

HYPOCALCEMIA DUE TO HYPOPARATHYROIDISM IN β -THALASSEMIA MAJOR PATIENTS

Aamer Aleem, MBBS, MRCP; Abdul-Kareem Al-Momen, MD, FRCPC;
Mohammed S. Al-Harakati, MD, FRCPC; Asim Hassan, MBBS, MRCP;
Ibrahim Al-Fawaz, MD, FRCPC

Background: This is a retrospective analysis of case records of β -thalassemia major patients who developed hypoparathyroidism (HPT). The objective of this study was to assess the prevalence of hypocalcemia and hypoparathyroidism in β -thalassemia major patients being followed at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia.

Patients and Methods: Diagnosis was based on low serum calcium (S/Ca), high serum phosphate (Po_4), normal serum magnesium and alkaline phosphatase, and low serum parathyroid hormone levels. Other parameters analyzed included age, sex, serum ferritin levels, age of onset of HPT, any symptoms of hypocalcemia, and presence of other complications in these patients.

Results: Out of 40 patients, eight (20%) were diagnosed to have HPT. The mean age at diagnosis was 13.6 years (range 11-16 years), mean serum calcium was 1.88 mmol/L (range 1.58-2.04), mean serum ferritin was 7490 μ g/L (range 2000-23,064) and mean serum phosphate was 1.88 mmol/L (range 1.50-2.73). Serum parathyroid hormone (PTH) levels were low in most of the patients. Only two patients (25%) had mild symptoms of hypocalcemia. Growth retardation was present in all patients, while four patients had liver dysfunction, two had diabetes mellitus and two had cardiac dysfunction.

Conclusion: HPT due to iron overload may develop in a significant number of thalassemia major patients, especially when chelation therapy is not optimal, therefore, all thalassemics should be carefully watched for this complication from early in their second decade.

Ann Saudi Med 2000;20(5-6):364-366.

Key Words: Hypocalcemia, hypoparathyroidism, β -thalassemia major.

Hypoparathyroidism (HPT) secondary to siderosis in thalassemia patients was first described by Gabriele in 1971.¹ It was later detected in more patients and more reports appeared in the literature.²⁻⁶ It is now a well-recognized complication of blood transfusion therapy, secondary to iron deposition in parathyroid glands. It was possibly more common in patients born or treated before the era of intensive chelation therapy.⁷ It has also been documented that asymptomatic hypocalcemia is much more common,^{4,7,8} and can be missed for some time unless specifically looked for.

Materials and Methods

We retrospectively searched the records of patients with thalassemia major who were diagnosed to have hypocalcemia due to hypoparathyroidism at some stage during the follow-up at adult and pediatric hematology

clinics at KKUH, Riyadh. Ten patients were identified from a total of 40 being followed at our center. Two patients were excluded: one who was initially misdiagnosed as having β -thalassemia major, but later on proved to have sickle/ β -thalassemia, and another who was HIV-positive with many HIV-related complications, and who despite being significantly hypocalcemic, did not fulfil the criteria for HPT.

Desferrioxamine mesylate (Desferal, Ciba-Geigy, Basel, Switzerland) chelation therapy was started at variable intervals from the beginning of blood transfusions because of initial parental refusal or noncompliance, and many patients were given intravenous Desferal along with blood transfusions during this period. The dose of Desferal ranged from 20-50 mg/kg body weight subcutaneously by pump infusion overnight five times weekly, but many patients received a dose of 2 g daily regardless of weight.

Patients were diagnosed with HPT if they had low serum calcium, high serum phosphate, and normal serum magnesium and alkaline phosphatase. Serum calcium levels were corrected for serum albumin levels. Serum PTH was measured in seven patients by radioimmunoassay to confirm the diagnosis. Blood samples were taken after

From the Departments of Medicine and Pediatrics, King Khalid University Hospital, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Aleem: 18 Sovereign Way, Trafalgar Road, Moseley, Birmingham, B13 8AT, U.K.

Accepted for publication 9 July 2000. Received 20 February 2000.

overnight fasting. The other parameters analyzed included

TABLE 1. *Characteristics of the patients.*

Age (years)	Sex	S/Ca (mmol/L)	S/PO ₄ (mmol/L)	S/Ferritin (μmol/L)	S/PTH (nmol/L)	Age Desferal started	Age of onset of HPT (years)	Symptoms of low Ca
17	F	1.58	2.73	12,000	Undetectable	10	15	Yes
16	M	1.70	1.63	7080	Undetectable	6	15	Yes
16	M	1.90	1.54	4440	0.7	10	16	No
13	F	1.94	1.50	23,064	0.9	5	13	No
12	M	1.95	1.90	2925	1.1	3.5	12	No
16	M	1.95	1.95	4000	2.0	5	15	No
12	F	1.99	1.80	4416	–	4	12	No
12	F	2.04	2.02	2000	4.0	5	11	No

S/Ca=serum Ca.

age, sex, serum ferritin levels, age at starting regular Desferal treatment, age at the onset of HPT and any symptoms of hypocalcemia. The characteristics of the patients are shown in Table 1. Other observations included presence or absence of growth retardation, hypogonadism, hypothyroidism and diabetes mellitus (DM). Evidence of liver disease and cardiac dysfunction was also sought by measuring liver enzymes and performing echocardiography.

Results

HPT was diagnosed in eight patients (20% of total patient population). The median age at diagnosis was 15 years (mean 13.6 years, range 11-16 years). The lowest level of calcium recorded was 1.58 mmol/L and the highest was 2.04 mmol/L, with a mean of 1.88 mmol/L (normal range 2.10-2.60 mmol/L). The mean serum phosphate level was 1.88 mmol/L (range 1.50-2.73, normal range 0.87-1.45 mmol/L). Mean serum ferritin level at diagnosis was 7490 μg/L (range 2000-23,064, normal less than 300 μg/L). There was no consistent relationship between serum ferritin levels and degree of hypocalcemia. The age at which Desferal was started regularly ranged from 3.5-10 years, and the maximum lag period between regular blood transfusions and starting chelation therapy was six years (Patient 1 in Table 1). Serum PTH was undetectable in two patients and was low in five others (normal range, 10-65 ng/L).

The majority of our patients were asymptomatic, and only two patients with the lowest levels of serum calcium had mild symptoms in the form of paresthesia of the hands. Growth retardation was present in all patients (100%). DM was present in two patients (25%), liver dysfunction (diagnosed by raised transaminases on more than one occasion, each taken three months apart) in four patients (50%), and two patients (25%) had cardiac involvement, while none had hypothyroidism.

Discussion

HPT is well known to occur in thalassemia major patients, but it is thought to be uncommon and its incidence is considered to be decreasing with improvements in chelation therapy.⁷ In the few published studies, the prevalence varies greatly from very low to as high as 22.5%.⁹ The largest study on endocrine problems in thalassemia published to date included 1861 patients from 25 centers, and it recorded HPT in 3.6% of patients (mean age at diagnosis 18.7 years), although the percentage varied from center to center.¹⁰ In our group of thalasseemics, the percentage of HPT (20%) seems to be quite high, and this could partly be explained by the delay in starting chelation therapy, the causes of which have been described earlier, as well as noncompliance with treatment.

The cause of HPT in thalassemia is assumed to be iron deposition in parathyroid glands,⁶ but the reason why some patients develop HPT and others do not is not exactly known. A number of possible mechanisms have been described to be responsible for glandular damage through iron overload. These include free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage,¹¹ and a number of surface transferrin receptors in the cell, and the ability of the cell to protect itself against inorganic iron.¹²

From the above discussion it seems logical to consider that patients with high levels of serum ferritin are more likely to develop endocrine complications, and the data from an Italian study⁷ is indicative of this, but others found no such correlation. Our study also does not show a good correlation between serum ferritin levels and development of HPT, but the number of patients is small and single readings at the time of diagnosis are probably less important than mean ferritin levels over longer periods.

It has been shown that prognosis for survival is best for those thalassemia patients in whom serum ferritin levels can be maintained below 2500 μg/L,¹³ but at the same time some patients who receive ideal management in terms of present standards do develop significant endocrine damage.¹⁴ A multicenter study¹⁰ found that 22% of their thalassemia patients had endocrine complications, with a

serum ferritin level below 2000 µg/L. Thus it is very reasonable to believe that there are other possible factors as well responsible for organ damage. Previous investigators have postulated different mechanisms, including individual sensitivity to iron damage,⁷ increased collagen deposition secondary to increased activity of the iron-dependent procollagen proline hydroxylase enzyme, with subsequent disturbed microcirculation in the parathyroid and pancreas,^{12,15} and chronic anemia.⁶

All the thalassemia patients reported who developed HPT were above the age of 10 years except for one,¹⁰ so HPT is primarily a disease of the second decade. From the preceding discussion, it is quite obvious that although optimal chelation therapy does reduce the incidence of HPT and other endocrine complications, nonetheless some patients will continue to develop HPT. Noncompliance is also common and will continue to compromise optimal therapy until some effective oral chelating agent is found. We often found it quite difficult to convince parents to start chelation therapy. Desferal also has different side effects, one of which is lens opacification, and it is important to note that HPT can give rise to cataract formation. Many thalasseemics have impaired cardiac function, and hypocalcemia in these patients can precipitate or aggravate cardiac failure.

In conclusion, despite the best management of thalassemia major patients, some cases of HPT will continue to arise and as most patients are asymptomatic, it is very important to actively look for them, starting from the early second decade of life, so that the treatment can be initiated without delay. If endocrinopathies can be prevented by bone marrow transplant (BMT) (which remains to be seen by longer follow-ups), this would be another point in favor of BMT, especially in those patients who are noncompliant with Desferal therapy.¹⁴

References

- Gabriele O. Hypoparathyroidism associated with thalassemia. *South Med J* 1971;64:115-6.
- News GH. Endocrinopathies in thalassemia major. *Acta Paediatr Scand* 1973;62:91.
- Oberklaid F, Seshadri R. Hypoparathyroidism and other endocrine dysfunction complicating thalassemia major. *Med J Aust* 1975;1:304-6.
- Flynn DM, Fairney A, Jackson D, Clayton DE. Hormonal changes in thalassemia major. *Arch Dis Child* 1976;51:828-36.
- McIntosh N. Endocrinopathy in thalassemia major. *Arch Dis Child* 1976;51:195-201.
- Costin G, Kogut MD, Hyman CB, Ortega JA. Endocrine abnormalities in thalassemia major. *Am J Dis Child* 1979;133:497-502.
- De-Sanctis V, Vullo C, Bagni B, Chiccoli L. Hypoparathyroidism in beta thalassemia major: clinical and laboratory observations in 24 patients. *Acta Haematol* 1992;88:105-8.
- Gertner JM, Broadus AE, Anast CS, Grey M, Pearson H, Genel M. Impaired parathyroid response to induced hypocalcemia in thalassemia major. *J Paediatr* 1979;95:210-3.
- Perignon F, Brauner R, Souberbielle JC, de-Montalembert M, Giroit R. Growth and endocrine function in major thalassemia. *Arch Fr Paediatr* 1993;50:657-63.
- Multicenter study of prevalence of endocrine complications in thalassaemia major. Italian Working Group On Endocrine Complications in Non-Endocrine Diseases. *Clin Endocrinol (Oxf)* 1994;42:581-6.
- Gutteridge JM, Halliwell B. Iron toxicity and oxygen radicals. In: Hershko C, editor. *Iron chelating therapy*. London: Baillière Tindall, 1989:195-256.
- Iancu T. Ultrastructural pathology of iron overload with special reference to endocrine glands. In: Pintor C, Corda R, De-Sanctis V, editors. *Workshop on endocrine problems in thalassemia*. Venezia: San Marco Scientific Publications, 1990:19-28.
- Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous β thalassemia. *N Eng J Med* 1994; 331:574-8.
- Grundy RG, Woods KA, Savage MO, Evans JPM. Relationship of endocrinopathy to iron chelation status in young patients with thalassemia major. *Arch Dis Child* 1994;71:128-32.
- Weintraub LR, Goral A, Grasso J, Franzblau C, Sullivan A, Sullivan S. Collagen biosynthesis in iron overload. *Ann N Y Acad Sci* 1988; 526:179-84.