



# Transfusion-Related Hemochromatosis Involving Pituitary Gland in a Patient of Beta-Thalassemia Major

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## Abstract

**Introduction:** Hemochromatosis of the pituitary gland is a form of iron overload disease which occurs in different clinical conditions related to multiple blood transfusions.

**Case Presentation:** We present a case of secondary hemochromatosis involving the pituitary gland and choroid plexus in an eight-year-old female with imaging findings and a review of the relevant literature. Our patient has had a history of cessation of growth in height for the last 1 year. She was diagnosed with a thalassemia major at the age of 6 months. She has been on regular blood transfusions since then. Magnetic resonance imaging (MRI) revealed evidence of iron deposition in the pituitary gland.

**Conclusion:** This diagnosis should be suspected on clinical presentation and history of multiple blood transfusions. It can be confirmed based on characteristic imaging findings. The patient should be strictly monitored with serum iron levels, and a tailored iron chelation therapy should be initiated.

**Keywords:** Hemochromatosis, Blood Transfusion, Thalassemia, Chelation Therapy, MRI Scans

## 1. Introduction

Defective synthesis of the beta chain of hemoglobin results in hereditary blood disorders known as beta-thalassemia, ranging from asymptomatic conditions to severe anemia. Thalassemia major, intermedia, and minor are the three recognizable forms of thalassemia. A beta-thalassemia major diagnosis is typically made over the first two years of life with anemia and individuals require multiple blood transfusions.<sup>1</sup>

Excessive iron deposition at the cellular level leading to cell damage and organ dysfunction is hemochromatosis. One of the leading causes of hemochromatosis is beta-thalassemia, in which multiple blood transfusions are required to maintain adequate levels of hemoglobin. Despite iron chelation therapy, iron accumulation occurs in these patients in various organs.<sup>2-4</sup> Increased iron deposition in the anterior pituitary gland results in hypogonadotropic hypogonadism and growth failure. Cell death probably due to iron toxicity plays a vital role in this failure of the anterior pituitary gland.<sup>5</sup>

We present a case of transfusion-related hemochromatosis of the anterior pituitary, which led to short stature in an eight-year-old child. This case shows the rare finding of pituitary iron deposition and reinforces the role of MRI in the early diagnosis of this condition.

## 2. Case Presentation

An eight-year-old girl presented with short stature with

stationary height for 2 years. She was diagnosed with a case of beta-thalassemia major at the age of 6 months. Later, her parents were also detected to have beta thalassemia trait, which was unknown to them before their marriage.

At the age of 6 months, the child presented with failure to thrive, poor appetite, and lethargy. On hematological evaluation, she was found to have anemia with a hemoglobin (Hb) level of 8 g/dL. On Hb electrophoresis, she was found to have beta-thalassemia major. Blood transfusion was started regularly at a dose of one unit of blood every 20 days. Oral iron chelation therapy was started at the age of 2 years.

Recently, the child presented with an inability to gain any height from the age of 6 years, with the height being constant at 119 cm, which was lower than standard for the present age of 8 years. On clinical examination, the patient was mildly icteric and pale. She had malar prominence with slight frontal bossing. Per abdominal examination revealed hepatosplenomegaly (Figure 1). The rest of the clinical examination was normal.

Her height and weight were average from birth up to 6 years of age. Her parents and younger brother were of average height. Also, there was no history of any skeletal dysplasia in the family. X-ray wrist joint showed bone age of 8 years. There was no history or clinical features of nutritional deficiency disorder or a metabolic disorder. There was no pre-existing cardiac or liver disease.

The patient had an Hb level of 10.3 mg/dL. Her serum

ferritin levels were >1200 ng/mL. In addition, she had raised serum iron with a reduced total iron-binding capacity (TIBC). The rest of the biochemical parameters, including liver and renal function tests, were within normal limits. In addition, the patient underwent an ultrasound abdomen which revealed hepatosplenomegaly with a liver span of 16 cm and spleen span of 16.5 cm (Figure 2).

Because of the short stature, magnetic resonance imaging (MRI) of the brain was performed to evaluate the pituitary gland. Multiplanar T1-weighted images (T1W1), T2 weighted images (T2W1), gradient echo (GRE) images, and diffusion-weighted images (DWI) followed by post gadolinium T1 weighted fat-saturated images were acquired. The anterior pituitary showed an altered signal intensity with a diffuse signal loss on T2WI and GRE sequences. There was also focal signal loss in the infundibular stalk. Choroid plexus in lateral ventricles, third ventricle, and fourth ventricle showed susceptibility artifacts on GRE sequences. A mild signal loss was also

noted in the pineal gland (Figure 3). The rest of the visualized structures revealed normal morphology. These findings were suggestive of iron deposition in the anterior pituitary gland, infundibular stalk, and choroid plexus.

The patient is planned for splenectomy to reduce both the destruction of red blood cell (RBC) and the iron load. In addition, her iron chelation therapy is being optimized under the consultation of a hematologist.

### 3. Discussion

There are multiple genetic forms of thalassemia like  $\alpha$ -thalassemia,  $\beta$ -thalassemia, hemoglobin E/ $\beta$ -thalassemia, and others. Mutation in an  $\alpha$ -globin gene cluster on chromosome 16 and  $\beta$ -globin gene cluster on chromosome 11 leads to alpha and beta-thalassemia.<sup>6</sup> The defective and decreased alpha/beta chain leads to early apoptosis of mature red blood cells, leading to chronic hemolytic anemia and hematopoietic expansion for compensation of ineffective erythropoiesis.<sup>1,6,7</sup> Most



Figure 1. Frontal photograph of the patient shows the presence of frontal bossing and abdominal distension due to hepatosplenomegaly.

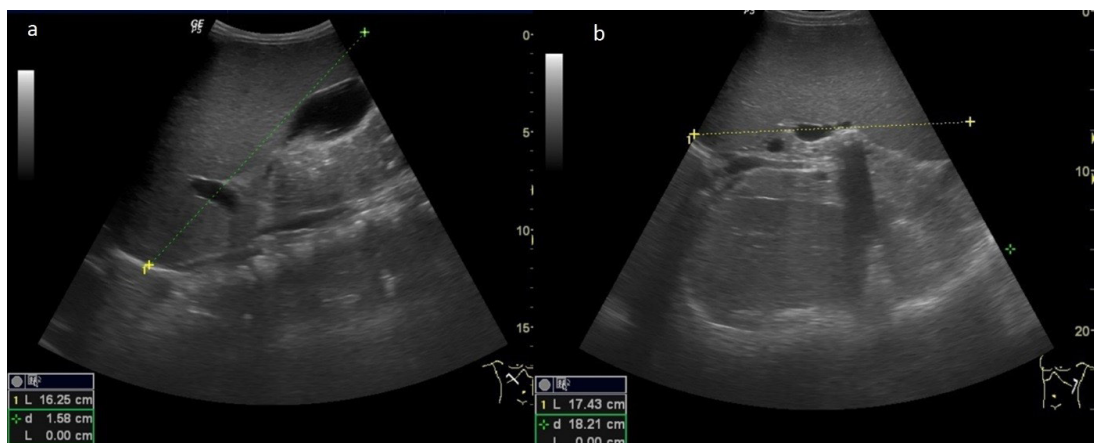
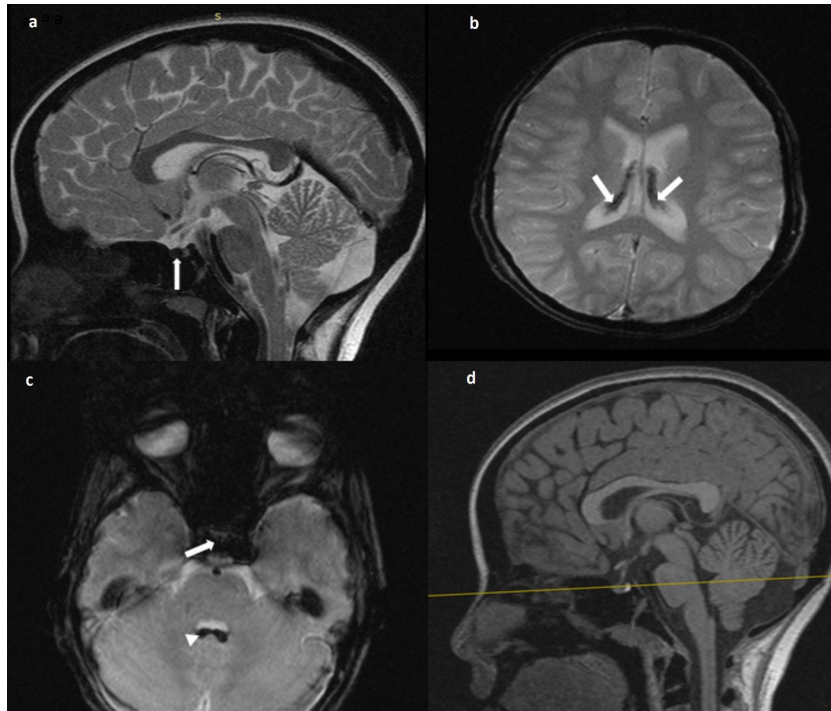


Figure 2. USG Abdomen Images Showing (a) Hepatomegaly and (b) Splenomegaly.



**Figure 3.** MRI Images of the Brain. (a) T2 weighted sagittal image shows diffuse T2 hypointensity in the anterior pituitary - suggestive of iron deposition. Gradient Echo (GRE) axial images at the level of the lateral ventricles (b) and the 4<sup>th</sup> ventricle (c) respectively show susceptibility artefacts in the pituitary gland (white arrows in c) and the choroid plexus of bilateral lateral ventricles (white arrows in b) & 4<sup>th</sup> ventricle (arrowhead in c). (d) T1 weighted sagittal image is provided to display the axial level of the section for image (c).

thalassemia is inherited as recessive trait thalassemia.<sup>1,6</sup> Beta thalassemia major variably referred to as “Cooley’s anemia,” is the most severe form of beta-thalassemia among the three different forms.

The Mediterranean, Middle Eastern, and Asian descent have the highest prevalence of beta-thalassemia.<sup>6</sup> The migration of population and intermarriage between different races and ethnic groups has introduced thalassemia in all parts of the world. The annual incidence of this disease having symptomatic individuals is estimated at 1 in 100 000 throughout the world.<sup>1,6</sup> There is no sex predilection for beta-thalassemia. The most common combination of beta-thalassemia with abnormal Hb is HbE/beta-thalassemia, most prevalent in Southeast Asia.<sup>1</sup>

The clinical presentation of beta-thalassemia major is between 6 and 24 months. Failure to thrive and progressive pallor is the main presentation. There is hypertrophy of the erythroid marrow, which results in medullary and extramedullary hematopoiesis. It leads to decreased bone density. Extramedullary hematopoiesis occurs in the form of masses of erythropoietic tissue primarily affecting the spleen, liver, lymph nodes, chest, and spine. Typical facial changes (chimpanzee facies- bossing of the skull, prominent malar eminence, depression of the bridge of the nose, tendency to a mongoloid slant of the eye, and hypertrophy of the maxillae, which tends to expose the upper teeth) are seen in this condition<sup>1</sup>. Other complications like gallstones, painful leg ulcers, and increased predisposition to thrombosis are due to excessive RBC destruction due to defective Hb.<sup>1,6</sup>

Increased iron in patients with thalassemia occurs as a

result of increased iron absorption from the gastrointestinal tract due to ineffective erythropoiesis and regular blood transfusions. There is 200-250 mg of elemental iron in every unit of transfused blood which amounts to 0.3-0.6 mg/kg/day on an assumed transfusion of 2-4 units every month. When macrophages phagocytize senescent transfused RBCs, this caused the release of labile cellular iron from RBCs. This iron is released into the circulation and it binds to transferrin. When transferrin gets saturated, the free iron is transported to various organs (liver, heart, and endocrine gland) known as hemosiderosis. Cellular dysfunction and necrosis of the target organ occur due to reactive oxygen species produced during the metabolism of iron.<sup>2,5,7</sup> This target organ damage is hemochromatosis, whereas hemosiderosis is iron accumulation without organ damage.

When the peripheral organs get saturated, deposition occurs in other tissues. Excessive iron deposition in the central nervous system (CNS) is rare. However, it sometimes occurs in the brain outside the blood-brain barrier in the choroid plexus, the pituitary gland, pineal gland, and area postrema and less frequently in the basal ganglia.<sup>8</sup> The choroid plexus plays a vital role in protecting the brain from iron overloading by buffering mechanism, so the presence of hemochromatosis in the choroid plexus is considered an early signal of CNS iron deposition. Hemochromatosis occurring in the choroid plexus is almost always asymptomatic in transfusion-dependent patients.<sup>8</sup>

Brain MRI, including GRE sequence, has high sensitivity in detecting hemochromatosis in the brain due to its

ability to detect hemosiderin based on the susceptibility effect.<sup>8</sup> The deposited iron preferentially accumulates in the gonadotropin-secreting cells and, less commonly, in growth hormone-secreting cells.<sup>9</sup> The most common manifestation is hypogonadism, followed by growth failure.

Chelation therapy aims to balance the rate of the iron accumulation from blood transfusion by increasing the rate of iron excretion. Only a tiny fraction of body iron is available for iron chelation at any moment as the chelating agent interacts with 'labile' iron pools better than that with iron stored as ferritin or haemosiderin. The amount of iron chelation is different from every chelator and depends upon the type of chelator. In addition to the liver, it takes longer to remove iron from other parts of the body as a meager amount of iron is available at the cellular level for chelation.<sup>10,11</sup> Chelation therapy has dramatically improved the prognosis of patients with iron overload leading to an 80% reduction in the risk of death from cardiac disease at 20 years.

Previous studies have confirmed that MRI is a valuable and non-invasive tool for diagnosing pituitary iron overload.<sup>12</sup> The present case illustrates this beautifully. We recommend the early use of MRI to diagnose pituitary iron overload in thalassemia patients who present with short stature, growth delay, or growth cessation.

#### 4. Conclusion

In a patient with beta-thalassemia requiring multiple blood transfusions, hemochromatosis occurs in various organs; however, it is rare in the pituitary gland. We reported a case of iron deposition in the pituitary gland, which led to short stature. MRI brain with GRE sequences is the most sensitive way to detect iron deposition in the pituitary gland. Since iron deposition and the organ damage occurring due to iron deposition is irreversible, the early detection of iron deposition in the various organs and commencing iron chelation therapy at an early stage is essential to prevent organ damage.

#### Authors' Contributions

BG: Conceptualised the case report and acquired patient data and images; SM: Drafted the case report; DSG: Approved the final version; PR: Acquired and edited the images; and AK: Assisted in acquiring patient data and images.

#### Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

#### Ethical Approval

The current study was approved by the Institutional Ethical Committee (IEC), Armed Forces Medical College vide approval letter no. 721/2020 dt 10 Sep 2020.

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