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Growth And Puberty In Girls With B-Thalassemia Major And it's Correlation With Chelation Therapy And Serum Ferritin Levels.

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ABSTRACT

Background: (1) To study FSH, LH and Estrogen levels and it's correlation with Serum Ferritin levels in Female Beta Thalassemia Major patients. (2) To study the correlation of these hormones and SMR with Serum Ferritin. (3) To compare these hormone levels and SMR of Patients with Controls. Study Design: It was a cross-sectional case control study done in a tertiary care centre in a large Metropolitan city over a period of 2 years. **Methods:** The study was approved by the Institutional ethical committee. The patients attending the Emergency, in-patient and outpatient Departments of Pediatrics Division of our institute were enrolled for the study as per the criteria given. It was a cross-sectional case control study done in patients who had already been diagnosed with beta thalassemia major (cases) and healthy girls (controls). The demographic data, ferritin levels, chelation therapy, SMR staging and hormonal essays of FSH, LH, estrogen and their correlation with blood transfusions and serum ferritin levels was studied. Also the hormone levels and SMR staging of patients with thalassemia major were compared with control group. **Results:** 56 girls having beta thalassemia major (cases) and 50 healthy girls not suffering from any ailments as (controls) per inclusion and exclusion criterion were enrolled in this study. Estimation of FSH in test and control subjects revealed that The difference was not significant in the age group of 8-12 years (P=0.323). The FSH values of cases >12 years were significantly lower than those of controls (P<0.001). Estimation of oestrogen and LH revealed that these values were significantly lower in Thalassemics as compared to non thalassemics in both age groups (P<0.001). 0% Cases and 26.3% Controls had attained Menarche in the age group of 8-12 years whereas 11.4% Cases and 93.3% Controls in the age group of >12 years had attained Menarche . In our study the mean age of attainment of menarche was 14.5 in thalassemics and 11.5 in non thalassemics. The differece was found to be very highly significant (P<0.001). The association of serum ferritin and FSH, LH and oestrogen levels revealed that a statistically significant association was found in between Sr ferritin and FSH (P=0.015) and oestrogen (0.008). While for LH the difference was insignificant (P=0.174). Association of FSH,LH and oestrogen with duration of chelation therapy showed that there was no significant difference in between FSH,LH and oestrogen levels with respect to duration of chelation therapy. **Conclusion:** Our study concluded that Delayed growth and Puberty is a common complication of beta thalassemia major. Regular chelation therapy reduces serum ferritin levels and improves FSH, LH and estrogen levels.

Keywords: B-thalassemia major, Delayed puberty, Growth retardation, Iron overload, Hormonal levels.

INTRODUCTION

Thalassemia is the most common heterogeneous group of genetic disorders in which the production of normal hemoglobin (Hb) is partly or completely suppressed because of defective synthesis of one or more globin chains that vary widely in severity from asymptomatic forms to severe or even fatal entities.[1] Thalassemia is classified into different types depending on one of two things: the specific part of hemoglobin that is affected (usually either "alpha" or "beta"), or the severity of thalassemia, which is noted by words like trait, carrier, intermedia, or major. Hemoglobin, which carries oxygen to all cells in the body, is made of two different parts, called alpha and beta chains. When Thalassemia is called "alpha" or "beta," this refers to the part of hemoglobin that isn't being made. If either the alpha or beta part is not made, there aren't enough building blocks to make normal amounts of hemoglobin. Low alpha is called alpha thalassemia.[2] Low beta is called beta thalassemia (a).

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Beta Thalassemia Major causes profound anemia that kills untreated affected children before the age of 3 years. However, the life expectancy of patients treated with regular blood transfusion and iron-chelation

therapy, or bone-marrow transplantation is approaching normal. Alpha thalassemia major causes hydrops fetalis and perinatal death, often with life-threatening obstetric complications for the mother and prenatal diagnosis usually leads to termination of pregnancy. Some cases have recently been saved by intrauterine transfusion, despite a high risk of severe mental and physical handicap.[3]

With regular monthly blood transfusions, quality and duration of life of thalassemic patients has been transformed over the last few years, with their life expectancy increasing well into the third decade and beyond with a good quality of life of patients.[4] But Infections such as HBV, HCV, and HIV can be observed through frequent transfusions in children with Beta Thalassemia major (BTM).[5] Various endocrine, cardiac, and hepatic diseases may occur depending, on excessive iron-loading. Failure of pubertal growth, delay or absence of sexual development, amenorrhea, sexual dysfunction and infertility due to hypogonadism are well recognized disturbances of the hypothalamic – pituitary – gonadal axis in Beta Thalassemia patients.[6] Hence we intend to study the gonadotropins, estrogen and SMR in female Beta Thalassemia Major Patients.

MATERIALS AND METHODS

This was a cross-sectional case control study done at a tertiary care hospital in a large Metropolitan city over a period of 2 years. Before enrolling the patients in the study informed Consent was taken from parents of patients by explaining about the purpose of the study, the outcome and also explaining that the respondent can refuse and withdraw from study at anytime. All this information was conveyed in local language.

Inclusion criteria –

1) All female patients diagnosed with Beta Thalassemia Major in the age group of 8 years to 16 yrs.

Exclusion criteria –

1) Females having hormonal imbalance due to other proven causes eg:-congenital anomalies, tumors, precocious puberty, polycystic ovarian syndrome etc.

2) Patients having additional hemolytic anemias like sickle cell disease, autoimmune hemolytic anemia etc.

Approval of Institutional Ethical Committee was obtained. Study group comprised 106 female children, 56 children aged 8 years to 16 years with diagnosed Thalassemia major receiving regular blood transfusions in tertiary care hospital and 50 controls. Controls will be patients not suffering from disease ailment causing derangement in gonadotropins and Estrogen levels and SMR. Written consent of parents of patients was taken. All details were recorded in a pre-decided pro-forma which included personal information, transfusion history, clinical examination, anthropometric evaluation and SMR of all patients and serum levels of FSH, LH, Estrogen and Serum Ferritin of the patients. Anthropometric parameters like weight were taken on a Digital Weighing Scale. Height was measured by Stadiometer. SMR staging was done using the Tanner's scale. Duration of blood transfusion and chelation therapy was recorded in months and years along with their regularity. Regularity of chelation therapy was assessed for preceding 6 months, those taking the drugs in prescribed doses and not missing more than 5 doses per month were said to be on regular Chelation Therapy the rest were classified as taking irregular Chelation. Assessments of the serum levels of FSH, LH, Estrogen of all Cases and Controls was done, Serum Ferritin was measured only in the Cases and not in Controls. To assess Hormone and Ferritin levels, blood samples were drawn between 8am-9am by venous prick and collected in the plain bulbs. For those who had attained menarche, samples were collected in the follicular phase of the menstrual cycle. These samples were analyzed for FSH, LH, Estrogen and S. Ferritin in Cases and FSH, LH, Estrogen in controls. About 5 ml of serum was withdrawn and subjected to above mentioned tests, using Cobas E 114 immunoassay analyzer. Data analysis was done with the use of SPSS and Microsoft Excel. Graphs and tables were prepared by Microsoft Excel.

RESULTS

For present Case Control study 56 diagnosed female cases of Beta Thalassemia Major receiving blood transfusions at regular intervals in a tertiary care hospital were enrolled in Cases group and 50 healthy girls not suffering from any ailments as per inclusion and exclusion criterion were enrolled in the Control group. Analysis was done and results are presented. The cases and controls were further divided into 2 more groups based on age from 8-12 years and >12-16 years to study the pubertal status and hormonal levels. Amongst cases 67.9 % were in the age group of 8-12 years while 33.9 % were >12 years. Amongst controls 70% were in the age group 8-12 years and 30 % were >12 years.

Table 1: Age distribution of Thalassemic and Non-Thalassemic patients.

Disease	Age in years		Total
	8-12 years	>12 years	
Yes	37	19	56
No	35	15	50
Total	72	34	106

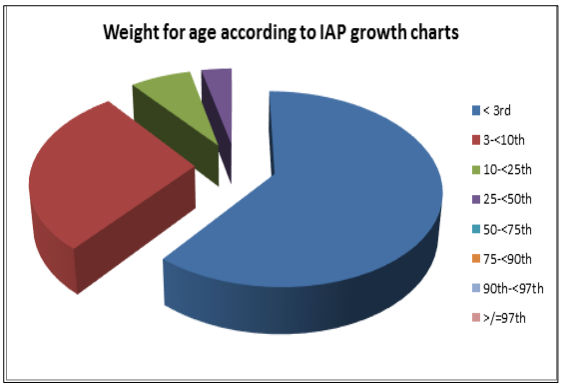

Figure 1: Frequency distribution of cases in various centiles for weight for age (IAP).

Table 2: Comparison of Mean Height of Thalessemic and Non-Thalassemic group.

Age Group	Disease			P Value
		Mean	SD	
8-12 years	Yes	122.6	13.43	< 0.001 (Very highly significant)
	No	137.5	11.98	
> 12 years	Yes	133.7	8.15	< 0.001 (Very highly significant)
	No	160.0	7.98	

Table 3: Height for Age according IAP growth charts.

Percentile for Height for age	Frequency in cases (n)	Percentage	Frequency in controls (n)	Percentage
< 3rd	42	75%	0	0
3rd- <10th	9	16%	2	4%
10th- < 25th	3	5.4%	3	6%
25th-< 50th	1	1.8%	10	20%
50th-<75th	1	1.8%	14	28%
75-<90th	0	0	15	30%
90th-<97th	0	0	4	8%
>/=97th	0	0	2	4%
TOTAL	56	100%	50	100%

Table 4: Comparison of Hemoglobin of Thalassemic and Non-Thalassemic group.

Age Group	Disease			P Value
		Mean	SD	
8-12 years	Yes	8.10	0.81	< 0.001 (Very highly significant)
	No	12.58	0.94	
> 12 years	Yes	8.41	0.92	< 0.001 (Very highly significant)
	No	12.33	0.97	

The pre-transfusion hemoglobin values of cases were significantly lower than those of controls for both the age groups.

Table 5: Comparison of FSH, LH and Estrogen levels of Thalassemic and Non-Thalassemic group.

Age Group	Disease	FSH (mIU/ml)			LH (mIU/ml)			Esterogen (pMol/l)		
		Mean	SD	P Value	Mean	SD	P Value	Mean	SD	P Value
8-12 years	**Yes**	2.37	0.69	0.323	1.04	0.35	<0.001	121.14	40.08	<0.001
	No	2.55	0.87	Not significant	2.83	1.38	Very highly significant	211.77	45.80	Very highly significant
> 12 years	**Yes**	2.28	0.62	<0.001	1.02	0.37	<0.001	101.16	26.88	<0.001
	No	4.40	0.75	Very highly significant	4.66	0.51	Very highly significant	297.33	67.50	Very highly significant

Comparison of FSH, LH and estrogen levels was done. The difference was not significant in the FSH levels in the age group of 8-12 years. The FSH values of cases >12 years were significantly lower than those of controls. LH values were significantly lower in Thalassemics as compared to non thalassemics in both age groups. Estrogen values were significantly lower in Thalassemics as compared to non- Thalassemics in both age groups. Overall for all 3 hormones i.e. FSH, LH and Estrogen, when compared between Cases and Controls, it was found that the hormonal level were significantly lower in the girls with Thalassemia as compared to those without the Disease in age group of 12-16 years. However the FSH levels although lower in cases in the age group of 8- 12 years as compared to controls the difference was not statistically significant.

When attainment of Menarche was compared between Thalassemics and non Thalassemics it was observed that:- 0% Cases and 26.3% Controls had attained Menarche in the age group of 8-12 years whereas 11.4% Cases and 93.3% Controls in the age group of >12 years had attained Menarche . This difference was not significant in the age group of 8-12 years (p value=0.051) but was statistically significant in the age group of > 12 years (p value <0.001). The mean age of attainment of menarche was studied in Cases and Controls, it was found that Thalassemics attained menarche at a greater age (14.5 years) as compared to Non-Thalassemics (11.5 years) and the difference was statistically significant. (p value <0.001).

SMR staging was compared between Thalassemics and non-Thalassemics In the age group of 8-12 years 94% Cases 31.4% Controls had an SMR of stage I. None of the cases had an SMR of stage IV whereas 2.8% Controls had an SMR of stage IV.

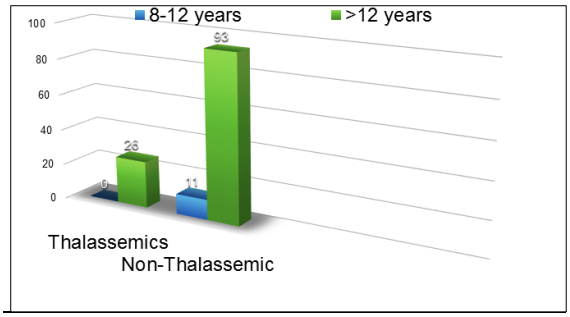

Figure 2: Comparison of attainment of menarche between thalassemic and Non-Thalassemic group.

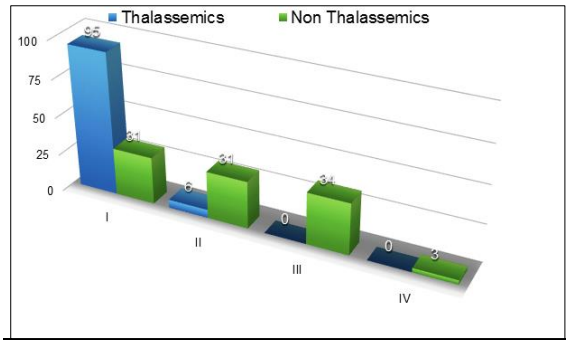

Figure 3: Association between SMR staging and thalassemia in patients of 8-12 yeaars.

In the age group of >12 years 52.6% Cases and 0% Controls had an SMR of stage II. None of the cases had an SMR of stage V whereas 33.3% Controls had an SMR of stage IV. In both the age groups the P value was highly significant.

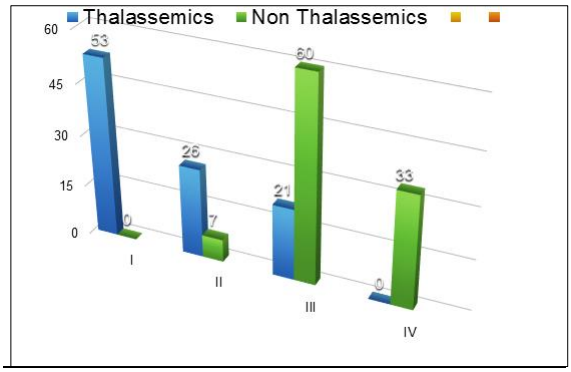

Figure 4: Association between SMR staging and thalassemia in patients of > 12 years of age.

All patients had hepatomegaly, splenomegaly was found in 71.4% patients, while 28.6% patients were splenectomised. 17 patients were receiving blood transfusion for less than 7 years while 39 patients were receiving blood for more than 7 years. 87.5% of patients were receiving chelation Therapy while 12.5% patients were not receiving any Chelation Therapy. It was statistically observed that those who received blood transfusion for a longer duration had higher ferritin values. Those who received transfusion for more than 7 years 82 % of those had ferritin values more than 2000ng/ml , whereas those receiving blood transfusion for more less than 7 only 23.5 % had values more than 2000ng/ml. The association between Ferritin and Hemoglobin values was not statistically significant. To study the association of S.Ferritin and hormonal levels the cases were divided into 2 groups based on their S.Ferritin levels, Those with Ferritin levels more than >2000ng/ml and those with S.Ferritin < 2000ng/ml.

Table 6: Association of Serum ferritin with FSH,LH and Esterogen levels.

Serum Ferritin (ng/ml)	FSH (mIU/ml)			LH (mIU/ml)			Esterogen (pMol/l)		
	Mean	SD	P Value	Mean	SD	P Value	Mean	SD	P Value
< 2000 ng/ml	2.81	0.95	0.015 t=2.508 df=54	1.12	0.40	0.174 t= 1.482 df= 54	135	45.8	0.008 t=2.897 df= 54
> 2000 ng/ml	2.27	0.64		0.99	0.32		102.9	25.5	

The association of Serum Ferritin and FSH levels was studied and the FSH values were found to be significantly lower in those with S.Ferritin >2000ng/ml (mean= 2.27mIU/ml) as compared to those with S.Ferritin <2000ng/ml (mean=2.81mIU/ml). P value= 0.015. The LH values were Lower in those with S.Ferritin > 2000ng/ml (mean=0.99mIU/ml), as compared to those with S.Ferritin <2000ng/ml (mean=1.12mIU/ml) however the difference was not statistically significant (P value=0.174). The Estrogen levels were also significantly lower in those Cases with S.Ferritin >2000ng/ml (mean=102.9 pmol/l) than those with S.Ferritin < 2000ng/ml (mean=135 pmol/l) .P value=0.008. The Ferritin values were higher in those receiving Chelator therapy for more than 5 years as compared to those receiving chelation for less than 5 years.

P value= 0.044 statistically significant. This could be because those receiving chelation for a longer time were also receiving blood transfusion for a longer duration.

There was no statistically significant difference when duration of chelation was compared to FSH, LH and estrogen levels. The analysis of chelation therapy and mean ferritin levels revealed that in patients who had been receiving regular chelation therapy mean Ferritin level was 1746.2ng/ml and those who were receiving irregular chelation had mean ferritin levels of 3417.The difference was found to be very highly significant(P value <0.001) .Those taking irregular or no chelation had mean

FSH, LH and estrogen levels of 2.3 mIU/ml, 2.9mIU/ml and 104.07 pmol/l while those taking irregular or no chelation had mean FSH,LH and estrogen levels of 1.17 mIU/ml, 0.98 mIU/ml and 142.4 pmol/l. The difference was found to be statistically significant in all these cases.

Table 7: Association of duration of chelation therapy and FSH, LH and Estrogen Levels.

Duration of chelation therapy (years)	FSH (mIU/ml)			LH (mIU/ml)			Esterogen (pMol/l)		
	Mean	SD	P Value	Mean	SD	P Value	Mean	SD	P Value
< 5 years	2.59	0.74	0.341 t=0.9607 df=47	1.07	0.35	0.685 t=0.4071 df= 47	117.9	37.68	0.105 t=1.6521 df= 47
> 5 years	2.37	0.72		1.02	0.38		101.6	16.6	

DISCUSSION

This research was performed to study the pubertal status and growth and development of female patients with Beta Thalassemia Major, age group included was 8-16 years .The pubertal status of these patients was also compared with normal girls. FSH, LH and Estrogen levels were done in both the groups whereas ferritin was done only in the cases as the controls were normal females without history of blood transfusions or any diagnosed hematological disorders; therefore it was assumed that the Ferritin levels in this group would be insignificant. From our study it was found that, menarche as well as other pubertal parameters such as pubic hair and breast development (SMR) as assessed by Tanners staging was significantly lower in Thalassemics. Apart from this, the expected height for age and weight for age was also less as assessed by IAP growth charts and were significantly lower than the controls. This points out to the fact that iron deposition as evidenced by high ferritin levels in the thalassemics due to repeated blood transfusions causes endocrine dysfunction.[7] In this study, it refers to pituitary dysfunction causing hypogonadotropic hypogonadism due to low FSH and LH levels, and lower height and weight possibly due to growth hormone deficiency (GH hormone not included in this study).[8] Ovarian failure as evidenced by low Estrogen levels in cases as compared to controls could be because of hypogonadotropic hypogonadism or due to deposition of iron in the ovaries itself which could lead to pubertal failure.[9] Although the exact mechanism in which iron overload causes tissue damage is not completely understood, there are evidences that free radical formation and lipid peroxidation can lead to the damages of mitochondrial, lysosomal, and sarcoplasmic membranes. The presence of iron deposits and oxidative damage by free radicals affects the pituitary and ovarian follicles.[10] As a result, the hypothalamic- pituitary-gonadal axis function is disturbed which eventually leads to delayed puberty.[11] In our study, most patients had low levels of serum LH, Estrogen and low serum FSH level as compared to normal subjects. This showed a dysfunction of the hypothalamic-pituitary-gonadal axis.[12] Consequently, gonadal stimulation was reduced which caused estrogen secretion to decrease. This result was in accordance with the study performed by Jose Batubara who studied prevalence of delayed puberty in Beta Thalassemia Major patients and he found that the prevalence of delayed puberty in Beta Thalassemia Major patients was high (56%).In his study, delayed puberty was defined as the absence of any breast development at the age of 13 years in girls,he found that 78 % of girls who had delayed puberty had low LH, 57% had low FSH and 73% had low estrogen.[13] Our study also showed similar results where we compared the pubertal status of thalassemics with those of normal subjects (using Tanners staging, and hormonal levels) and found similar results wherein there was significantly lower SMR stages in Cases as compared to Controls, there was delay in attainment of menarche and also significantly lower levels of FSH, LH and Estrogen all these cases had iron overload as evidenced by very high Ferritin levels.[14] Periodic examination and recording of pubertal stage needs to be done in girls who have reached 8 years of age so that early detection and management of delayed puberty can be done.[15] Actually, in order to differentiate hypothalamic from pituitary defects, determination of LH and FSH responses to gonadotropin-releasing hormone (GnRH) stimulation is needed. Moreover, in this study, it was not known whether the low serum levels of estradiol was also caused by gonadal failure, because stimulation tests with human chorionic gonadotropin (HCG) or human menopausal gonadotropin (HMG) were not performed. Amongst the Thalassemics it was found that those having serum Ferritin levels >2000ng/ml had lower levels of gonadotropins and as compared to those having < 2000ng/ml. This implies that if the ferritin levels are maintained at lower levels preferably below 2000ng/ml may prevent pituitary dysfunction and thus pubertal delay as well as it may improve the growth status of these patients.[16, 17] When the levels of S. Ferritin were compared in those receiving chelator therapy < 5 years and those receiving it for > 5 years it was found that those with chelation therapy > 5 years had higher ferritin levels than those receiving it for less than 5 years. This could be because of the fact that those receiving chelation for a longer duration were also receiving

blood transfusion for a greater number of years which meant that they had a greater iron overload as well.[18,19] When Regularity of chelation therapy was assessed with ferritin levels it was found that those taking regular chelation therapy irrespective of the drug which was used had significantly lower Ferritin levels as compared to those taking chelation irregularly.(regularity was defined as those taking chelation therapy in the prescribed doses and not missing >5 doses per month for the preceding 6 months.[20] The levels of FSH, LH and Estrogen also showed no significant difference between those receiving chelation for >5 years and those receiving it less than 5 years. When regularity of Chelation Therapy was compared with hormones not taking into account the of duration and type of drug it was found that those taking Chelation Therapy regularly had significantly higher hormonal levels than those taking it irregularly or taking no therapy. This means that regular chelation therapy could improve the hormonal levels of the patient.

CONCLUSION

Our study concludes that delayed growth and delayed Puberty are common complications seen in female beta thalassemia major Patients. Regular Chelation therapy is necessary to reduces serum ferritin levels which improves FSH, LH and Estrogen levels.

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