The Prevalence of Nonalcoholic Steatohepatitis in Thai Patients with Non-HBV, Non-HCV Chronic Hepatitis

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This study aimed to determine the prevalence of nonalcoholic steatohepatitis in Thai patients with non-HBV, non -HCV chronic hepatitis. The clinical and laboratory findings associated with non alcoholic steatohepatitis were discussed. Forty-six patients with negative markers for viral hepatitis B and viral hepatitis C and no history of alcohol consumption or consumption less than 20 grams of ethanol per day were recruited. The informed consent for liver biopsy and blood collecting to identify the etiology of chronic hepatitis was performed. Most patients (76.1%) exhibited fatty metamorphosis of the liver which included steatosis (21.8%) as well as steatohepatitis (54.3%). Eleven of 46 patients (23.9%) were classified as cryptogenic chronic hepatitis. There were statistically significant differences between the fatty metamorphosis group and the cryptogenic chronic hepatitis group with regard to the fasting blood sugar, serum alkaline phosphatase, serum ferritin and histologically necroinflammatory grading score ($p < 0.05$). Between the steatosis group and the steatohe-patitis group, body mass index (BMI) was the only factor showing statistically significant difference ($p = 0.02$). Eight from 25 NASH-patients had diabetes mellitus (32.0%) and the AST to ALT ratio in this group was 0.6. The histopathological assessment for inflammation and fibrosis by using Knodell score, the fibrosis score which equal or higher than 3 was found in 20.0% of NASH- patients.

***Conclusion** : The prevalence of NASH-patients In Thai patients,with non HBV, non HCV chronic hepatitis was 76.1%,while the liver biopsy can add the diagnostic yield especially in the group of unexplained chronic hepatitis with obesity, diabetes mellitus and dyslipidemia.*

***Keywords** : Prevalence, Nonalcoholic steatohepatitis, Chronic Hepatitis*

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Desmet et al defined cryptogenic chronic liver disease as liver disease whose cause can not be established from the patient's history, physical examination, laboratory data or histology[1]. The global prevalence of cryptogenic liver disease is unknown because the variation is diagnostic capability and demographic among nations. In Thailand, there was a report that stated that 39.5% of cirrhosis was cryptogenic[2]. The prevalence of the indeterminate causes of chronic liver diseases including cirrhosis varies from 5-90.1%[3-7]. Cirrhosis is considered to be a risk factor for hepatocellular carcinoma; the characteristic histological changes seen in cirrhosis can not be predicted by changes in the level of serum aminotransferase, making it impossible to chart the progression of chronic hepatitis by monitoring the elevation of aminotransferase[3,8-11]. Long-term follow-up has shown that cryptogenic chronic liver diseases had a propensity for progression to cirrhosis despite having an asymptomatic clinical course[12-14]. Moreover, the now routine biochemical assays conducted during annual check ups have led to an increasing number of incidental findings of abnormal liver function tests (LFT)and found that 18.7% of patients undergoing routine medical check ups in the preventive medicine clinic of the King Chulalongkorn Memorial Hospital, Bangkok, had abnormally elevated levels of liver enzymes[15-16].

A chronically abnormal LFT is defined as an elevation of either AST or ALT for more than 6 months. In these cases, a liver biopsy is recommended[4,17-19]. Diagnoses of cryptogenic chronic hepatitis have to be viewed with a certain caution; hepatitis with an identifiable etiology may have been overlooked, especially in facilities that lack the capacity for sophisticated investigative techniques. There is a new form of chronic

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hepatitis, non-alcoholic steatohepatitis (NASH), which presents as a syndrome of obesity, diabetes or dyslipidemia and is confirmed by histological findings, including Mallory bodies, fatty changes and lymphocytes infiltration[20]. The prevalence of NASH in Thai patients with chronic hepatitis is unknown. In the present study, the authors determined the prevalence of NASH among patients at the King Chulalongkorn Memorial Hospital and Hospital for Tropical Medicine, Mahidol University. The authors also describe the clinical, biochemical, and histological findings in patients with NASH.

Material and Method

Patients

This study was a prospective study of patients of the King Chulalongkorn Memorial Hospital and Hospital for Tropical Medicine, Mahidol University, Bangkok, Thailand. The patients, aged between 18 and 65 years, were referred to the Liver Unit between June 1998 and January 2002. The patients had been referred for further investigation of chronically abnormal liver function tests (> 6 months duration). Abnormal LFT_s were defined as the elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to more than 1.5 times the upper limit of normal (40 units/liter); each patient,s abnormal, LFT_s had been assayed at least twice within 6 months. No patient had viral hepatitis B or viral hepatitis C or a history of alcohol consumption exceeding 20 gram /day. Patients eligible for the study gave their consent for a liver biopsy. The study was approved by the Chulalongkorn Hospital ethics committee. The patients' clinical data included demographic information, symptoms and signs related to liver disease, concurrent illnesses and current medication. The exclusion criteria were symptomatic HIV infection; clinical manifestations of cirrhosis; history of malignancy; history of intravenous drug use; chronic renal failure; pregnancy; contraindications to liver biopsy. All of the patients had an ultrasonographic examination prior to the liver biopsy. Slit lamp examination of the eyes for Kayser-Fleischer rings was conducted in the hypoceruloplasmin case. Obesity was defined as a body mass index (BMI) of ≥ 25 kg/m^2, the cut-off point proposed by the World Health Organization. A full history was taken and a thorough physical examination was conducted; height and weight were recorded. Conventional laboratory tests were ordered: the tests were intended to ensure that no specific etiological factors had been overlooked and gave an overview of hepatic function. The LFT included AST, ALT, alkaline phosphatase, bilirubin, albumin, globulin, prothrombin time, antinuclear, antibodies, antismooth muscle, antibodies and antimitochondrial antibodies were measured and were considered positive with a rising titer of ANA, SMA or AMA at least 1:40. Serologic markers of HBV infection comprised of hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (AntiHBc), and antibody to hepatitis B surface antigen (AntiHBs) were performed. HCV screening was done by using second generation enzyme-linked immunosorbent assay (ELISA-II). Serum cerulo-plasmin, ferritin, and alpha-fetoprotein were also tested. Diabetes mellitus (DM) was defined as a fasting blood sugar $\geq$ 126 mg/dl; dyslipidemia was defined as a serum cholesterol > 220 mg/dl, or serum triglycerides > 155 mg/dl, according to our reference laboratory values. Data were recorded in the case record forms.

Procedure

Liver biopsy was carried out on an in-patient basis using a 16-18 Fr. Hepafix disposable biopsy needle under ultrasonographic guidance; tissue samples were preserved in 10% formalin. All of the liver biopsies were reviewed by one hepatopathologist. Knodell score criteria were applied during the determination of the histology activity indices (HAI) of necroinflammatory and fibrotic changes. Steatosis was defined as the fatty metamorphosis of more than 50% of a hepatic lobule and there was no infiltration by inflammatory cells. Steatohepatitis was defined as the fatty metamorphosis of more than 50% of a hepatic lobule which presented at least one of the following: infiltration by inflammatory cells (mostly in centrilobular area); hyaline Mallory bodies; centrilobular fibrosis. Bridging fibrosis was defined as the extension of fibroses from one portal tract to another. A diagnosis of cryptogenic chronic hepatitis was made once the hepatitis of known cause had been excluded.

Statistical analysis

Data were analyzed using descriptive and inferential statistics. The difference in the continuous variables was compared by using the t-test (SPSS for window version 10.0).

Results

Forty-six patients of non viral hepatitis B, non viral hepatitis C and non alcoholic chronic hepatitis were included. The clinical and demographic data of each group of chronic hepatitis are summarized in Table 1. Forty-two patients (91.3%) lived in Bangkok

Table 1. The demographic and clinical data of 46 cases of non viral hepatitis B, and non alcoholic chronic hepatitis categorized by the causes of hepatitis during June 1998-January 2002

Demographic and clinical data	Total (%)	Cryptogenic (N = 11)	Steatosis (N = 10)	NASH (N = 25)
Sex				
- male	30(65.2%)	N(50%)	N(25%)	N(44.0%)
- female	16(34.8%)	N(50%)	N(75%)	N(56.0%)
Age mean ± SD	44.7±12.4	42.7±15.7	44.8±12.64	5.7±11.9
range (years)	19-64	19-64	32-62	23-62
History of blood transfusion	3(6.5%)	2	0	1
Jaundice	3(6.5%)	1	0	2
Pale	1(2.2%)	1	0	2
BW mean ± SD (kg)	77.4±35.4	60.9±23.4	67.8±11.6	87.2±45.6
BMI mean ± SD (kg/m^2)	26.8±3.8	25.3±5.6	25.7±1.9	28.2±3.2

or nearby provinces in the central region while the rest lived in northern, northeastern or in southern parts of the country. Most of the patients were asymptomatic (88.9%). None of the patients had history of intravenous drug use,being homosexual, or a family history of psychiatric disorder but there were 3 patients (6.5%) who had a history of blood transfusion. Only one male patient had a family history of an elder sister dying from liver failure but the definite diagnosis was not known.

Table 2 shows the laboratory findings. The mean ALT was about four times higher than the upper limit of normal. The mean duration from the detection of abnormal LFT until the liver biopsy was 21.9 ± 15.2 months. The ratio of mean AST to mean ALT in patients with NASH was 0.6.

The abnormal serological markers for autoimmune liver diseases were positive ANA (13 patients, 28.2%), but most of them were weakly positive. Only one patient had a very low serum ceruloplasmin level (5 mg/dl). Thirteen patients (28.3%) had a high level of ferritin (> 400 ng/ml). Hypergammaglobulinemia occurred in 8.4%. Most of the patients (76.1%) displayed fatty metamorphoses of the liver which were steatosis and steatohepatitis (NASH). There were 11 patients (23.9%) who had no specific etiology for the abnormal LFT and so were labelled as cryptogenic chronic hepatitis.

The number of associated diseases which classified to the histological diagnosis is shown in Table 3. Comparing the 35 patients who had fatty metamorphosis of the liver with the eleven cryptogenic chronic hepatitis patients showed that the fatty metamorphosis group had statistically significant differences for the presence of higher fasting blood sugar, higher ferritin level, higher HAI scores and lower alkaline phosphatase as shown in Table 4. Comparing the characteristics of the patients between the steatosis and the steatohepatitis groups, most had no statistically significant difference except NASH-patients had the higher BMI (28.2 and 25.7, p = 0.02, 95% CI = 0.4 to 4.7) and the higher HAI score (2.3 and 1.0, p = 0.01, 95% CI = 0.3 to 2.3)

For these 35 patients who had fatty metamorphosis of the liver, comparison between the obese group (BMI ≥ 25 kg/m^2) and the normal BMI (< 25 kg/m^2) showed that the obese group had higher fasting blood sugar (116.0 and 97 mg/dl, p = 0.038; 95% CI = 1.12 to 36.96), lower total bilirubin level (0.7 and 1.0

Table 2. The laboratory findings of 46 cases of non viral hepatitis B, C and non alcoholic chronic hepatitis categorized by the cause of hepatitis during June 1998-January 2002

Laboratory parameters (normal value)	Total Mean ± SD	Cryptogenic CH (N = 11)	Steatosis (N = 10)	NASH (N = 25)
Hematocrit (%)	41.2 ± 4.6	41.5 ± 4.9	43.2 ± 3.2	41.2 ± 4.1
Total bilirubin (<1 mg/dl)	1.6 ± 3.4	1.7 ± 2.7	0.8 ± 0.4	0.8 ± 0.3
Direct bilirubin (0-0.25 mg/dl)	0.8 ± 2.5	1.1 ± 2.5	0.2 ± 0.1	0.2 ± 0.1
Alkaline phosphatase (98-279 U/L)	302.4 ± 461.7	416.9 ± 594.5	158.9 ± 53.1	181.2 ± 64.5
AST (0-38 U/L)	110.3 ± 115.6	103.4 ± 143.0	69.1 ± 29.4	106.2 ± 88.1
ALT (0-38 U/L)	155.0 ± 84.9	115.0 ± 66.0	139.7 ± 69.2	170.8 ± 92.3
Albumin (3.4-5.5 g/dl)	4.6 ± 0.6	4.6 ± 0.7	4.8 ± 0.3	4.7 ± 0.5
Globulin (2.0-4.0 g/dl)	3.4 ± 0.8	3.1 ± 0.5	3.0 ± 0.7	3.4 ± 0.7
Cholesterol (< 220 mg/dl))	253.5 ± 151.3	326.5 ± 315.1	234.9 ± 41.4	227.4 ± 45.9
Triglyceride (< 155 mg/dl)	195.37 ± 95.4	176.9 ± 120.6	221.9 ± 114.6	197.1 ± 77.3
Fasting blood sugar (< 110 mg/dl)	104.7 ± 35.2	81.6 ± 29.3	94.3 ± 6.3	120.4 ± 39.9
Ceruloplasmin (25 ± 6mg%)	30.0 ± 10.4	28.9 ± 15.4	29.1 ± 5.6	31.0 ± 10.1
Ferritin (100-400 ng/ml)	374.9 ± 347.6	241.1 ± 98.5	590.2 ± 604.8	375.1 ± 226.3

Table 3. The associated diseases of 46 cases of non viral hepatitis B, C and non alcoholic chronic hepatitis categorized by the causes of hepatitis during June 1998-January 2002

Associated diseases	Number (%)			Total
	Cryptogenic (N= 11)	Steatosis (N= 10)	NASH (N= 25)	
- DM	1 (9.1%)	1 (10.0%)	8 (32.0%)	10 (21.7%)
- Obesity (BMI > 25 kg/m^2)	4 (36.3%)	6 (60.0%)	23 (92.0%)	33 (72.0%)
- Dyslipidemia	8 (72.7%)	8 (80.0%)	24 (96.0%)	40 (86.9%)
- Positive ANA	4	4	5	13 (28.3%)

Table 4. Comparison the mean values of variables between the cryptogenic chronic hepatitis and fatty metamorphosis of liver group during June 1998-January 2000

	FBS mean ± SD	ALP mean ± SD	Ferritin mean ± SD	HAI mean ± SD
- Cryptogenic CH (N=11)	81.6 ±	416.9 ±	241.1 ±	0.9 ±
- Fatty metamorphosis of liver (N=35)	112.4 ±	174.3 ±	441.3 ±	1.9 ±
- P value	0.027	0.042	0.022	0.005
- 95% CI	-57.5 to -4.0	9.3 to 475.8	-369.2 to -31.1	-1.7 to -0.4

mg/dl, p = 0.021; 95% CI = -1.07 to 3.24). Comparing the patients who had ALT ≥ 160 U/L and ALT < 160 U/L, it was found that the higher ALT group had a shorter duration from abnormal LFT detected until liver biopsy was done (13.7 and 26.6 months, p = 0.034; 95% CI = 1.1 to 24.7), lower cholesterol level (206.4 and 242.1 mg/dl, p = 0.047; 95% CI = 5.2 to 70.7) and also a higher level of AST (158.8 and 60.9 U/L, p = 0.001; 95% CI = 45.9 to 149.8). The HAI score and the fibrosis score of both groups revealed no statistically significant difference (p = 0.31 and 0.96 respectively).

Discussion

The present study indicates that those patients with no viral hepatitis B, no viral hepatitis C and without a history of excessive alcohol consumption with LFT, were chronically abnormal and often had histological evidence of chronic active hepatitis, most of these patients had some degree of fibrosis (86.1%). Eight patients had a fibrosis score at, suggesting that asymptomatic illness coupled with or without biochemical abnormality does not herald the benign process of liver disease[21,22]. The majority of the presented patients had associated diseases, including DM, obesity, and dyslipidemia similar to those reported in the patients with chronic non-A, non-B hepatitis. The prevalence of cryptogenic chronic hepatitis was only 23.9% while the group of fatty metamorphosis of the liver was 76.1% which was the most common etiological diagnosis.

In the NASH group, only two patients had a BMI of less than 25 kg/m^2 (23.1 and 24.7 kg/m^2). Eight NASH-patients had diabetes mellitus (32.0%) and had the average duration from diagnosis until liver biopsy of 1.6 years. The AST to ALT ratio of NASH-patients in the present report was 0.6 which corresponded with a previous study and considered to be useful in distinguishing steatohepatitis from alcoholic liver disease[23]. The histopathological assessment for inflammation and fibrosis in the present study used the Knodell score which is commonly used in chronic viral hepatitis. Currently, there are no specific systems for assessment of histological necroinflammation and fibrosis for the NASH group. By using the Knodell score,the fibrosis score which was equal or higher than 3 was found in 5 patients (20%NASH). This group of patients with NASH and severe fibrosis pattern should be followed long term because there were reports of cirrhosis occurring in NASH in about 20-30% after 10 years of follow up[24-25]. There were other important causes of chronic hepatitis such as chronic hepatitis C (CHC) which is frequently associated with histological changes similar to steatohepatitis[26]. The second-generation ELISA anti HCV test was used to detect HCV infection the present our study because of high sensitivity, high specificity and low costs. The false negative result of the anti HCV test may be as high as 10%[27-28] but Kodali reported no increase in diagnostic yield in the HCV detection by using the PCR technique despite 46% of his patients having been blood transfused[7].

The limiting factors of the present study are the small number of cases, the lack of specific medication for treatment and lack of long term follow up. However, in the group of the fatty metamorphosis of liver, The authors can advise them to modify their life style including weight reduction, lowering high fatty diet, control related diseases and regular exercise which can improve the LFT and the pathological findings of the liver. The medications such as ursodeoxycholic acid and vitamin E still have limited results[29-32]. Liver biopsy also increased the diagnostic yield in the

present study but the necessity of this procedure is debatable[33,34]. It should be weighted between the benefit from the definite diagnosis and the risk from the liver biopsy with reported a mortality rate of less than 0.02% and a complication rate of less than 0.2%, especially if done with ultrasonographic guidance[35,36].

At present, the prevalence of steatohepatitis is increasing. This may be due to the higher incidence of obesity and the increased awareness of health care. However, the mechanisms which can explain the hypothesis of the transitional change from steatosis to NASH is unclear. Three factors which were studied and supported this hypothesis are the oxidative stress and subsequent lipid peroxidation, the factors associated with abnormal cytokine production such as tumor necrosis factor and the factors associated with disordered fatty acid metabolism and insulin resistance[37-39]. This advanced knowledge should be further studied and aimed to prevent the progression to cirrhosis.

In conclusion, NASH are commonly found in the group of chronic hepatitis patients with negative markers for viral hepatitis B, C and alcohol while the liver biopsy can add the diagnostic yield especially in the group of unexplained chronic hepatitis with obesity, diabetes mellitus and dyslipidemia.

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ความชุกของโรคตับอักเสบเรื้อรังจากไขมันสะสม ในกลุ่มผู้ป่วยโรคตับอักเสบเรื้อรังที่ไม่พบสาเหตุจากแอลกอฮอล์และไวรัสตับอักเสบชนิดบี, ไวรัสตับอักเสบชนิดซี

นุสนธิ์ กลัดเจริญ, สมบัติ ตรีประเสริฐสุข, วโรชา มหาชัย, พลรัตน์ วิไลรัตน์, พินิจ กุลละวณิชย์

เพื่อศึกษาถึงความชุกของโรคตับอักเสบเรื้อรังจากไขมันสะสมในกลุ่มผู้ป่วยโรคตับอักเสบเรื้อรังที่ไม่พบสาเหตุจากแอลกอฮอล์ และไวรัสตับอักเสบชนิดบี,ไวรัสตับอักเสบชนิดซี รวมทั้งข้อมูลทางด้านลักษณะทางคลินิกที่สัมพันธ์กันผลตรวจของเนื้อเยื่อตับทางพยาธิวิทยาของ ผู้ป่วยไทยที่มีตับอักเสบเรื้อรังจากโรคตับอักเสบจากไขมันในโรงพยาบาลจุฬาลงกรณ์มหาวิทยาลัยและมหาวิทยาลัยมหิดล จากผู้ป่วยจำนวน 46 คนที่เข้าร่วมในการศึกษาผู้ป่วยเป็นชายและหญิงอายุระหว่าง 18-65 ปี โดยได้รับการซักประวัติ พบว่าไม่มีประวัติการดื่มแอลกอฮอล์เป็นประจำ ตรวจร่างกายไม่มีลักษณะของโรคตับแข็งและมีผลตรวจทางห้องปฏิบัติการที่ยืนยันว่าไม่มีเชื้อไวรัสตับอักเสบชนิดบี, ไวรัสตับอักเสบซี และตรวจอัลตราซาวนด์และทำการเจาะตับ นำผลที่ได้บันทึกเก็บข้อมูล และวิเคราะห์ทางสถิติชนิดไปข้างหน้า ผลการศึกษาพบว่า ความชุกของการตรวจพบผู้ป่วยไทยที่มีตับอักเสบเรื้อรังจากไขมันสะสมสูงถึงร้อยละ 76.1 โดยแบ่งเป็นกลุ่มที่มีภาวะอักเสบน้อย ร้อยละ 21.8 และกลุ่มที่มีภาวะอักเสบมาก ร้อยละ 54.3 ส่วนอีกร้อยละ 23.9 จัดเป็นกลุ่มที่มีตับอักเสบเรื้อรังที่ไม่ทราบสาเหตุ เมื่อวิเคราะห์เปรียบเทียบกลุ่มผู้ป่วยไทยที่มีตับอักเสบเรื้อรังจากไขมันสะสมกับกลุ่มที่มีตับอักเสบเรื้อรังที่ไม่ทราบสาเหตุ พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในค่า ตรวจวัดระดับน้ำตาล, ค่าการทำงานตับได้แก่ค่า serum alkaline phosphatase, ค่าระดับสารเหล็กในเลือด และค่าคะแนนการอักเสบของตับที่ได้จากการตรวจทางพยาธิวิทยา ($p < 0.05$) นอกจากนี้ยังวิเคราะห์เปรียบเทียบในกลุ่มผู้ป่วยไทยที่มีตับอักเสบเรื้อรังจากไขมันสะสมชนิดที่มีภาวะอักเสบน้อยกับกลุ่มที่อักเสบมากพบว่าค่าดัชนีมวลกายเป็นปัจจัยเดียวที่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p = 0.02$) กลุ่มผู้ป่วยที่มีตับอักเสบเรื้อรังจากไขมันสะสมชนิดที่มีภาวะอักเสบมากนั้นพบว่ามีเพียง 2 รายที่มีค่าดัชนีมวลกายน้อยกว่า 25 กก/ม^2 (23.1 และ 24.7 กก/ม^2) และหนึ่งในสามหรือร้อยละ32.0 ของกลุ่มผู้ป่วยที่มีตับอักเสบเรื้อรังจากไขมันสะสมชนิดที่มีภาวะอักเสบมากสัมพันธ์กับโรคเบาหวาน และค่าอัตราส่วนระหว่าง AST กับ ALT นั้นมีค่าเท่ากับ 0.6. ส่วนผลการเจาะตับทำให้ตรวจพบพังผืด หรือ วัดเป็นคะแนนของพังผืดที่ตรวจพบสูงกว่าหรือเท่ากับ 3 ถึงร้อยละ 20