

Endocrine investigation and follow up in thalassaemia. Time for specific guidelines

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Abstract

Iron overload due to multiple transfusions affects the endocrine glands especially the anterior pituitary, the pancreas, the thyroid and the parathyroids. This leads to a variety of endocrinopathies and growth failure. Delayed puberty, hypogonadism, growth hormone deficiency in adults, hypothyroidism, hypoparathyroidism and diabetes are common and around 20% of patients have more than one endocrinopathy. In this paper suggestions for guidelines concerning diagnosis, investigation and treatment are proposed for the following clinical entities encountered in thalassaemia patients: i) Growth failure: after the age of 9-10 years there is a slowing of growth velocity, the pathogenesis of which is multifactorial and anaemia, folate deficiency and hypersplenism are implicated. Desferrioxamine toxicity has been reported as cause of the abnormal upper to lower segment ratio. Growth hormone is given in selected cases. ii) Delayed puberty and hypogonadism: are the most obvious clinical consequences of iron overload in both sexes. Primary and secondary amenorrhoea are very common in women. Sex steroid replacement therapy is the optimal therapeutic regime which has a great impact on the quality of life of adult thalassaemia patients. iii) Fertility: Women with TM, who are regularly transfused and are well chelated can now become pregnant either spontaneously or by inducing ovulation. Pregnancy must carefully monitored. iv) Growth hormone deficiency in adult thalassaemics: This occurs in a high prevalence and since GH in adults is involved in numerous biological functions, especially of the heart, proper assessment of this hormone is needed and consideration of the need for replacement. v) Hypothyroidism and hypoparathyroidism: these deficiencies are also discussed.

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Introduction

Patients with multi-transfused Thalassaemia Major (TM) develop severe endocrine complications as seen in Figure 1. Iron overload due to multiple transfusions is the main cause of such complications hence proper and effective iron chelation therapy is essential for the reduction of iron deposition on various endocrine glands. Iron accumulates in tissues with high levels of transferrin-receptor such as liver, heart and endocrine glands especially anterior pituitary, pancreas, thyroid, and parathyroids.^{1, 2, 3}

A. Growth failure

Growth retardation is commonly reported in children and adolescents with TM. The child with TM has a particular growth pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. The pathogenesis of growth failure is multifactorial.^{4, 5}

Key contributing factors to stunted growth in patients with TM may include chronic anaemia, transfusional iron overload, hypersplenism, and chelation toxicity. Other contributing factors include hypothyroidism, delayed puberty/hypogonadism, Growth Hormone (GH) deficiency, zinc deficiency, chronic liver disease, undernutrition and psychosocial stress.⁶

Subnormal sitting height is characteristic in patients with TM as seen in Figure 2. The abnormal Upper to Lower segment ratio is seen not only in pubertal but also in prepubertal children with TM leading to the conclusion that delayed puberty is not the only cause of truncal shortening.^{7, 8, 9} Furthermore truncal shortening was observed in children with good chelation therapy compliance and low ferritin levels. It has been suggested that growth retardation may be precipitated as a result of Desferrioxamine (DFX) toxicity. The clinical outcome of DFX toxicity is platyspondylosis and shortening of the vertebrae.

Diagnosis requires careful clinical evaluation that would establish: i) short stature (height below the 3rd percentile for sex and age based on national growth charts); ii) slow growth rates (growth velocity expressed in cm/year less than - 1 SD for age and sex based on growth velocity charts); iii) signs of other pituitary hormone deficiencies; iv) other possible causes of retarded growth

Investigation of a child with Thalassaemia who has stunted growth is generally similar to that of the non-Thalassaemic child: i) routine biochemical analysis - elements; ii) bone age (X-ray of wrist and hand); iii) thyroid function (TSH and FT4); iv) transglutaminase antibodies (TGA) to exclude coeliac disease; v) in selected cases, GH stimulation test; vi) in selected cases, Insulin Growth Factor-I (IGF-I), Insulin Growth Factor Binding Protein-3 (IGFBP-3).

Treatment

Anaemia, folate deficiency and hypersplenism are traditional causes of poor growth in TM where transfusion is not regular. In countries where DFX is regularly used, this is a major cause of growth retardation and should be monitored. In peri-pubertal patients, hypogonadism

should be carefully investigated before starting treatment with GH.

GH treatment often with high dose is not always as effective as expected and may result in decreased insulin sensitivity and abnormal glucose tolerance. Oral zinc sulphate supplementation should be given to patients with proven zinc deficiency.^{10, 11, 12}

Can children with TM attain normal stature and develop normally with early and reasonable DFX treatment? Although iron chelation can decrease the frequency of endocrinopathies, early DFX treatment may result in growth impairment. On the other hand poor compliance with DFX may eventually lead to severe iron burden, gonadal dysfunction and eventually growth failure. The benefits of treatment should be weighed against the potential adverse effects and the caring physician should balance between the efficacy and the injudicious use of DFX. It is therefore recommended that growth in both standing and sitting position should be assessed at 6-month intervals in order to detect early growth failure. Alternative oral chelation agents are often an option in cases of DFX toxicity, although some bone lesions remain irreversible. The effect of new chelating agents on growth is still under investigation.

Growth failure in TM has been well known for many years. During the last decades therapeutic progresses resulted in a prolonged life expectancy in TM patients. However, despite significant advances in transfusion programs and regimens, chelating agents and hormonal replacement, iron overload is still a major consequence leading to endocrine dysregulation. Growth retardation continues to be a significant challenge in TM patients due to interrelated factors, affecting their social adjustment and quality of life. Close follow up, early recognition and proper management is crucial for every patient. New transfusion protocols and chelators such as Deferiprone and Deferasirox could be used in order to minimize the serious complications of iron deposition and side effects of DFX on growth. Finally the therapeutic use of Growth Hormone should be viewed as not a panacea and judiciously given in selected cases with proven GH deficiency.

B. Delayed puberty and hypogonadism

Iron deposition on gonadotrophic cells leads to disruption of gonadotrophin (FSH and LH) production. In the majority of patients the function of gonads is normal; however, gonadal iron deposition occasionally occurs. TM patients with a favorable genotype manifest less severe gonadal dysfunction, due to less iron loading.^{13, 14, 15}

Delayed puberty and hypogonadism are the most obvious clinical consequences of iron overload. Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13 years, and in boys by the age of 14 years. Hypogonadism is defined in boys by the absence of testicular enlargement (less than 4 mL), and in girls by the absence of breast development by the age of 16 years.

Adolescent thalassaemics may present with delayed puberty or slowly progressive puberty. Arrested puberty is a relatively common complication in moderately or grossly iron overloaded patients with TM. This is characterised by the lack of pubertal progression over a year or longer. In such cases, the yearly growth velocity is either markedly reduced or completely absent.

Most women with TM present with Primary Amenorrhea (PA), whereas Secondary Amenorrhea (SA) will invariably develop with time especially in patients poorly compliant to chelation therapy. Ovarian function of these women is normal as they produce the expected number of ova after stimulation therapy. Damage of the ovaries by iron deposition is rarer and is more likely to appear in women of 25-30 years of age because of high vascular activity on the ovaries at this age.

Investigation

i) Hypothalamic-pituitary-gonadal function with Gn-RH, stimulation test for LH and FSH measurement; ii) sex steroids (Serum Testosterone, Serum 17- β Estradiol); iii) pelvic ultrasound to assess ovarian and uterine size.

Incidence/prevalence of endocrinopathies in iron-overloaded β -thalassaemia major patients across various countries

Endocrine complications (% in both sexes)	Country					
	Cyprus (n = 435)	Greece (n = 262)	Italy (n = 1,861)	N. Am. (n = 262)	Iran (n = 220)	Turkey (n = 252)
Hypogonadism	32.5	42	49	42	35.1	50
Diabetes mellitus/IGT	9.4	5/27	4.9	5	8.7	9.3/6.6
Short stature/GHD	35	32	12.4 (GHD)	32 /3	39.3	10 (GHD)
Primary hypothyroidism	5.9	4	6.2	4	7.7	29
Hypoparathyroidism	1.2	4	3.6	4	7.6	4

**More than 1 endocrinopathy: 13%;
2 endocrinopathies: 6%; 3 endocrinopathies: 1%**

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Figure 1. The incidence of endocrine complications in patients with Thalassaemia Major

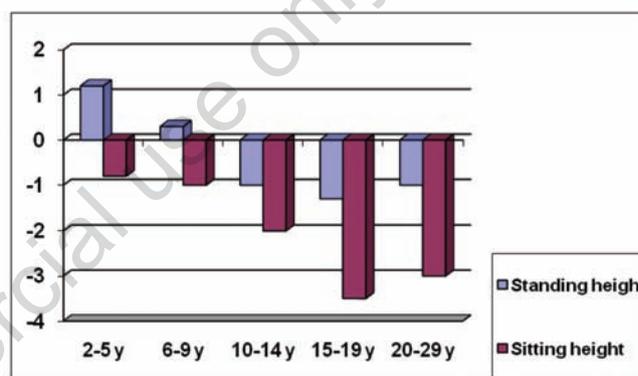


Figure 2. Standing height and sitting height is SDS in different age-groups.

Treatment

The treatment of delayed or arrested puberty, and hypogonadotrophic hypogonadism depends on factors such as age, severity of iron overload, damage to the hypothalamo-pituitary-gonadal axis, chronic liver disease, and the presence of psychological problems resulting from hypogonadism. Collaboration between endocrinologists and other doctors is critical. Intensive chelation therapy is reported to ameliorate or even completely reverse gonadal dysfunction.

For girls, therapy may begin with the oral administration of Ethinyl Estradiol (EE) 2.5-5 μ g daily for 6 months, followed by hormonal reassessment. If spontaneous puberty does not occur within 6 months after stopping the treatment, oral estrogen is re-introduced with gradually increasing dosages EE from 5-10 μ g daily for another 12 months and to 20 μ g for additional 12 months. If breakthrough uterine bleeding does not occur, then low estrogen-progesterone hormone replacement is the recommended treatment for induction of menarche and subsequent maintenance of the menstrual cycles.¹⁶

For delayed puberty in males, low dosages of intramuscular depot-testosterone esters (25 mg) are given monthly for 6 months. This is followed by hormonal re-assessment. In patients with hypogonadotrophic hypogonadism, therapy with 50 mg can be continued until the growth rates wane. The fully virilising dose is 75-100 mg of depot-testosterone esters every 10 days administered intramuscularly. The same effects can be achieved with topical testosterone gel. For pubertal arrest, the treatment is similar to that of delayed puberty if growth potential is

present or to that of Hypogonadotropic Hypogonadism in cases where growth has been completed.¹⁷ Induction of spermatogenesis has been successfully achieved with the combination of hormonal preparations mimicking FSH and LH.¹⁸

The treatment of hypogonadism is a complex issue as sex steroids have a great impact on the quality of life of the adult Thalassaemic and each patient has to be assessed individually. Therefore guidelines are needed in regard to the best therapeutic regimen and the duration of treatment.

C. Fertility

Women with TM, who are regularly transfused and are well chelated can now become pregnant either spontaneously or by inducing ovulation. The presence of gonadal dysfunction can be overcome with proper combination treatment. It is necessary that all pregnant women with TM be followed up very closely. Apart from the routine pregnancy follow-up, the thalassaemic pregnant woman needs additional medical care. Haemoglobin levels should be maintained at 10 g/dL and careful monitoring of vital signs during transfusion is required. Ferritin levels should also be measured and observed to avoid iron overload. Careful monitoring of the transfusion regime and regular evaluation of cardiac function should be done in all pregnant thalassaemic women to prevent fluid overload. Cardiac function should be evaluated periodically by a cardiologist.^{19, 20}

Iron chelation therapy, due to its possible teratogenic effects, is withheld as soon as the pregnancy is planned or identified. It has been assumed that pregnancy is an efficient chelator of iron due to its haemodilution effect and the fetal consumption of free iron. Although DFX therapy has not been implicated for any deleterious effect on the fetus the current recommendation is its discontinuation, both once pregnancy is identified and during the induction period.

Chronic maternal anaemia in the thalassaemic pregnant woman may result in fetal hypoxia, which predisposes to premature labour, intrauterine growth retardation and death.

The desire of the female Thalassaemic to procreate should be viewed with special caution and sensitivity by all physicians who are involved in her medical care. Medical reasons often impose a barrier to this wish and specific criteria that have been established are as follows:

Eligibility

i) Cardiac function: electrocardiogram, echocardiogram; ii) liver function: liver function test, ultrasound; iii) vessels: clotting factors, doppler; iv) pancreas: oral glucose tolerance test; v) viral infections: hepatitis B and C virus, HIV; vi) iron status.

Feasibility

i) Hypothalamic–pituitary–gonadal axis; ii) ultrasound of uterus and ovaries; iii) postcoital test; iv) hysterosalpingography; v) complete endocrine assessment; vi) genetic counselling: partner's carrier status and fertility.

During pregnancy there are a number of issues that need to be taken into consideration. Accumulated knowledge over the years has helped physicians to form guidelines regarding the management of the pregnant Thalassaemic woman, as follows.

i) Maintenance of haemoglobin level at 10 g/dL; ii) frequent low volume blood transfusions; iii) discontinue iron chelation therapy; iv) regular cardiac monitoring every 3 months; v) assessment of endocrine function, including oral glucose tolerance test; vi) multidisciplinary approach by all specialist involved in the medical care of TM

The strong desire of the Thalassaemic woman to become pregnant must not be viewed as an emotional defiance of the stigma of her chronic disease, but recognized, respected and approached with sensitivity by all specialties involved in her medical care.

D. Growth hormone deficiency in adult thalassaemics

Clinical advances in the treatment of TM patients have helped to increase substantially the life expectancy of patients, so that the TM patients in our days represent the first generation of adult thalassaemics. The dysfunction of GH-IGF 1 axis in TM may be secondary to a neurosecretory dysfunction, hypothalamic GH-releasing hormone deficiency, pituitary deficiency, increased somatostatin activity and GH resistance.²¹

The results of our recent study are consistent with a high prevalence of severe Growth Hormone deficiency in adult TM patients (54.5%). This percentage is higher compared to previous reports and may be related to the older age (37.8±8.5 years) of our patients and to the GH stimulation test employed in our study.²²

Nevertheless these findings raise a vital question regarding GH administration, as GH in the adults is involved in numerous biologic functions, most importantly that of cardiac morphology and function. Interestingly 3 patients with GH deficiency and normal myocardial MRI T2* (16.6%) were found to have a reduced LVEF. There are not yet guidelines in literature for the use of growth hormone treatment in TM patients with GH deficiency. The American Association of Clinical Endocrinologists (AACE), recommend that one GH stimulation test is sufficient if clinical suspicion is high, such as in patients with at least one other pituitary hormone deficiency and low or low-normal IGF-1 level are present. In TM patients however with chronic liver disease IGF-1 levels are low and have a low diagnostic sensitivity for the GH deficiency diagnosis.

E. Hypothyroidism

Primary hypothyroidism is one of the most common complications in TM patients, usually appearing in the second decade of life related to iron overload. The reported prevalence depends on the number as well as on the age composition of the study population. Some studies reported low prevalence from 0% to 6.2% and some others from 11% to 18%. It is more common in girls than in boys. A positive correlation between serum ferritin levels and primary hypothyroidism was reported. Primary thyroid dysfunction occurs before any iron-induced damage of the TRH-TSH axis thus secondary hypothyroidism due to pituitary haemosiderosis is rare.

Abnormal thyroid function may be reversible at an early stage by intensive chelation; however the progression of subclinical hypothyroidism to overt disease may take many years. Symptoms and signs of primary hypothyroidism in children and adolescents such as growth retardation and weight increase may develop. Thyroid function tests should be checked in children with TM every year. Ultrasound of the thyroid gland is not diagnostic. Good chelation therapy compliance may prevent or improve hypothyroidism. A notable caution in thalassaemics with subclinical hypothyroidism and cardiomyopathy treated with amiodarone may result in a rapid progression of severe disease, which in turn deteriorates cardiac function. The question is often raised regarding the initiation of treatment in so called *subclinical hypothyroidism*, where TSH is borderline or slightly elevated with Free T4 being within the normal range.

F. Hypoparathyroidism

Hypoparathyroidism is a rare complication in TM, which develops, in late adolescence. A recent study reported prevalence up to 13.5% with no sex differences. Iron overload with deposition on parathyroid cells and tissue fibrosis are the main causes of hypoparathyroidism. Chronic anaemia is an additional factor causing parathyroid dysfunction.

The condition presents with the typical biochemical picture of hypoparathyroidism of low calcium and high phosphate levels. Parathormone may be normal or low and Vitamin D is low. Low calcium and phosphorus is found in 24hour urine collection. Bone x-rays are

characteristic for osteoporosis and malformations. Recently abnormal cerebral CT findings have been reported to be related with hypoparathyroidism in TM. If hypoparathyroidism is suspected, there is always the risk of hypocalcaemia which has to be treated with no delay. Vitamin D and calcium are the choice of treatment

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