



Study of Growth Hormone Levels in Thalessemia Major Patients in Children

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Abstract

Introduction: *Thalassemia is an inherited disorder of hemoglobin synthesis. Regular blood transfusions and chelation therapy have notice ably prolonged survival in thalassemic patients.^[1] Despite a significant increase in the life span of these patients, they suffer from multiple abnormalities probably due to iron over load, including endocrinal abnormalities such as hypogonadism, diabetes mellitus, hypothyroidism and hyperparathyroidism.^[2] The pattern of levels of growth hormone levels among the patients with thalassemia major undergoing repeated blood transfusions remain unexplored. Very few studies have been undertaken among Indian population.*

Methodology: *It is a prospective study and was conducted at St George hospital, Mumbai, on diagnosed patients of thalassemia major admitted to the paediatric wards. Duration of the study was 3 months and 20 patients were included.*

Inclusion Criteria

1. All admitted patients of thalassemia major aged 18 years and below.

Exclusion Criteria

1. Chronic haemolytic anemia apart from thalassemia major
2. Those that was very sick
3. Those suffering from malnutrition
4. Those who were on supplementation of growth hormone.

Patients who were willing to participate and sign the inform consent were enrolled in the study.

Growth hormone levels were done using CLIA.

Results: *The mean age of the studied thalassemia patients was 9.65 ± 4.23 years with no gender preponderance. Mean (SD) Growth hormone levels was $0.769 \text{ ng/dl} \pm 0.540 \text{ ng/dl}$ and was not found to be statistically significant ($p > 0.001$).*

Conclusion: *It is evident from the present study that the levels of Growth Hormone are normal among β -thalassemia major patients on repeated blood transfusion. But GH supplementation can help these patients. Frequent monitoring and supplementation in deficient states is recommended.*

Keywords: *Beta Thalassemia major, Growth Hormone levels.*

Introduction

Thalassemias are a group of autosomally recessive inherited conditions characterised by the absence or reduced synthesis of The one of the two polypeptide chains (alpha (α) or beta (β)) that form the normal adult human haemoglobin molecule (haemoglobin A, $\alpha_2\beta_2$) leading to reduced haemoglobin in red cells and anaemia . The thalassaemia syndromes are named according to the globin chain affected or the abnormal haemoglobin involved; mutations of the α globin gene cause α thalassaemia, while the β globin gene defects give rise to β thalassaemia. It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of β thalassaemia, with approximately 60,000 symptomatic individuals born annually.^[1]

Similarly, α thalassaemia occurs at high frequencies throughout tropical and subtropical regions of the world. The thalassaemias can be classified according to phenotype (clinical severity) or genotype (type of mutation) in which clinical presentation can be highly variable ranging from asymptomatic carriers to transfusion-dependent thalassaemia. The more clinically severe forms of thalassaemia affect multiple systems, where the manifestations are either caused by the condition itself or by the complications from various treatments such as frequent blood transfusions. These individuals usually present within the first two years of life with severe anaemia and if untreated or poorly transfused, they suffer from growth retardation, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis and skeletal changes due to bone marrow expansion. Regular blood transfusions will improve growth and development, reduce hepatosplenomegaly as well as bone deformities, but can lead to complications of iron overload such as cardiomyopathy, liver cirrhosis and endocrinopathies.^[1]

Growth hormone deficiency (GHD) has been recognised as one of the endocrine complications among this population as the anterior pituitary is

particularly sensitive to free radical oxidative stress secondary to iron overload .Studies in many people with thalassaemia who are of short stature have shown dysfunction of the growth hormone releasing hormone-growth hormone-insulin-like growth factor 1 (GHRHGH-IGF-1) axis. Growth hormone reserve, which is defined biochemically by the peak serum concentration after stimulation with a known secretagogue, was reported to be normal or reduced with a wide variability (8% to 80%) in people with thalassaemia who are of short stature due to defects in the pituitary gland or hypothalamus or both.^[1]

The major concerns with GHD in children surround their growth and height attainment; and among people with thalassaemia, GHD has been recognised as a cause for growth and maturational delay . In adults, GHD has been associated with: an adverse lipid profile; increased cardiovascular and cerebrovascular events; and decreased bone mineral density, muscle strength, exercise capacity, cognitive function and quality of life. Although predominantly seen in those with thalassaemia major, GHD may affect those with thalassaemia intermedia where it manifests with a less severe form of anaemia.^[1]

Short stature is very common amongst people with thalassaemia. It may be caused by various factors including problems with growth hormone or other hormones, insufficient blood transfusions or poor nutrition. Synthetic growth hormone is one way of treating short stature in thalassaemia, especially in children with defective growth hormone production. This usually involves an injection of growth hormone under the skin (subcutaneously) several days a week over a period of time. However, it is unclear whether the use of synthetic growth hormone provides any consistent or clear benefits to people with thalassaemia.^[2]

Growth issues in people with thalassaemia should be addressed with measures such as ensuring optimal transfusion and chelation therapies, treating nutritional deficiencies and prompt diagnosis and treatment of endocrinopathies such

as hypothyroidism, abnormal glucose homeostasis, pubertal delay and GHD). As many of these aspects (such as proper transfusion regimens and chelation therapies) have been addressed, attempts to improve linear growth has increasingly included the used of GH replacement therapy.^[1]

Materials and Methods

A prospective study was conducted in the department of pediatrics, St George hospital Mumbai. The study was conducted on diagnosed patients of thalassemia major admitted to the pediatric wards. Duration of the study was 3 months. Taking into consideration of availability of patients within data collection period, a total of 20 children, diagnosed with β thalassemia major were enrolled in the study. All the necessary information regarding the study was explained to the parents and informed written consent was taken from the parents who were willing to participate in the study. After obtaining written informed consent in local vernacular language, the patients who were fulfilling the inclusion criteria were included in the study.

Inclusion Criteria

1. All admitted patients of thalassemia major aged 18 years and below.

Exclusion Criteria

1. Chronic haemolytic anemia apart from thalassemia major
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Table no. 1

Range of Growth Hormone levels(ng/dl)	Interpretation	Frequency (n=20)	Chisquare	P value
<0.09 ng/ml	deficient	2	166.0384	>0.001
>0.09 ng/ml	sufficient	18		

Discussion

Mean (SD) Growth Hormone levels was 0.769 ± 0. 0540 ng/dl. The cut off GH deficiency is 0.09 ng/ml. Similar lower GH deficiency was found in other studies as well.

4. Those who were on supplementation of growth hormone.

Statistical Analysis

All the data collected were entered in to a spreadsheet on Microsoft office Excel Sheet and then transferred to SPSS IBM version 21.0 for analysis. Significance of p value was taken as p<0.001.

Results and Observation

The mean age of the studied thalassemia patients was 9.65 ±4.23 years with no gender predilection. Mean (SD) Growth Hormone levels was 0.769 ± 0.540 ng/dl. Only 2 out of 20 samples were found to be low normal levels of growth hormone. As per Indian pediatric population, Growth Hormone concentrations of >0.09 ng/mL (4.06 pmol/L) are considered as sufficient, and <0.09 ng/mL (<4.06 pmol/L) as deficient [] as shown in figure 1and table 1.

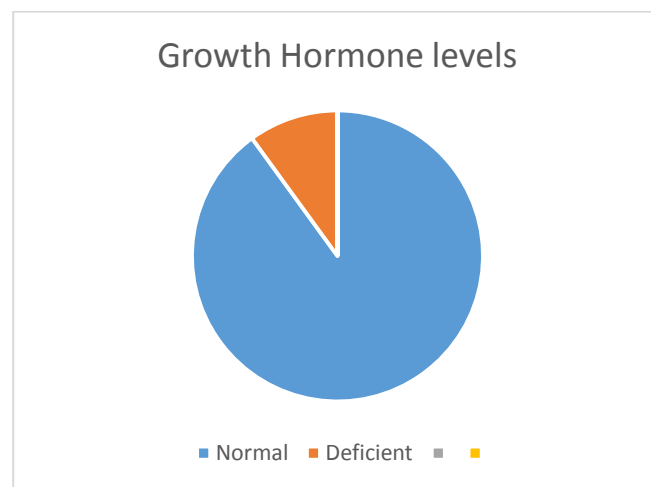


Figure 1: Growth Hormone levels

In our study, it is found that only 10 % patients had growth hormone levels lower than required. This was not found to be significant with p value >0.001. Several studies have reports low growth hormone levels in thalassemia patients.^[10-14] These

were attributed to hepatic dysfunction and dysfunctions of endocrine tissues.^[12]

This shows that thalasseemics are at a little risk for growth hormone deficiency and hence may require a need for growth hormone supplementation.

Conclusion and Recommendations

We can conclude that the levels of growth hormone are not deficient among β -thalassemia major patients on repeated blood transfusion. There is no need to give growth hormone supplement considering the untoward side effects of growth hormone supplementation. But, it is important to emphasize that treatment of thalassaemia patients with aggressive nutritional support which include fortified cereals, fortified milk are highly recommended.

Supplementation with GH in these children would also help in normalisation of various other growth markers such as calcium, phosphorous and ALP.

We should try to screen all B-thalassaemic children for growth hormone abnormalities, other hormone, vitamin D levels, calcium, and phosphorus levels as well.

References

1. Ngim CF, Lai NM, Hong JY, et al. Growth hormone therapy for people with thalassaemia. *Cochrane Database Syst Rev*. 2017;9(9):CD012284. Published 2017 Sep 18. doi:10.1002/14651858.CD012284.pub2
2. Ngim CF, Lai NM, Hong JYH, Tan SL, Ramadas A, Muthukumarasamy P, Thong MK. Growth hormone therapy for people with thalassaemia. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012284. DOI: 10.1002/14651858.CD012284.pub2.
3. Shruti Dhale, Subash Valinjar, Jyothi Janardhan, Sagar Walhekar. Study of Vitamin D levels in Thalessemia Major Patients in Children. Volume07Issue07 July 2019.
4. De Sanctis V, Soliman AT, Elseidfy H, et al. Growth and endocrine disorders in thalassaemia: The international network on endocrine complications in thalassaemia (I-CET) position statement and guidelines. *Indian J Endocrinol Metab*. 2013;17(1):8–18. doi:10.4103/2230-8210.107808.
5. Vogiatzi MG, Macklin EA, Trachtenberg FL, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. *Br J Haematol*. 2009;146(5):546–556. doi:10.1111/j.1365-2141.2009.07793.x
6. Raiola, Giuseppe & Galati, M & Sanctis, Vincenzo & Caruso-Nicoletti, Manuela & Pintor, C & Simone, M & Arcuri, Vincenzo & Anastasi, Salvatore. (2003). Growth and puberty in Thalassaemia major. *Journal of pediatric endocrinology & metabolism : JPEM*. 16 Suppl 2. 259-66.
7. Karimi, Mehran & Karamifar, Hamd-Allah. (2004). Short stature in beta-thalassaemia minor subjects. *Medical science monitor : international medical journal of experimental and clinical research*. 10. CR603-5.
8. Low, Louis. (2005). Growth of children with β -thalassaemia major. *The Indian Journal of Pediatrics*. 72. 159-164. 10.1007/BF02760702.
9. C. PINTOR, S. G. CELLA, PAOLA MANSO, R. CORDA, C. DESSI, V. LOCATELLI, E. E. MÜLLER, Impaired Growth Hormone (GH) Response to GHReleasing Hormone in Thalassaemia Major, *The Journal of Clinical Endocrinology & Metabolism*, Volume 62, Issue 2, 1 February 1986, Pages 263–267.
10. Wu, Kang-Hsi & Tsai, Fuu-Jen & Peng, C. (2003). Growth hormone (GH) deficiency in patients with β -thalassaemia major and the efficacy of recombinant GH treatment.

- Annals of hematology. 82. 637-40.
10.1007/s00277-003-0712-3.
11. Karamifar, H & Karimi, Mehran & Amirhakimi, G & Badiei, M. (2006). Endocrine Function in Thalassemia Intermedia. International journal of biomedical science : IJBS. 2. 236-240.
 12. Vidergor, G., Goldfarb, A.W., Glaser, B. *et al.* Growth hormone reserve in adult beta thalassemia patients. *Endocr* 31, 33–37 (2007) doi:10.1007/s12020-007-0018-7
 13. Fahim FM, Saad K, Askar EA, Eldin EN, Thabet AF. Growth Parameters and Vitamin D status in Children with Thalassemia Major in Upper Egypt. *Int J Hematol Oncol Stem Cell Res.* 2013;7(4):10–14.
 14. Kyriakou A, Skordis N. Thalassaemia and aberrations of growth and puberty. *Mediterr J Hematol Infect Dis.* 2009;1(1):e2009003. Published 2009 Jul 27. doi:10.4084/MJHID.2009.003.
 15. Aydinok, Yesim. (2002). Endocrine Complications in Patients with - thalassemia Major. Journal of Tropical Pediatrics - J TROP PEDIAT. 48. 50-54. 10.1093/tropej/48.1.50.
 16. Soliman AT, De Sanctis V, Elalaily R, Yassin M. Insulin-like growth factor- I and factors affecting it in thalassemia major. *Indian J Endocrinol Metab.* 2015;19 (2):245–251. doi:10.4103/2230-8210.131750.
 17. Soliman A, De Sanctis V, Yassin M, Abdelrahman MO. Growth hormone - insulin-like growth factor-I axis and bone mineral density in adults with thalassemia major. *Indian J Endocrinol Metab.* 2014;18 (1):32–38. doi:10.4103/2230-8210.126525.