

# DIFFUSE HEPATIC CALCIFICATION - A MARKER OF HYPOPARATHYROIDISM IN BETA THALASSEMIA DUE TO IRON OVERLOAD

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## ABSTRACT

Iron overload can occur in beta thalassemia. The iron overload can damage liver, heart and endocrine organs. Non- endocrine complications due to iron overload are liver fibrosis and cirrhosis, skeletal manifestations and dilated cardiomyopathy. Endocrine manifestations are pituitary insufficiency, failure of sexual maturation, delayed puberty and hypogonadism, diabetes mellitus and glucose intolerance due to pancreatic insufficiency, dyslipidaemia, hypoadrenalism, hypothyroidism and hypoparathyroidism. Hypoparathyroidism is seen upto 6.7 % of thalassemia major (TM) patients and is the most prevalent endocrine complications of thalassemia major. Diffuse hepatic calcification and calcification in the brain occur in beta thalassemia due to hypoparathyroidism. Isolated intracerebral calcification due to hypoparathyroidism has been reported previously. Isolated hepatic calcification is infrequent with only one reported case in thalassemia. We report the first case of an 18- year old beta-thalassemia major patient, with hypoparathyroidism with extensive diffuse hepatic calcification and brain calcification.

**Keywords:** Thalassemia, liver calcification, hypoparathyroidism, haemochromatosis, iron overload

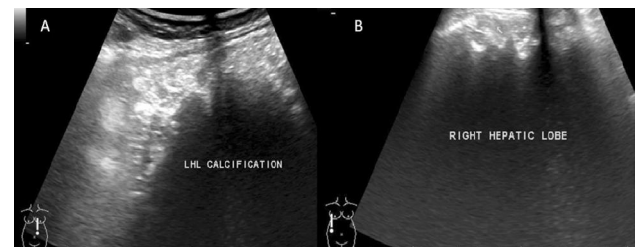
## Case Report

An 18- year old female patient known case of Beta thalassemia was referred to our hospital for iron chelation therapy with desferrioxamine (0.5 mg x 6 with 500 ml normal saline for 10 days). She was receiving blood transfusion of one unit of packed cell volume, once a month. There was a previous history of splenectomy in 2007.

On examination, she was pale, with depressed nasal bridge and short stature. Her haemoglobin was 6.8 GM%, serum ferritin -220.6 (normal range 10-120ng/ml), vitamin D was 32.8 (normal), serum calcium was 7.1mg% (normal range was - 8.8 to 10.5mg%), serum bilirubin was 1.3mg%, SGOT, SGPT and serum alkaline phosphate were normal. Her blood was B positive.

Her USG abdomen shows evidence of splenectomy. Liver was enlarged and showed marked diffuse coarse echotexture with multiple echoreflective calcific foci

in both right and left lobes with posterior acoustic shadowing (Fig. 1). There was no ascites, portal vein was not well visualised.



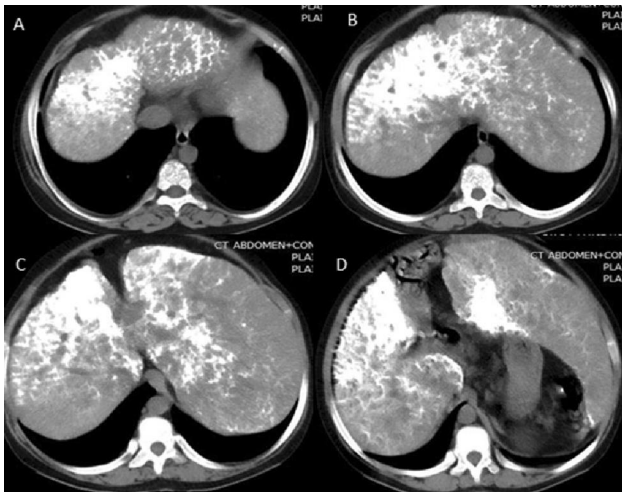
**Figure 1:** USG of liver showing extensive echoreflective calcific foci in both left (A) and right hepatic lobes (B).

CT scan of the abdomen and pelvis showed hepatomegaly with extensive calcification. Both right and left hepatic lobes were enlarged and showed extensive calcification with slight nodular surface (Fig. 2). Spleen was not visualised (History of splenectomy). Portal

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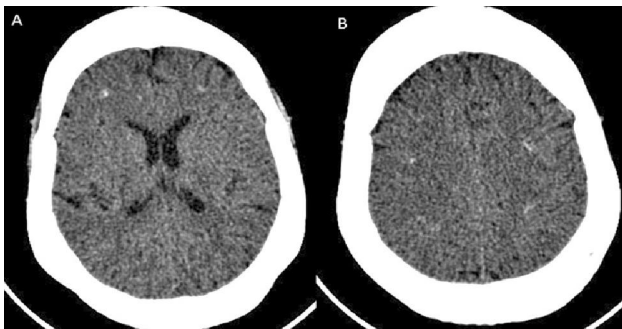
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vein and gall bladder were normal. There was no ascites.

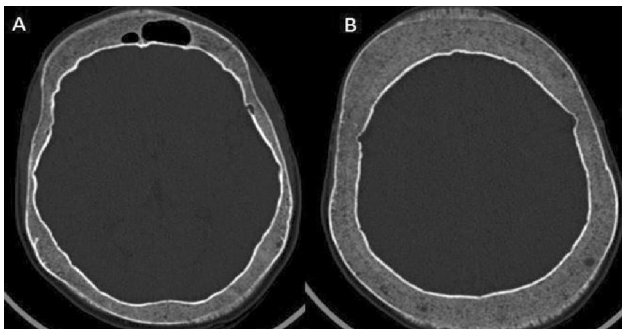


**Figure 2:** Plain CT scan of the abdomen showing extensive calcific foci in both right and left hepatic lobes (A-D) and evidence of splenectomy (D).

Plain CT scan of the brain was done. It showed multiple calcific foci in bilateral frontal lobes and parietal lobes in subcortical white matter (Fig. 3). The cranial vault was thickened and showed multiple small osteolytic lesions with pepper pot skull (Fig. 4).



**Figure 3:** Plain CT scan of brain showing calcific foci in bilateral fronto-parietal subcortical white matter (A-B).



**Figure 4 :** Plain CT scan of brain bony windows showing the thickened vault with multiple small osteolytic lesions with pepper pot skull (A-B).

A radiograph of skull, lateral and antero-posterior view showed thickened vault with thinning of inner and outer tables with hair on end sign due to thickening of trabeculae having perpendicular orientation with sparing of occipital bone (Fig. 5).

In view of hepatic and brain parenchymal calcification hypoparathyroidism was suspected. Serum parathyroid was 2.5 pg/ml (normal 15 to 16 pg/ml) suggestive of hypoparathyroidism.



**Figure 5:** Plain radiograph of skull, lateral and antero-posterior view showing the thickened vault with thinning of inner and outer tables with hair on end sign due to thickening of trabeculae having perpendicular orientation with sparing of the occipital bone (A-B).

## Introduction

Beta thalassemia is a hereditary blood disorder which occurs due to defect in the synthesis of the beta globin chain. It is a common monogenetic disease.<sup>1,2</sup> Due to this defect there is a disproportionate ratio of alpha-and beta-globin chain synthesis leading to ineffective erythropoiesis (IE) and a chronic haemolytic anaemia. It has three categories -thalassemia major, thalassemia intermedia, and thalassemia minor.<sup>1</sup>

$\beta$ -thalassemia major ( $\beta$ -TM) harbour two defective copies of the  $\beta$ -globin chain. They present during the first two years of life with microcytic haemolytic anaemia and need lifelong blood transfusion. symptomatic beta thalassemia needs regular blood transfusions.<sup>2</sup>

Iron overload occurs due to inability to excrete iron. The iron overload can damage liver ,heart and endocrine organs. Non- endocrine complications due to iron overload are liver fibrosis and cirrhosis, skeletal manifestations and dilated cardiomyopathy. Endocrine manifestations are pituitary insufficiency, failure of sexual maturation, delayed puberty and hypogo-

nadism, diabetes mellitus and glucose intolerance due to pancreatic insufficiency, dyslipidaemia, hypoadrenalism, hypothyroidism and hypoparathyroidism. Hypoparathyroidism is seen upto 6.7% of thalassemia major (TM) patients.<sup>1</sup>

## Discussion

Frequent blood transfusion with more than 40 units can cause haemochromatosis (non-RES iron deposition) with iron deposition in the reticuloendothelial system (RES). Ineffective erythropoiesis, high erythrocytic requirements leads to increased duodenal iron absorption, which lead to haemochromatosis, in the non reticuloendothelial system. There is increased accumulation of iron, increased in total body iron stores and abnormal deposition in non reticuloendothelial system leading to haemochromatosis and organ dysfunction. There is increased gastrointestinal absorption of iron, increased cellular uptake of iron into the known reticuloendothelial system. The liver is the primary organ of deposition followed by the pancreas and myocardium. Once hepatic deposition is extensive, iron is deposited in periportal hepatocytes leading to peribulbar fibrosis and formation of eventually liver cirrhosis with broad fibrous septa.<sup>3</sup>

USG assesses cirrhotic changes and presence of focal lesions. MR imaging is extremely useful in detecting and estimating the extent of iron deposition. It is non-invasive, widely accessible and has replaced liver biopsy in hepatic iron overload assessment.<sup>4</sup> It gives an indication of hepatic iron deposition and aids in chelation therapy dose adjustment thus preventing under or over treatment and risk of therapy related toxicity.<sup>2</sup>

Iron deposition occurs secondary to ineffective erythropoiesis, which triggers increased gastrointestinal absorption of iron due to increased marrow demand. As in primary haemochromatosis iron deposition occurs in liver, thyroid, adrenal glands, pituitary gland, pancreas, myocardium, and musculoskeletal system. Iron deposition in bone marrow leads to loss of bone. Marrow expansion occurs secondary to red marrow activation from chronic anaemia. This interrupts bone formation with cortical thinning and increased fragility. Osteoporosis seen in beta thalas-

semia is multifactorial and occurs due to bone marrow expansion, iron overload and endocrine dysfunction. The most prevalent endocrine complications of thalassemia major is hypoparathyroidism which leads to hypocalcemia, tetanus, and seizure.<sup>5</sup> Isolated intracerebral calcification due to hypoparathyroidism has been reported previously. Isolated hepatic calcification is infrequent with only one reported case in thalassemia.<sup>5-7</sup>

Iron deposition in parathyroid gland occurs in thalassemia major patients causing hypoparathyroidism. This results in suppression in parathyroid hormone secretion. Laboratory findings seen in hypoparathyroidism are hypocalcemia, hyperphosphatemia, normal or low serum level of alkaline phosphatase, and normal or low serum level of parathyroid hormone. As a result metastatic calcification can occur in central nervous system mainly in the basal ganglia and rarely outside the extra pyramidal system. Metastatic calcification in hypoparathyroidism is due to decrease bone reservoir for the absorption of calcium and phosphate from the intestine causing extra osseous calcification.<sup>3</sup>

Hepatic calcification is usually seen in both inflammatory and neoplastic conditions. Inflammatory conditions are tuberculosis, histoplasmosis, brucellosis, schistosomiasis, hydatid cyst, cytomegalovirus, toxoplasmosis, Pneumocystis carinii infection, chronic amoebic or pyogenic abscess, and chronic granulomatous disease of childhood. Vascular causes are hepatic artery aneurysm, portal vein thrombosis, and hematoma. Neoplastic conditions are hemangioma, hepatocellular adenoma and carcinoma, infantile hemangioendothelioma, cholangiocarcinoma, hepatoblastoma, and metastasis. Extensive diffuse hepatic calcification is rare with very few causes. It can occur after ischemic insult in patients with end stage renal disease on hemodialysis and as a sequel of shock liver.<sup>8,9</sup> Hyperparathyroidism occurring as an endocrine complication in thalassemia major due to iron overload is an extremely rare cause of extensive diffuse hepatic calcification.

## Conclusion

Diffuse hepatic calcification is extremely rare. Detection of diffuse hepatic calcification and calcification in brain in beta thalassemia on radiological investi-

gations are markers of hypoparathyroidism in beta thalassemia due to iron overload .

**Conflicts of interest:** None

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