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Oral Glucose Tolerance Test in Blood Transfusion Dependent Thalassemic Patients

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Abstract: ***Background: Beta thalassemia major is a common clinical problem we are facing it in our country, present transfusion protocols have increased the life expectancy of patient with beta thalassemia major, but iron overload is a major clinical complication of the treatment. Aim of the Study: This study is to determine the prevalence of diabetes mellitus and association of some factors with impaired glucose tolerance test in transfusion dependent beta thalassemia major. Patients and Methods: A case control study was done on a randomized group of patient with beta thalassemia major diagnosed by hemoglobin electrophoresis registered in thalassemia center in AL–Zahraa Teaching Hospital for Maternity and Children in AL- Najaf AL- Ashraf, during a period from 15 of January 2016 to 1st of May 2016. According to inclusion and exclusion criteria, a total number of 50 thalassemic patients included in this study all of them on blood transfusion as part of their treatment. And 50 patient control are healthy children chosen from visits to schools, with same age. Consent was obtained from the patients' first-degree relatives (mother or father) these patients were also informed that the results of the study would be provided to them as free useful laboratory tests. The patients were diagnosed with beta thalassemia major as recorded in their files(by Hemoglobin electrophoresis). The patients name, age, gender, time of first blood transfusion ,number of blood transfusion , time of starting of chelation treatment, period of chelation therapy, history of previous splenectomy ,hepatitis state, and family history of diabetes mellitus was taken and relevant systemic examination was done. Patient suffering from any acute illness, liver disease and previously diagnosed case of diabetes mellitus, were excluded, we define impaired Oral glucose tolerance according to World Health Organization. Results: There was Statistically significant association of Diabetes and glucose intolerance in thalasemic children (p-value<0.001), and significant association with higher age (p-value<0.001) and with low Hemoglobin (p-value<0.001) with prevalence of Diabetes and glucose intolerance in thalassemic children. Conclusion: The study showed increasing incidence of Diabetes mellitus and glucose intolerance in thalassemia children and this probability increases with low Hemoglobin and higher age.***

Keywords: Oral glucose tolerance test, thalassemia

1. Introduction

Thalassemia syndromes are the most common genetic disorder on worldwide bases, which is inherited on autosomal recessive bases.[(1)]Beta Thalassemia was first described by Cooley in 1925[(2)]. It is a genetic disorder of hemoglobin synthesis, characterized by absence or reduction in the synthesis of beta globin chain[(3,4)].

Beta thalassemia classified according to the severity into[(5)]:
1) Beta Thalassemia major (Homozygous or Cooley's anemia)
2) Beta Thalassemia minor (Heterozygous).
3) Beta Thalassemia intermedia.

Diabetes is a significant complication of beta thalassemia major. The cause may be cell destruction due to iron deposition, autoimmune disease, resistance to insulindue to hepatic disease and development of diabetes. Theestimates of prevalence are variable, ranging between 1% to 21% of patients attending a thalassemia service[(6,7)].Various etiological factors may contribute to development of diabetes in thalassemia. Transfusion iron overload is a key factor damaging pancreatic beta cells and causing diabetes.

Factors that increase the risk for occurrence of impaired glucose metabolism in thalassemia include :poor compliance to iron chelatingdrugs and late onset of chelation therapy[(8)]

Other possible etiological factors include abnormal insulin production from beta cell,[(9)] autoimmune disease,[(10)] insulin resistance due to hepatic diseases and Hepatitis C virus infection that affect glucose metabolism.[(11)]Furthermore, with the worldwide epidemic of diabetes.

2. Aim of the Study

To determine the prevalence of diabetes mellitus with impaired glucose tolerance test among patient with transfusion dependent beta thalassemia major.

3. Patients and Methods

3.1 Study Design

A case control study done on a group of patient with beta thalassemia major selected randomly by their file number by rule 3 to 1 diagnosed by hemoglobin electrophoresis registered in thalassemia center in AL– Zahraa Teaching Hospital for Maternity and Children in AL- Najaf AL-ashraf Iraq ,during a period from 15 of January 2016 to 1st of May 2016, 50 patient with thalassemia and 50 control group.

Inclusion criteria
All patients with thalassemia major were subjected to a blood transfusion as part of their treatment ,not diabetic.

Exclusion criteria
Acute illness, liver disease and previously diagnosed case of diabetes mellitus, were excluded.

3.2 Data Collection

A total of 50 patients with thalassemia were studied (27males and 23 females), aging from(5year to 15 years).

The patients name, age, gender, time of first blood transfusion ,number of blood transfusion , time of starting of chelation treatment, period of chelation therapy, history of previous splenectomy ,hepatitis state, and family history of diabetes mellitus was taken and relevant systemic examination was done.

A 50 patient control with same age(28male and 22 females) randomly selected from school. None of them had history of previous blood transfusion and they had no family history of hemoglobinpathies.

A detailed history and clinical examination was obtained for every patient (thalassemic children and control group).Consent was obtained from the patients' first-degree relatives (mother or father). These patients were also informed that the results of the study would be provided to them as free useful laboratory tests. The patients were diagnosed with beta thalassemia major as recorded in their files(by Hemoglobin electrophoresis) We define impaired Oral glucose tolerance according to World Health Organization. Oral glucose tolerance test was done after6-8 hour of overnight fast. A blood sample was drawn and glucosewas taken in a dose of 1.75 gram/kilogram up to a maximum of 75 gram, and serum glucose was measured 2 hours later ,the glucose level wasmeasured by glucometer machine. Impaired glucose tolerance test defined as the 2 hour plasma glucose was >140 milligram/deciliters and less than200 mil/deciliters (7.8- 10.3 mile mole/liter) and fasting plasma glucose was <126mili gram/dl (7.0 mole/liter). Diabetes diagnosed as the fasting plasma glucose was > 126 milligram/deciliters (7.0millemol/Liter) and 2 hour post glucose plasma glucose >200 milegram/deciliter (11.1 millemol/Liter).

3.3 Statistical analysis

Statistical analysis was done by using SPSS (statistical package for social sciences) version 20 in which we use frequencies, percentages, mean and standard deviation as descriptive statistics. Independent sample t-test, analysis of variance(ANOVA) and chi square test for comparison between groups.P value≤0.05 regarded signify.

4. Results

Table 1: Comparison between cases and controls in basic characteristics

Patients characteristics		Thalassemic children (n=50)	Control (n=50)	P value
Age(years) (Mean±SD)		9.36±3.74	4.38±3.06	<0.001
Gender	Male	27(54%)	28(56%)	0.841
	Female	23(46%)	22(44%)	
Family history of DM		7(14%)	8(16%)	0.779
Mean Hb		8±1.6	10±1.8	<0.001

Table 2: Association between blood glucose status and thalassemia

	Impaired Glucose Tolerance or Diabetes Millitus (n=22)	Normal (n=78)	Total	P value	OR (95%CI)
Thalassemia	22(44%)	28 (56%)	50 (100%)		
Control	0(0%)	50 (100%)	50 (100%)	<0.001	79.7 (6.09-inf.)

Table 3: Comparison between cases and controls in blood sugar level.

	Thalasemia (n=50)	Control (n=50)	
	Mean±SD	Mean±SD	P value
FBS mg/dl	125.22±26.04	112.1±8.68	0.001
Blood sugar After 2 hour	161.62±49.91	121.98±9.69	<0.001

Table 4: Fasting blood sugar, Blood sugar after 2hours, Age and duration of disease and serum ferritin among thalassemic children, significant in fasting and after 2hours and age of patient but not significant in duration of illness and serum ferritin.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		P value
					Lower Bound	Upper Bound	
Fasting Blood Sugar	thalassemia Diabetes Mellitus	12	167.08	16.70	156.4707	177.6960	<0.001
	Thalassemia impaired glucose	10	111.6	9.70	104.6545	118.5455	
	thalassemia normal	28	112.14	7.81	109.1140	115.1717	
After 2 hour	thalassemia Diabetes Mellitus	12	240.08	29.72	221.1993	258.9674	<0.001
	Thalassemia impaired glucose	10	165.3	15.26	154.3829	176.2171	
	thalassemia normal	28	126.6	8.73	123.2898	130.0673	
Age/years	thalassemia Diabetes Mellitus	12	12.00	3.30	9.90	14.10	<0.001
	Thalassemia impaired glucose	10	12.30	2.16	10.75	13.85	
	thalassemia normal	28	7.18	2.85	6.07	8.29	
Duration of disease/years	thalassemia Diabetes Mellitus	12	8.42	4.25	5.71	11.12	0.009
	Thalassemia impaired glucose	10	7.90	3.92	5.09	10.71	
	thalassemia normal	28	4.96	3.01	3.80	6.13	
serum ferritin	thalassemia Diabetes mellitus	12	3290.50	1877.542	2097.56	4483.43	0.483
	Thalassemia impaired glucose	10	3795.40	2578.529	1950.83	5639.96	
	thalassemia normal	28	4250.96	2393.686	3322.78	5179.13	

5. Discussion

The present study has assessed Oral glucose tolerance test in blood transfusion dependent children with thalassemia major

The results of this study showed that statistically significant difference between thalassemic patient and control regarding blood glucose (p value <0.001) In comparison to control group (0.0% diabetes) 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[12] leading to progressive organ dysfunction.

This result comparable to study done in Egypt,Khalifa AS1 et al[13] which show The results of diabetes are 10.4% [14], and abnormal glucose tolerance is common in multiply transfused beta thalassemia patient ,which could be attributed to progressive and early loss of beta cell mass, along with persistent insulin resistance.

The result incomparable to study done in India,Bablu Kumar Gaur1 et al,[15]which show 12 were found to have an impaired glucose tolerance, (p value <0.001) while none were found to be diabetic.

The result comparable to study done in Iran, Karamifar H et al[16], which show type 1diabetes mellitus is 7.3%in thalassemic patient, may be a result of poor disease control and management in early life when irreversible tissue damage due to iron overload.

The result incomparable to study done in Iraq, Ahmed Shemran M. Al-Wtaify,et al[17]which show There was no significant difference of diabetes among thalassemic patients.

And comparable to study done in Iraq, Shiama'aabia Alhamid Ahmed et al[18] which show10 patients (8.9%) were found to have impaired glucose tolerance and 7 patients (6.25%) with diabetes mellitus. Patients with abnormal glucose tolerance(P <0.001).

Our study is higher ,may be due to under transfusion or to late onset administration of chelation therapy ,which as risk factor for development of diabetes mellitus[19,20].

Regarding age and hemoglobin parameter,our study demonstrate highly significant difference between cases and controls regarding age which is higher among cases(p value <0.001) and Hemoglobin which is low(p value <0.001).Which may be explain by fact that chronic hypoxia and longer period of time on blood transfusion therapy may directly or indirectly affect the function of insulin on peripheral tissue causing abnormal oral glucose tolerance test and clinical diabetes mellitus[21].

This study comparable to study done in India,Bablu Kumar Gaur1 et al,[15] which show age significant for impaire glucose tolerance and study done in Iraq, Ahmed Shemran M. Al-Wtaify,et al[17] show There was highly significant increase of diabetes mellitus with increasing age(p value0.001) this similar to our study in which age of patient risk factor for develop diabetes.

Regarding serum ferritin, our study show no significant difference for our group of thalassemic patient in respect to control group(p value0.483).This may be explain by fact that serum ferritin not good parameter for extent of tissue iron over load including pancreas, for its action as acute phase reaction which may rise in various pathological inflammatory problem although iron over load in pancreas may disturb its function causing decrease insulin level, peripheral tissue resistance to insulin due to precipitation of iron may manifested itself as clinical diabetes mellitus[22].

This incomparable to study done in India,Bablu Kumar Gaur1 et al,[15]which show the risk of development Impaired Glucose Tolerance increase with increasing serum ferritin (p-value <0.001) highly significant.

And incomparable to study done in Iraq, Ahmed Shemran M. Al-Wtaify,et al[17]show highly significant increase of Diabetes mellitus with increasing level of serum ferritin more than 1000µicrogram/liter (P < 0.001).

Regarding other parameters there is no significant difference between the two groups regarding gender (male or female)(pvalue0.841)regarding family history of Diabetes mellitus(p value0.779) not significant.

6. Conclusions

1) Our study demonstrate there is direct association between thalassemia major and abnormal glucose tolerance test and clinical diabetes in significant percentage in thalassemia patient.
2) Incidence higher among thalassemic patient who are older age group and low hemoglobin level.

7. Recommendations

1) Education of the families and the patients for good follow up and good transfusion may improve likelihood of occurrence of diabetes mellitus.
2) Cooperation between thalassemia center and endocrinologist for early detection of abnormal oral glucose tolerance may improve the life style of thalassemia patient.
3) New effort to detect tissue iron overload by noninvasive method for liver and heart(magnetic resonance cholangiography)T2* for early management of iron overload.

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