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IMPAIRED GLUCOSE TOLERANCE TEST IN BLOOD TRANSFUSION DEPENDENT BETA THALASSEMIC CHILDREN

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ABSTRACT

Impaired glucose tolerance and Serum ferritin level in transfusion-dependent β-thalassemic children was studied. Known case of beta Thalassemia major childrens 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 and S.ferritin levels were measured.

The prevalence of impaired glucose tolerance was 20%, the Serum ferritin was highly raised in all thalassaemic children, with highly statistical significant differences between normal and impaired GTT patients.(p.value<0.001) Mean serum ferritin was found to be 2089 ± 690 µg/l in patients with normal GTT while it was 4100 ± 518 µg/l in Impaired GTT. Significant variation was found (p value<0.05) 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).

Most of patients with impaired glucose tolerance in present study had received more then 100 blood transfusion and serum ferritin level >3000µg/L with mean age of 13.0 years indicating that abnormal glucose homeostasis begin after 10 year of age.

Key words: beta-Thalassemia major, impaired glucose tolerance, Serum ferritin,chelation therapy.

INTRODUCTION

Thalassmia the commonest congenital hemolytic anemia is first described by Cooley and Lee[1] . It is characterized by anemia, hepatosplenomegaly, growth retardation, jaundice, and bone changes. The cause is a genetic mutation that reduces or even halts the synthesis of β-globins chains. There are about 65,000-67,000 β-thalassemia major patient in India, with around 9,000-10,000 cases being added every year[2,3,4.] The progressive iron overload in beta thlalssaemia major patients is the consequence of multiple blood transfusion, ineffective erythropoiesis, increased gastrointestinal absorption of iron, lack of physiologic mechanism for excreting excess iron. Iron overload may cause deposition of iron in parenchyma tissue of liver and other tissues like heart and pancreas and leads to endocrine complications, common manifests as cirrhosis, cardiomyopathies and damage to pancreas[5-8] .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 to insulin deficiency resulting from the toxic effects of iron deposited in the pancreas,and insulin resistance[9,10,11,12]. 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

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muscle damage)[13] .Persistent insulin resistance along with a progressive reduction in circulating insulin levels may lead to glucose intolerance and overt diabetes[14] .If it is not diagnosed timely, these children may land up with fatal complications hence this necessitates the need of oral glucose tolerance test and serum ferritin level for early diagnosis, monitoring and prevention of these complications. Therefore, this study was undertaken to assess the effect of various factors on oral glucose tolerance test.

METHODS

This study was conducted on 60 children with β-thalassemia major (only as confirmed by Hb electrophoresis) aged between 3-17 years being regularly transfused at department of Pediatrics, Kamala Raja Hospital, G.R Medical College Gwalior for the period of one year. Ethical approval was obtained by the institutional ethical committee. Written consent was obtained from guardians. Information regarding name, age, sex, age at the first blood transfusion, frequency of blood transfusion per year, age at the start of iron-chelation therapy, duration of chelation therapy, compliance with iron-chelation therapy, history of previous splenectomy and family history of DM was taken and anthropometry and relevant systemic examination was done . Patient suffering from any acute illness, liver disease and previously diagnosed case of diabetes mellitus, were excluded

Oral glucose tolerance test was estimated using 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 hour 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 estimation was done by glucose oxidase peroxidase method (GOD-POD Method). Impaired glucose tolerance test was diagnosed if the 2 hour plasma glucose was >140 mg/dL and less than 200 mg/dL (7.8-10.320222.231.1 mmol/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). Serum ferritin level was assessed by Automated Biosystem Machine by using s.ferritin kit based on Chemiluminiscence.

Statistical analysis:

Differences between patients with and without abnormal glucose tolerance were tested with x2 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. All the statistical analysis were conducted by using Epi Info ™ software version 3.5.3.

RESULTS

Table-1: Mean value of different Variables and GTT in Thalassemic children.

Patient characteristics	Normal GTT	Impaired GTT	p value
Age(yr) (mean ± sd)	7.3 ± 4.36	13.0 ± 2.5	<0.001
Gender 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
Hight(cm) (mean ± sd)	95.7± 17.5	122.7± 3.5	0.006
Age of 1st blood transfusion (mean ± sd)	12.6 ± 0.9 mnth	8.2 ± 1.8 mnths	0.049
Serum Ferritin level (mean ± sd)	2089 ± 690	4100 ± 518	<0.001

In the present study, 60 thalassemic children were studied, out of them 11 were females and 49 were males. 29 patients were of age group 3-5 yrs, 14 patients of age group 6-10 yrs and 17 were of age group 11-17 years. Impaired glucose tolerance was observed in 12 of thalassemic 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). mean height was 95.7±17.5cm in normal GTT and122.7±3.5cm in IGT respectively,(p.value=0.006)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))(Table 1) No case of diabetes was detected. Serum ferritin were also analyzed in thalassemic children based on the number of transfusions. Children with >100 transfusions had serum ferritin higher when

Table-2 Correlation between Numbers of blood transfusion and GTT in thalassemic children.

Frequency of BT	Normal GTT	IGT	p value
≤100	38	1	0.0000051
>100	10	11	.0000051

Thalassemic children with frequent blood transfusion have impaired glucose tolerance, the difference was found to be statistically highly significant (p value.<0.001)

compared to those with <100 transfusions, the difference in values between the two groups was found to be highly significant (p value=0.0000051)) (Fig. 1). Mean value of serum ferritin, was found to be 3601 ± 775 µg/l, in patients who received more than 100 transfusions while it was 1906 ± 563 ug/l in patients who receive less than 100 transfusions. Of the 21 patients who had received >100 transfusion, 11 had Impaired Glucose Tolerance(IGT). while out of 39 patients who received <100 transfusions,only 1 had Impaired Glucose Tolerance(Table 2). Mean serum ferritin was found to be 2089 ± 690 µg/l in patients with normal GTT while it was 4100 ± 518 µg/l in Impaired glucose tolerance.42 children had <3000µg serum ferritin among them only 1 had impaired glucose tolerance while 18 children had serum ferritin >3000 µg among them 11 children developed impaired glucose tolerance test. Significant variation (p value<0.001) in ferritin levels were observed when values in patients with normal GTT was compared with those having IGT (Table 3).

Table-3 Correlation between Serum ferritin with GTT in Thalassemic children.

S.ferritin (ug)	Normal GTT	Impaired GTT	Total
≤3000	41	1	42
>3000	7	11	18

This table shows the risk of development Impaired Glucose Tolerance increase with increasing s. ferritin (p-value <0.001 highly significant)

Among 60 thalassemic children 42 were receiving chelation therapy, out of 42 patients who received chelation therapy, only 5 patients had impaired Glucose Tolerance Test, 18 patients had no chelation therapy, among non chelator group 7 had impaired Glucose Tolerance Test, the difference was found to be statistically significant.(p value-0.0135)(Fig. 2). Age of initiation of iron- chelation therapy was 3.8±0.98yrs in normal GTT and4.0±1.5yrs in IGT(p.value=0.042)(Fig. 3). Significant variation was found (p value<0.05) in children with impaired glucose tolerance compared to normal glucose tolerance with respect to age, weight, height, age at first blood transfusion,no of blood transfusion,s.ferritin level and age at starting chelation therapy.

DISCUSSION

Total 60 patients studied, 12 were found to have an impaired glucose tolerance while none were found to be diabetic. Of the 12 patients with impaired glucose tolerance, 9 were males and 3 were females. In our study prevalence of impaired glucose tolerance (IGT) was 20%, which is nearly similar to the study done by Hafez et al[15], in which prevalence was 24.1%.Varying prevalence of impaired glucose tolerance has been previously reported by other workers, El-Hazmi[16] reported in 24% patients. khalifa[17] 14.6%, de sanctic[18] reported it to be 37%,.

Mean serum ferritin was found to be 2089 ± 690 µg/l in patients with normal GTT while it was 4100 ± 518 µg/l in IGT. Out of 60 children, 18 had serum ferritin level >3000µg/l in which 11children developed impaired glucose tolerance, while in other group (<3000µg/l) only one had IGT, which was statistically significant (p value<01)(Table 3).This result is similar to the result of a study done by Suvarna et al[19] and Christoforidis[20] Jimmy PS et al[21] in which serum ferritin was a risk factor .The no. of IGT was more in age group>10 years in comparison to <10 years age group. Mean age of patients who had IGT was 13 years .and with increasing age the possibility of development of impaired glucose tolerance increase ,which indicate age as a risk factor for IGT, which is similar to the result of study done by Najafipour et all[22] and Saudek CD et al[11] .Significant variation (p<0.05) was found in glucose tolerance test and age of first blood transfusion, number of transfusions, compliance with chelation therapy, age of start of 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.. This is similar to

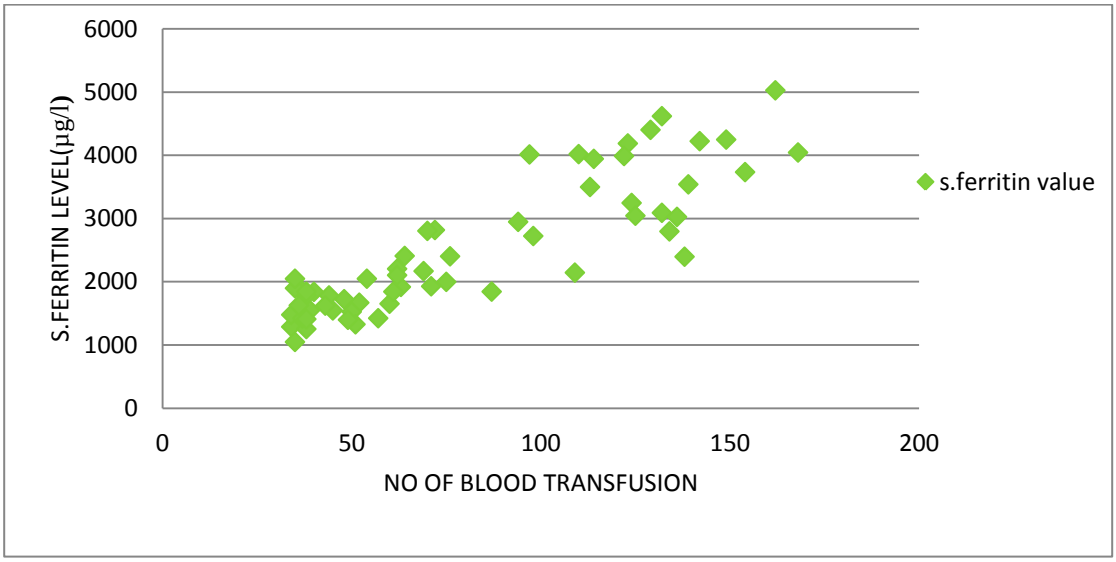

Fig.1- Correlation between serum ferritin and number of blood transfusion

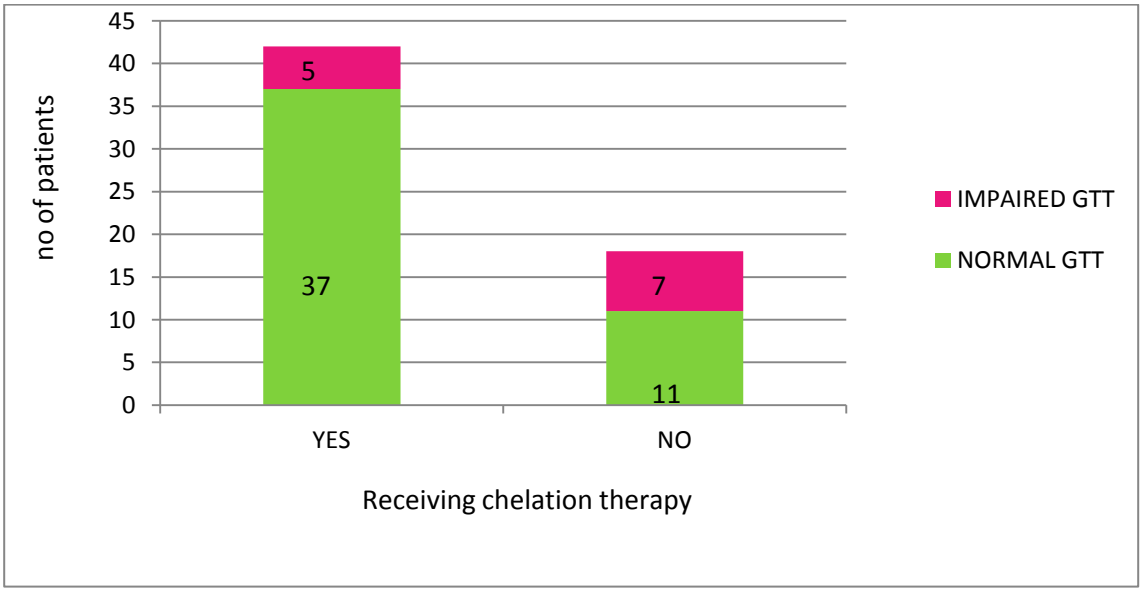

Fig.-2 Correlation of chelation therapy with GTT

the result obtained by Hamdoon et al[23] .Those who required frequent blood transfusions >100 blood transfusion(mean of 15.5 transfusion/year) had impaired glucose tolerance in comparison to those who required <100 blood transfusions (mean of 13.7 transfusions/year) the glucose tolerance was normal(Table 2). This agrees with the result obtained by Najafipour et al[22] Khalifa AS et al[17],Saudek CD et al [11,] in which the number of blood transfusions was a risk factor,. One another study conducted by Mona Hafez et al[24] on 54 beta thalassemia major patients, also shows similar correlation. These patients were started on regular blood transfusions before their first birthday, and the total amount of blood received per year ranged from 60 to 240 mL/kg/year (mean142.8 ± 51.4 mL/kg/year) with transfusion intervals from 2 to 8 week (mean 3.9 ± 1.4 weeks).

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 belonged to adolescent age group(Fig 2). Those children who started chelation therapy before the age of 5.0 years had better glucose tolerance than those who started

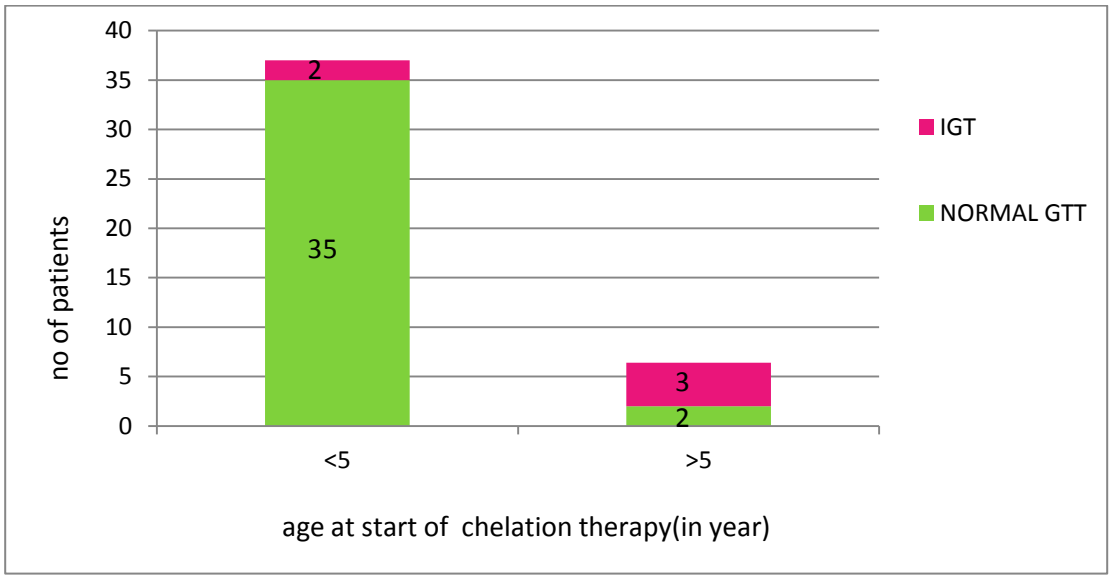

Fig.-3 Correlation of age of starting chelation therapy with GTT

after the age of 5.0 years.(Fig 3). This is similar to a study done by Jimmy et al [20] and Ferjade , Christoforidis a et al[21] 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. The presence of impaired glucose tolerance along with elevated ferritin level may be attributed to the glucose intolerance associated with insulin resistance and may be direct or indirect consequence of hepatic damage.[25]

Patients with impaired glucose tolerance had ferritin level higher than those patients with normal glucose tolerance, difference in that values was found to be highly significant ($p<0.001$). The risk factors for impaired glucose tolerance found in transfusion-dependent β-thalassemic patients were age, no of blood transfusion, initiation of chelation therapy and serum ferritin concentration. Frequently transfused patients with under or poor compliance with iron chelation therapy increased the risk of development of impaired glucose tolerance. Timely intervention with adequate chelation therapy can decrease the effect of iron overload and increase the life expectancy of the patients.

CONCLUSION AND RECOMMENDATION

Prevalence of Impaired glucose tolerance in this study is 20%. Risk of Impaired glucose tolerance develops when serum ferritin level exceeds 3000µg/L. Those children not receiving chelation therapy may develop impaired glucose tolerance at early age, before 10 years of age. Increasing age, number of blood transfusion and levels of serum ferritin are risk factors for impaired glucose tolerance.

Oral glucose tolerance test should be mandatory in all Transfusion dependent β-thalassemic children when Serum ferritin level exceeds 3000µg/l or Age of children >10 years or Number of blood transfusion >100. If child is not on iron-chelation therapy or late initiation of chelators than Oral glucose tolerance should be done even before 10 years of age.

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