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Hypogonadism in thalassemia major patients

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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.

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

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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