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Hypogonadism in thalassemia major patients

Sasima Srisukh *, Boonsong Ongphiphadhanakul, Pongamorn Bunnag

Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, 10400, Thailand

ABSTRACT

Despite recent advances in iron chelation therapy, excess iron deposition in pituitary gonadotropic cells remains one of the major problems in thalassemic patients. Hypogonadism, mostly hypogonadotropic hypogonadism, is usually detected during puberty. Early diagnosis and treatment are crucial for normal pubertal development and to reduce the complications of hypogonadism. The risks and benefits of hormonal replacement therapy, especially regarding the thromboembolic event, remain a challenge for providers caring for thalassemic patients.

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Introduction

Thalassemia refers to a group of inherited diseases characterized by decreased or absent synthesis of normal globin chains [1]. The direct consequence is an imbalance of the alpha and beta globin chain synthesis that results in anemia from ineffective erythropoiesis and hemolysis. The term thalassemia major refers to the severe form that is often associated with life-long transfusion dependent anemia.

Hypogonadism is the most frequently reported endocrine complication, affecting 70–80% of thalassemia major patients. Hypogonadism is likely to be caused by iron deposits in the gonads, pituitary gland or both. However, hypogonadotropic hypogonadism resulting from iron deposition in the pituitary gonadotrope is more commonly found. Gonadal iron deposition in ovaries or testes occurs less frequently, as the majority of amenorrheic women can still ovulate after hormonal treatment.

In normal individuals, iron homeostasis is controlled mainly by iron absorption, not excretion. Lacking adequate excretory mechanisms, thalassemic patients receiving a blood transfusion (usually 1 mg of iron per 1 mL of blood) inevitably experience significant iron overload. Normally, iron is bound to transferrin and transported to bone marrow and tissue, where transferrin receptor takes up iron and stores it as ferritin. Transferrin saturation is usually maintained at 10–50%, and less than 1% of total body iron is found in the blood. As a consequence of iron overload in thalassemic patients, either from blood transfusion or excessive iron absorption, transferrin is fully saturated and non-transferrin-bound iron (NTBI) is found excessively in the blood. Instead of using the transferrin receptor,

NTBI enters non-hematopoietic cells by other cellular channels in forms that can possibly damage cells [2]. NTBI is also a catalyst for the formation of reactive oxygen species, causing oxidative damage [3]. The anterior pituitary gland is sensitive, in a dose-dependent fashion, to the effects of iron overload from transfusions [4]. Studies of human anterior pituitary adenomas showed that gonadotropes require more iron as compared with other pituitary cell types [5]. Thus, these cells are most affected, resulting in declining synthesis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Hypogonadotropic hypogonadism in thalassemia is related not only to iron toxicity on gonadotrope cells but also to adipose tissue and leptin. In addition to its effects on carbohydrate and fat metabolism and appetite, leptin also acts on the hypothalamic–pituitary–gonadal (HPG) axis, indirectly stimulating Kiss1 neurons in the arcuate nucleus [6]. In normal girls and boys, leptin concentrations rise before pubertal transition, followed by an initial increase of LH and FSH. In normal girls, serum leptin concentrations continue to rise as pubertal development proceeds due to the effect of estrogen, while the levels decrease in boys due to the inhibitory effect of testosterone [7,8]. To our knowledge, several studies have been conducted on leptin levels in different age groups of thalassemic patients, and in all of them low leptin levels were observed [9]. Therefore, low circulating leptin may be one of the factors causing delayed puberty in thalassemic patients.

The direct effect of iron, in particular that of NTBI, on the ovaries and testes is currently unknown. The ovarian reserve is preserved in the majority of female thalassemia patients, even in women with amenorrhea. In males, histological examination of testicular tissues from autopsies demonstrated testicular interstitial fibrosis with small, heavily pigmented, undifferentiated seminiferous tubules and an absence of Leydig cells [10].

Iron deposition in the anterior pituitary gland can be demonstrated beginning in the first decade of life, but clinical manifestations

* Corresponding author. Fax: 66 2 201 1647.
  E-mail address: sasima_kim@yahoo.com (S. Srisukh).

are usually not evident until the onset of puberty. At the earlier stage, only a diminished gonadotropin reserve with intact gonadotropin pulse was observed [11]. There may be an asymptomatic phase of pituitary siderosis before hypogonadism occurs. Later, the gonadotropin reserve significantly diminishes, with markedly reduced spontaneous pulsatile gonadotropin activity which may lead to irreversible damage of the HPG axis. However, additional studies are still required before the natural history can be conclusively determined.

Hematologic phenotypes were significantly associated with hypogonadotropic hypogonadism. A majority of patients (86.4%) with the β^0/β^0 hematologic phenotype developed hypogonadotropic hypogonadism, while there was only a 25% occurrence in the β^0/β^+ phenotype [12]. High serum ferritin levels of more than 2500 ng/mL during puberty was also found to be a risk factor for hypogonadism [13], with a 2.75 times greater likelihood of having hypogonadism compared with patients with serum ferritin levels less than 1000 ng/mL [14]. Nevertheless, splenectomized individuals who had serum ferritin levels less than 2500 ng/mL also had high rates of endocrine disorders.

The prevalence and severity of hypogonadism in thalassemia major varies among studies, depending on the age group studied, genotype of thalassemia [12,15–17], extent of transfusion, age at the beginning and type of iron chelation therapy [15,18]. Differences are also observed between those born before and after the introduction of iron chelation therapy; desferoxamine was introduced in 1975 as an intramuscular injection and in 1980 as a subcutaneous route.

Data from 7 Italian hospitals showed that the percentage of patients affected by hypogonadism was the same among those born in 1970–1974 and 1975–1979 (64.5% and 56.3%, respectively); however, it was much lower among those born during 1980–1984 (14.3%) [19]. Data from 29 centers in 2004 with a total of 3817 patients revealed that hypogonadism in adolescents and adults with thalassemia major had a prevalence of 38% in females and 43% in males [20,21]. The widespread heterogeneity in epidemiological data is also due to differences in clinical characteristics.

Treatment and care of thalassemic patients have been much improved in the last few decades, with treatment modalities such as transfusion, iron chelation and bone marrow transplantation. The concept of aggressive blood transfusion in the late 1960s and iron chelation therapy with desferoxamine, introduced in 1975, improved overall median survival and decreased endocrine disturbances. Bone marrow transplantation became available later in 1981 as the only curative treatment.

Clinical manifestations

There are three main clinical presentations of the HPG axis derangement in thalassemia major, including delayed puberty, arrested puberty and hypogonadism. Delayed puberty is defined as the absence of any pubertal signs by 14 years in boys and 13 years in girls [20]. Arrested puberty is defined as the absence of further pubertal progression for more than 1 year after puberty has started.

In patients with hypogonadism, spontaneous fertility is possible in well-chelated and well-transfused patients, but others with hypogonadotropic hypogonadism may need assisted reproductive techniques. Gonadal function is usually intact in patients with hypogonadotropic hypogonadism, indicating that ovulation or spermatogenesis can be induced by exogenous gonadotropin therapy. Hypothyroidism and diabetes mellitus also influence the outcome of fertility treatment, and specific treatments are needed. Origa et al. studied 58 pregnancies in thalassemia major patients. There were 25 spontaneous pregnancies, 6 in oligomenorrhea patients and 1 in a patient with secondary amenorrhea. The remaining 33 pregnancies were achieved following gonadotropin-induced ovulation [22]. According to data from the Royal Hospital in London, 29 pregnancies in 22 thalassemia major patients occurred during a 15-year period (1989–2004). Of these 29 pregnancies, 16 followed spontaneous ovulation, 12 followed gonadotropin injection for induction of ovulation, and 1 followed clomiphene therapy [23].

Diagnosis

HPG axis dysfunction can manifest as low estradiol or testosterone with low to normal serum LH and FSH as commonly seen in hypogonadotropic hypogonadism. Low estradiol and testosterone accompanied with increased serum LH and FSH indicates primary gonadal failure.

Evaluation of testicular function during childhood is difficult since serum testosterone, LH, and FSH remain very low until the onset of puberty. Anti-Müllerian hormone (AMH) is a hormone that is mainly secreted by the Sertoli cells. Serum AMH level is high during childhood and declines during puberty. In a study of 28 patients with thalassemia major in Thailand, 15 in prepuberty, circulating AMH was not significantly different from controls, suggesting normal Sertoli cell function in patients with thalassemia major [24]. However, serum testosterone levels in pubertal patients were lower than in controls, which suggested that their testicular function is diminished, despite a normal pubertal onset. In women, AMH corresponds well with antral follicle count and can be used to accurately assess the ovarian reserve, independent of gonadotropin levels. AMH levels in thalassemia patients are overall normal, signifying that ovarian reserve is preserved and possibly serving as an important biomarker for reproduction [25].

The role of pituitary magnetic resonance imaging (MRI) in thalassemic patients has been studied in recent years. Hypogonadotropic hypogonadism is often hard to recognize before puberty because of the immaturity of the HPG axis [26]. Early detection of pituitary iron overload is important since hypogonadism is not fully reversible by iron chelation [27]. MRI has been used to predict asymptomatic iron deposition in the heart, liver, pancreas, and pituitary gland [28–30]. Decreased pituitary volume has been observed, which may be due to apoptosis of gonadotropic cells, failure of gonadotropic cells to grow properly, and also the possibility of suppressed leptin level. Patients with transfusion iron overload begin to develop pituitary iron deposition since during the first decade of life. However significant pituitary volume loss, using mean and standard deviation for a particular age, is not observed until the second to third decade of life. Thus, the critical time for MRI surveillance may be at 10–20 years of age when many patients rapidly accumulate pituitary iron [26]. For children under the age of 7 years, MRI data are lacking. Pituitary volume loss is also an independent predictor of hypogonadism [30], especially a Z-score of pituitary volume lower than –2.5 [26] or pituitary height less than 4.4 mm [31]. However, MRI results reveal that many patients with moderate to severe pituitary iron overload retain normal gland volume, representing an opportunity for iron chelation treatment and potential improvement in pituitary function [26].

Iron deposition in the anterior pituitary gland can decrease pituitary MRI signal intensity significantly in the T2-weighted image [30]. MRI signal hypointensity is due to the paramagnetic effect of iron [15], and serves as a useful tool for early detection of pituitary iron overload [30]. In a study of 33 patients with homozygous β-thalassemia, MRI results correlated well with GnRH stimulation tests, but not the clinical pubertal status of patients [28].

Although liver iron concentration has been considered to be an excellent marker of total body iron load, no relationship has been found between liver and pituitary iron deposit using MRI [32,33]. No association between MRI parameters of siderosis in the pituitary

gland and in other solid organs has been demonstrated [33,34]. The lack of correlation may be due to differences in transferrin receptor concentration, iron kinetics, and the degree of organ inflammation or fibrosis.

Hypogonadism after iron chelation therapy and bone marrow transplantation

In chronic iron overload, when transferrin is completely saturated, NTBI, the form of iron that causes toxicity, is found in the plasma. Intensification of chelation therapy has been shown to improve cardiac function, but not in the liver. The mechanism proposed was that the heart and also endocrine tissue, including the pituitary gland, take up circulating labile iron species that are non-transferrin-bound iron, while liver iron uptake is mediated via transferrin.

Chelation therapy with desferoxamine before the age of puberty has helped patients to attain normal sexual maturation in some studies but not in others. In a study of 40 patients with transfusion-dependent thalassemia major, 90% of 19 patients who began treatment with desferoxamine before the age of 10 had normal sexual development compared with only 38% of those treated after the age of 10 [18]. In contrast, another study reported no difference in the frequency of pubertal maturation when iron chelation therapy was started at the age of 10 or earlier [19]. Serum ferritin levels were still higher than normal in previous studies, a recent study targeted the achievement of normal ferritin levels. Desferoxamine, in combination with deferiprone, was orally administered to fifty two thalassemic patients, aged 10–49, until the serum ferritin levels were normal; the clearance of liver and heart iron was demonstrated by MRI. After a period of 5–7 years, 50% of hypogonadal males achieved normal testosterone levels and 32% of amenorrheic women became pregnant, either spontaneously or using in vitro fertilization [27]. With modern medications, iron-induced hypogonadism may be reversible with intensive iron chelation regimens.

Two major concerns for hypogonadism in transplanted thalassemics are iron overload and conditioning regimen. Busulfan plus cyclophosphamide and cyclosporine used in transplantation may be responsible for gonadal damage, which was observed primarily in prepubertal girls, whereas the same study found no obvious gonadal damage in boys [35]. Since ovarian failure is common, it is important to counsel patients on the pros and cons of bone marrow transplantation regarding fertility issues. In contrast, patients undergoing conventional treatment usually have hypogonadotropic hypogonadism, but pregnancy is still possible using hormonal stimulation.

Despite early successful bone marrow transplantation, only some patients reach puberty spontaneously. In a series involving 50 thalassemia patients who received a transplant before puberty (3.6–14.5 years old), 40% entered puberty normally despite most of them showing clinical and hormonal evidence of gonadal dysfunction. No correlation was found between the pubertal stage and age at bone marrow transplantation [36]. De Sanctis studied 68 thalassemic patients who had successfully undergone bone marrow transplantation during childhood; 34% of females (mean age 16 years) attained pubertal maturation, while 63% of males (mean age 18 years) also reached puberty [37].

Treatment

Sex steroid or pulsatile GnRH can be utilized to induce puberty if the HPG axis is functionally intact, especially at an early stage of hypogonadotropic hypogonadism. Later on, if the HPG axis is irreversibly damaged, sex steroid replacement therapy is the only option to induce puberty. Generally, it is advisable to initiate puberty with sex steroid replacement therapy by age 13 in women and age 14

in men [38]. Factors such as severity of iron overload, liver disease and growth hormone deficiency should be considered before pubertal induction [20].

Treatment in women

According to the Thalassaemia International Federation recommendations [20], therapy in women may begin with oral ethinyl estradiol (2.5–5 µg daily) for 6 months, followed by hormonal reassessment. If spontaneous puberty does not occur within 6 months after the end of treatment, oral estrogen is reintroduced in gradually increasing doses (ethinyl estradiol from 5–10 µg daily) for another 12 months. If patients do not experience breakthrough uterine bleeding, low-dose estrogen–progesterone hormone replacement is the recommended treatment.

Treatment in men

For treatment of delayed puberty in men, intramuscular testosterone enantate or cypionate (30–50 mg) are given monthly for 6 months, followed by hormonal reassessment. In patients with hypogonadotropic hypogonadism, treatment at a dose of 50 mg monthly can be continued until growth rates wane. The fully virilizing dose is 75–100 mg of testosterone esters every 10 days, administered intramuscularly after growth is almost completed and afterwards. Other preparation of testosterone such as topical testosterone gel can be used as well.

The risks and benefits of hormone replacement therapy should be discussed with patients. The high incidence of thromboembolic event in thalassemia, 1–29% from various studies [39], has led to the identification of a hypercoagulable state in thalassemic patients. The absence of the spleen can contribute to and increase the risk of thrombosis in many hematologic diseases. From the treatment of symptoms of the menopause clinical practice guideline of the Endocrine Society, randomized controlled trials (RCT) demonstrated that oral estrogen increases venous thromboembolism (VTE) risk in women aged 50 to 59 [40]. Observational studies and meta-analyses suggest that transdermal estrogen therapy does not increase VTE risk, even in women with thrombophilia. No RCTs were conducted in thalassemic patients; thus, hormonal replacement therapy in hypogonadal thalassemic patients should be used cautiously, preferably in transdermal form.

Many factors contribute to the high prevalence of low bone mineral density, fractures and bone pain in thalassemia patients. Hypogonadism might be the main determinant of reduced bone mass, but other causes include ineffective erythropoiesis, alteration in the growth hormone/insulin-like growth factor I axis, thalassemia genotypes, vitamin D status, iron overload and treatment with iron chelation therapy [41]. The studies of hormonal replacement in thalassemia patients have yielded inconsistent results. An improvement in bone mineral density after gonadal hormone replacement has been reported in some but not all studies [41]. Carmina et al. studied bone mass in 30 adult women, average age 28.5 years, with thalassemia major; 13 of 24 hypogonadal patients received hormone replacement therapy beginning at an average age of 15 years, but their bone mass and bone turnover markers were not different from untreated patients [42]. Anapliotou et al. followed 27 thalassemia major patients (12 without treatment, 7 on continuous replacement and 8 on on/off schemes followed by continuous therapy). The regimen comprised either transdermal estradiol (100 µg) plus medroxyprogesterone for females, or hCG to produce serum testosterone concentrations within the normal range for males. Continuous hormone replacement therapy with transdermal estrogen for females or hCG for responding males best improved the bone density parameters [43]. Lasco

et al. studied 40 thalassemia patients, 20 of whom had been receiving sex hormone replacement therapy for 3 years on average. Early hormone replacement therapy was able to improve the pattern of bone loss significantly at L2–L4 and the femoral neck. Osteoporosis was only observed at the lumbar spine in treated patients, while in untreated patients, it also involved the femoral neck [44].

Tanner staging should be performed every 6 months in prepubescent children, as well as annual monitoring for LH and FSH between 8 and 10 years of age [45]. The ultra-sensitive assays, the Immunochemiluminometric (ICMA) LH and FSH assays, should be carried out when testing puberty in children.

Conclusions

Hypogonadotropic hypogonadism resulting from iron deposition in the pituitary gonadotrope is commonly found in thalassemia major patients. Early diagnosis and treatment are crucial for normal pubertal development and to reduce the complications of hypogonadism.

Conflict of Interest

The authors declare they have no conflicts of interest.

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