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Original Article

Hepatobiliary Abnormalities in Pediatric and Adolescent Hemoglobin Ebeta-thalassemia Detected by Ultrasonography

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Abstract

Background/Aims;

1. To detect hepatobiliary abnormalities in hemoglobin Ebeta-thalassemia pediatric and adolescent patients by ultrasonography
2. To identify correlation between ultrasonographic findings, serum ferritin and liver function test

Material and method: Abdominal ultrasonography serum ferritin and liver function test were performed in 64 DNA analysis proven hemoglobin Ebeta-thalassemia pediatric and adolescent patients, age ranging between 5-18 years (mean 14.1 years). Ultrasonographic parameters include: gallbladder length, width, cross section, gallstone, height of left lobe of the liver, diameter of the aorta, liver parenchymal echoes, cranio-caudal length of spleen, and splenic echoes. Liver function test includes; cholesterol, total protein, albumin, globulin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP).

Result: Statistical analysis, using factor analysis and discriminant analysis, showed negative correlation between serum ferritin and age of the patients. Gallbladder sludge and stone correlated with splenic length and cross section of the gallbladder. Splenic parenchyma abnormality correlated with height of left lobe of the liver/aorta diameter, total protein albumin and AP and length of spleen/aorta.

Conclusion: Gallbladder hypomotility may contribute to stone formation. Total protein albumin and AP showed correlation with hepatobiliary abnormalities detected by ultrasonography. Negative correlation of serum ferritin and patient's age may be due to increased iron absorption from gastrointestinal tract in younger age.

Keywords: hemoglobin Ebeta-thalassemia, hepatobiliary abnormalities, liver function test, ultrasonography, gallstone

Introduction

Thalassemia is a class of genetic disease of abnormal globin chain synthesis and remain a significant health problem in several regions of the world. The incidence is highest in Southeast Asia, the Middle east and Africa. Clinical manifestations result from the decrease or absent production of normal globin chain of hemoglobin.[1] Thalassemia is classified according to deficient globin chain. Main subtypes are alpha and beta thalassemia. Hemoglobin Ebeta-thalassemia is an important cause of childhood chronic disease in Southeast Asia. The patients are generally classified as having thalassemia intermedia because they have inherited a beta-thalassemia allele and hemoglobin E, which acts as a mild beta^{+}-thalassemia. However, a remarkable variability in the clinical expression, ranging from a mild form of thalassemia intermedia to transfusion-dependent conditions, is observed.[2] Iron overload occurs without exception in hemoglobin Ebeta-tha-lassemia.[3-5] Excessive iron accumulates because of blood transfusion and enhanced gastrointestinal absorption. Liver fibrosis from iron overload is common whereas ascites and other signs of cirrhosis are rare.[6-7]

Gallstone is also known to have high incidence in hemolytic disease.[8] Liver biopsy is an invasive and high risk procedure for children. Ultrasonography has made the study of liver and biliary tract easier and is wildly available in all hospitals. Ultrasonography may be used to identify hepatobiliary abnormalities that might reduce liver biopsy and reduce cost of unnecessary liver function test in routine follow up of the patients.

Method

Patients

This study is a part of prospective study of illness in hemoglobin Ebeta-thalassemia patients. Sixty-four hemoglobin Ebeta-thalassemic pediatric and adolescent patients diagnosed by DNA analysis, age ranging between 5-18 years (mean 14.1 years), were enrolled in the study. They had received regular leukocyte-poor packed red cell transfusion 10 ml/Kg every time at 3-4 weeks interval. Their pre-transfusion hemoglobin was < 9 g/dL. This allows thalassemia patients to have normal growth and suppress over-erythropoiesis.[9] Desferrioxamine (Desferal^{R}) was given by their parents at home (20-40 mg/Kg/d using subcutaneous infusion in 8-10 hr, 2-7 times/wk, depending on the level of serum ferritin). Informed sign consent was obtained from the parents of each subject before ultrasonography. The study was approved by the Ethics Committee of Khon Kaen University (HE451032). The study was performed during March 2003 to June 2004.

Ultrasonography

Abdominal ultrasonography was performed after at least 4 hours fasting. We used a full size high resolution machine, Acuson model Aspen, with a 4 MHz convex array probe. The maximum height of left lobe of the liver above the abdominal aorta was determined. The diameter of aorta below left lobe of the liver was recorded in order to use as an internal reference for other parameters. The maximum gall bladder length width and cross section were measured after locating the largest images in all planes of view. Cranio-caudal length of spleen,

parenchymal echoes of liver and spleen were also recorded. During the investigation, the radiologist was unaware of the serum ferritin or liver function test results of the subjects. The sonographic criteria to use in diagnosis of hepatobiliary status are listed in table 1.

Biochemical study

Serum ferriitin and liver function test were performed in each subject the same day as ultrasonography. The liver function test includes cholesterol, total protein, albumin, globulin, total bilirubin, direct bilirubin, ALT, AST, AP. The mean values are listed in table 2.

Statistical Analysis

Factor analysis and discriminant analysis were performed. The number of factors was determined on the basis of eigen values (ie, >1.0)

Result

Patient characteristics

There were 3 cases of gallbladder sludge (4.69%), 5 cases of gallstones (7.82%) and 24 previous splenectomy patients (37.50%).

Factor analysis showed negative correlation between serum ferritin and age of the patients. Discriminant analysis showed standardized Canonical-function Coefficients as:

Gallbladder abnormality = .712 cross section of gall bladder ± .675 splenic length

Splenic parenchyma abnormality = -.449 left lobe of the liver/aorta - 1.023 total protein + 1.157 albumin -0.94 AP +1.129 splenic length/ aorta ($p<0.01$)

Table 2 Mean values of hemoglobin, serum ferritin and liver function test

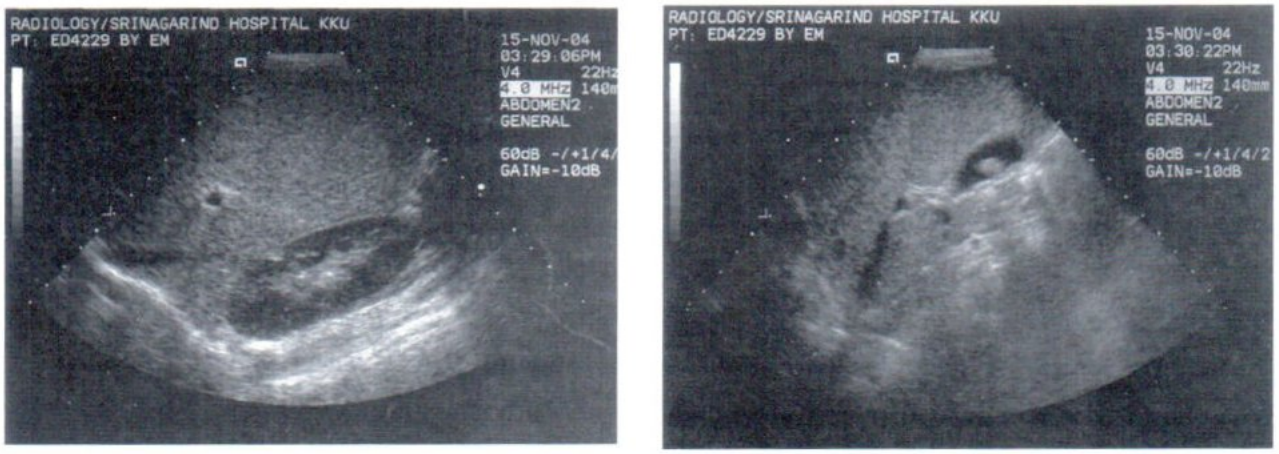
	Mean value	normal value
Hemoglobin	7.31	12 g/dL
Ferritin	2063.64	12-122 ng/ml
Cholesterol	98.11	127-262 mg/dL
Total protein	7.62	6.5-8.8 g/dL
Albumin	4.14	3.8-5.4 g/dL
Globulin	3.56	2.6-3.4 g/dL
Total bilirubin	1.67	0.25-1.50 mg/dL
Direct bilirubin	0.34	0-0.5 mg/dL
ALT	47.96	4-36 U/L
AST	53	12-32 U/L
AP	142.93	42-121 U/L
Volume of transfusion	90.69 ml/Kg/yr	

Table 1 Diagnostic criteria for ultrasonography

Gall bladder abnormality	normal (0) minimal sludge* (1) obvious sludge (2) gall stone (3)
Liver parenchyma	normal (0) slightly increased as compared to kidney (1) markedly increased as compared to kidney (2)
Splenic parenchyma abnormality	normal (0) slightly increased as compared to kidney (1) markedly increased as compared to kidney (2) previous splenectomy (3)

Scores were given for statistical analysis

* Sludge is defined as low intensity gravity dependent echoes within the gallbladder with a fluid-fluid level



A B

Fig.1 Ultrasonography (US) of a typical case of thalassemia. A) US shows diffusely and homogeneously increased liver parenchyma. B) US shows a gallstone.

Where: Cumulative percentage = 69.3
Canonical Correlation = .498
Wilks lambda = .719

Discussion

In children and young adult with thalassemia major, liver disease remains a common cause of morbidity and mortality. The major factor in the generation of liver damage is iron overload. The iron loading in thalassemia depends on both volume of blood transfused and the amount accumulated from gastrointestinal absorption.[10] In beta-thalassemia intermedia, some patients do not require frequent transfusion but progressive iron overload occurs due to increased intestinal absorption.[11] Our patients who had serum ferritin more than 1,000 ng/ml had received iron chelator still had high serum ferritin level.

In this study we present complication of hemoglobin Ebeta-thalassemia in Northeast Thailand. We identified the correlation between ultrasonographic findings, serum ferritin, and liver function test. It is well recognized that level of serum ferritin is poorly correlated with hepatic iron content.[12] Ferritin is an iron storage protein complex found principally in the intestinal mucosa, spleen and liver that functions as the primary form of the iron storage in the body. In assessment of iron overload it can be misleading. There are many inflammatory conditions that can elevate the serum ferritin including viral hepatitis, fatty liver and arthritis.[13] This study showed that serum ferritin did not correlate with liver or splenic parenchyma abnormality detected by ultrasonography. Serum ferritin showed negative correlation with patient's age. This could be explained that in younger age the iron absorption is faster than adult. Animal model showed increased iron absorption in younger animal com-pared to the older group.[14]

Gallbladder abnormality, sludge and stones

correlated with cross section of the gallbladder and splenic length. There are 3 factors that may involve in gallstone formation: cholesterol supersaturation, accelerated nucleation, and gallbladder hypomotility.[15-16] Our patients did not have significant high cholesterol or bilirubin level. Statistical analysis did not show correlation between gallbladder abnormality and serum cholesterol or bilirubin either. Hypomotility or stasis of the gall bladder may play an important role in Ebeta-thalassemia patients. As indicated by correlation with cross section of the gallbladder, bile flow in static gallbladder stagnates and renders biliary sludge formation. Bililary sludge can be an antecedent to gallstones. The abnormal erythrocytes of thalassemia in the circulation are taken up by liver and spleen with ensuing enormous hepatosplenomegaly. Hepatosplenomegaly may cause stasis of the blood circulation (congestion) of the gallbladder resulting in hypomotility. Our study also showed correlation of splenic length with gallbladder abnormality. Splenic parenchyma abnormality correlates with liver size, total protein, albumin and AP. As mentioned previously, both liver and spleen take up abnormal erythrocystes, thus splenic parenchyma abnormality relates with liver size. protein albumin and AP are the component of liver function test that could be used as indicators for severity of the disease. With progressive parenchymal liver disease, albumin synthetic capacity decreases. Although, serum albumin concentration reflects a variety of extrahepatic factors, including nutritional and volume status, vascular integrity, catabolism, hormonal factors and loss in the urine and stool.[17] The patients in this study did not have other diseases. The correlation of total protein and albumin with splenic parenchyma abnormality should be due to corresponding chronic liver impairment.

AP comprises a group of enzymes present in a variety of tissues, including liver, bone, intestine, kidney, placenta, leukocytes and various neoplasms. AP production tends to increase in tissue undergoing metabolic stimulation. Bone and liver are the major sources of serum AP. Thalassemia affects both bone and liver of the patients. Increased AP in thalassemia patients should reflect both bone and liver impairment.

Conclusion

Serum ferritin did not correlate with liver or splenic parenchyma abnormality. It showed negative correlation with age of the patient, which could be due to increased iron absorption in younger age.

Gallbladder hypomotility might contribute to the formation of sludge and gallstone in Ebeta-thalassemia patients. Gall bladder sludge, gall stone, size of liver, size of spleen total protein albumin and AP can be used as indicators for severity of the disease. Blood chemistry components other than total protein albumin and AP of the liver function test may be skipped from the routine follow up of the patients.

References

1. Weatherall DJ. Pathophysiology of thalassemia. Bailliers Clin Haematol 1998;11:127-46.
2. Fucharoen S, Winichagoon P. Thalassemia in Southeast Asia: Problem and strategy for prevention and control. Southeast Asian J Trop Med Public Health 1992;23: 647-55.
3. Brittenham G, Pootrakul P, Finch CA, et al. Iron overload in HbE β-thalassemia: magnetic measurement of hepatic iron store (abstract). Blood 1986;68:72.
4. Pootrakul P, Huebers HA, Finch CA, Pippard MJ, Cazzola M: Iron metabolism in thalassemia. Birth Defects 1988;23: 3-8.

5. Pootrakul P, Kitcharoen K, Yamsukon P, et al. The effect of erythroid hyperplasia on iron balance. Blood 1988; 71:1124-9.
6. Thakerngpol K, Sonakul D, Fucharoen S, Vathanapas V, Stinimankan T: Histochemical study of liver tissue from thalassemic patients. Birth defects 1988;23:199-206.
7. Thakerngpol K, Sonokul D, Fucharoen S, et al. Electron microscopic study of liver tissue from 30 thalassemic patients. Birth defects 1988;23:199-206.
8. Dewey KW, Grossman H, Canale VC. Cholelithiasis in thalassemia major. Radiology 1970;96:385.
9. Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion 1997;37(2):135-40.
10. Weatherall DJ, Clegg JB. The thalassemia syndrome. 4th edition, London: Blackwell Science Ltd. 2001. P.311.
11. Cossu P, Toccafondi C, Vardue F, et al. Iron overload and desterrioxamine chelation beta-thalassemia intermedia. Eur J Pediatr 1981;137:267-71.
12. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complication of beta-thalassemia major in North America. Blood 2004;104:34-9.
13. Wong K, Adams PC. The diversity of liver diseases associated with and elevated serum ferritin. Can J Gastro 2007;20:467-70.
14. Gardenghi S, Marongiu M, Ramos P, et al. Ineffective erythropoiesis in β-thalassemia is characterized by increased iron absorption mediated by down-regulation of hepcidin and up-regulation by ferroportin. Blood 2007; 109(11):5027-35.
15. Sedaghat A, Grundy SM: Cholesterol crystals and the formation of cholesterol gallstones. N Engl J Med 1980; 302:1274.
16. Holan KR, Holzbach RT, Hermann RE, et al. Nucleation time: A key factor in the pathogenesis of cholesterol gallstone disease. Gastroenterology 1979;77:611.
17. Timothy J, Davern and Bruce F Schrschmidt. Biochemical liver tests. In: Feldman M, Freidman L, Sleisenger MH, editors. Gastrointestinal and Liver Disease, Vol.2. Philadelphia: Saunders, 2002. p. 1230-1.