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Parathyroid Hormone Profile In Sickle Cell Disease In School Aged Children

Hosny Mohamed Ahmed El-Masry[1], Mostafa Abd-Elazeem Hassan[1], Alaa Mohamed Hashem[2], Abdullah Arafa Shaban[1]*

Departments of [1]Pediatrics and [2]Clinical Pathology, Faculty of Medicine, Al-Azhar University, Assiut, Egypt

***Corresponding author**: Abdullah Arafa Shaban, **Mobile:** (+20) 01007558708, **E-Mail:** abdullaharafa@gmail.com

ABSTRACT

Background: Sickle cell disease (SCD) is group of hemoglobinopathies associated with hemolytic anemia and vaso-occlusive complications. All forms of SCD are inherited in an autosomal recessive fashion. Parathyroid hormone plays an essential role in calcium and phosphorus homeostasis, which is achieved by its action on target organs (intestine, bone and kidney), leading to normal bone formation and mineralization and normal physiological concentration of calcium and phosphorus.

Objectives: This study aimed to detect the effect of sickle cell disease on parathyroid hormone and consequently on serum calcium (S.Ca), phosphorus (ph), alkaline phosphatase (alk.Ph) and magnesium (Mg) on patients with sickle cell anemia.

Subjects and Methods: Forty children known as sickle cell disease patients, twenty of them were SCD (HbSS) (11 males and 9 females). The other twenty were known SC trait (10 males and 10 females). The ages of the children ranged from 5 to 15 years old. All were in non-crises state in routine Outpatient Clinic visits, compared to twenty apparently healthy, age matched and with normal hemoglobin from Atfal Masr Hospital as control. Neither patients nor control received calcium supplementation before the study.

Results: The results indicated that sickle cell patients and sickle cell trait patients had hypocalcaemic tendency associated with supernormal parathyroid hormone level and implied impaired calcium absorption from intestine leading to disturbed calcium metabolism, which might contribute in skeletal changes seen in sickle cell patients.

Conclusion: We found that there was statistically significant decrease in serum Ca levels accompanied with increase in serum PTH, ph, alk Ph and Mg levels in SCD and Sickle cell trait patients compared to control group.

Keywords: Sickle cell disease, Sickle cell trait, Parathyroid hormone profile, Serum calcium, phosphorus.

INTRODUCTION

Many studies have been made in the management of both acute and chronic complications of sickle cell disease with a significant improvement in the life expectancy of a child born today. In sickle cell anemia, HbS is commonly as high as 90% of the total hemoglobin while in sickle cell trait, HbS is ≤ 50% of all hemoglobin [(1)]. Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the sixth codon of the β-globin gene. This change encodes valine instead of glutamine in the 6th position in the β-globin molecule [(2)].

In red blood cells, the hemoglobin molecule has a highly-specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain mutations, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the hemoglobin tetramer and in the deoxygenated state. HbS molecules can now interact with each other forming rigid polymers that give the red blood cell its characteristic "sickled" shape. The lung is the only organ capable of reversing the polymers, and any disease of the lung can be expected to compromise the degree of reversibility [(2)].

The most commonly used procedures for newborn diagnosis is high-performance liquid chromatography (HPLC). A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit and after 6 months of age to determine the final hemoglobin phenotype. In addition, a complete blood cell count (CBC) and hemoglobin phenotype determination is recommended for both parents to confirm the diagnosis and to provide an opportunity for genetic counseling [(3)].

Physiological concentrations of plasma calcium and phosphorus are necessary to ensure skeletal integrity and to maintain vital physiological processes, including muscle contraction, coagulation, energy metabolism, and neuronal excitation. Calcium and phosphorus homeostasis is regulated by both hormonal and non-hormonal factors. Increased appreciation of these complex interactions allows for a deeper understanding of the pathophysiology of the clinical disorders that occur with disturbance of this delicate balance [(4)].

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases. PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1, 25-dihydroxycholecalciferol (1, 25(OH) 2D3). The increased level of 1, 25(OH) 2D3 induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa resulting in absorption of calcium.

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PTH also mobilizes calcium by directly enhancing bone resorption and increase calcium level [5].

This study aimed to detect the effect of sickle cell disease on parathyroid hormone and consequently on serum calcium (S.Ca), phosphorus (ph), alkaline phosphatase (alk.Ph) and magnesium (Mg) on patients with sickle cell anemia.

SUBJECTS AND METHODS

Forty children known as sickle cell disease patients, twenty of them were SCD (HbSS) (11 male and 9 female). The other twenty were known SC trait (10 male and 10 female). They were aged from 5 to 15 years old. All were in non-crises state during routine Outpatient Clinic visits compared to twenty apparently healthy, age matched and HbAA as control from Atfal Masr hospital. Neither patients nor control received calcium supplementation before the study. Subjected patients were divided into three groups, group one with normal Hb, group two with HbS > 90%, and group three with HbS < 50%. All of them were subjected to full history taking, clinical examination and investigation in the form of serum calcium, phosphorus, alkaline phosphatase, magnesium and parathyroid hormone levels.

Inclusion criteria: Children aged from 5 to 15 years old with Hb electrophoresis to distinguish between normal children and children with SCD and sickle cell trait. All of them are symptom free and have no any acute illness.

Exclusion criteria: Children out of age range, suffering from any SCD symptoms or having any acute illness.

Ethical consideration: Oral and written consent was taken from parents or guardians of each patient. The aim of the work was explained to the parents before collection of the data. The privacy of the collected data were assured. **An approval of the study was obtained from Al- Azhar University academic and ethical committee.**

All children included in this study were subjected to the following:

Full history: including family history, hospitalization, medications, and low serum calcium manifestation.

Clinical assessment: including general examination, vital signs, and detection of any exclusion criteria.

Investigations: including serum calcium, serum phosphorus, serum alkaline phosphatase, serum parathyroid hormone, and serum magnesium.

Statistical analysis

Data were analyzed by using SPSS version 22. Summary of measures was reported as mean ± standard deviation (SD) for quantitative variables such as age and weight, while categorical variables such as sex and Tanner stage were represented as percentages. A comparison between 2 quantitative data was analyzed by independent t-test. The correlation between two variables was done by using the Pearson correlation test to identify the degree of correlation of numerical variables. P-value ≤ 0.05 was considered statistical significance and highly significant when $P \leq 0.001$.

RESULTS

The results of our study are illustrated in tables (1-3)

Table (1): Mean age and sex distribution

	Group 1	***Group 2***	***Group 3***	**Significance (P-value)**		
				Group 1 vs. Group2	**Group 1 vs. Group3**	**Group 2 vs. Group 3**
Age (years) Mean ± SD	10.90 ± 5.66	11.55 ± 2.9	11.25 ± 3.09	0.618	0.788	0.818
Sex: Male	11	10	10	Total 31		
Female	9	10	10	29		

Group 1= control group. Group 2 = HbSS. Group 3 = sickle cell trait.

Concerning age and sex, table (1) showed that there was no difference between the studied groups.

Table (2): comparison between studied groups regarding hemoglobin level (gm/dl)

	Group 1	***Group 2***	***Group3***	***Significance (P- value)***		
				Group 1 vs. Group2	**Group 1 vs. Group3**	**Group 2 vs. Group 3**
Mean ± SD	12.12 ± 1.53	6.90 ± 0.69	7.38 ± 0.62	0.001	0.001	0.148

Group 1= control group. Group 2 = HbSS. Group 3 = sickle cell trait.

Regarding Hb, table (2) showed that there was significant p-value between group1 vs. group 2 and group 1 vs. group 3 and insignificant p-value between group 2 vs group 3.

Table (3): Comparisons between studied groups concerning s. Ca, s. ph, s. alk. ph. parathyroid hormone and s.Mg

Chemical measures	*Control (G1)*	*HbSS (G2)*	*Sickle cell trait (G3)*	*Significance (p-value)*		
				Group 1 vs. Group2	Group 1 vs. Group3	Group 2 vs. Group 3
***S. Ca* (mg/dL)** Mean ± SD	9.14 ± 0.67	7.41 ± 0.62	8.09 ± 0.78	0.001*	0.001*	0.003*
S. ph. Mean ± SD	2.53 ± 0.35	4.06 ± 0.69	3.90 ± 0.45	0.001*	0.001*	0.345
***Alk. ph.* (IU/L)** Mean ± SD	67.70 ± 19.73	150.50 ± 29.23	149.75 ± 27.41	0.001*	0.001*	0.927
***S. PTH* (pg/mL)** Mean ± SD	34.55 ± 3.04	65.20 ± 2.41	53.35 ± 6.96	0.001*	0.002*	0.041*
***S. Mg* (mg/dL)** Mean ± SD	2.01 ± 0.21	2.41 ± 0.27	2.18 ± 0.35	0.001*	0.063	0.013*

S.ca= serum calcium, s.ph= serum phosphorus, alk ph = alkaline phosphatase, s.PTH = serum parathyroid hormone, S.Mg = serum magnesium

Group 1= control group, – Group 2 = HbSS and Group 3 = sickle cell trait.

Comparisons between parathyroid hormone profiles in studied groups showed significant p-value in S.ca, S.ph, alk.ph, S. Mg, S.PTH.

DISCUSSION

The results presented showed the concentrations of some biochemical parameters related to calcium metabolism in SCD. There were no sex or age differences in these concentrations in either the control or the patients.

Sickle cell disease is a phenotype that results from different genotypes. Although the complications of disease are found in all genotypes while genotypes with higher cellular concentration of HbS are clinically more severe. Within milliseconds to seconds after HbS deoxygenation, depending on the intracellular concentration of HbS, HbS polymer appears in the sickle erythrocyte and cause sickling [(6)].

Vasoocclusion by sickle shaped RBCs and their hemolysis are the hallmarks of SCD. Acute and chronic body pains which are common clinical symptoms in SCD are understood to be due to vasoocclusion. All painful events in SCD may not be sickle cell related. Other systemic disorders including some endocrine disorders like hyperparathyroidism, which commonly cause musculoskeletal pain may be present concurrently with SCD[(7)]. Hyperparathyroidism may be primary, secondary, or tertiary. Primary hyperparathyroidism (PHPT) is due to over secretion of PTH most commonly from a parathyroid adenoma [(8)]. Most new patients are asymptomatic at the time of diagnosis with PHPT. The classical symptoms of PHPT are due to combined effects of increased PTH and calcium. Complaints of weakness and fatigue are common among patients with PHPT [(9)].

Other manifestations include nephrolithiasis, bone disease, constipation, polyuria, and polydipsia. There is a wide spectrum of involvement of the skeletal system in hyperparathyroidism. Effects can range from generalized bone pains to asymptomatic patients with decreased bone densitometry and increased risk of fractures [(10)].

Secondary and tertiary hyperparathyroidism occur in patients with chronic kidney disease. Tertiary hyperparathyroidism is characterized by severe parathyroid hyperplasia with autonomous secretion of PTH that is no longer adequately responsive to the plasma calcium concentration. This causes high bone turnover and abnormal mineralization [(10)].

In our study regarding serum calcium, there was significant decrease in SCD patients more than sickle cell trait group (P value 0.003) and control group (p value 0.001). In addition, there was decrease in serum calcium in sickle cell trait and control group (p value 0.001) and that finding is in agreement with **da Silva *et al.*** [(7)] and **van der Dij *et al.*** [(12)].

As regards serum phosphorus and alkaline phosphatase, there was significant increase in sickle cell group more than control (p value 0.001). Sickle cell trait group was also significantly increased more than control (p value 0.001). There was no significant difference between sickle cell group and sickle cell trait group (p value 0.345 & 0.927) respectively.

Regarding parathyroid hormone, there was significant increase in sickle cell group more than control group (p value 0.001). Also, PTH level was significantly increased in sickle cell trait group (p value 0.002). Our findings are in agreement with **Elshal *et al.*** [(13)] and **van der Dij *et al.*** [(12)] who reported increase in S. PTH level in patients with sickle cell anemia and

referred that to other factors specially to low S. Ca in long period.

Although dietary intake of calcium and vitamin D (in the form of milk and milk-products) by both sickle cell patients and controls were not included by our study, but it seems to be adequate, most of the studied patients had an altered status of calcium. Therefore, subnormal dietary calcium intake neither explains the hypocalcaemic tendency.

Hence, it is possible that intestinal absorption of calcium is impaired in some of the patients which agree with previous reports of abnormal digestive and absorptive functions in SCD. Abnormal absorption of fat and fat-soluble materials, such as vitamin E, increased fecal fat excretion associated with bulky stool. It is also well known that non-sickle cell patients suffering from fat mal-absorption usually have poor absorption of calcium. With all of the above-mentioned abnormalities in SCD, it is likely that digestive and the absorptive function is impaired, which would explain the low serum calcium observed in some of the studied SC patients.

It can be concluded that more than one factor is playing a role in the disturbance of calcium metabolism seen in our patients.

However, the digestive and absorptive malfunctions may remain the major ones. The impaired calcium absorption leads to decreased ionized calcium in the plasma, which in turn stimulates the secretion of PTH in an attempt to correct the disturbance. The elevated levels of PTH in our patients may be seen as appropriate resulting from the physiological adjustment in response to a hypocalcaemic tendency [(14)].

CONCLUSION

Our study demonstrated that there was a significant decrease in serum Ca, in patients with SCD and Sickle cell trait in comparison with control group. That was accompiend with high level of PTH, S.Ph, alk. phosphatase and S. Mg in patients with SCD and sickle cell trait in comparison with control group**.**

RECOMMENDATION

- S.ca S.ph and PTH follow up is mandatory to all patients with SCD or SC trait to be warned early.
- Calcium supplementation for affected children is needed.
- Further studies with more investigation are needed to evaluate the effect of SCD on more systems of the body.

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