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Risk Factors Causing Diabetes Mellitus in Beta Thalassemic Major Children

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Abstract: To study the impaired glucose tolerance and serum ferritin level in transfusiondependent β-thalassemic children. A prospective and hospital based study.Setting: Kamala Raja Hospital, G.R.Medical College, Gwalior. Known case of beta Thalassemia major children being regularly transfused in Department of Pediatrics, Kamla Raja Hospital, Gwalior. This study was done on 60 children between 3-17 years of age with β thalassemia. Major information regarding name, age, sex, height, body weight, age at the first blood transfusion, frequency of blood transfusion per year, age at the start of iron-chelation therapy, compliance with chelation therapy, H/O Diabetes mellitus and history of previous splenectomy was taken. For each patient glucose tolerance test was performed. Significant variation was found (p value<0.001) in children with impaired glucose tolerance compared to normal glucose tolerance with respect to age, age of first blood transfusion, age of starting chelation therapy. Patients with impaired glucose tolerance had a mean transfusions of 137.58±20.15 times while those with normal glucose tolerance had 58.85±39.80 times of transfusions.(p.value<0.001) Conclusion: Most of patients with impaired glucose tolerance in present study had received more then 100 blood transfusion with mean age of 13.0 years indicating that abnormal glucose homeostasis begin after 10 year of age.
Keywords: Beta thalassemia major, impaired glucose tolerance, chelation therapy.

INTRODUCTION

Beta thalassemia was first described by Cooley and Lee [1] and is characterized by anemia, hepatosplenomegaly, growth retardation, jaundice, and bony changes. The cause is a genetic mutation that reduces or even halts the synthesis of β-globins chains.

The progressive iron overload in beta thalassemia major patients is the consequence of multiple blood transfusions, ineffective erythropoiesis, increased gastrointestinal absorption of iron, and lack of physiologic mechanism for excreting excess iron. Iron overload may cause deposition of iron in parenchyma tissue of liver and other organs like heart, pancreas and leads to endocrine complications, commonly manifests as cirrhosis, cardiomyopathies and damage to pancreas [2-5]. The commonest endocrine complication is abnormal glucose tolerance. The mechanism of abnormal glucose homeostasis in patients with beta thalassemia major is still unknown but is attributed mainly due to insulin deficiency resulting from the toxic effects of iron deposited in the pancreas, and insulin resistance [6-9**]**. Insulin resistance may come from iron deposition in both liver (where iron deposits may interfere with insulin's ability to suppress hepatic glucose production) and muscle (where iron deposits may decrease glucose uptake because of muscle damage [10]. Persistent insulin resistance along with a progressive reduction in circulating insulin levels may lead to glucose intolerance and overt diabetes [11]. If it is not diagnosed early, these children may land up with fatal complications hence this necessitates the need of oral glucose tolerance test for early diagnosis, monitoring and prevention of these complications.Therefore, this study was done to detect factors that may land up with diabetes mellitus in such children.

MATERIALS AND METHODS

This study was done on 60 children already diagnosed β-thalassemia major confirmed by hemoglobin electrophoresis between 3-17 years of age being transfused in department of Pediatrics, Kamala Raja Hospital Gwalior after approval by the Institutional ethical committee of our institute. Informed written consent was obtained from guardians. Information regarding, age, sex, weight, age at the first

blood transfusion, age at the start of iron-chelation therapy, duration of chelation therapy and its compliance, family history of diabetes mellitus in first degree relatives was taken and relevant systemic examination was done .

Exclusion criteria

- Children with any acute illness,
- Liver disease,
- Known case of diabetes mellitus
- Treatment with drugs causing diabetes.

Oral glucose tolerance test was performed as per World Health Organization's definition of impaired glucose tolerance and diabetes. An oral glucose tolerance test (OGTT) was performed in the morning after 3 days on carbohydrate diet and 8-10 hours overnight fast. A fasting blood sample was drawn and glucose was ingested in a dose of 1.75 g/kg up to a maximum of 75 g, and plasma glucose was estimated 2 hours later. Blood glucose estimated by glucose oxidase peroxidase method. Impaired glucose tolerance test was diagnosed if the 2 hour plasma glucose was >140 mg/dL and less than 200 mg/dL (7.8- 11.1mmol/L) and fasting plasma glucose was <126 mg/dl (7.0 mmol/L). Diabetes was diagnosed if the fasting plasma glucose was > 126 mg/dL (7.0 mmol/L) and 2 hour post glucose plasma glucose >200 mg/dL (11.1 mmol/L).

Statistical analysis

Differences between patients with and without abnormal glucose tolerance were tested with x^2 test, and Fisher's exact test to identify the potential risk factors. A two-tailed P.value of <0.05 was considered to be statistically significant. Statistical analysis was done with EpiInfo ™software version 3.5.3.

RESULTS

In the present study, 60 thalassemia children were studied, out of them 11 were females and 49 were males. 29 patients were of age group 3-5 yrs (48.3%),. 14 patients of age group 6-10 yrs(23.3%) and 17 were of age group 11-17 years(28.3%). Impaired glucose tolerance was observed in 12 of thalassemia children studied, of which 9 were males and 3 were females and 48 patients had normal glucose tolerance test.Mean weight was 15.7 ± 8.4 kg and 25.5 ± 4.2 kg in normal and impaired glucose tolerance respectively(p.value=0.010)(Table 1). Age at first blood transfusion was 12.6 ± 0.9 months in children with normal glucose tolerance and 8.2 ± 1.8 months' with impaired glucose tolerance.(p.value=0.049) No case of diabetes was reported. Out of 60 patients 42 receiving chelation therapy, and only **5** had impaired GTT, 18 were not on chelation therapy, among which **7** had impaired GTT, the difference was found to be statistically significant.(p value-0.0135)$_{(table\ 2).}$ Age at start of iron-chelation therapy was 3.8±0.98yrs in normal GTT and 4.0±1.5yrs in IGT(p.value=0.042)(table 1). Age at first blood transfusion was 12.6 ± 0.9months in children with normal glucose tolerance and 8.2 ± 1.8 months' with impaired glucose tolerance.(p.value=0.049)(table 1). Out of 21 patients who had received >100 transfusions, 11 patients had impaired glucose tolerance test, while out of 39 patients who received <100 transfusions 1 patient had impaired glucose tolerance test (table 1).

Table-1: Characteristics of cases of normal GTT and impaired GTT in thalassemia children

Patient characteristics	Normal GTT	Impaired GTT	p value
Age(yr) (mean ± sd)	7.3 ± 4.36	13.0 ± 2.5	<0.001
Sex male female	 41 (83.7)% 7 (63.7%)	 8 (16.3%) 4 (37.3%)	 0.26
Body weight (kg) (mean ± sd)	 15.7± 8.4 kg	 25.5± 4.2 kg	 0.010
Age at first blood transfusion	12.6+_0.9 mnth	8.2+_1.8 mnth	0.049
Total number of blood transfusions	58.85+_39.85	137.58+_20.1	<0.001
Age at initiation of iron chelation therapy	3.8+_0.98 yrs	4+_1.5 yrs	0.042

Table-2: effect of chelation therapy on glucose tolerance test

Chelation therapy	Normal GTT	Impaired GTT	P value
Receiving	37	5	0.0135
Not receiving	11	7	

Table-3: Comparison of GTT on the basis of age at start of chelation therapy

Age at start of chelation therapy	Normal GTT	Impaired GTT	P value
Less than 5 years	35	2	0.00431
More than 5 years	2	3	

DISCUSSION

In this study we found that incidence of impaired glucose tolerance was high in age group of more than 10 years as compared to less than 10 years age . Mean age of patients who had IGT was 13 years which indicates age as a risk factor for IGT, which was similar to the result of study done by Najafipour *et al*. [15] and Saudek CD *et al*. [8]. In this study, we found that out of 60 patients, 42 patients were receiving chelation therapy in which 5 patients had developed IGT, while out of 18 patients, who had not received chelation therapy, 7 patients had developed IGT and all of them were of adolescent age. Those children who started chelation therapy before the age of 5 years had better glucose tolerance than those who started after the age of 5 years [Table-3]. This is similar to a study done by Christoforidis A *et al*. [13], Jimmy PS *et al*. [14]. Abnormal glucose homeostasis in patients with beta thalassemia major is attributed mainly to insulin deficiency resulting from toxic effect of iron deposited in pancreas and from insulin resistance. The insulin resistance may come from iron deposition in liver.

Patients with impaired glucose tolerance had a mean transfusions of 137.58±20.15 times while those with normal glucose tolerance had 58.85±39.80 times of transfusions. This is similar to the result obtained by Hamdoon *et al*. [16] in which patients who required frequent blood transfusions (mean of 15.5 transfusion/year) had impaired glucose tolerance in comparison to those with less blood transfusions. This also agrees with the result obtained by previous studies[8,12]in which the number of blood transfusions was a risk factor for developing diabetes in beta thalassemic children. In a study by Hafez Mona *et al*. [17] similar correlation was found suggesting increased frequency of blood transfusions to be a major risk factor for developing impaired glucose tolerance test in beta thalassemic children.

Age, number of blood transfusions, late initiation of chelation therapy along with its poor compliance were found to be the risk factors causing impaired glucose tolerance.

CONCLUSION

Advancing age, number of blood transfusion and delayed initiation of chelation therapy with its poor compliance are risk factors for impaired glucose tolerance, may be due to pancreatic dysfunction and may result in diabetes mellitus in beta thalassemic children.

WHAT THIS STUDY ADDS

- Oral glucose tolerance test is to be mandatory in all regularly transfused beta thalassemic children.
- Initiation of chelation therapy at early age (<5 years) and its good compliance may reduce the incidence of impaired glucose tolerance.

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