

Endocrine Complications in Thalassaemia Major

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Patients with multi-transfused Thalassaemia Major (TM) develop severe endocrine complications. 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 [1].

The anterior pituitary gland is particularly sensitive to free radicals oxidative stress, resulting in hormone secretion disorders mainly gonadotrophins : FSH and LH and Growth Hormone (GH). Consequently patients with TM develop hypogonadism and short stature. Other endocrine organs plagued by iron deposition secondary to multiple transfusions include the pancreas, thyroid, and parathyroid glands leading to Diabetes Mellitus (DM), acquired hypothyroidism and hypoparathyroidism respectively. Despite good chelation therapy begun early in life, problems such as delayed sexual maturation and impaired fertility may persist [2].

A. GROWTH

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.

Key contributing factors to stunted growth in patients with TM may include chronic anaemia, transfusional iron overload, hypersplenism, and chelation toxicity [3]. Other contributing factors include hypothyroidism, hypogonadism, GH deficiency/insufficiency, zinc deficiency, chronic liver disease, undernutrition and psychosocial stress.

Subnormal sitting height is characteristic in patients with TM as seen in figure 1 [4]. 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. 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. DFX inhibits cell proliferation, protein synthesis and mineral deposition and decrease the activity of alkaline phosphatase. The clinical outcome of DFX toxicity is platyspondylosis and shortening of the vertebrae.

Diagnosis and investigations

Diagnosis requires careful clinical evaluation that would establish:

- short stature (height below the 3rd percentile for sex and age based on national growth charts)
- slow growth rates (growth velocity expressed in cm/year less than – 1 SD for age and sex based on growth velocity charts)
- signs of other pituitary hormone deficiencies (e.g., gonadotrophins)
- 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.

- Routine biochemical analysis - elements
- Bone age (X-ray of wrist and hand)
- Thyroid function (TSH and FT4)
- Transglutaminase antibodies (TGA) to exclude coeliac disease
- In selected cases, GH stimulation test
- 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 [5]. Oral zinc sulphate supplementation should be given to patients with proven zinc deficiency.

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 [6]. 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.

B. DELAYED PUBERTY AND HYPOGONADISM

Iron deposition on gonadotrophic cells leads to disruption of gonadotrophin 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 [7] .

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 [8].

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 [9].

Investigation

- Hypothalamic-pituitary-gonadal function with Gn-RH, stimulation test for LH and FSH measurement
- Sex steroids (Serum Testosterone, Serum 17- β Estradiol)
- Pelvic Ultrasound to assess ovarian and uterine size

Treatment

The treatment of delayed or arrested puberty, and hypogonadotropic 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.

For girls, therapy may begin with the oral administration of Ethinyl Estradiol (EE) 2.5-5 μg 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 μg daily for another 12 months and to 20 μg 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. .

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 hypogonadotropic hypogonadism, the therapy (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.

Sex steroid replacement therapy cannot adversely affect body disproportion, as truncal shortening at final height is evident in patients with either spontaneous or induced puberty [10]. Body disproportion therefore is independent of pubertal or prepubertal period of greater height gain.

The treatment of pubertal disorders is a complex issue due to the many associated complications; therefore, each patient has to be assessed individually.

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 [11].

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 (IUGR) and death. Luckily in our study the incidence of such complications is relatively small [12].

The desire of the female Thalassaemic to procreate should to 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

- Cardiac function: electrocardiogram, echocardiogram.
- Liver function: liver function test, ultrasound.
- Vessels: clotting factors, doppler.
- Pancreas: oral glucose tolerance test.
- Viral infections: hepatitis B and C virus, HIV.
- Iron status.

Feasibility

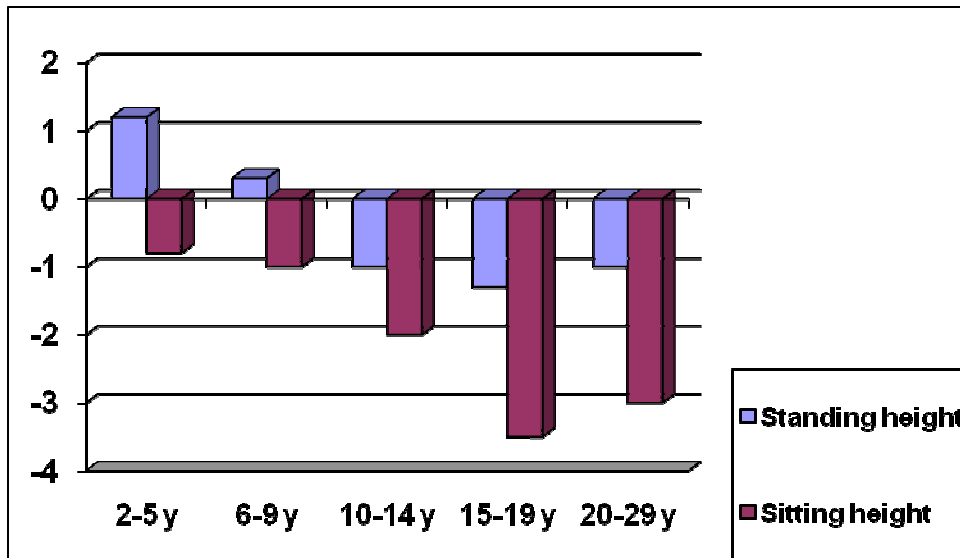
- Hypothalamic–pituitary–gonadal axis.
- Ultrasound of uterus and ovaries.
- Postcoital test.
- Hysterosalpingography.
- Complete endocrine assessment.
- Genetic counselling: partner's carrier status and fertility.

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 thalassaemia patient, as follows.

- Maintenance of haemoglobin level at 10 g/dL.
- Frequent low volume blood transfusions.
- Discontinue iron chelation therapy.
- Regular cardiac monitoring every 3 months.
- Assessment of endocrine function, including oral glucose tolerance test.
- Multidisciplinary approach by all specialist involved in the medical care of thalassaemia.

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.

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



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