International Journal of Research in Medical Sciences
Gupta R et al. Int J Res Med Sci. 2016 Aug;4(8):3632-3635
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162344

Case Report

Dark liver on MRI: throwing light on clinically unsuspected hemochromatosis in double heterozygote HbE-beta thalassemia

Rohini Gupta*, Sagar Tomer, Amit Kumar, Pooja Jain, Ritu Nair Misra

Department of Radiodiagnosis, VMMC and Safdarjung Hospital, New Delhi, India

Received: 16 June 2016
Revised: 18 June 2016
Accepted: 06 July 2016

***Correspondence:**
Dr. Rohini Gupta,
E-mail: rohini1912@gmail.com

ABSTRACT

Secondary hemochromatosis is a well-known complication in thalassemic patients under regular blood transfusions and can be diagnosed based on clinical suspicion and biochemical tests in this setting. However, double heterozygote HbE-β thalassemic is an uncommon form of thalassemia where the clinical course is highly variable and iron deposition in liver, endocrine glands and myocardium similar to primary hemochromatosis can occur in non-transfused patients. We report the MRI diagnosis of erythropoietic hemochromatosis involving liver and adrenal gland in one such rare case presenting in adulthood with severe anemia.

Keywords: HbE beta thalassemia, Hemochromatosis, Iron overload, MRI

INTRODUCTION

Secondary hemochromatosis is a well-known condition in thalassemic patients undergoing regular blood transfusions. It has serious complications like hepatic failure, cirrhosis and hepatocellular carcinoma. Clinical diagnosis is mostly possible in this setting. But imaging features may help to raise a suspicion in atypical clinical scenarios.[1-3]

CASE REPORT

A 25 year old female patient, resident of Bihar, India presented with a history of epistaxis for 2 years, generalized weakness for 5months, jaundice for 3 months, and joint pains in shoulders, wrist, metacarpals and cervical spine for 15 days. She also had amenorrhea for 8 months. She had undergone an uneventful pregnancy with normal vaginal home delivery 3 years back. On examination, there was severe pallor. Icterus was present. Skin pigmentation was also noted which had developed over the past few months. There was a pan systolic murmur over mitral and pulmonary area and hyper dynamic apex. Abdomen was non-tender and the spleen and liver were enlarged and palpable. Her Hb was 3.8 g/dl and she was referred for an USG examination for 'anemia under evaluation'.

Ultrasound abdomen revealed an enlarged liver with coarsened echotexture, although the liver outline was maintained. Cardiomegaly was present. Spleen was moderately enlarged with normal echotexture. In addition, the right adrenal gland was enlarged and hypoechoic with preserved adrenal shape (Figure 1).

Laboratory examination findings are summarized in Table I.

Skeletal survey for bone and joint pains showed features of erythroid hyperplasia like generalized trabecular coarsening, metaphyseal widening and diploic thickening.

CT abdomen was done which showed an enlarged liver which was homogenously hyperdense as compared to the spleen; mean HU being 82. Right adrenal and spleen were enlarged with normal attenuation.

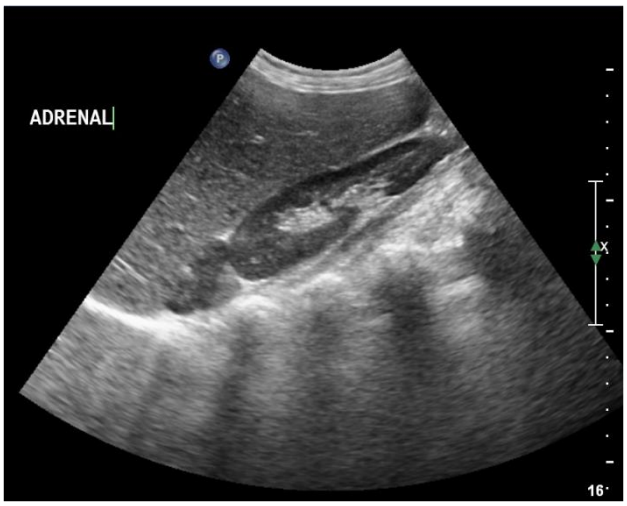

Figure 1: Ultrasound image showing enlarged hypoechoic adrenal gland. Pyramidal adrenal shape is preserved.

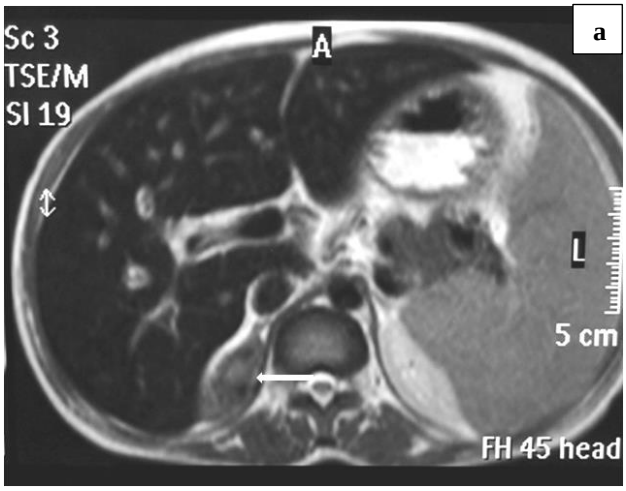

Figure 2a: Axial t2-weighted mri image shows hepatomegaly with marked diffuse reduction in hepatic signal intensity. The right adrenal (arrow) shows normal triangular shape but the size is enlarged with reduced signal intensity. Splenomegaly is seen with preserved parenchymal signal intensity.

In the presence of a blood picture of iron overload, a diagnosis of hemochromatosis with multiple organ involvement was suspected. However, there was no history of any prior blood transfusions or iron supplementation. MRI abdomen was done to confirm the diagnosis. Marked diffuse reduction in hepatic signal intensity was seen on T1W, T2W and T2 fat saturated images. Liver was enlarged with a normal shape and outline. Moderately splenomegaly was seen with normal signal intensity of splenic parenchyma. The right adrenal gland was enlarged with normal shape but dark signal intensity (Figure 2a). The signal intensity of pancreas and myocardium was normal (Figure 2b). A diagnosis of hemochromatosis with hepatic and right adrenal involvement with extra medullary hematopoietic nodules in spleen was made on MRI.

Hb electrophoresis using high performance liquid chromatography (HPLC) revealed:

- HPLC FOR Hb:
- Hb A: 58.60% ↓↓
- Hb F: 10.40% ↑
- Hb A2: 31% ↑
- Hb D: Absent
- Hb S: Absent
- Hb C: Absent
- Hb E: Present

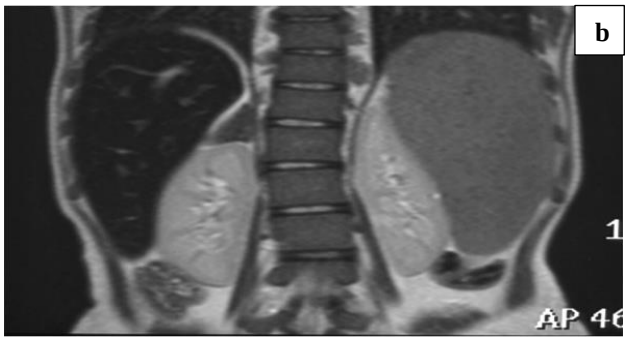

Figure 2b: Coronal T2-weighted MRI image shows dark hepatic right adrenal signal intensity.

Bone marrow biopsy revealed hypercellular bone marrow with increase in erythroid precursors and adequate iron stores. Hormonal profile for thyroid (T3, T4, TSH), adrenal (cortisol), pituitary (prolactin, ACTH, LH, FSH), ovaries (estrogen, progesterone) and pancreas (blood sugar fasting and post prandial) were normal.

HPLC for Hb of the parents was also done:

Father:	Mother:
Hb A : 66.40% ↓↓	HbA: 85.0%
↓	
HbA2+E : 23% ↑	HbA2: 4.6%
↑	
HbF: <1%	Hb F : <1%
↓	↓
HbE trait heterozygous (ββE)	β-thalassemiaminor (ββ0)

The inheritance can be explained as below.

Father (β βE)			Mother (β β0)
↓	↓	↓	↓
β β	βE β0	β β0	βE β

Final diagnosis of double heterozygote HbE- β0 thalassemia with severe anaemia and erythropoietic hemochromatosis with liver and right adrenal involvement was made.

Table 1: Relevant laboratory findings.

CBC	
Hb	3.8g/dl
Platelet	1,29,000
WBC	4700
DLC	P37 L41 M16 E2 B0
INR	1.29
PT	14s
aPTTK	40s
P.S.	Dimorphic anemia Rouleaux +, nucleated RBCs+Poikilocytosis+, tear drop cells+
LFT	
S.Bilirubin	S.bil.2.0 ALT 135 AST 140 ALP 113
S.electrolytes	Na^+ 136 K^+ 4.5
Reticulocyte count	0.8%
Reticulocyte Hb	16pg
Immature reticulocyte count	9%
Viral markers	HBsAg, HCV, HIV :-ve
Iron studies	
S.Iron	212µg/dl (highly raised)
S.ferritin	1254 ng/ml (highly raised)
TIBC	188µg/dl (low)
Vit.B12	745pg/ml (normal)
Folic acid	8.96 ng/ml (normal)

During the course of admission, Hb of the patient dropped to 2g/dl and she underwent 2 pint packed RBC transfusion. The S. ferritin level increased to 1500ng/ml after the transfusion and she was started on oral deferoxamine therapy. Splenectomy was done later and patient was maintained on deferoxamine therapy.

DISCUSSION

Hemochromatosis occurs due to accumulation of iron in the body from any cause. Primary hemochromatosis results from an autosomal recessive genetic disorder due to abnormal HFE gene that alters a protein involved in the regulation of iron absorption from the gastrointestinal tract.[1,2] The excess iron binds to proteins in parenchymal organs like liver, pancreas, myocardium. Secondary hemochromatosis or hemosiderosis results from non-genetic causes like myelodysplastic syndromes, anaemia related to ineffective erythropiesis like thalassemia, and exogenous increase by ingestion, parenteral infusion or multiple blood transfusions. The erythrocytes are ingested into the reticuloendothelial (RE) macrophages (Kupffer cells) and excess iron is bound to ferritin and hemosiderin in RE cells of spleen, lymph nodes, bone marrow, and to a lesser degree in the liver.[2]

Iron overload due to mechanism and increased gastrointestinal absorption similar to hereditary primary hemochromatosis also occurs in non-transfused thalassemic patients because of increased erythopoiesis and high iron demand.[2,3]

Serum ferritin and transferrin are screening tests for body iron stores, but may give false positive results in alcoholism and infection. Liver biopsy is confirmatory but invasive and preferred only in cases with strong suspicion based on clinical or biochemical evidence.[2]

Imaging offers non-invasive diagnostic solution in hemochromatosis. Ultrasound findings are non-specific, but can raise a suspicion in presence of abnormal S.iron studies as in our case. Non-contrast CT scan shows a diffusely hyperattenuating liver, but this can also be seen in storage disorders, Wilson's disease, drugs like thorotrast, amiodarone, colloidal gold, and cisplatin. Also, CT cannot differentiate hemochromatosis from hemosiderosis.[4]

MRI abdomen is best suited for diagnosis because iron is a paramagnetic substance. Intracellular iron in the form of deoxyhemoglobin, methemoglobin, ferritin, or hemosiderin causes local field inhomogeneities leading to signal loss on MRI. Primary hemochromatosis can be demonstrated with decreased signal intensity of the liver, pancreas, and heart muscle; while the signal intensity of the spleen remains unchanged. This is in contrast with secondary hemochromatosis due to blood transfusions where the excess iron is accumulated in the RE cells. Therefore, the signal intensity of both the liver and the spleen decreases.[2,4] Quantitative assessment of iron overload based on MR imaging sequences has been demonstrated by correlating the T2 and T2* relaxation times to specific measures of liver iron content.[2]

MR imaging is a noninvasive alternative test that allows a comprehensive evaluation of organ iron overload, liver cirrhosis and its complications, such as portal hypertension and HCC, in a single examination. Serial MRI can be used to monitor the efficacy of phlebotomy therapy 2. Differential distribution of iron among various organs on T2 and T2* W has given new insights to pathways of iron metabolism. This also helps to personalise the chelating agent for each patient as each drug has preferential action on some organs over the others.[5]

The diagnosis of iron overload is mostly clinical in transfusion dependent thalassemic patients. However, the diagnosis may not be apparent clinically in a non-transfused patient in rare Hb-E β thalassemia presenting late in adulthood. HbE is an extremely uncommon structural haemoglobin variant caused by base

substitution of lysine for glutamic acid. HbE variant is resistant to P.Falciparum and is therefore more prevalent in areas where malaria is endemic like many South Asian countries like Laos, Cambodia and Thailand 3. The incidence is rising globally. Indian data published by a genetic clinic of a tertiary care centre reported only 26 patients in 12 years, while another study found 30 patients over 14 years.[6,7] Most of the patients were from UP and few from Bihar and Haryana.

HbE mutation results in an extremely varied clinical presentation depending on its combinations with other Hb subtypes and mutations. Hb- β thalassemia is the most severe of all HbE syndromes. Severe transfusion dependent patients of homozygous β thalassemia mostly present early in childhood. But the clinical course of Hb E β-thalassemia is highly variable 3. Various factors like HbF level, β+ / β0 combination, environmental factors including malaria are known to change the chronic phenotypic expression of the disease. Fall in erythropoietin levels with age can also explain worsening of anaemia in adulthood. Iron overload due to increased gastrointestinal absorption in non-transfused HbE-β thalassemia patients is reported.[3,7]

Splenomegaly to increase the haemoglobin level was routinely done previously. However, it is now controversial due to increased risk of thromboembolism. Management for iron overload is regular phlebotomies and chelating agents like deferoxamine, deferasirox and deferiprone.[3]

Unusual findings in our case were late presentation in female patient at 25 years with severe transfusion dependent anaemia, although the patient had uneventfully survived childbirth 3years earlier. Hemochromatosis in our case was clinically unsuspected because of no history of previous blood transfusions and was diagnosed radiologically. Awareness of the radiologist that rare double heterozygote E- β thalassemia can present late and iron overload can occur in such cases even without transfusions can help in alerting the physician for appropriate therapy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Buljubasic D, Ladenhauser-Palijan T, Debeljak Z. Homozygous form of hereditary hemochromatosis in a patient with beta-thalassemia minor: case report. Biochemia Medica. 2009;19(2):199-205.
2. Ito K, Hussain SM, Mitchell DG. Diffuse liver disease. In: Edelman RR, Hesselink J, Zlatkin M, eds. Clincial Magnetic Resonance Imaging.3rd edn. Saunders; 2005.
3. Vichinsky E. Hemoglobin E. syndromes. Hematology Am Soc Hematol Educ Program. 2007:79-83.
4. Boll DT, Merkle EM. Liver: normal anatomy, imaging techniques and diffuse diseases. In: Haaga JR, Dogra VS, Forsting M et al, editors. CT and MRI of the Whole Body.5th edn. Elseviers; 2008.
5. Kontoghiorghe CN, Kontoghiorghes GJ. New Developments and controversies in iron metabolism and iron chelation therapy. World J Methodol. 2016;6(1):1-19.
6. Agarwal S, Gulati R, Singh K. Hemoglobin E beta thalassemia in Uttar Pradesh. Indian Pediatrics. 1997;34:287-92.
7. Panigrahi I, Agarwal S, Gupta T, Singhal P, Pradhan M. Hemoglobin E-beta thalassemia: factors affecting phenotype. Indian Pediatrics. 2005;42:357-62.

Cite this article as: Gupta R, Tomer S, Kumar A, Jain P, Nair Misra R. Dark liver on MRI: throwing light on clinically unsuspected hemochromatosis in double heterozygote HbE-beta thalassemia. Int J Res Med Sci 2016;4:3632-5.