HYPOGONADISM IN MULTIPLY TRANSFUSED ß-THALASSEMIA SYNDROME PATIENTS

Humaira Khan*[1], Maria Kamran[1], Ubaidullah[2], Tariq Masood[1], Jawad Ahmed[1], Shoaib Shah[3], Abid Sohail Taj[1]

[1] Institute of Basic Medical Sciences, Khyber Medical University Peshawar Pakistan
[2] Suwair General Hospital Al-Jouf, Kingdom of Saudi Arabia
[3] Institute of Radiotherapy and Nuclear Medicine (IRNUM) Peshawar Pakistan
Address for correspondence: Humaira Khan Institute of Basic Medical Sciences,

Khyber Medical University Peshawar Pakistan E-mail: humairaubaid18@gmail.com

ABSTRACT

Background: Beta thalassemia syndrome represents a wide spectrum and clinically diverse group of recessively inherited dyserythropoietic anaemias including beta thal-assemia major, beta thalassemia intermedia and beta- thalassemia compound hetero-zygotes. The group is signified by defective synthesis of one or more globin subunits of the hemoglobin tetramer requiring blood transfusions. Human body does not have an internal mechanism to eliminate the surplus iron, thus iron overload and its se-quelae follow, effecting complexion, growth, vital organs, sexual maturity, calcium metabolism and vulnerable endocrine functions.

Objectives: To determine the frequency of hypogonadism in multi-transfused beta thalassemia syndrome patients in Khyber Pakhtunkhwa province of Pakistan.

Materials and Methods: This cross sectional descriptive study included 97 patients, 55 males and 42 females aged 15 to 32 years, regularly transfused at Fatimid foun-dation Hayatabad Peshawar. Patients' data was recorded in questionnaires. Clini-cal characteristics relevant to growth and puberty were recorded. Serum Ferritin, FSH, LH, Testosterone and Estradiol assays were performed using Chemilumines-cence (CLIA) technique. Data was analyzed by SPSS version 20. Means, standard deviation and frequencies were calculated for numerical variables.

Results: Hypogonadism was seen in 40.2% of the whole population (56.4% in males and 19.04% in females). Amongst 42 females, 32 were above 16 years. 43.7% had primary amenorrhoea while 12.5% had secondary amenorrhoea, with an average age of menarche 16±2 years. Delayed puberty was observed in 54.7% of females and 83.6% of males

Conclusion: Delayed puberty and hypogonadism are obvious endocrinopathies showing higher frequencies in iron overloaded thalassemic patients of Khyber Pakhtunkhwa. In this study, frequency of hypogonadism was found more in males as compared to females. Regular endocrine evaluation and timely in-tervention can ensure sexual maturity and improved quality of life for these patients.

Key words: Beta Thalassemia Syndrome, Puberty, Hypogonadotropic Hypo-gonadism, Ferritin.

This article may be cited as: Khan H, Kamran M, Ubaidullah, Masood T, Ahmed J, Shah S, Taj AS. Hypogonadism in multiply transfused β - thalassemia syndrome patients. Adv Basic Med Sci. 2017;1(2):55-60.

INTRODUCTION

Beta-thalassemia has been encountered in every ethnic group and geographical location, not only con-fined to Mediterranean countries, but also common in Africa, the Middle East, South east Asia including south-ern China, Indian subcontinent, Burma and Peninsula of Indonesia[1,2]. The maximum carrier frequency has been reported (14%) in Cyprus, (10.3%) in Sardinia and in Southeast Asia[3]. Globally the estimated prevalence of thalassemia trait is 1.5%.

Thalassemia International Federation (TIF) docu-mented that the number of thalassemia major patients who are alive and enrolled in the list of patients getting regular treatment is merely about 200,000 around the world[4]. Estimated number of patients suffering from

thalassemia across Pakistan is 70,000. Whereas number of new cases of thalassemia coming for treatment each year is estimated to be 6000[5].

Beta thalassemia syndrome represents a wide spectrum and clinically diverse group of recessively inherit-ed dyserythropoietic anaemias. The group is signified by defective synthesis of one or more globin subunits of the hemoglobin tetramer[6-9]. At one end of the spectrum are patients suffering from thalassemia major also called "Cooley's Anemia"[10] or "Mediterranean Anemia". In the middle are non-transfusion dependent thalassemia ma-jor or thalassemia intermedia and compound heterozy-gotes like HbE/β thalassemia, HbC/β thalassemia and HbS/β thalassemia. A great majority of affectees carry a single gene defect, referred to beta thalassemia car-riers or beta thalassemia trait. These disorders are of varying clinical severity in which patients are inappro-priately diagnosed, poorly managed, inadequately che-lated and have multi-system anomalies like cardiac fail-ure, retarded growth, osteopenia, multiple fractures, delayed puberty et cetera (etc).

TIF has recommendations of regular blood transfu-sions to transfusion dependent thalassemic patients at an interval of two to five weeks, in order to maintain pre transfusion Hb at 9-10.5g/dl[11] while every single unit of blood has 200mg of iron[12].

Although blood transfusions are crucial in the surviv-al of such patients, humans have no internal mechanism to eliminate the surplus iron, rendering these regularly transfused patients vulnerable to the risk of developing iron toxicity. Blood transfusion on regular basis of up to 12 transfusions will result in iron overload and its com-plications, including endocrinopathies involving short stature, diabetes mellitus, hypogonadism, insufficiency of pituitary, hypothyroidism and hypoparathyroidism[13]. Hypogonadism is a frequent complication due to iron deposition in hypothalamus, pituitary and gonads[14]. Hypogonadotropic hypogonadism resulting from trans-fusional iron overload is the most evident endocrinopa-thy[15] although in time use of chelation drugs can bring improvement in survival[16].

This study was conducted due to the fact that there are no published results or studies looking at gonadal functions in beta thalassemia syndrome patients in Khy-ber Pakhtunkhwa (KPK) province of Pakistan. This study aimed to evaluate hypogonadism in a single centered, iron overloaded thalassemia syndrome patients of KPK province of Pakistan, enabling practitioners and phy-sicians to prioritize comprehensive molecular diagno-sis and management of such patients accordingly, thus ensuring their sexual maturity and gonadal wellbeing. Inadequate chelation due to financial constraints was a perplexing situation faced by our young patients and thus the aim was to use serum ferritin as a prognostic marker.

METHODOLGY

This cross sectional (Descriptive) study was conduct-ed at Institute of Basic Medical Sciences (IBMS), Khyber Medical University (KMU) Peshawar from March 2014 to March 2015 after the permission of Advance study and Research Board (AS&RB) and Ethical board of KMU. The study consisted of 97 pre-diagnosed multi-transfused be-ta-thalassemic patients. The study participants were 55 males and 42 females between the ages of 15-32 years. Participants who were below 15 years or had received any hormone replacement therapy or had some co-mor-bid condition were excluded from the study. Sampling was done at Fatimid foundation Hayatabad Peshawar. Patients were enrolled in the study after taking permis-sion from relative authorized personnel. Blood sampling and data collection was performed from patients after taking prior written informed consent from the patients or guardians. A total of 3 ml blood samples were col-lected in red top vacutainers which after clotting were centrifuged at 10,000 RPM (Revolutions per minute) for 5 minutes. The clear serum extracted was stored at – 40_0 C. The samples were brought to room temperature prior to conduct analysis, then were centrifuged and analyzed on Lumax analyzer. Serum Ferritin, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Es-tradiol (E2) and Testosterone (T) were analyzed by Che-miluminescence immunoassay (CLIA) technique (17) us-ing kits manufactured by Monobind Incorporation USA.

STATISTICAL ANALYSIS

Data was analyzed using SPSS software (version 20). Numerical data was represented as mean ± standard de-viation, frequencies and percentages.

RESULTS

In study sample size of 97 patients, males were 55 (56.7%) while females were 42 (43.3%). Age range was 15-32 years. Mean was 18 ± 3. The distribution of age groups of patients showed that highest number of pa-tients 71.1% were in more than (>16) years age group whereas 28.9% of patients were in less than (<) 16 years age group.

DEMOGRAPHIC CHARCTERISTICS

Majority of patients were from Peshawar district fol-lowed by Charsadda. Commonest spoken language was Pushto followed by Urdu. Blood groups O_+ and B_+ were the commonest blood groups.

CLINCICAL CHARACTERISTICS

Mean height of study patients was 144 ± 8 cm. BMI of patients in > 16 years group indicated that more than half of patients were underweight while in < 16 years age group half of patients were normal and half had low percentile. The lowest mean Ferritin detected for short stature was 3000ng/ml in this study.

Mostly patients were chelated, although regularly chelated was only a small proportion. Compliants were only 3%. Most of the patients had splenomegaly followed by hepatomegaly. Splenectomised patients were 24.7 %. Viral profile of majority of patients was unknown, al-though HCV_+ had a higher frequency.

Delayed puberty was found more in males (absence of facial hair development) as compared to females (ab-sence of breast development) even at the ages of 15 years. Mean age of menarche was 16 ± 2 SD.

Females who reached pubertal age of 16 years were 32, in which 14 (43%) had primary amenorrhoea and 4 (12%) had secondary amenorrhoea.

Transfusion frequency was variable but mostly patients were taking two times transfusion per month followed by three times transfusion per month.

All of patients were iron overloaded with serum ferritin minimum value 1500 ng/dl, maximum value of 27042ng/ml and mean value 12848ng/ml. Iron overloaded patients were divided into four groups however maximum number of patients 69 out of 97 (71.1%) were in a group with very severe iron overload (more than 10,000ng/ml).

Frequency of hypogonadism was 40.2% in study patients. 56.36% in males on the basis of low Testosterone and 19.04% in females on the basis of low Estradiol.

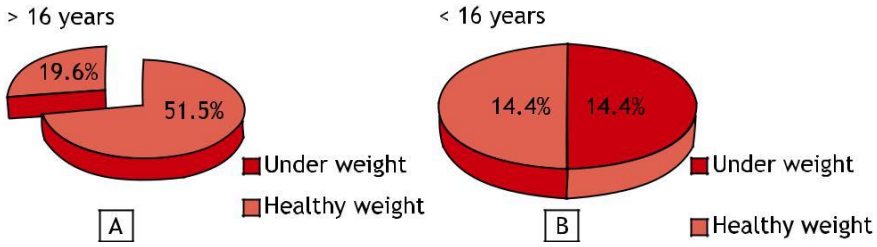

Fig 1 A. Percentages of healthy and normal weight on > 16 years group
B. Percentages of healthy and normal weight on < 16 years group

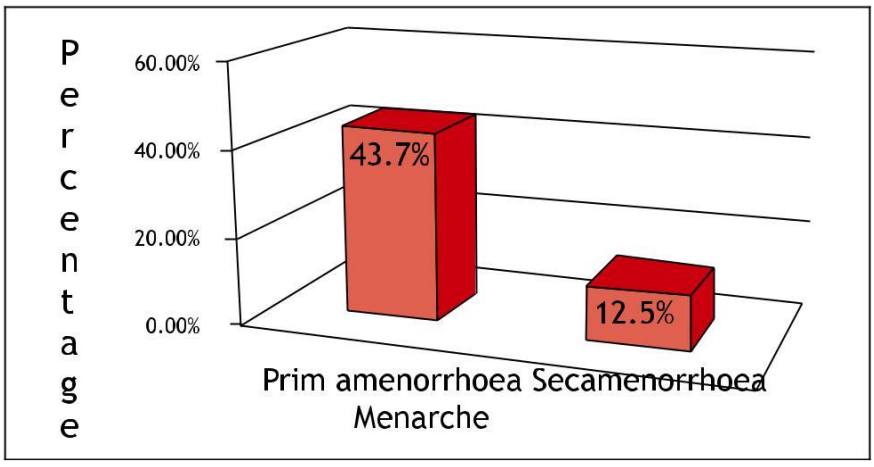

Fig 2 Frequencies of patients with primary and secondary amenorrhoea

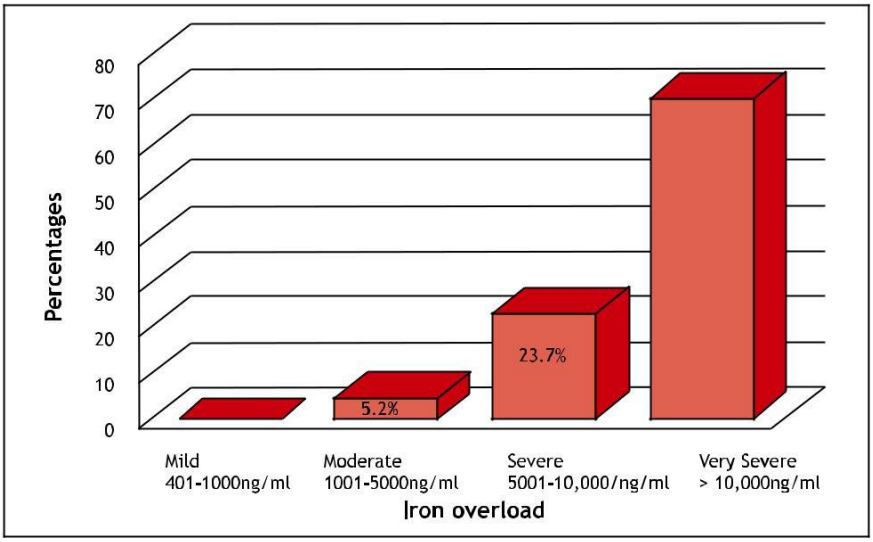

Fig 3 Grouping of iron overload

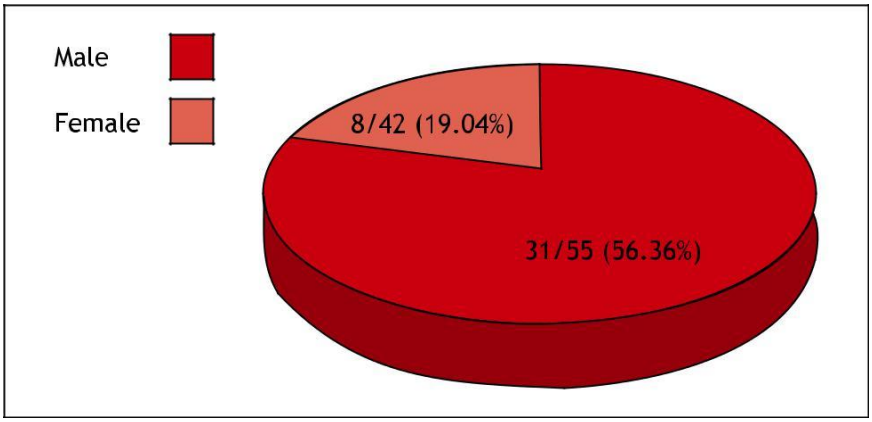

Fig 4 Frequency of hypogonadism in study sample

Table 1 Clinical characteristics of study sample

Variables		Mean+ SD or n (%)
Height (cms)		144.9 + 10.8
Chelation	Yes	73 (75.3)
	No	24 (24.7)
Chelation Status	Compliant	3 (3.1)
	Non-compliant	70 (72.2)
Splenectomy	Yes	24 (24.7)
	No	73 (75.3)
HBV/HCV Status	Unknown	63 (64.9)
	Both positive	1 (01)
	Both negative	4 (4.1)
	HBsAg+	2 (2.1)
	HCV+	27 (27.8)
Delayed Puberty	Males	46 (83.65)
	Females	23 (54.7)

Table 2 Frequency of hypogonadism in male population (n=55)

Groups	Gonadal function tests			Hypogonadism
	Low Testosterone	Low FSH	Low LH	
Paediatri Group (n=17)	9 (52.9%)	4(23.5%)	9(52.9%)	9(52.9%)
Adult Group (n=38)	22 (39.2%)	17(44.7%)	14(36.8%)	22(39.2%)

Table 3 Frequency of hypogonadism in female population (n=42)

Groups	Gonadal function tests			Hypogonadism
	Low Estradiol	Low FSH	Low LH	
Paediatric Group (n=11)	3(27.3%)	3(27.3%)	4(36.4%)	3(27.3%)
Adult Group (n=31)	5(16.1%)	3(9.7%)	5(16.1%)	5(16.1%)

Male as well as female population was stratified into two groups < 16 years and >16 years. Frequency of hy-pogonadism was calculated in both of the groups sepa-rately.

DISCUSSION

Hypogonadism is one of the most evident endocr-inopathy encountered in multi-transfused thalassemic patients[14], the cause is mainly deposition of iron in the hypothalamus-pituitary gonadotrophic cells along with gonads[18].

Growth retardation was an obvious finding in this study, with an incidence of 51.5% in >16 years age group while 14.4% in <16 years age group (Fig 1). Same was described in a study of Greek patients[19] with highest frequency observed in 15 to 20 years of age group. The lowest mean Ferritin detected for short stature was 3000ng/ml in present study. This is consistent with find-ings of study from Israel[16].

Viral profile of patients showed that 27.8% of the pa-tients were HCV positive followed by 2.1% HBsAg pos-itive (Table 1), which is comparable to Iranian multi-centre study[20]. These findings accomplished that blood transfusion is a major risk factor for hepatitis C virus acquisition among our thalassemic patients.

Primary amenorrhoea was found to be 43.7% while 12.5% had secondary amenorrhoea with an average age of menarche 16±2 years (Figure 2). Figures are compa-rable with Egyptian study by Abdelrazik and Ghanem[21].

Frequency of hypogonadism in study sample came out to be 40.2% (Fig 4). This is comparable with figures reported by multicentre study of Fung et al[22]. Frequency of hypogonadism in males was 56.4% while in females it was 19.04% which is comparatively low (Table 2 & 3).

This has also been reported before and is mainly due the fact that damage of ovaries owing to deposition of iron is rare before 25 to 30 years because of less vascularity of ovaries before this age[23].

In present study, all of the patients were diagnosed only on the basis of raised fetal haemoglobin when hae-moglobin (Hb) electrophoresis was performed. Thal-assemia diagnosis in high prevalence areas should be based on comprehensive set of testing including mo-lecular and conventional tests. It is imperative to have an exact diagnosis prior to planning out a management strategy. Gonadotropin releasing hormone (GnRH) stim-ulation test although cumbersome may point to the ex-act level of defect.

CONCLUSION

Delayed puberty and hypogonadism are obvious en-docrinopathies showing higher frequencies in iron over-loaded thalassemic patients of Khyber Pakhtunkhwa. In this study, frequency of hypogonadism was found more in males as compared to females. Regular endocrine evaluation and timely intervention can ensure sexual maturity and improved quality of life for these patients.

ACKNOWLEDGEMENT

I am grateful to Fatimid Foundation, Blood Bank and Haematological Services Hayatabad Peshawar especial-ly Afzal Hasan Khan (Admen Officer), Shagufta and all staff for their thorough support and facilitation. I am thankful to all the laboratory staff of pathology depart-ment of IBMS - KMU Peshawar especially Safi U Rehman and Kareem dil (Lab Technicians) who gave their con-stant technical support in the laboratory work. I wish to express my statement of gratitude towards IRNUM es-pecially Muhammad Rauf Khattak (Director Irnum) and staff for their support and attention. I would like to pay

thanks to Dr. Jehanzeb (Professor Biochemistry Department) Rehman Medical Institute Peshawar who gave his precious time and expertise regarding quality control.

REFERENCES

1. Galanello R, Origa R. Review: Beta-thalassemia. Orphanet J Rare Dis. 2010;5(11).
2. Olivieri NF. The ß-thalassemias. New England Journal of Medicine. 1999;341(2):99-109.
3. Flint J, Harding RM, Boyce AJ, Clegg JB. 1 The population genetics of the haemoglobinopathies. Baillière's clinical haematology. 1998;11(1):1-51.
4. Cappellini M-D, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Guidelines for the clinical management of thalas-saemia: Thalassaemia International Federation, Nicosia (CY); 2008.
5. Adil A, Sobani ZA, Jabbar A, Adil SN, Awan S. Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. Journal of the Pakistan Medical Association. 2012;62(3):307.
7. Srivatsa A, Marwaha R, Muraldharan R, Trehan A. Assessment of adrenal endocrine function in Asian thalassemics. Indian Pediatr. 2005;42(1):31-5.
8. Karamifar H, Shahriari M, Sadjadian N. Prevalence of endocrine complications in beta-thalassaemia major in the Islamic Republic of Iran. Eastern Mediterranean health journal. 2002;9(1-2):55-60.
9. Al-Elq AH, Al-Saeed HH. Endocrinopathies in patients with thalassemias. Saudi medical journal. 2004;25(10):1347-51.
10. Cooley TB, Lee P. A series of cases of splenomegaly in chil-dren with anemia and peculiar bone changes. Trans Am Pediatr Soc. 1925;37(29.1925).
11. Cappellini MD. Long-term efficacy and safety of deferasirox. Blood reviews. 2008;22:S35-S41.
12. Sway Lay Thein, David Rees In: A.Victor Hoffbrand, Daniel Catovsky, Edward G. D. Tuddenham, Green AR, editors. Postgraduate Haematology. 6th ed. London: Wiley-Black-well; 2011. p. 83-108.
13. Low LC. Growth, puberty and endocrine function in beta-thalassaemia major. Journal of Pediatric Endocrinology and Metabolism. 1997;10(2):175-84.
14. De Sanctis V. Growth and puberty and its management in thalassaemia. Hormone research. 2001;58:72-9.
15. Merchant RH, Shirodkar A, Ahmed J. Evaluation of growth, puberty and endocrine dysfunctions in relation to iron overload in multi transfused Indian thalassemia patients. The Indian Journal of Pediatrics. 2011;78(6):679-83.
16. Shalitin S, Carmi D, Weintrob N, Phillip M, Miskin H, Kornreich L, et al. Serum ferritin level as a predictor of im-paired growth and puberty in thalassemia major patients. European journal of haematology. 2005;74(2):93-100.
17. Chen W, Jie W, Chen Z, Jie X, Huang-Xian J. Chemiluminescent immunoassay and its applications. Chinese Journal of Analytical Chemistry. 2012;40(1):3-10.
18. Berkovitch M, Bistritzer T, Milone S, Perlman K, Kucha-rczyk W, Koren G, et al. Iron deposition in the anterior pituitary in homozygous beta-thalassemia: MRI evaluation and correlation with gonadal function. Journal of Pediat-ric Endocrinology and Metabolism. 2000;13(2):179-84.
19. Kattamis C, Liakopoulou T, Kattamis A. Growth and devel-opment in children with thalassaemia major. Acta Paedi-atrica. 1990;79(s366):111-7.
20. Mirmomen S, Alavian S-M, Hajarizadeh B, Kafaee J, Yektaparast B, Zahedi M-J, et al. Epidemiology of hepatitis B, hepatitis C, and human immunodeficiency virus infecions in patients with beta-thalassemia in Iran: a multicenter study. Arch Iran Med. 2006;9(4):319-23.
21. Abdelrazik N, Ghanem H. Failure of puberty in Egyptian beta thalassemic patients: Experience in north east region—Dakahlia province. Hematology. 2007;12(5):449-56.
22. Fung EB, Harmatz PR, Lee PD, Milet M, Bellevue R, Jeng MR, et al. Increased prevalence of iron-overload associat-ed endocrinopathy in thalassaemia versus sickle-cell dis-ease. British journal of haematology. 2006;135(4):574-82.
23. Toumba M, Kanaris C, Simamonian K, Skordis N. Outcome and management of pregnancy in women with thalassaemia in Cyprus. Eastern Mediterranean Health Journal. 2008;14:628-35.