n=413) | Non-fatty liver group (n=200) |
|--------------------------------|--------------------------|------------------------------|
| Alcohol abuse                  | 51(12.4)                 | 7(3.5)                      |
| Obesity                        | 244(59.1)                | 17(8.5)                     |
| Type 2 diabetes mellitus       | 206(49.9)                | 15(7.5)                     |
| Hyperlipidemia                 | 276(66.8)                | 63(31.5)                    |
| Hypertariglyceridemia          | 92(23.3)                 | 17(8.5)                     |
| Hypercholesterolemia           | 64(15.5)                 | 35(17.5)                    |
| Mixed Hyperlipidemia           | 120(29.1)                | 11(5.5)                     |
| HBV infection                  | 50(12.1)                 | 31(15.5)                    |
| HCV infection                  | 34(8.2)                  | 10(5.0)                     |
| History of drugs and toxins    | 6(1.5)                   | 2(1.0)                      |

Table 2 Multivariate stepwise logistic regression

| Variables                        | β      | SE     | OR      | 95%CI        | P-value |
|----------------------------------|--------|--------|---------|-------------|---------|
| Obesity                          | 3.054  | 0.354  | 21.204  | 10.539-42.429 | 0.000   |
| Alcohol abuse                    | 2.923  | 0.509  | 18.601  | 6.585-50.432  | 0.000   |
| Type 2 diabetes mellitus         | 1.496  | 0.354  | 4.461   | 2.228-8.952  | 0.022   |
| TG                               | 1.365  | 0.268  | 3.916   | 2.316-6.621  | 0.000   |
| LDL-C                            | 0.610  | 0.184  | 1.840   | 1.283-2.640  | 0.001   |
| FPG                              | 0.429  | 0.094  | 1.535   | 1.278-1.846  | 0.000   |
| Apo B                            | -1.590 | 0.530  | 0.204   | 0.072-0.576  | 0.003   |

Abnormal liver function in patients with fatty liver

Using χ² test, abnormal frequencies of ALT, AST/ALT and GGT showed significant differences between the patients with and without fatty liver (Table 3).

Comparison of serum biochemical features between alcoholic fatty liver (AFL) group and nonalcoholic fatty liver (NAFL) group

The abnormal frequencies of serum TG, CHOL, LDL-C and Apo B were higher in NAFL group than those in AFL group. The proportion of HDL-C < 1.0, AST ≥ 40 and AST/ALT ≥ 2 were higher in patients with AFL than with NAFL (Table 4).

Table 3 Abnormal liver function in the patients with fatty liver and non-fatty liver (%)

| Liver function | Fatty liver group (n=413) | Non-fatty liver group (n=200) |
|----------------|---------------------------|------------------------------|
| AST (≥40 U)   | 85(20.6)                  | 38(19.0)                     |
| (40-80 U)     | 65(15.7)                  | 26(13.0)                     |
| (≥80 U)       | 20(4.8)                   | 12(6.0)                      |
| ALT (≥40 U)   | 129(31.2)                 | 37(18.5)                     |
| (40-80 U)     | 84(20.3)                  | 26(13.0)                     |
| (≥80 U)       | 45(10.9)                  | 11(5.5)                      |
| AST/ ALT (<2) | 161(39.0)                 | 28(14.0)                     |
| (≥2)          | 23(5.6)                   | 54(27.0)                     |
| ALB (<35 g/L) | 16(3.9)                   | 15(7.5)                      |
| GLB (≥30 g/L) | 42(10.2)                  | 29(14.5)                     |
| A/G (<1.5)    | 84(20.3)                  | 47(23.7)                     |
| GGT (≥50 U/L) | 145(35.1)                 | 46(23.0)                     |
| TBIL (≥17.1 μmol/L) | 75(18.2) | 39(19.5) |

Table 4 Comparison of laboratory abnormalities among AFL, NAFL and control groups (%)

| Biochemical index | AFL group (n=28) | NAFL group (n=301) | Control group (n=413) |
|-------------------|------------------|--------------------|-----------------------|
| TG (≥1.7 mmol/L)  | 2(7.1)           | 16(56.2)           | 27(17.7)              |
| CHOL (≥5.2 mmol/L)| 2(7.1)           | 14(48.9)           | 35(22.9)              |
| HDL-C (≥1.0 mmol/L)| 9(32.1)       | 35(11.6)           | 27(17.7)              |
| LDL-C (≥2.6 mmol/L)| 12(42.9)       | 214(71.1)          | 97(63.4)              |
| Apo A (≥1.2 mmol/L)| 13(46.4)      | 118(39.2)          | 45(29.4)              |
| Apo B (≥1.1 mmol/L)| 4(14.3)         | 149(49.5)          | 53(34.6)              |
| UA (<452 mg/dL)   | 5(17.9)          | 89(29.6)           | 18(11.8)              |
| AST (≥40 U)       | 12(42.9)         | 51(16.9)           | 24(15.7)              |
| ALT (≥40 U)       | 10(35.7)         | 87(28.9)           | 26(17.0)              |
| AST/ ALT (<2)     | 11(39.3)         | 168(55.8)          | 31(20.3)              |
| (≥2)              | 5(17.9)          | 15(5.0)            | 40(26.2)              |
| ALB (<35 g/L)     | 3(10.7)          | 9(3.0)             | 7(4.6)                |
| GLB (≥30 g/L)     | 3(10.7)          | 32(10.6)           | 20(13.1)              |
| A/G (<1.5)        | 7(25.0)          | 64(21.3)           | 31(20.3)              |
| GGT (≥50 U/L)     | 10(35.7)         | 95(31.6)           | 30(19.6)              |
| TBIL (≥17.1 μmol/L)| 6(21.4)         | 50(16.6)           | 30(19.6)              |

DISCUSSION

In recent years, the prevalence of fatty liver is constantly increasing along with the improvement of life-style, the change of dietetic structure, the aged population and the application of new diagnostic technique. The incidence of fatty liver in 3432 Japanese adults thorough medical examination was 21.8%[1]. In China, fatty liver affected 10.2% of cadres in Nanjing[2] with 11.4% of male and 6.8% of female. There were no data to show the prevalence of fatty liver in the southern China. Because of distinct life-style and climate feature in Guangzhou, the pattern...
of fatty liver could be different from other area. Among 413 patients with fatty liver, the gender ratio (M/F) was 1.02:1. The age ranged widely, the median age was 57 years.

Fatty liver may be an independent disease, but more generally, it is a lesion of the liver in certain systemic diseases. Fatty liver may be caused by many diseases and risk factors, and can progress from mild steatohepatitis to severe fibrosis and cirrhosis[9]. The etiological prevention is very important because of the lack of effective therapy. Although the etiology of hepatic steatosis is explored extensively, the complicated and multi-factor pathogenesis make it remain poorly understood. The possible related risk factors include: alcohol abuse, diabetes mellitus, obesity, hyperlipidemia, drugs and toxins, hepatitis virus infection (especially HCV), rapid weight loss, jejuno-ileal bypass surgery, total parenteral nutrition, pregnancy and so on[10-16].

413 patients with fatty liver were diagnosed mainly according to the history, clinical manifestations, laboratory and ultrasound examination. Liver biopsy was the best method of diagnosing fatty liver. But it was difficult to carry out in large sample of populations. This was the possible limitations of the study.

Our data from 413 patients with fatty liver showed that obesity, alcohol abuse, type 2 diabetes mellitus, hyperlipidemia and elevation of fasting plasma were independent risk factors confirmed by a multivariate logistic analysis. These correlations were similar to the researches at home and abroad[3,4]. It suggested that the pathogenesis of fatty liver in southern China might have a similar pattern to other area in China and abroad.

Obesity was easily accompanied with fatty liver[17]. The percentage of the obese patients with fatty liver (59.1%) was significantly higher than controls (8.5%). Obesity is a very common phenomenon in the developed countries. 60-100% of patients of non-alcoholic steatohepatitis (NASH) were proved to have obesity[18]. This situation was also found in developing country, especially in China. According to the data in 11 provinces/autonomous regions/municipalities of China from July 1995 to July 1997, the prevalence rate of overweight and obesity among 42 751 Chinese adults aged 20-74 years were 21.51% and 2.92% respectively[19]. There were about 200-300 million of overweight and 30-40 million of obese populations in China. With the odds ratio of 21.204, obesity was a predictor of fatty liver. The practice of prevention for overweight and obesity was very important for control of fatty liver.

Alcohol liver disease was the major medical complications of alcohol abuse. Alcohol abuse was one of the major causes of fatty liver and cirrhosis in the Western countries. At least 80% of heavy drinkers developed fatty liver, 10-35% of alcoholic hepatits, and approximately 10% cirrhosis[20]. Alcohol drinkers were not as common in southern China as in northern China[19]. Based on our data, there were only 12.4% patients with alcoholic fatty liver among 413 patients with fatty liver. This proportion was much lower than the diagnostic standard of China in 2002. But, the proportion of alcoholic abuse was still higher in patients with fatty liver than those without fatty liver. Alcoholic abuse contributed to a risk factor of fatty liver.

Type 2 diabetes mellitus usually accompanied insulin resistance[12,21]. Both peripheral and hepatic insulin resistance were present in almost all patients with nonalcoholic fatty liver disease, irrespective of the coexistence of related risk factors[21]. Above findings, together with the associated hyperlipidemia, obesity, hypertension and herperurisemia, were considered as the manifestations of the metabolic syndrome that was associated with insulin resistance[22,23]. In this study, either type 2 diabetes or elevation of fasting plasma glucose was related to fatty liver. It suggested that insulin resistance might be a risk factor of fatty liver.

The role of serum lipids in fatty liver remained controversial[16,24]. Some researches showed that the effects of hyperlipidemia on fatty liver were complicated and difficult to be dissociated with obesity and type 2 diabetes mellitus. Among the 413 patients with fatty liver, the total incidence of hyperlipidemia was 66.8%, which consisted of 22.3% of hypertriglyceridermia, 15.5% of hypercholesterolemia and 29.1% of mixed hyperlipidemia. TG and LDL-C were independent risk factors and ApoB was a protective factor confirmed by multivariate logistic analysis. TG and LDL-C stimulated the proliferation and collagen synthesis of hepatic stellate (HSC) and increased deposition of extracellular matrix (ECM) in the liver by means of lipid peroxidation[25,26]. This process was related to hepatic fibrosis and effected prognosis of patients with fatty liver.

The correlation between hepatitis virus infection (especially HCV) and hepatic steatosis was found[27]. Although the incidence of chronic HBV and HCV infection in China remained the highest proportion in the world, there was no significant difference in the incidence of HBV or HCV infection between patients with and without fatty liver. The infection of HBV and HCV was excluded from the model of multivariate stepwise logistic regression.

The clinical and laboratory features varied greatly with different causes and degree of hepatic steatosis in patients with fatty liver[28]. The elevation of serum TG, CHOL and LDL-C was more common in patients with NAFL than those with AFL. Most patients with fatty liver had no obvious symptoms and signs of liver disease at the time of diagnosis. But a higher proportion of patients with cryptogenic cirrhosis shared many of the clinical and demographic features of patients with fatty liver. NASH played an under-recognized role in many patients with cryptogenic cirrhosis[29]. Mild elevation usually less than 2 folds of the normal limit of serum ALT and GGT was showed in this investigation. The mitochondria was the most likely source of the reactive oxygen species (ROS) leading to lipid peroxidation in patients with fatty liver[30]. AST, a mitochondrial enzyme, was more easily affected by ethanol[31]. Among the abnormal hepatic functions, the higher AST levels with AST/ALT more than 2 were found in those with AFL. The increases of serum lipids and AST/ALT ratio might be useful in differentiating NAFL from AFL.

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