International Journal of Advances in Medicine
Sharma S et al. Int J Adv Med. 2017 Jun;4(3):673-677
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20171587

Original Research Article

Prevalence of hypothyroidism, diabetes mellitus and delayed puberty in patients of thalassemia major in a tertiary care center of Jammu province, Jammu Kashmir, India

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Received: 09 April 2017
Accepted: 13 April 2017

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ABSTRACT

Background: Thalassemia is a common genetic disorder which is associated with a lot of complications. Frequent blood transfusions result in increased iron deposition in various tissues leading to dysfunction of many organs of our body. Endocrine disorders constitute a major part of such complications increasing the morbidity of thalassemia manifold in the affected patients.
Methods: This is a prospective study carried out in 64 thalassemia major patients attending thalassemia day care centre at SMGS Hospital Jammu from December 2014 to November 2015. Patients were examined and investigated for presence of one or more endocrine disorders including diabetes mellitus, hypothyroidism and delayed puberty.
Results: Endocrine disorders were detected in a total of 22 patients. Diabetes mellitus was detected in 4.7% (n=3) patients, hypothyroidism in 4.7% (n=3) patients and delayed puberty was found in 26.6% (n=17) patients. Mean serum ferritin level was found to be 2885.5 ng/ml and there was no significant difference in patients affected with endocrine disorder and those without any endocrine disorder.
Conclusions: Endocrine complications occur commonly in patients of thalassemia major. Increasing life span of thalassemia patients has increased the number of patients living with these disorders. A lot of morbidity occurs due to the presence of one or more of these disorders. Hence timely detection of these disorders by screening in all patients of thalassemia should be done to initiate treatment at the earliest so as to limit the morbidity caused by these disorders.

Keywords: Endocrine disorders, Serum ferritin, Thalassemia

INTRODUCTION

Thalassemia major is a common genetic disorder of haemoglobin synthesis with defect in production of one or more hemoglobin chains. The homozygous state results in severe anaemia and is known to affect a significant population in Mediterranean countries, middle East, northern India and parts of south east Asia. The combination of transfusion and chelation therapy has resulted not only in increased life expectancy of thalassemic patients but is also associated with various complications.

A number of these complications result from iron overload occurring due to repeated transfusions.[1] Excessive iron is deposited in most tissues of the body including the liver, heart and the endocrine glands.[2] Deposition of iron in tissues leads to endocrine dysfunction which is a well

recognised complication in patients with transfusion dependent thalassemia.[3-5] The effect of iron toxicity on endocrine glands has been well proven in various histological studies.[6,7]

Endocrine complications in thalassemia patients: Delayed puberty, diabetes mellitus, hypothyroidism and hypoadrenalism are some of the most common endocrine complications found in thalassaemia patients.[8] Of all these complications delayed puberty due to hypogonadism is the most common occurring in upto 50%-91% of patients.[8,9] Gonadal iron deposition resulting in primary gonadal failure is the most important cause of hypogonadism.[10]

Iron deposition in the pituitary gland can result in lowered Gonadotropin releasing hormone (GnRH) levels causing secondary hypogonadism.[11-13] The prevalence of diabetes is also very high and estimated to be between 2.3% to 24.1% in b-thalassaemia.[14,15] There are two main mechanisms resulting in glucose intolerance and subsequent development of diabetes mellitus. The first mechanism involves decrease in insulin production either by direct impairment of insulin excretory function by chronic iron overload or immune system activation against pancreatic b-cells in b-thalassaemia patients.[16,17]

The second mechanism involves decreased insulin sensitivity with reduced hepatic release of insulin.[8,18] Thyroid dysfunction is another frequently occurring endocrine complication. The natural history of thyroid dysfunction is not clearly understood and various studies have reported different incidences with almost 5 % thalassemia major patients having overt hypothyroidism and requiring treatment.[19,20]

To reduce iron overload in body and its resultant complications, all thalassemic patients need to be given Iron Chelation therapy. However, there are various issues with the available iron chelators at present. Desferoxamine has been used successfully in the treatment of beta thalassemia for quite a long time now and has been shown to be very effective in reducing both the hepatic and extra-hepatic iron stores and reducing the resultant complications including myocardial toxicity.[21] But the repeated parenteral therapy with desferioxamine results in poor compliance. Oral available chelators such as Deferasirox are expensive than the traditional chelators which makes it difficult for patients to afford in developing countries like India.[22]

Despite the well documented ability of desferioxamine to reduce hepatic and extrahepatic iron, its ability to prevent endocrine damage is less clear. It is but very logical that the prevention of excessive iron overload will decrease iron deposition in tissues, decrease free radical generation and thus improve the prognosis for the late sequelae of iron toxicity including endocrinopathies. Determining the exact prevalence of endocrinopathies is still difficult because of differences in age of first exposure to chelation therapy and improvement in survival in well-chelated patients.[23]

METHODS

This study was carried out from December 2014 to November 2015 in the department of Pediatrics, SMGS hospital Jammu which has a dedicated Thalassemia day care centre. Patients suffering from thalassemia major recieving regular blood transfusions and older than 10 years of age were included in this study.

A written informed consent was obtained from the guardians of the patients. Detailed history including age at first transfusion, total number of transfusions, frequency of transfusions, intake of any medicine for endocrine dysfunction, any chelation etc. were noted. Following investigations were done to for diagnosing any endocrine dysfunction or delayed puberty:

Hypothyroidism: A detailed history followed by thorough clinical examination were done to look for signs and symptoms of hypothyroidism. Thyroid stimulating harmone (TSH) levels were done in all patients and full thyroid profile was done in patients with elevated TSH. A diagnosis of hypothyroidism was established in children with TSH >5.4mIU/L and free T4 <0.5ng/dl (9) or in children with diagnosed hypothyroidism and on treatment.

Diabetes mellitus: After detailed history and examination, Fasting blood glucose and random blood glucose measurements were done. Glycosylated Haemoglobin (HbA1c) levels were done in those with elevated blood glucose levels. A fasting blood glucose level of more than 125 mg/dl or non-fasting level of more than 200 mg/dl was considered diagnostic of diabetes mellitus. Patients already diagnosed and on insulin therapy were also included.

Delayed puberty: Detailed menstrual history was obtained. Tanner's staging was done on all males older than 14 years and females older than 13 years of age. Delayed puberty was defined in females as age of more than 13 years and not having attained tanner B2 stage or age or more than 15 years with primary amenorrhea. In males it was defined as age of more than 14 years and not yet attained tanner G2 or on androgen replacement therapy.

Prevalence of hypothyroidism, diabetes mellitus and delayed puberty was reported using proportions and percentages.

RESULTS

There was a total of 64 patients included in this study which included 23 (36%) female patients and 41 (64%) male patients. The mean age was 17 years and mean serum ferritin level was 2885.53ng/ml.

Of the 64 thalassemia major patients, 3 (4.7%) patients had hypothyroidism. The mean age of patients with hypothyroidism was 23.3 years. It included 2 (66%) males and 1 (33%) female. The mean serum ferritin level was

2747.18 ng/ml. There were 3 (4.7%) patients who were detected to have diabetes mellitus. Again, there were 2 males and 1 female patient with diabetes. Mean age was 21 years and mean serum ferritin level was 2666.66ng/ml.

Table 1: Demographic and biochemical characteristics of 64 patients with thalassemia major.

Parameter	Minimum	Maximum	Mean (S.D.)
Age (in years)	10	32	16.9 (5.0)
FBS (mg/dl)	62	269	94.0 (35.5)
TSH (mIU/L)	0.5	52	4.6 (7.9)
S. Ferritin (ng/ml)	983.9	5066.5	2885.5 (1037.4)

FBS- fasting blood glucose, TSH- thyroid stimulating hormone, S. Ferritin-serum ferritin.

There was a total of 17 (26.6%) patients detected to be having delayed puberty. This included 11 males and 6 females with delayed puberty. Thus, delayed puberty occurred with equal preponderance in males i.e. 11 out of 41 (27%) and females i.e. 6 out of 23 (26%). The mean age was 18.65 years. There was a total of 32 patients who were above 15 years of age in our study. Of these 32 patients in age group 15 years and above, 17 patients (53.1%) had delayed puberty. Thus, more than fifty percent of patients above 15 years of age were detected to have delayed puberty. The mean serum ferritin level was 2885ng/ml. There was one patient having both delayed puberty and diabetes mellitus. Thus, a total of 22 patients out of 64 (34%) were found to be having some endocrinopathy (Table 1, Figure 1).

Mean Serum ferritin levels of patients with diabetes (2666.6 ng/ml) and hypothyroidism (2747.1 ng/ml) were similar to those patients who had no diabetes and hypothyroidism whereas mean serum Ferritin levels of patients with delayed puberty (3308.7ng/ml) were found to be only slightly higher than those without delayed puberty. Furthermore 50% of patients with serum ferritin levels above 3500ng/ml had delayed puberty (Table 2).

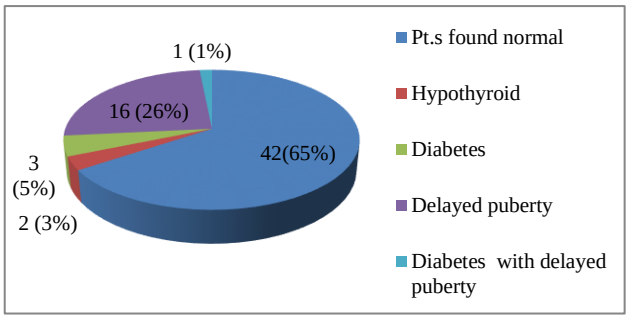

Figure 1: Prevalence of various abnormalities as found in this study.

Table 2: Relation of serum ferritin levels with various abnormalities.

	S. Ferritin 500-1500ng/ml (n=6)	S. Ferritin 1500-2500ng/ml (n=19)	S. Ferritin 2500-3500ng/ml (n=23)	S. Ferritin>3500 ng/ml (n=16)
No. of hypothyroid patients	0	2 (10.4%)	0	1 (6.25%)
No. of diabetic patients	0	1 (5.2%)	2 (8.7%)	0
No. of patients with delayed puberty	1 (16.6%)	6 (31.5%)	4 (17.3%)	8 (50%)

DISCUSSION

Repeated blood transfusions in patients suffering from thalassemia major result in various complications. Increasing life expectancy of thalassemia patients has resulted in a variety of complications including endocrine abnormalities causing a lot of morbidity in these patients. The complications include hypo-gonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and other endocrine abnormalities.[12] In present study 3 (4.7%) patients were found to be suffering from diabetes. Previous studies have reported prevalence of diabetes ranging from 2.3% to 24.1% in these patients.[24,25] Ong et al. reported diabetes mellitus prevalance of 8% in these patients while Jaruratanasirikul et al. found prevalence of impaired glucose metabolism of 12.5% in such patiens.[26,27] Najafipour et al. on the other hand reported prevalance of diabetes at 8.9% in Iran.[28] No correlation was found between serum ferritin levels of patients having diabetes and those without diabetes. The reason for this could be that in addition to chronic iron overload that results in diabetes, immune system activation against pancreatic beta cells also plays a significant role resulting in impaired insulin secretion.[17,18]

Hypothyroidism was found in 3 (4.7%) of patients in our study. This was similar to the findings of Zervas et al. who reported prevalence of hypothyroidism in 4% of patients and Karamifar et al who reported that 6% of patients had hypothyroidism.[29,30] Again in present study we could not find any relation of hypothyroidism with increasing levels of serum ferritin. There has been consistent occurrence of hypothyroidism in patients of thalassemia but still its causation is poorly understood and there is a lot of variation in its reported prevalence ranging from 4% to 60 %.[29,31]

There is thus a high prevalence of endocrine abnormalities in multi transfused patients of beta thalassemia owing partly to direct deposition and toxicity of serum ferritin and partly to some immune and as yet to be understood mechanisms.[28-30] There were 17 (27%) patients in our study who had clinical evidence of delayed puberty as assessed by tanner staging with equal male female preponderance. This percentage increased to 53% percent when patients younger than 15 years of age were excluded. Thus, more than half of the patients otherwise expected to have attained puberty had delayed puberty. Again, there is wide variation in reported prevalence of delayed puberty ranging from 50% to 100%.[8] High serum ferritin leading to gonadal iron deposition is thought to cause primary gonadal failure.[10] Iron deposition in pituitary gland can lead to secondary gonadal failure due to decrease in Follicle stimulating harmone (FSH) and Leutenizing harmone (LH) levels.[11,12] More commonly there may be both primary and secondary gonadal failure occurring together.[32]

CONCLUSION

Endocrine dysfunction occur in a large number of patients suffering from thalassemia. Present study has also found a high prevalence of these disorders. Early detection of these disorders can result in timely interventions including specific treatment of each disorder and more vigorous control of total body iron content. Although our study has failed to demonstrate any significant increase in serum Ferritin in affected patients as compared to unaffected patients pointing towards a multifactorial etiogenesis, the findings of our study are limited by small sample size and other factors including chelation. The findings therefore cannot be extrapolated and the fact that it is a single center study restricts the generalization of results to the entire population.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Sharma S, Dutt N, Sidhu M, Digra S, Meenia R. Prevalence of hypothyroidism, diabetes mellitus and delayed puberty in patients of thalassemia major in a tertiary care center of Jammu province, Jammu Kashmir, India. Int J Adv Med 2017;4:673-7.