ASSESSMENT OF SERUM CALCIUM AND PHOSPHORUS LEVELS AMONG TRANSFUSION-DEPENDENT BETA THALASSEMIA MAJOR PATIENTS ON CHELATION THERAPY

Salva Shah

[1] Kabir Medical College, Peshawar - Pakistan.
Address for correspondence:
Dr. Salva Shah
Kabir Medical College, Peshawar - Pakistan.
E-mail: adeel.gillani123@gmail.com
Date Received:
December 7, 2014
Date Revised:
September 12, 2015
Date Accepted:
November 10, 2015

ABSTRACT

Objectives: to determine the levels of calcium and phosphorus in transfusion-dependant β-thalassemia major patients who were on chelation therapy being followed at Fatimid Foundation, Peshawar.

Methodology: This study included 100 β-thalassemia major patients who were diagnosed by Hb electrophoresis and were receiving regular blood transfusions for anemia and chelation therapy for prevention of iron overload related complications. Detailed history and examination including height and weight were recorded on pre-designed questionnaire and blood samples were taken for measurement of serum calcium and phosphorus. These tests were performed on "Microlab 200" via commercially available kits. Data was analysed using SPSS version 20.

Results: Frequency of hypocalcemia was 49% in our study. Hyperphosphataemia was associated with 53% of hypocalcemic patients (Hypoparathyroidism was suspected in 26 patients). Mean serum calcium was 8.46±0.94mg/dl while mean phosphate level was 5.33±0.77mg/dl in the subjects. Mean age of positive cases was 13.84 ± 3.98 years.

Conclusion: Low serum calcium is very prevalent in transfusion-dependent beta thalassemia major patients in our set up possibly due to poor chelation as was confirmed by our study where 49% of patients had hypocalcemia. Hypocalcemia in iron overload patients is mostly chronic and asymptomatic.

Key Words: Thalassemia, Transfusion dependent, Chelation

This article may be cited as: **Shah S. Assessment of serum calcium and phosphorus levels among transfusion-dependent βeta thalassemia major patients on chelation therapy. J Postgrad Med Inst 2015; 29(3): 168-71.**

INTRODUCTION

The term Thalassemia was coined by George Whipple in 1936. The name is derived from Greek: thalassa, meaning "sea" and haima meaning "blood", probably based on the observation that most early cases were of the Mediterranean origins[1]. Thalassemias, autosomal recessive disorders, are among the most prevalent genetic[1,2] and major hemoglobin disorders globally[3].

β-thalassemia results from defective synthesis of beta globin units of hemoglobin, resulting in reduced or absent synthesis of beta globin leading to a spectrum of phenotypic manifestations[4]. In Southern Asia, the prevalence of β thalassemia has been reported to be from as low as 2% to as high as 28% in various studies[5,6]. In Pakistan, 70000 people are estimated to be suffering from thalassemia and new cases reported annually are about 6000[7].

β-thalassemia major patients present within the first year of their life and require regular lifelong blood transfusions for correction of anemia[8,9]. These frequent transfusions lead to iron overload which itself is fatal by the second decade of life[10]. With the advent of chelation therapy, the survival of thalassemia major patients have increased and they are entering even into third and fourth decades of life[11]. Desferrioxamine is the preferred chelating agent used[12].

Inspite of chelation therapy, iron overload related complications like endocrinopathies are still occuring. It is recommended that serum ferritin (Marker of iron overload) should be maintained below 2500 µg/L for good prognosis, however it is shown that in patients whose serum ferritin level was below 2000 µg/L, even they developed endocrine problems. Thus there might be other mechanisms too responsible for these problems. Common endocrine disorders reported in β-thalassemia major patients are short stature, hypogonadism, hypoparathyroidism, hypothyroidism and diabetes mellitus[13].

Many studies have been done on endocrine disor-

ders including hypoparathyroidism in thalassemia patients and frequency reported varies from centre to centre but largest study so far done included 1861 patients from 25 centres and showed that 3.6% β -thalassemia major patients had hypoparathyroidism[14]. In Pakistan a study showed a very high prevalence of hypoparathyroidism of 40%[7].

Hypocalcemia occurring in β-thalassemia major is attributed to hypopoparathyroidism mainly. Low parathyroid hormone levels lead to excessive calcium loss in urine, decrease bone remodeling and decreased intestinal absorption of calcium[15]. Hypocalcemia is a common biochemical abnormality which may be asymptomatic in mild cases or present as acute life threatening crisis. Chronic hypocalcemia complications are mainly those of bone disease. In addition, severe hypocalcemia can result in cardiovascular collapse, hypotension which does not respond to fluids and dysrrythmias. Neurological complications of low serum calcium are acute seizures, tetany, basal ganglia calcification, parkinsonism, hemiballismus and choreoathetosis[16].

The current study was designed for assessment of serum calcium and phosphorus among transfusion-dependent β thalassemia major patients in our set up where delay in starting chelation therapy and non-compliance is common. This study will be useful in setting recommendations regarding Calcium and Vitamin D supplementation and periodic assessment of calcium levels among transfusion-dependant β thalassemia major.

Transfusion-dependant patients were defined as those who require regular blood transfusions for their survival after every 2-4 weeks with the aim of maintaining pre-transfusion Hb of 9-10 g/dl[17].

METHODOLOGY

It was a descriptive cross-sectional study conducted on 100 patients who were attending Fatimid Foundation, Peshawar, regularly for their follow up. Ethical approval was taken. Patients included were those who were diagnosed as β-thalassemia major on haemoglobin electrophoresis, transfusion-dependant and on chelation therapy, aged between 5 to 20 years of age and patients giving informed consent. Patients excluded were those suffering from renal disease, patients having malabsorption syndrome, seriously ill patients, or those taking drugs that effect serum calcium level like antiepileptics, bisphosphonates, diuretics, proton pump inhibitors, aminoglycosides and cisplatin and patients who were not willing for participation in this study.

Patients who were receiving frequent blood transfusions to maintain a pre-transfusion haemoglobin level of 9 g/dL and were on chelation therapy with Desferrioxamine or Deferiprone were selected for this study. Detailed information of the patients was recorded on pre-designed questionnaires. 3 ml of blood was taken from patients in plain tubes with gel through venipuncture. Blood was allowed to clot at 37 degree centigrade for 10-15 minutes and then centrifuged for separating the ser um for 10-15 minutes approximately at 1800 rpm. Sera obtained were stored at -20 degree centigrade till further analysis. Serum calcium and phosphate were measured on semi-automated analyzer through commercially available kits.

Data was analyzed using SPSS version 20. Results were analyzed via descriptive statistical methods employing mean, standard deviation and range.

RESULTS

Mean serum calcium levels of participants of this study was 8.46±0.94 mg/dl. The range observed was 6-11mg/dl whereas the normal range of serum calcium are 8.6 to 10 mg/dl, so the frequency of hypocalcemia was very high in this study i.e. 49%. The mean phosphorus level was 5.33±0.77mg/dl and the range being 4 to 6.90 mg/dl. 26 out of 100 patients had hypocalcemia associated with hyperphosphatemia, the cause of which was hypoparathyroidism most probably, however, confirmation is required by doing parathyroid harmone assay (PTH).

The age range was 5 to 20 years in this study and the mean age noted was 13.62±3.78 years. 53 patients were males and 47 were females. Mean age at start of blood transfusions was 5.8±4.027 months and mean age at start of chelation therapy was 6.54±3.24 yrs. Deferrioxamine was the most frequent chelating agent used by 45% of participants of the study. Symptoms of hypocalcemia were positive only in 15 patients while 34 patients were asymptomatic.

Table 1: Serum calcium and phosphorus levels (n=100)

	Mean	Std. Deviation
S. Calcium	8.469	0.9419188
S. Phosphorus	5.334	0.77241

DISCUSSION

Beta thalassemia major is the most prevalent hemolytic anemia in children and adolescents specially in areas where consanguinity is common. The use of regular transfusions with chelation has improved the quality of life in such patients but endocrine complications due to iron overload still do occur in these patients[18]. Hypoparathyroidism leading to low calcium and high phosphorus levels is one of these complication typically occuring in second decade of life[19]. Many mechanisms have been proposed so far for elaboration of glandular damage occuring via iron overload. These include formation of free radicals and lipid peroxidation leading to lysosomal, sarcolemmal and mitochndrial membrane damage and a number of cell surface transferrin receptors and cell's ability of protection against inorganic iron[20]. Serum calcium and phosphate levels have been determined by many before in thalassemic patients. Many of them found hypocalcemia associated with hyperphosphatemia[18,19,21] but few reported no change in mean calcium and phosphate levels[22,23]. Hypocalcemia is reported to be 16.6% by Dresner et al,[24] while Gulati et al,[25] reported it to be 13.5% and hyperphosphatemia was found in 60% of those who had hypocalcemia. Hypocalcemia and hyperphosphatemia was detected in 22% and 18% respectively by Mirrhosseini et al,[26]. In Pakistan hypocalcemia in thalassemic patients is reported to be 35.3%[7]. In our study the mean serum calcium levels came out to be very low. The reason for this might be delay in starting chelation therapy and poor compliance with the therapy.

Patients with low serum calcium increased with age and it was noted that at age of 13 or above percentage of hypocalcemics increased to 50%.

Hypocalcemia increases as the patient grows older because the need for transfusions also rises as a consequence of increasing growth, expansion of bone marrow, hypersplenism or from auto antibody production which causes hemosiderosis and organ dysfunction.

Hypocalcemia was mostly asymptomatic in such patients. This was in agreement with the previous studies who also proposed that iron overload related hypocalcemia is mostly chronic and symptomless.

CONCLUSION

Low serum calcium is very prevalent in transfusion-dependant beta thalassemia major patients in our set up possibly due to poor chelation as was confirmed by our study where 49% of patients had hypocalcemia. Hypocalcemia in iron overload patients is mostly chronic and asymptomatic, therefore such patients should be periodically assessed for calcium and PTH and where needed calcium and vitamin D supplements should be advised.

REFERENCES

1. Marengo-Rowe AJ. The thalassemias and related disorders. Proc (Bayl Univ Med Cent) 2007; 20:27-31.
2. Lahiry P, Al-Attar SA, Hegele RA. Understanding Beta-Thalassemia with Focus on the Indian Subcontinent and the Middle East. Open Hematol J 2008; 2:5-13.
3. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86:480-7.
4. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis 2010; 5:11.
5. Mohanty D, Colah RB, Gorakshakar AC, Patel RZ, Master DC, Mahanta J, et al. Prevalence of ß-thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. J Community Genet 2013; 4:33-42.
6. Uddin MM, Akteruzzaman S, Rahman T, Hasan AK, Shekhar HU. Pattern of ß-Thalassemia and Other Haemoglobinopathies: A Cross-Sectional Study in Bangladesh. ISRN Hematol 2012; 2012:659191.
7. Adil A, Sobani ZA, Jabbar A, Adil SN, Awan S. Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. J Pak Med Assoc 2012; 62:307-10.
8. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. Am Fam Physician 2009; 80:339-44.
9. Thalassemia International Federation. Endocrine complications of thalassemia major; Guidelines for clinical management of thalassemia. Thalass Int Feder 2000:41.
10. Lokeshwar MR. Progress in the Management of Thalassemia. Indian Pediatr 2006; 43:503-6.
11. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedqilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in β thalassemia major: a multicenter study in Tehran. BMC Endocr Disord 2003; 3:4.
12. Maggio A, D'Amico G, Morabito A, Capra M, Ciaccio C, Cianciulli P, et al. Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. Blood Cells Mol Dis 2002; 28:196-208.
13. De Sanctis V, Eleftheriou A, Malaventura C. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev 2004; 2:249-55.
14. Aleem A, Al-Momen AK, Al-Harakati MS, Hassan A, Al-Fawaz I. Hypocalcemia due to hypoparathyroidism in β thalassemia major patients. Ann Saudi Med 2000; 20:364-6.
15. Cooper MS, Gittoes NJ. Diagnosis and management of

hypocalcemia. Br Med J 2008; 336:1298-302.

16. Liamis G, Millionis HJ, Elisaf M. A review of drug induced hypocalcemia. J Bone Miner Metab 2009; 27:635-42.
17. Thein SL, Rees D. Haemoglobin and the inherited disorders of globin synthesis. In: Hoffbrand AV, Catovsky D, Tuddenham EGD, Green AR, editors. Postgraduate hematology. 6th ed. London: Wiley Blackwell Publishing; 2011: 83-108.
18. Sleem GAAM, Al-Zakwani IS, Almuslahi M. Hypoparathyroidism in adult patients with B thalassemia Major. Sultan Qaboos Uni Med J 2007; 7:215-8.
19. Goyal M, Arora P, Lal H. Parathyroid and calcium status in patients with thalassemia. Indian J Clin Biochem 2010; 25:385-7.
20. Aleem A, Al-Momen A K, Al-Harakati M S, Hassan A, Al-Fawaz I. Hypocalcemia due to hypoparathyroidism in β thalassemia major patients. Ann Saudi Med 2000; 20:364-6.
21. Angelopoulos NG, Goula A, Rombopoulos G, Kaltzidou V, Katounda E, Kaltsas D, et al. Hypoparathyroidism in transfusion-dependent patients with β thalassemia. J Bone Miner Metab 2006; 24:138-45.
22. Mahachoklertwattana P, Sirikulchayanonta V, Chuansumrit A. Bone histomorphometry in children and adolescents with β thalassemia disease: Iron-associated focal osteomalacia. J Clin Endocrin Metabol 2003; 88:3966-72.
23. Dandona P, Menon RK, Houlder S. Serum 1,25 dihydroxyvitamin D and osteocalcin concentration in thalassemia major. Archives of disease in childhood 1987; 62:474-7.
24. Dresner Pollack R, Rachmilewitz E, Blumenfeld A, Idelson M, Goldfarb AW. Bone mineral metabolism in adults with beta-thalassaemia major and intermedia. Br J Haematol 2000; 111: 902-7.
25. Gulati R, Bhatia V, Agarwal SS. Early onset of endocrine abnormalities in β thalassemia major in a developing country. J Pediatr Endocrinol Metab 2000; 13:651-6.
26. Mirhosseini NZ, Shahar S, Ghayour-Mobarhan M, Banihashem A, Kamaruddin NA, Hatef MR . Bone-related complications of transfusion-dependent β thalassemia among children and adolescents. J Bone Miner Metab 2013: 31:468-76.