Serum Ferritin in Cirrhosis: The Preliminary Report

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Abstract:

Introduction: Primary hemochromatosis is opposed to the hepatitis B virus as the cause of chronic liver diseases in Thailand. When the cirrhotic patients are shown to have HBsAg, the iron study will be automatically neglected.

Patients and Methods: This cross-sectional study was performed to explore the serum ferritin, hepatitis B and C viruses in the cirrhotic patients who were proved to be free from severe thalassemian or chronic kidney disease.

Results: Thirty cirrhotic patients, 15 males, mean age 57.2±9.8 years, were enrolled. The serum ferritin was found to range from 15.1 to 9,455, mean 1,685.5±2,335.7 ng/ml, the transferrin saturation ranged from 23.6 to 54.8, mean 38.6±8.4% while HBsAg and HCV were found in 6 (20.0%) and 2 patients (6.7%), respectively. The hyperferritinemia (serum ferritin >1,000 ng/ml) was found in 14 patients (46.7%). Four from 6 patients with HBsAg had the hyperferritinemia but the prevalence was not different from the patients without HBsAg (p=0.272).

Conclusion: The hyperferritinemia is found in nearly half cases of cirrhotic patients regardless of hepatitis B virus and its prevalence is 2-fold and 7-fold of hepatitis B and C viruses respectively.

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บทคัดย่อ: ระดับ Serum Ferritin ในผู้ป่วยตับแข็ง: รายงานเบื้องต้น

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**หน่วยโรคทางเดินอาหาร กลุ่มงานอายุรกรรม, โรงพยาบาลมหาราชนครราชสีมา จ.นครราชสีมา 30000
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ภูมิหลัง: ภาวะเหล็กเกินชนิดปฐมภูมิ พบได้น้อยในคนไทย ในขณะที่ไวรัสตับอักเสบชนิดบีพบได้ชุกชุม เมื่อพบผู้ป่วยตับแข็งว่ามีไวรัสตับอักเสบชนิดบีแล้ว การตรวจเหล็กจึงมักจะถูกละเลย **ผู้ป่วยและวิธีการ:** เป็นการศึกษาภาคตัดขวาง เพื่อหาระดับ serum ferritin, ไวรัสตับอักเสบชนิดบีและซีในผู้ป่วยตับแข็ง ที่ไม่มีธาลัสซีเมียชนิดรุนแรงและไตวายเรื้อรัง **ผลการศึกษา:** จากผู้ป่วยตับแข็ง 30 ราย เพศชาย 15 ราย อายุเฉลี่ย 57.2±9.8 ปี พบระดับ ferritin ระหว่าง 15.1 ถึง 9,455, เฉลี่ย 1,685.5±2,335.7 ng/ml, transferrin saturation ระหว่างร้อยละ 23.6 ถึง 54.8 เฉลี่ยร้อยละ 38.6±8.4 ขณะที่ไวรัสตับอักเสบชนิดบีและซีพบ 6 (ร้อยละ 20.0) และ 2 ราย (ร้อยละ 6.7) ตามลำดับ มีผู้ที่มีเหล็กเกิน (ระดับ ferritin >1,000 ng/ml) 14 ราย (ร้อยละ 46.7) เป็นผู้ที่มีเชื้อไวรัสตับอักเสบชนิดบี 4 ราย ความชุกของภาวะเหล็กเกินในผู้ป่วยที่มีเชื้อไวรัสตับอักเสบชนิดบีไม่แตกต่างจากกลุ่มที่ไม่มี (p=0.272) **สรุป:** ภาวะเหล็กในเลือดเกินพบได้เกือบครึ่งของผู้ป่วยตับแข็ง ไม่ว่าจะมีไวรัสตับอักเสบชนิดบีหรือไม่ก็ตามและภาวะเหล็กเกินนี้พบมากกว่าเชื้อไวรัสตับอักเสบชนิดบีและซี ถึง 2 และ 7 เท่า ตามลำดับ

Introduction

Hemosiderosis or hemochromatosis is the state of excess body iron storage, which is represented by the serum ferritin more than 1,000 nanogram/ml, the level of the risk for damaging many organs such as liver leading to cirrhosis[1]. It is classified as primary if the cause cannot be identified and secondary from chronic hemolytic diseases or regular blood transfusion. In Thailand, the primary hemochromatosis is rather rare[2], opposed to the secondary hemochromatosis which is very common because of the strikingly prevalent severe thalassemia especially beta thalassemia/hemoglobin E disease[3].

Cirrhosis is highly prevalent in Thailand, its occurrence is 75.3 per 100,000 population[4]. It is found to be 5.1% of death and it is 6th common causes of death for males[5]**.** The most common cause of cirrhosis is related to alcohol, i.e. 53.6 from 75.3 per 100,000 population whereas other causes are hepatitis virus B, C and G[6], Wilson's disease or copper toxicity and alpha-1 antitrypsin deficiency. The hemochromatosis in cirrhosis among Thai people has never been mentioned although it can be solely responsible for cirrhosis itself or it can be co-incidentally found in cases of cirrhosis due to viral hepatitis, e.g. high serum

ferritin (>350 ng/ml in females and >450 ng/ml in males) was found in 20.7% of virus C[7].

In Thailand, the various metals in the serum of the patients with viral cirrhosis, was investigated except the iron[8] while the study of anemia among cirrhosis in Thailand in 1998 showed that the serum ferritin of more than 1,000 ng/ml was found to be 12.8%[9]. This study was aimed to study the serum ferritin and other iron parameters among the patients with cirrhosis.

Patients and Methods

This was the cross-sectional study. The patients who were newly diagnosed as cirrhosis, both compensated and uncompensated, depending on the combination of clinical manifestations, such as jaundice, edema of legs, ascites, hepatosplenomegaly and the laboratory results i.e., reverse albumin globulin ratio, with or without hypocholesterolemia were consecutively recruited. And they all were confirmed by the ultrasonography or the computerized tomography which was performed and interpreted by the well trained radiologists. They all were admitted at the medical ward of Maharat Nakhon Ratchasima Hospital. Their ages would be more than 20 years of age. They were investigated for CBC, BUN, creatinine, liver function test, HBsAg, anti-HCV, anti-HIV antibody and hemoglobin typing, using the standard methods.

The iron study consisted of the serum ferritin which was quantified with Microplate Chemiluminescence Immunoassay (CLIA) method, its normal range was between 15-230 ng/ml for male and 10-126 ng/ml for females and the serum iron and the total iron binding capacity (TIBC). The patients who had serum ferritin of more than 1,000 ng/ml, would be considered having excessive iron storage.

The exclusion criteria were thalassemia major including beta thalassemia/hemoglobin E disease, beta thalassemia major and hemoglobin H and related diseases, HIV infection, chronic kidney disease, regular blood transfusion or malignant diseases[10].

Depending on the prevalence of hyperferritinemia (ferritin >1,000 ng/ml) in the cases of cirrhosis of 12.8 % in Thais[9], the sample size was calculated according to the formula

$N = Z^2pq/d^2$, if $d = 0.1$, $N = 43.0 \simeq 45$

Here was the preliminary report of the first 30 participants.

The study was approved by the ethic committee of Maharat Nakhon Ratchasima Hospital.

Results

Thirty consecutive patients who were newly diagnosed as cirrhosis, 15 males and 15 females, admitted at the medical ward were recruited. Ages ranged from 45 to 66, mean 57.2±9.8 years. Their diagnoses of cirrhosis were all confirmed using the ultrasonography. Among them, the HBsAg and HCV were found in 6 (20.0%) and 2 patients (6.7%) respectively. Alcohol was not studied because of the unreliability of the data. Hb typing was found to be Hb A_2A in 28 cases (93.3%), Hb AE in 1 case (3.3%) and Hb EE in 1 case (3.3%). The general characteristics of the patients would be shown as in the table 1.

The mean of serum ferritin level was 1,685.5± 2,335.7 ng/mL while the transferrin saturation ranged from 23.6 to 54.8%, mean 38.6±8.4 %. If the per-

Table 1 The general characteristics of the patients with cirrhosis

	Min	Max	Mean±SD
Hb (g%)	5.0	12.4	9.2±2.9
Hct (%)	8.1	39.4	27.6±7.3
MCV (fL)	66.0	133.0	90.5±12.3
MCH (pg)	21.0	39.0	30.9±4.7
Albumin (g%)	1.7	3.8	2.8±0.5
Globulin (g%)	1.7	5.7	3.8±1.2
Cholesterol (mg%)	40	318	113.4±56.4
AST (unit/L)	22	348	117.4±86.5
ALT (unit/L)	5	683	75.6±130.8
AP (unit/L)	25	752	215.1±159.4
Transferrin sat (%)	23.6	54.8	38.6±8.4
Ferritin (ng/ml)	15.1	9,455	1,685.5±2,335.7

centage of transferrin saturation which could cause the liver damage, was 60% for male and 50% for female, only 1 female patient had the transferrin saturation above such level (52.6%) while the maximal value of 54.8% was found in 1 male.

When the serum ferritin was classified to be low or iron depletion (<20), normal (20-500), high normal (501-1,000) and hyperferritinemia (>1,000) ng/mL, our patients could be categorized as shown in table 2.

Table 2 The number of the cirrhotic patients in each interval of the serum ferritin

Serum ferritin	No (%)
<20	1 (3.3)
20-500	10 (33.3)
501-1,000	5 (16.7)
>1,000	14 (46.7)

There were 14 patients with the hyperferritinemia (46.7%), 5 with the high serum ferritin (16.7%) and 1 patient with iron depletion (3.3%).

From the 6 patients who had HBsAg, 4 of them had the serum ferritin more than 1,000 ng/mL (66.7%) however when the percentage of hyperferritinemia in the patients with HBsAg was compared with that of the patients without HBsAg, there was no difference (p=0.272). Both of the 2 patients who had anti-HCV antibody, had serum ferritin less than 1,000 ng/mL.

Discussion

In Thailand the hemochromatosis genes itself is very rare with variable or low penetrance until the authorities do not recommend for population screening[2] but in cases of cirrhosis, the prevalence of hyperferritinemia is 2-fold and 7-fold of hepatitis B and C viruses respectively. Therefore, the screening of the serum ferritin should be particularly considered because of its high prevalence in this group.

Although the hepatitis virus B is very common in Thailand, i.e. 8-10% of males and 6-8% of females, among cases of cirrhosis, the hepatitis B virus is found only in 30% of the patients[11]. As compared with our study, it seems that the cirrhotic patients in Thailand more commonly suffer from hyperferrititnemia than from hepatitis B virus.

The excessive iron can enhance the liver cell damage from alcohol[12] or from hepatitis B[13] or C virus infection[14]. But the necessity to treat it is still inconclusive, one authority suggests the transferrin saturation should also be studied because it is the most sensitive method for predicting whether the elevated serum ferritin represents iron overload due to

hemochromatosis. The cut point of transferrin saturation of >60% in males and >50% in females in combination with high serum ferritin is shown to be correlated with hemosiderosis, just only high serum ferritin can be found in various conditions such as non-alcoholic hepatitic steatosis (NASH), viral hepatitis (B/G), alcohol excess, chronic inflammations and familial hyperferritinemia[15]. Furthermore, the high serum ferritin can spontaneously decrease within 12 months after treating the cirrhosis due to virus B with lamivudine[16], or within 6 weeks after abstinence of alcohol in the case of alcoholic cirrhosis[17].

On contrary, the patients who have serum ferritin more than 1,000 ng/ml are at risk of hemosiderosis[1]. Furthermore, the men who persistently have chronic hepatitis B virus infection as well as the serum ferritin more than 300 ng/ml, have a 50% chance of developing primary hepatocellular carcinoma within 2-17 years[18].

This controversy should be verified in further studies. One cases had rather low ferritin (5.1 ng/ml) (normal 21.81-274.66 ng/ml for male, 4.63-204.0 ng/ml for female) and the oral iron therapy has been administered.

Conclusion

The hyperferritinemia is found in nearly half cases of cirrhosis, regardless the presence or absence of hepatitis B virus. When the clinical diagnosis of cirrhosis is established, whether the hepatitis viral cause can be identified, the iron study including the serum ferritin is still in necessity for more proper diagnosis.

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