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Prepubertal Hypertransfusion in Thalassemia Intermedia: A Case Report of Sustained Positive Effects on Growth, Splenic Function and Endocrine Parameters

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Abstract

We report a known case of thalassemia intermedia (Hb Dhofar) who in spite of mild thalassemic facies, attained his normal genetic height, pubertal maturity and improved self-image with minimal splenomegaly through a hypertransfusion/chelation regimen that was started just before puberty and maintained for 5 years. As there are no clear guidelines in the management of patients with thalassemia intermedia, the option of hypertransfusion/chelation during the pubertal growth spurt may alleviate some of the complications associated with thalassemia intermedia.

Keywords: Thalassemia Intermedia; Prepuberty; Hypertransfusion.

Introduction

Thalassemia intermedia (TI) is a clinical designation often used to characterize individuals who are homozygous for beta-thalassemia genes but maintain hemoglobin levels of 6-9 g/dl without regular transfusions. The term TI has been used to describe the clinical and hematologic findings in patients whose disease is not as severe as that which characterizes homozygous beta-thalassemia, but is more severe than the heterozygous carrier.[1] Hb Dhofar is a variant hemoglobin (beta[29 (GGC-GGT) gly-gly], beta[58 (CCT-CGT) pro-arg]) associated with a thalassemic phenotype and unique to the Sultanate of Oman. Clinical and hematological data suggest that this mutation behaves like a moderately severe beta (+) thalassemia allele resulting in a TI phenotype.[2] The available options in the management of TI patients include splenectomy, transfusion therapy, iron chelation therapy and the use of cytotoxic drugs such as hydroxyurea to increase the Hb F level.[3] We report of a 19 year old Omani male with known Hb Dhofar, who was initiated on hypertransfusion regimen at the age of 11 years (prepubertal) for 5 years.

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Case Report

The patient was a 19 year old boy, diagnosed with Hb Dhofar at the age of 6 years. We offer most of our moderately severe TI patients the option of hypertransfusion/chelation early in life (when they present at 5-6 years) and it is acceptable in most of the cases. In our patient, the family refused this option for some cultural beliefs and fear of risks of chronic transfusion. He was put on hydroxyurea 15 mg/kg/day for three months. The drug was stopped on parent's request for fear of cytotoxic agent and results of XMN1 polymorphism was negative as well. He was started on folic acid and regular follow-up of his clinical condition. He maintained a steady state Hb of 9 g/dl, however at the age of 11 years, his Hb started to drop to 7-8 g/dl (hypersplenism) and his growth parameters were far below the 3rd centile. His bone densitometry was very low with evidence of osteoporosis (Z-score: -2.5).

He was started on a hypertransfusion regimen for 5 years (11-16 years of age), aiming to improve his growth and reverse the other complications he suffered. The child was maintained on deferiprone 75 mg/kg/day throughout his transfusion years and thereafter. The patient attained normal puberty with all secondary sexual characteristics, and achieved his genetic height (75th centile, Fig. 1). His bone densitometry did not show much improvement (Z-score: -2.8). His spleen size regressed to 2 cm below the left costal margin with no evidence of hypersplenism. Transfusion was stopped after he achieved his genetic height and is currently on follow-up for 3 years with no further transfusions, and is maintaining steady hemoglobin state of 9.5 g/dl. (Table 1)

The following tests were used for the diagnosis and follow-up of the patient: Genetic study for Hb Dhofar. DNA was extracted from blood, the interest region of beta globin gene was amplified by PCR. The product was visualized on a 2% agarose gel electrophoresis followed by purification with ExoSap (USB, Cleveland, OH, USA). Purified PCR products were sequenced on the ABI 3100 automated Sequence Analyzer (Applied Biosystems Inc) using the BigDye Terminator Version 3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems Inc). Then XMN1 polymorphism was done by RFLP, and 10µl aliquots of the amplified DNA is digested with 2-5 units of XmnI restriction enzyme and its reaction buffer in a 20µl reaction volume. The mixture was incubated at 37°C for overnight. The digested DNA was applied onto a 2% agarose gel and electrophoresis was carried out at 100V for 45 minutes. The band pattern was visualized in a

gel documentation system

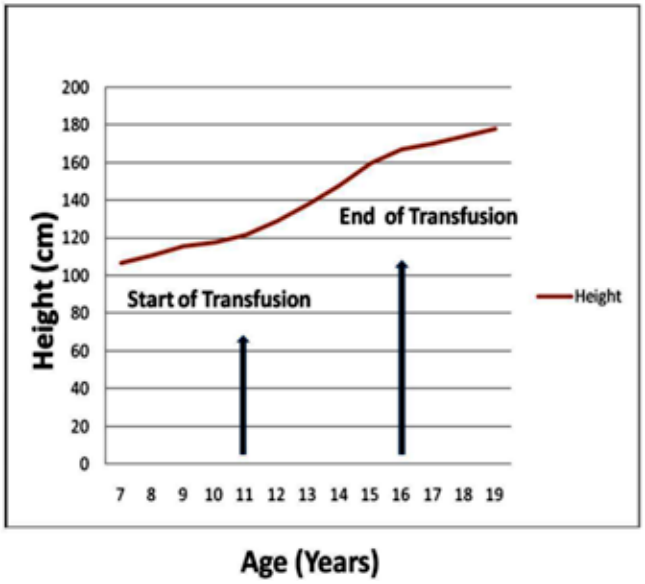

Figure 1: Radiology Bone densitometry and MRI T2* heart and liver.

Table 1: Patient characteristics.

Characteristics	Prepubertal	Postpubertal
Hb (Mean g/dl)	7.4	9.5
Spleen (cms below left costal margin)	4	2
Height (cms)	122 (11 years)	167 (16 years) 178 (19 years)
Weight (centile)	<3rd centile	50th centile
Ferritin (Mean ng/ml)	980	527
FSH (1.3-19.3 IU/L)	0.8	3.3
LH (1.2-8.6 IU/L)	0.8	1.5
Testosterone (6-27 nmol/L)	<0.4	13.4
TSH (0.34-5.6 mIU/L)	1.16	1.57
T4 (7.9-14.4 pmol/L)	7.1	14.1
PTH (1.6-9.3 pmol/L)	2.8	3.4
Bone densitometry	Z-score: -2.5	Z-score: -2.8

Discussion

Non-transfused children with TI are very likely to develop serious complications including marked thalassemic facies, which are usually irreversible growth retardation with marked short stature, splenomegaly, hypersplenism, hypercoagulabilty, pulmonary hypertension, heart failure, cholelithiasis, diabetes mellitus, hypothyroidism, osteoporosis and hypogonadism,[4-7] and some of these complications can be avoided by a hypertransfusion/chelation regimen.

In spite of mild thalassemic facies, our patient with TI (Hb Dhofar) attained normal genetic height, pubertal maturity, and improved self-image with minimal splenomegaly through a hypertransfusion/chelation regimen that was started just before puberty and maintained for 5 years. Regular hypertransfusion with good chelation is the only explanation for the reversal of all the complications. Of interest is the longstanding effect of his hypertransfusion, as still 3 years after stopping the hypertransfusion, the patient maintains a steady state of Hb of 9.5 g/dl with minimal splenomegaly.

Currently, there are no clear guidelines on the treatment of moderately severe thalassemia intermedia.[4] The available options in the management of TI patients include splenectomy, transfusion therapy, iron chelation therapy, and modulation of fetal hemoglobin production with the use of cytotoxic drugs such as hydroxyurea.[3,8] However, it is well known that splenectomised patients have a higher rate of complications in terms of infections and increased susceptibility to thrombosis.[4,9,10] Many studies have shown that patients with TI who are not on regular blood transfusion because of their milder symptoms nevertheless develop major complications related to their chronic anemia and ineffective erythropoiesis. TI patients would benefit from transfusion therapy to prevent such complications.[11,12] Although early introduction of blood transfusions will increase the rate of iron accumulation, with effective iron chelation, the benefits of transfusion therapy greatly outweigh the cost and inconvenience of iron chelation therapy.

In this patient, transfusion therapy was initiated at the age of 11 years for a period of 5 years, coinciding with the pubertal growth spurt. The patient achieved pubertal maturity, genetic height, euthyroid and normal parathyroid status. The transfusions in this patient has definitely alleviated complications of facial bone deformities, growth retardation and hypersplenism. However, endocrine deficiencies were not tested in our patient. The bone densitometry did not show any improvement. The patient attained his puberty at normal time. Since many patients with thalassemia intermedia achieve normal puberty, the normal pubertal maturation in our patients cannot be attributed to hypertransfusion. Although we practice transfusion/chelation therapy in our moderate to severe TI patients at presentation, transfusion therapy during the pubertal growth spurt nevertheless needs to be explored in the group of TI patients not maintaining their hemoglobin levels at puberty.

Conclusion

We would like to highlight the importance of starting hypertransfusion in children with milder forms of TI (who are usually not considered for transfusion) at the prepubertal age. This option will allow them to attain their genetic height, pubertal maturity, better self-image and reversal of some complications such as hypersplenism.

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