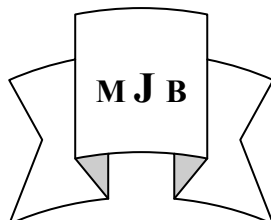


Prevalence of Diabetes and Hypocalcemia among Thalassemic Patients in Thalassemia Center in Babylon Governorate

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Abstract

A prospective study was conducted on 129 patients with thalassemia, classified as 67 patients with β -thalassemia major, 52 patients β -thalassemia intermedia and 10 patients with sickle cell thalassemia, who were attending the thalassemia center at Babylon Maternity and Children teaching Hospital, from period of July 2008 to April 2009, their age ranged from 6 months – 26 years with mean age of 10.9 years. They were studied for diabetes and hypocalcemia. Four patients (3.1%) have diabetes and 28 patients (21.7%) have hypocalcemia with a mean level of serum calcium 1.61 ± 0.23 mmol/L in comparison to control group where they have 0 % diabetes and 10 patients (10%) hypocalcemia with mean level of serum calcium 1.9 ± 0.16 mmol/L.

Risk factors for diabetes are age older than 15 years, frequent blood transfusion of more than 200 units and S. ferritin of more than 2000 μ g/L. While, in hypocalcemia, the risk factors are age older than 5 years, blood transfusion of more than 50 unit and S. ferritin of more than 1000 μ g/L.

Also the study showed that diabetic patients associated with 100% short stature, 75% (hepatitis, heart failure, and delay sexual development) and 25% hypothyroidism. While in hypocalcemic patients associated with 75% short stature, 50% delay sexual development, 32.2% heart failure, 21.4%hepatitis, and 17.8% hypothyroidism.

الخلاصة

دراسة مستقبلية، اشتملت على ١٢٩ مريضاً مصاباً بفقر الدم البحرى نوع بيتا صنفوا إلى ٦٧ مريضاً مصاباً بفقر دم البحرى الكبير، و ٥٢ المتوسط و ١٠ مريضاً مصاباً بفقر دم البحرى المنجلي. الذين راجعوا مركز فقر الدم الوراثى في مستشفى الولادة والأطفال في مدينه الحلة (محافظة بابل) للفترة من تموز ٢٠٠٨ إلى نيسان ٢٠٠٩. تراوحت أعمارهم من ٦ شهر إلى ٢٦ سنة وبمعدل عمري ١٠,٩ سنة. تمت الدراسة عليهم لتحديد المصابين بمرض داء السكرى وانخفاض نسبة الكالسيوم في مصل الدم. اربعة مرضى (٣,١ %) مصابين بداء السكرى و ٢٨ مريض (٢١,٧ %) مصابين بانخفاض الكالسيوم في مصل الدم. المعدل الحسابى لمستوى الكالسيوم في مصل الدم (1.61 ± 0.23 مل مول / لتر)، مقارنة بمجموعه السيطرة الذين ليس بينهم مصابين بداء السكرى (٠,٠٠ %) وبينهم (١٠ %) مصابين بانخفاض مستوى الكالسيوم والمعدل الحسابى للكالسيوم بمصل الدم (1.9 ± 0.16 مل مول / لتر). عوامل الخطورة للمصابين بداء السكرى هو العمر (أكبر من ١٥ سنة)، تكرر نقل الدم لأكثر من ٢٠٠ وحدة، ومستويات الفيريتين في مصل الدم أكثر من ٢٠٠٠ مايكروغرام / ليتر. بينما عوامل الخطورة للمصابين بنقص مستوى الكالسيوم في مصل الدم هو العمر (أكثر من ٥ سنة)، تكرر نقل الدم أكثر من ٥٠ وحدة ومستوى الفيريتين في مصل الدم (أكثر من ١٠٠٠ مايكروغرام / ليتر). التهاب الكبد الفيروسي، عجز القلب و، أيضاً الدراسة أظهرت بان المرضى المصابين بداء السكرى يعانون من قصر القامة (١٠٠ %) تاخرالنمو التناسلي (٧٥ %) و نقص إفراز الغدة الدرقية (٢٥ %). بينما المصابين بانخفاض مستوى الكالسيوم بمصل الدم يعانون من قصر القامة (٧٥ %)، تاخرالنمو التناسلي (٥٠ %)، عجز القلب (٣٢,٢ %) التهاب الكبد (٢١,٤ %) و (١٧,٨ %) قصور في إفراز الغدة الدرقية.

Thalassemia are genetic disorder in globin chain production, resulting

Introduction

from either a complete absence of β -globin chain production (β o thalassemia) or a partial reduction (β + thalassemia), while in α thalassemia, the α globin gene production is either absent or partially reduced.[1]

Anemia is resulting from ineffective erythropoiesis and from hemolysis[2], presents clinically in β - thalassemia major within first year of life (commonly in second six month) and subsequently require regular blood transfusion to survive, or those presented later after two years which seldom needs transfusion are said to have thalassemia intermedia.[3]

A decision to initiate regular transfusion may be difficult and based on the presence and severity of symptoms and signs of anemia including failure of growth and development.[4]

The goals of transfusion include correction of anemia, suppression of erythropoiesis and inhibition of increased gastro-intestinal absorption of iron.[5]

Regular red blood cells (RBC) transfusions eliminate the complication of anemia, compensatory bone marrow expansion and permit normal development through out children and extend survival [4]. In parallel, transfusion result in a second disease while treating the first, that of the inexorable accumulation of tissue iron that without treatment is fatal in the second decade of life.[4] The toxicity of iron is mediated by its catalysis of reactions which generate free hydroxyl radicals propagators of oxygen related damage which induce lipid peroxidation of cell organelles including mitochondria, lysosomes and sarcoplasmic membrane.[4]

Iron unbound to storage or transport proteins is particularly toxic in this regard, while in normal individuals, tight binding of plasma iron to the transport protein transferrin, prevent

the catalytic activity of iron in free radical production.[4] In very heavily iron loaded patients, transferrin become fully saturated and non transferrin bound fraction of iron become detectable in plasma [4] which accelerate the formation of free hydroxyl radical, facilitate uptake of iron by tissue [4]. The effectiveness of an iron chelating agents depends in part on its ability to bind non transferrin bound iron over sustained period of time, therefore decreasing tissue uptake and iron catalyzed toxic reaction.[4]

Iron overload before introduction of iron chelating agent was a frequent cause of morbidity and mortality [6], death was often due to cardiac failure, which typically before the patients reached 20 years of age [6]. Iron chelating agents has improved the prognosis [7] and resulted in one of the most dramatic alterations in morbidity and mortality[4].

Inspite of blood transfusion and iron chelating agent, iron related complications still common [6]. Growth, sexual development, fertility, bone mineral density, diabetes, hypothyroidism, hypoparathyroidism and hypogonadism are the main issue be addressed in the long term follow up of patients with thalassemia [8]. Increased echogenicity of the pancreas due to hemosiderosis is a frequent laboratory finding in children and adolescent with β - thalassemia [9].

Diabetes mellitus in patients with thalassemia major is caused by secondary hemochromatosis due to transfusional iron overload, its mechanism from siderosis are still poor understood [10], has been attributed to impaired secretion of insulin secondary to chronic pancreatic iron overload [4] and to insulin resistance which interfere with the insulin ability to suppress hepatic

glucose uptake or decrease glucose uptake by muscle [11].

With advancing age, a persistent insulin resistance along with decrease in the circulating insulin level (due to declining beta cell function) leads to onset of glucose intolerance and frank diabetes mellitus [11].

However, even in the face of adequate chelating, a significant amount of carbohydrate metabolism dysfunction occurs [11], suggesting that the development of diabetes might be complicated by other factors like pancreatic autoimmunity, liver abnormality (cirrhosis, fibrosis, hepatitis C infection), family history of diabetes [11].

Thyroid function is usually well preserved in patients with iron overload, in contrast to parathyroid activity is frequently compromised (Functional hypo-parathyroidism can be demonstrated in many patients by inducing hypocalcemia with an intra venous bolus of ethylene-diamine tetra acetic acid (EDTA) which monitoring the production of parathyroid hormone) [12]. Also, it is well recognized complication of blood transfusion therapy secondary to iron deposition in parathyroid gland and was possibly more common in patients born or treated before given intensive chelating therapy [13].

Damage of parathyroid gland is through many factors like individual sensitivity to iron damage, increased collagen deposition secondary to increased activity of iron dependent procollagen proline hydroxylase enzyme with subsequent disturbed micro-circulation in the parathyroid [13].

Aim of Study

This study was carried out to determine:

1- The prevalence of diabetes and hypocalcemia among thalassemic patients in babylon thalassemic center.

2- The correlation of diabetes and hypocalcemia with certain variable factors including age, number of blood transfusion, serum ferritin, type of thalassemia and residence.

Patients and methods:

I- A total of 129 patients with thalassemia were studied (74 males and 55 females), aging from 6 months to 26 years with a mean age of 10.9 years, attending babylon thalassemic center in Babylon Maternity and Children teaching Hospital from period of July 2008 to April 2009.

II- Control group consisted of 100 randomly selected, healthy children visiting the out patients department for minor illness and some were admitted for other illness like urinary tract infection and respiratory tract infection, their ages ranged from 6 month to 14 years with mean age of 7.6 years. None of them had history of previous blood transfusion and they had no family history of hemoglobinopathies.

III- A detailed history and clinical examination was obtained for every patient (thalassemic children and control group).

IV- All patients were investigated by:

A- Blood aspiration for blood sugar, serum calcium, serum phosphorus, alkaline phosphatase, serum ferritin, PCV, WBC, infection screen for (Hepatitis Bs antigen, hepatitis C virus).

B- Urine analysis was done for all patients and controls.

C- Blood aspiration for thyroid function test and liver function for positive cases

only.

V- Diabetes is diagnosed by: [14].

A- Clinical features (symptoms of diabetes are polyuria, polydipsia, unexplained

weight loss , glucosuria) plus
B- Random blood sugar (RBS) $\geq$ 200 mg/dl. (11.1 mmol/L), or Fasting blood sugar

(FBS) $\geq$ 126 mg/dl. (7 mmol/L).

VI- Hypocalcemia resulting from hypoparathyroidism is variable from:
A- Asymptomatic which diagnosed by blood investigation only to symptomatic hypocalcemia like numbness, parasthesia , tingling sensation with stiffness and Supported by blood Investigations (decrease serum calcium and increase serum phosphorus

with normal alkaline phosphatase).

Normal serum calcium is 2.1 – 2.6 mmol/L.

Normal phosphorus is 0.8 -1.4 mmol/L.

Normal alkaline phosphatase is 30 – 90 U/L.

Statistical analysis

The statistical analysis utilized was Fisher test and t- test. P-value of less than 0.05 is considered to be significant and of less than 0.001 is considered to be highly significant.

Results

Table 1 Distribution of positive cases among thalassemic patients and control group.

Case	Thalassemic patients					Control group				
	DM	%	Hypocalcem.	%	Mean value in mmol/L	DM	%	Hypocalcem.	%	Mean value in mmol/L
Negative	125	96.9	101	78.3	2.3	100	100	90	90	2.5 ± 0.10
Positive	4	3.1	28	21.7	1.6 ± 0.23	0	0.0	10	10	1.9 ± 0.16
Total	129	100	129	100		100	100	100	100	

1- There was no significant difference of diabetes among thalassemic patients and

2- There was a significant difference of hypocalcemic patients in comparison to control group. $P < 0.05$.

3- There was highly significant difference of mean value of serum calcium among thalassemia in comparison to control group. $P < 0.01$.

control group. $P > 0.05$.

Table 2 Age distribution of positive cases in thalassemic patients.

Age in years	DM	%	Hypocalcemia	%	Total
< 5	0	0.0	1	5.2	19
$\geq 5 - < 10$	0	0.0	7	16.2	43
$\geq 10 - < 15$	0	0.0	7	25	28
$\geq 15 - < 20$	3	12	8	32	25
≥ 20	1	7.1	5	35.8	14
Total	4	3.1	28	21.7	129

1- There was highly significant increased of diabetes mellitus (DM) with increasing age of patients. $P < 0.001$.

2- There was a significant increased of hypocalcemia with increasing age of patients (more than 15 years). $P < 0.05$.

Table 3 Comparison of positive cases and number of blood transfusion.

Number of blood transfusion	D.M	%	Hypocalcemia	%	Total
< 50	0	0.0	0	0	20
≥ 50 – 200	0	0.0	14	17.5	80
≥ 200	4	13.79	14	48.27	29
Total	4	3.1	28	21.7	129

1- Diabetes and hypocalcemia were increased with increasing number of blood transfusion.

2- Statically the results were highly significant. $P < 0.001$.

Table 4 Distribution of cases according to level of serum ferritin.

Level of ferritin (μg/dl)	D.M	%	Hypocalcemia	%	Total
< 1000	0	0	0	0.0	30
≥ 1000 – 2000	1	1.5	15	23	65
≥ 2000	3	8.8	13	38.2	34
Total	4	3.1	28	21.7	129

There was a highly significant increase of D.M and hypocalcemia with increasing level of serum ferritin more than 1000μg/L. $P < 0.001$.

Table 5 Distribution of cases according to residence.

Residence	D.M	%	Hypocalcemia	%	Total
Urban	1	2.5	8	20.5	39
Rural	3	3.3	20	22.2	90
Total	4	3.1	28	21.7	129

There was no significant difference of D.M and hypocalcemia among urban and rural area. $P > 0.05$.

Table 6 Distribution of positive cases according to types of thalassemia.

Types of thalassemia	D.M	%	Hypocalcemia	%	Total
β-thalassemia major	2	2.9	12	17.9	67
β-thalassemia intermedia	2	3.8	14	26.9	52
Sickle thalassemia	0	0	2	20	10
Total	4	3.1	28	21.7	129

There was no significant difference of D.M and hypocalcemia among different types of thalassemia. $P > 0.05$

Table 7 Associated complication with positive cases.

Type of case	Short stature		Delay sexual development		Heart failure		Hepatitis		Hypothyroidism	
D.M (4)	4	100 %	3	75 %	3	75 %	3	75%	1	25 %
Hypoc. (28)	21	75 %	14	50 %	9	32.2 %	6	21.4 %	5	17.8 %

Short stature was a common associated complication of thalassemic patients with D.M and hypocalcemia, while hypothyroidism was a least associated.

Discussion

Thalassemia is the commonest hemolytic anemia with prevalence 4 – 13% [15] and the use of regular, frequent blood transfusion in thalassemia has improved the span and quality of life [10]. It leads to chronic iron overload which frequently causes endocrine problems[10].The most clinical manifestation of iron overload does not appear until the second decade of life in patient with inadequate chelation [4].The result of this study showed that thalassemic patients developed 3.1 % diabetes and 21.7% hypocalcemia. In comparison to control group (0.0% diabetes and 10% hypocalcemia). This result is similar to study done in Iraq [16, 17]. This indicated that thalassemia is a risk factor for these complication as result from iron overload which caused by chronic blood transfusion or increased absorption of iron from the digestive tract [2 ,4] leading to progressive organ dysfunction [4].

Our results for diabetes are lower than the results done in other areas of word like Italia 5.4% [18], Hong Kong 8.6% [19], Egypt 10.4% [20], Saudia Arabia 5% [13], Lebanese 12.5% [21], Iran 7.3 [22] and India 7.4% [23]. Lower results in our study could be due to either from patient's age who included in the study are commonly 90 patients from total129 patients in first

15 years which reverse to other studies which commonly after 15 years and from small sample size.

Hypocalcemia results in our study are similar to other study done in Iraq 21.7% [17]. Saudia Arabia 20% [13] and India 18.5%[23]. Our results of hypocalcemia are higher than diabetes result. This is because hypoparathyroidism may produce from other factors in addition to hemosiderosis like individual sensitivity to organ damage, increased collagen deposition secondary to increased activity of iron dependent protocollagen protein hydroxylase enzyme with subsequent disturbances microcirculation in parathyroid gland [13].

Diabetes and hypocalcemia are increased with increasing age of patients due to increased requirement of blood transfusion as result from increased growth, bone marrow expansion, hypersplenism or from developing auto antibody [2] causing hemosiderosis and organ dysfunction [4] as result from catalysis of reaction generates free hydroxyl radicals [4].

Also these endocrine problems are associated with increased number of blood transfusion and level of serum ferritin. The patient who transfused 100 – 200 ml of the pure red blood cells/kg/year getting 116 – 232 mg of iron/kg/year, thus with regular blood transfusion, iron store increased to many time the normal unless chelating therapy is given leading to free radical causing organ dysfunction [4]. There was no significant difference of

these endocrine problems according to residence. The percentage are more on rural areas than urban which may due to low education, poor family income, their address away from thalassemia centers making them more neglect and delay center visiting leading to more anemia, more absorption of iron from intestine with decreasing iron chelation and more complication. There was no significant difference among all types of thalassemia as risk of iron induces endocrine dysfunction are the same [2].

Although the percentage are increased in both major and intermedia, in compare to sickle

Conclusion

- 1- This study has revealed that the prevalence of diabetes and hypocalcemia among thalassemia patients were 3.1% and 21.7% respectively. The prevalence of diabetes is lower than that in other areas of the world. While in hypocalcemia, it is similar to other studies done in multiple centers of world like Iraq (Ibn-Albalady) Saudia Arabia and India , and (prevalence of hypocalcemia is higher than diabetes).
- 2- The prevalence of endocrine problems (diabetes and hypocalcemia) is directly related to age of patients, number of blood transfusion and serum ferritin level.
- 3- Short stature is commonest associated problems, while hypothyroidism is a least associated.

Recommendation

- 1- All thalassemic patients should be assessed regularly for diabetes and hypocalcemia especially for hypocalcemia which should be started and treated early.
- 2- Iron overload studies, liver function test should be done regularly to correlate with parameters of glucose metabolism.

thalassemia which could be explained by small sample size and less requirement of blood transfusion in sickle thalassemia in comparison to others [2].

Short stature is commonest associated complication with diabetes and hypocalcemia while hypothyroidism are the least which could be explained that growth retard may be affected by other factors in addition to iron overload like chronic anemia, chelation toxicity, zinc deficiency, psycho-social stress, in compare to hypothyroidism which caused mainly by iron overload.[24].

- 3- Bone marrow transplantation and hopefully gene therapy should be available to prevent organ siderosis.

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