# Hypoparathyroidism in a Case of Transfusion Dependent Thalassemia

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## Abstract

Repeated blood transfusions in transfusion dependent thalassemia (TDT) leads to iron overload-related endocrine complications. Hypoparathyroidism (HPT) with severe signs of hypocalcemia is a recognized complication among these patients.

A 14-year-old thalassaemic boy, on regular transfusion and on anticonvulsant therapy with a presumptive diagnosis of epilepsy for the last 1 year, was admitted with high fever and severe muscle cramps with positive Trousseau's sign. He was diagnosed as a case of primary HPT and magnesium deficiency on the basis of low serum calcium, high phosphate, normal alkaline phosphates, very low intact parathyroid hormone (iPTH), normal serum vitamin D and very low serum magnesium level. His calcium, magnesium and phosphate level normalised following treatment with intravenous magnesium and calcium. His iPTH improved but remained at low normal. He was discharged from hospital with oral calcium, calcitriol, and magnesium supplementation. The anticonvulsant (Phenobarbitone) was successfully withdrawn gradually over the next six months without any recurrence of seizure in the subsequent 3 years of follow up.

Acquired HPT (apparently from hemosiderosis) is a common cause of hypocalcemia; and magnesium depletion further complicated the situation leading to severe hypocalcemia with recurrent episodes of convulsion. Magnesium replacement improved the parathyroid hormone (PTH) value proving its role in acquired HPT. Very high phosphate level on admission and poor PTH response with respect to the low serum calcium, indicates intrinsic parathyroid pathology. Metabolic abnormalities should always be evaluated in thalassaemic subject with seizure disorder and it appears that the initial convulsive episodes were due to hypocalcemia.

Muscle pain, cramps or convulsion may occur from HPT and simultaneous magnesium deficiency in transfusion dependent thalassaemic subjects. Metabolic correction is more important than anticonvulsant medication. Calcium and magnesium should both be assessed routinely in transfusion dependent thalassemic patients.

*Key words: hemosiderosis, hypomagnesemia, hypoparathyroidism, thalassemia*

## INTRODUCTION

Thalassemias are inherited blood disorders due to genetic defect in alpha globin (alpha thalassemia) or beta globin (beta thalassemia) protein chains of normal hemoglobin (hemoglobin A). Beta thalassemia results from several mutations in the beta globin gene in the short arm of chromosome 11[1] and presents as non-transfusion dependent thalassemia (NTDT) or transfusion dependent thalassemia (TDT), its most severe form. Clinical management of TDT consists of lifelong red blood cell transfusions and iron chelation therapy, to combat iron overload from excessive blood transfusions. The only definitive cure is bone marrow transplantation.[1] However, potentially curative gene therapy to treat transfusion-dependent β-thalassemia has recently been approved.[2]

Repeated blood transfusion therapy leads to iron overload-related complications including endocrine complications (growth retardation, failure of sexual maturation, diabetes mellitus, insufficiency of the parathyroid, thyroid, pituitary, and less commonly, of adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis.[3]

HPT in TDT is not an infrequently observed complication and is estimated in about 4.5% of thalassemia patients.[4] HPT is thought to be the consequence of iron deposition in the parathyroid glands but it has no clear relationship with serum ferritin levels and rarely presents with severe signs of hypocalcemia.[4]

## CASE

A 14-year-old boy was admitted in the hospital with high fever, pain in throat and cough associated with muscle cramps and generalized body pain for one week. He was a known case of transfusion-dependent β-thalassemia (detected at 9 months old), was regularly receiving packed red blood cell (RBC) transfusion (starting from 18 months old) and requiring, on average,

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4 units per month. He was maintained on Deferiprone (500 mg thrice daily) for a long time and was also put on deferoxamine mesylate since his serum ferritin went above 10000ng/dl one year prior to admission.

He was also treated conservatively for fever and muscle cramps about a year prior to admission, but no details were available. He had recurrent convulsive seizure at that time. Electroencephalography (EEG) showed nonspecific changes and Magnetic resonance imaging (MRI) brain was normal. Anticonvulsant therapy (Phenobarbitone 60 mg daily) was given since then, with a presumptive diagnosis of epilepsy along with other regular treatments for thalassemia.

Following this admission in the hospital for high fever, he experienced several episodes of severe muscle cramps and generalized body pain. He was conscious, febrile, anaemic and sick. The examination of the patient's pharynx revealed mild erythema with pharyngeal exudates. He was flushed, had hepatosplenomegaly, with no local muscle tenderness in limbs and positive Trousseau's sign. He had no other focal neurological deficit.

Laboratory evaluation showed hemoglobin: 10.5 gm/dl (13-16), leucocyte: 12,400/cumm (3500-9000), erythrocyte sedimentation rate: 44 mm (0-20), potassium: 2.45 meq/l (3.5-5.0), urea: 16 mg/dl (3.5-7.0) and creatinine: 0.83 mg/dl (0.7-1.3), serum ferritin: 8976 ng/dl (7-140), serum calcium: 3.8 mg/dl (9-10.5), phosphate: 11.53 mg/dl (2.7-4.5), alkaline phosphates: 86 U/L (53-141), serum albumin: 3.9 mg/dl, albumin corrected serum calcium: 3.98 mg/dl and repeat serum calcium: 4.1 mg/dl (9-10.5). His liver function test was abnormal with raised indirect bilirubin of 2.41 mg/dl (0.1-0.9) but normal direct bilirubin of 0.4 mg/dl (0-0.4) and normal aspartate transaminase 17 IU/L(8-40). His fasting plasma glucose and thyroid function test was normal.

Throat swab was obtained and was cultured. Gram-positive cocci suggestive of Streptococcus pyogenes grew in chains. No blood culture was done. His iPTH was very low: <2.5 (14-70 pg/ml) and serum vitamin D level was 34.62 ng/ml (30-100). The patient was diagnosed as a case of primary hypoparathyroidism and was evaluated for serum magnesium (Mg) which was also very low: 0.53 mg/dl (1.5-2.5).

He was treated with an antibiotic from day 1 for the fever and congested throat. Magnesium replacement (20 mmol/day for 6 days in intravenous route) along with calcium replacement (Ca-gluconate in intravenous route) was started on the second day of admission and daily monitoring of calcium, phosphate and magnesium was done. Calcium level and Magnesium level gradually improved from 2nd day to 6th day while serum phosphate level gradually

declined (Table 1). Hypomagnesaemia contributes to hypokalemia and he was closely monitored in the Intensive Therapy Unit. However, his serum potassium gradually improved from 2.45 meq/l (on admission) to normal levels (4.30 meq/l) on 6th day without potassium supplementation.

His episodes of severe muscle cramps and pain all over the body gradually improved, as well as the fever and congested throat. Intravenous calcium and magnesium replacement was stopped after 6th day and oral calcium (1000 mg daily), calcitriol (0.5 ug) and oral magnesium (400 mg daily) were started. On the 8th day, two days after oral supplementation was started, serum calcium was 6.7 mg/dl, magnesium 1.14 mg/dl and phosphate 4.9mg/dl. The iPTH was repeated and was at a low normal value of 16.5 (14 – 70 pg/ml). The dose of oral calcium (1500 mg daily) and calcitriol (1.5 ug) was then increased. Biochemical parameters improved further (Serum calcium 8.7 mg/dl, magnesium 1.24mg/dl and phosphate 4.4mg/dl) on the 12th day (Table 1). He had no further seizure and was discharged from the hospital. Repeat serum ferritin before his discharge came down to 7795 ng/dl.

On follow up, he was maintained on blood transfusions, deferiprone, deferoxamine mesylate, oral calcium and calcitriol without any history of muscle cramps or convulsion. The anticonvulsant (Phenobarbitone) was gradually withdrawn over the next six months. He did not have any further episode of convulsion over 3 years of follow up.

## DISCUSSION

Reduced or absent synthesis of the beta globin chains of the hemoglobin tetramer is the basic pathology of beta-thalassemia.[1] Regular red blood cell transfusions and iron chelation therapy to remove excess iron introduced with transfusions are the standard therapeutic interventions. Despite early establishment of chelation therapy, elevated ferritin is commonly due to iron overload from multiple blood transfusions; and in the long term may lead to cardiac, hepatic, or endocrine dysfunctions.[3] The patient presented with fever and very high serum ferritin (8976 ng/dl) level. Fever was due to throat infection which improved with antibiotic. Being an acute-phase reactant, serum ferritin settled down to 7795 ng/dl from 8976 ng/dl at the time of discharge from hospital. This high serum ferritin (7795 ng/dl) at the time of discharge indicates significant iron over loading. The clinical picture of TDT is often dominated by endocrine system abnormality, a consequence of iron overload and chronic hypoxemia.

As the survival of the TDT subjects improved with modern management, most (88.4%) suffer from at least one endocrine complication, the most common being hypogonadotropic hypogonadism (about 70% among male and 39.1% among female).[5] Type 1 Diabetes (18.6%), impaired glucose tollerance (34.8%), HPT (11.6%), subclinical hypothyroidism (20.9%), overt hypothyroidism (2.3%), central hypothyroidism (4.6%), and growth hormone deficiency (20%) are other common endocrine complications. Even some of them (11.6%) can have multiple (>3) endocrine complications simulteneously. Interestingly primary and secondary adrenal insufficiency appears very rare.[5]

**Table 1.** Changes in biochemical parameters during treatment of HPT

|                     | Day-1 | Day-2 | Day-4 | Day-6 | Day-8 | Day-12 |
|---------------------|-------|-------|-------|-------|-------|--------|
| Calcium (mg/dl)     | 3.8   | 5.57  | 6.08  | 6.59  | 6.7   | 8.7    |
| Magnesium(mg/dl)    | 0.53  | 0.87  | 1.04  | 1.09  | 1.14  | 1.24   |
| Phosphate(mg/dl)    | 11.53 | 8.09  | 5.79  | 4.97  | 4.9   | 4.4    |
| Potassium (meq/l)   | 2.45  | 2.57  | 2.63  | 4.30  | 4.2   | 4.3    |
| iPTH (pg/ml)        | < 2.5 | –     | –     | –     | 16.5  |        |

Oxidative damage by reactive oxygen species (ROS) is responsible for endocrine organ damage in patients with thalassemia. ROS generation is caused by two major mechanisms (Figure 1). The first is iron overload and the second, chronic hypoxia resulting from chronic anemia. Iron overload develops not only from secondary to regular transfusions but also from increased intestinal iron absorption. Normally about 1–2 mg of iron is lost daily and is balanced by intestinal absorption of 1-2 mg daily. On the other hand, each unit of transfused packed red blood cells contains 200 to 250 mg elemental iron and loads 400 mg to 1000 mg per month (13 to 33 mg per day) in the TDT patients with assumed monthly transfusion rate of 2 to 4 units. Moreover, the rate of intestinal iron absorption is much higher (3-4 times) among both TDT and NTDT due to ineffective erythropoiesis and chronic hypoxia.[6] Senescent transfused red blood cells are phagocytized by the macrophages and the labile cellular iron is released into the plasma to bind transferrin. As loading continues, the capacity of transferrin binding with released iron and intestinal absorbed iron get saturated and results in nontransferrin-bound iron fraction within plasma. Iron toxicity is primarily from non-transferrin bound iron which cannot be regulated, and hence, potentially damaging. It is avidly captured by hepatocytes and other parenchymal cells including endocrine glands and continues to accumulate in the cells and damage cell membranes, mitochondria, nuclei and other intracellular organelles by its propensity to generate ROS.[6]

In response to hypoxia from chronic anemia, several mechanisms are triggered to adapt cells to a low oxygen environment. As mitochondria are the major consumers of oxygen in the cell, they are severely affected by decreased oxygen availability. Mitochondria are also potential source of ROS. In response to hypoxia they modify cellular metabolism, especially lowering of the citric acid cycle. Intermediates of the citric acid cycle regulate hypoxia inducible factors (HIF), the key mediators for ROS-production by the HIF-pathway.[7] ROS are capable of causing oxidative damage to macromolecules leading to protein fragmentation and DNA damage. Cumulative oxidative damage produced both by iron and hypoxia lead to organelle collapse and dysfunction.

HPT is well known among the transfusion-dependent patients with beta-thalassemia[4,8] and commonly seen in iron-overloaded patients and is often accompanied by other endocrinopathies.[9] Acquired HPT from hemosiderosis (due to repeated blood transfusion) is always the first consideration for hypocalcemia in patients with TDT. However, the concentration of ferritin is not a valuable tool in the prediction of the development of HPT, as no significant differences have been reported in serum ferritin level in patients with HPT in the background of thalassemia in many studies.[10] Other factors, such as individual susceptibility to iron toxic effects and the hematological phenotype of the disease might play some roles in the development of HPT.[11,12]
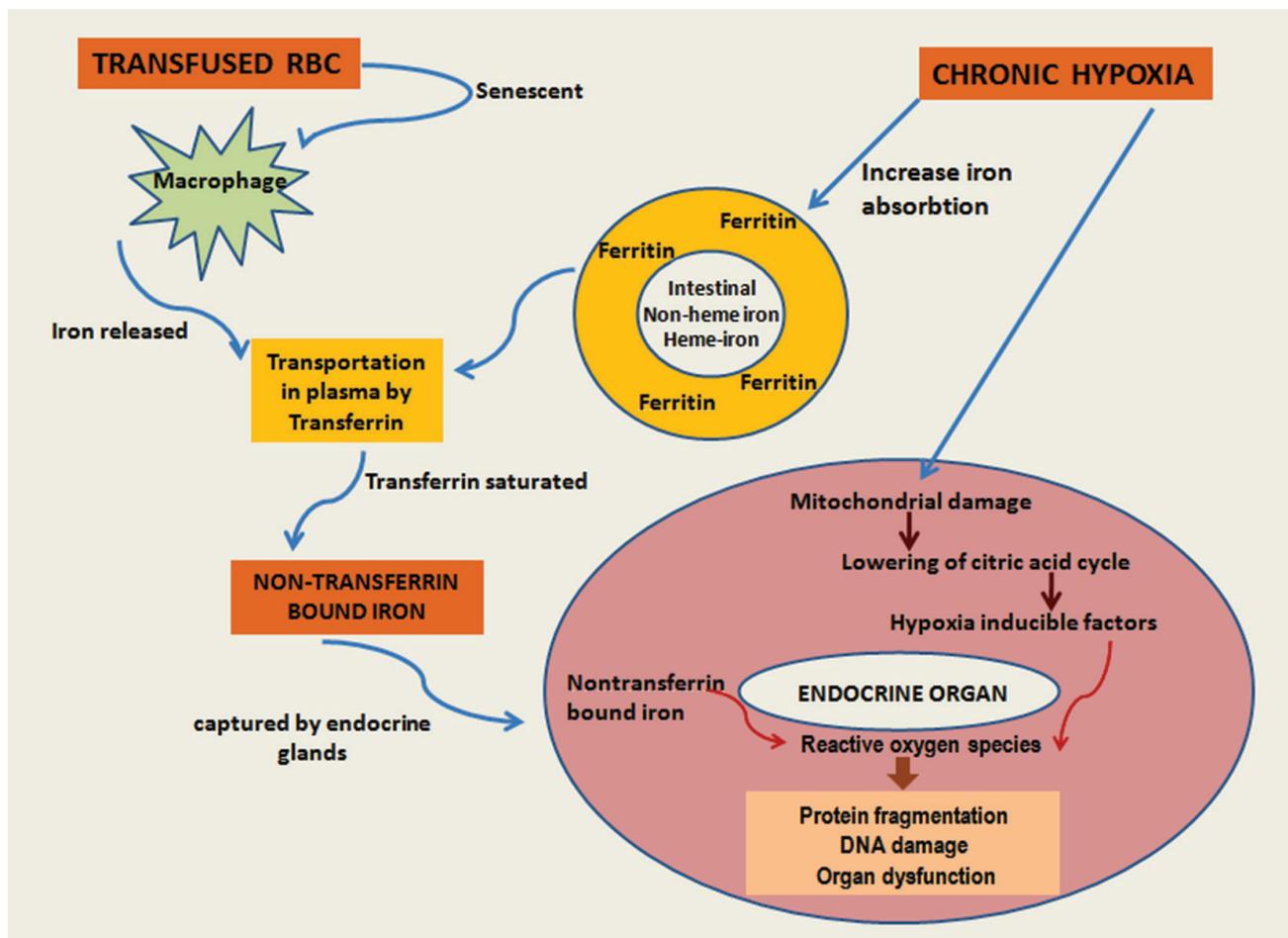


**Figure 1.** Mechanism of organ dysfunction from iron overload and chronic hypoxia in TDT.

Magnesium depletion is also associated with impaired PTH secretion, common among TDT subjects and is often present even in younger asymptomatic children,[13] Magnesium replacement in this patient improved the serum PTH value (from <2.5 pg/ml on admission to 16.5 pg/ml on 8th day) proving magnesium depletion as an important contributing factor for the acquired HPT. However, the PTH response was inappropriately low (16.5 pg/ml) in respect to the low serum calcium level (6.7 mg/dl), indicating intrinsic parathyroid pathology, probably from hemosiderosis. Moreover, phosphate level is usually not elevated (because phosphate deficiency is frequently associated with magnesium deficiency) in isolated magnesium deficiency states and very high phosphate level (11.53 mg/dl on admission) in this patient indicates significant intrinsic parathyroid defect. Magnesium deficiency further complicated the hypocalcemic state.

Hypokalemia is common in most hypomagnesemic subjects as both potassium and magnesium are the major intracellular cations. Excess renal potassium wasting in hypomagnesemic patients leads to hypokalemia.[14] Potassium secretion from the renal collecting tubular cells is mediated through luminal potassium channels and is inhibited by intracellular (collecting tubules) magnesium concentration. Hypomagnesemia leads to reduction in intracellular magnesium and releases this inhibitory effect on potassium efflux. This promotes potassium secretion from renal tubules and enhances urinary losses. Correction of the magnesium deficit and not potassium supplementation can reverse this effect as we have observed in our case.[14] Though the childhood seizure is mostly treated with anticonvulsant therapy,[15] metabolic abnormalities should always be looked into while evaluating a thalassaemic subject with seizure disorder. Anticonvulsant therapy was successfully withdrawn without any recurrence of seizure till last follow up and it appears that the initial convulsive episodes in this patient were probably due to hypocalcemia.

## CONCLUSION

Transfusion related hemosiderosis in thalassaemic subjects can cause HPT state with severe signs of hypocalcemia. Simultaneous magnesium deficiency may aggravate the HPT state. Muscle pain, cramps or convulsion can occur from these metabolic alterations and metabolic correction is more important than anticonvulsant medication. Assessment of both calcium and magnesium should be done routinely in the care of transfusion-dependent thalassemic patients.

### Ethical Consideration
Patient consent was obtained before submission of the manuscript.

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