Endocrinological Problems in Adult Thalassemia Patients

Erişkin Bir Talasemi Hastasında Endokrinolojik Sorunları

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ABSTRACT

Thalassemia refers to a group of genetic disorders associated with defective synthesis of alpha or beta subunits of globin chain of HbA. Patients with thalassemia major are transfusion dependent for life and they suffer from numerous problems associated with chronic anemia; extramedullary hematopoiesis and an iron overload. Several endocrine organs are affected by the iron overload. Hypogonadism is the most common endocrine complication in thalassemia. Diabetes, osteoporosis, growth hormone deficiency are other endocrine disorders seen among thalassemic patients. This review begins with a case and mainly focusses on diagnosis and treatment of endocrinological problems in adult thalassemia major patients.

Key Words: Thalassemia major, hypogonadism, diabetes, growth hormone deficiency

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ÖZET

Talasemi; HbA'nın alfa veya beta zinciri yapımında eksiklikle seyreden bir grup hastalığa işaret eder. Talasemi major hastaları ömür boyu kan transfüzyonuna bağımlıdırlar ve kronik anemi, demir yüklenmesi ve ilik dışı hematopoez ile ilişkili birçok sorunla karşı karşıyadırlar. Demir yüklenmesinden çeşitli endokrin organlar etkilenir. Talasemide en sık görülen komplikasyon hipogonadizmdir. Diyabet, osteoporoz ve büyüme hormonu eksikliği, talasemi hastalarında görülen diğer endokrin bozukluklardır. Bu derleme, bir vaka örneğiyle başlamaktadır ve erişkin talasemi major hastalarının başlıca endokrinolojik sorunlarının tanı ve tedavisine odaklanmıştır.

Anahtar Sözcükler: Talasemi major, hipogonadizm, diyabet, büyüme hormonu eksikliği

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INTRODUCTION

Thalassemia refers to a group of genetic disorders associated with defective synthesis of alpha or beta subunits of globin chain of HbA. The name originates from the Greek word *thalassa* meaning "sea" since the disease is prevalent around the Mediterranean (1). HbF is the main hemoglobin at birth and the disease is not manifest until around 6 months of age, at which Hb A becomes the predominant hemoglobin. Thalassemia is grouped into two according to the affected hemoglobin chain –alpha or beta (2). Alpha thalassemia is seen in Asians and blacks.

The clinical spectrum of alpha thalassemia ranges from asymptomatic mild microcytic anemia (alpha thalassemia trait) to intrauterine death when all four alpha globin chains are deleted (hydrops fetalis) (3). Absence of both copies of beta chain ($beta^0/beta^0$) or defect in both ($beta^+/beta^+$), results in beta thalassemia major (Figure 1). These patients suffer from numerous problems associated with chronic anemia, extramedullary hematopoiesis and iron overload, and are transfusion dependent for life (3). A milder form of mutation ($beta^+/beta^+$) results in beta thalassemia intermedia in which transfusion requirement is less frequent. The following review mainly focuses on beta thalassemia major.

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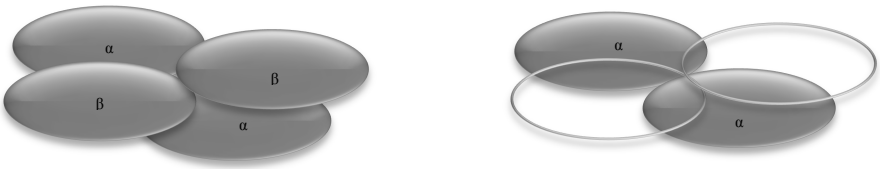

Figure 1: Schematic represantation of; A: normal hemoglobin chain, B: hemoglobin in beta thalassemia major

Although thalassemia had been considered a pediatric disease in the past, owing to advances in treatment, more than 75% of patients are estimated to survive to adulthood today (4). So physicians dealing with adults should be familiar with common medical problems of thalassemia patients.

How does endocrinopathies develop in thalassemia patients?

Iron overload is supposed to be the basic factor. The exact mechanism of endocrine dysfunction due to iron overload is unknown. When transferrin is saturated with iron, excess iron begins to circulate as non-transferrin bound species (NTBI) and NTBI can redox cycle between Fe 2+ and Fe +. This cycling generates reactive oxygen species which lead to lipid peroxidation and in turn cellular dysfunction and cell death (5,6) in susceptible organs, especially the pituitary (7). Other possible mechanisms implied for endocrine dysfunction are chronic hypoxia due to anemia (8), viral infections and individual susceptibility (9). The management of endocrinopathies in thalassemia is summarized in table 1.

Growth hormone deficiency

Growth retardation during childhood or failure of pubertal growth spurt is a common problem in thalassemia (7). In addition to chronic anemia, iron overload and toxicity of iron chelators are major factors for growth retardation. Hypothyroidism, hypogonadism and growth hormone (GH) deficiency also contribute to the picture (10). Regular assessment of growth is strongly recommended to pediatricians who deal with these children (11). However, at present, there is no guideline for the proper management of an adult thalassemia patient with GH deficiency. The American Association of Clinical Endocrinologists (AACE) recommends combination of one GH stimulation test and low IGF-1 level for the diagnosis of GH deficiency when at least one other pituitary hormone deficiency is present (12). One should bear in mind that low IGF-1 levels are not diagnostic for GH deficiency in thalassemia patients with chronic liver disease (13) A study in 25 adult thalassemia patients showed GH deficiency with two provocative tests in 8% of patients and IGF -1 deficiency in 72% of patients. Patients with hepatitis C virus infection had significantly lower IGF -1 levels when compared to non-infected patients (14). GH deficiency may affect bone density. Soliman et al. investigated the effect of GH deficiency on bone density in adult thalassemic patients. Thirty patients with a mean age of 31.5± 7.2 years are involved in the study. GH deficiency was detected in 12 patients. Thalassemic patients with GH deficiency had significantly lower BMD T score at the lumbar spine as compared to patients with normal GH and IGF-I levels (15). Another study on 25 adult thalassemia patients reported GH deficiency in 9 of them who showed a worse bone profile when compared to GH sufficient patients (16). More studies are needed to evaluate the effects of GH deficiency in adult thalassemia patients and possible treatments.

Hypothyroidism

In thalassemic children, hypothyroidism may present with growth retardation. The most common form of hypothyroidism in thalassemia is primary hypothyroidism but the prevalence of secondary hypothyroidism may increase with age. A cross sectional analysis of children and adults with thalassemia showed the central hypothyroidism prevalence to be 6% in patients younger than 21 years of age and 7,9% in patients who are older than 21 (17). The regular use of iron chelators may reverse or improve hypothyroidism in children (9). Autoimmunity does not seem to have a role in thyroid dysfunction (18,19). Thyroid echo pattern showing heterogeneity of the parenchyma is shown to be correlated with thyroid dysfunction (18). Adverse effects of amiodarone on thyroid in thalassemia patients who suffer cardiac failure should be considered in the management of these patients (20).

Hypoparathyroidism

Hypoparathyroidism is a relatively rare endocrine complication in thalassemia (21,22). It may be due to iron deposition in parathyroid glands or suppression of parathormone (PTH) as a consequence of increased bone resorption due to increased hematopoiesis (23). Patients may present with paresthesias, low serum calcium and low serum parathormone levels. Cranial imaging may reveal intracerebral calcifications (24). Treatment of hypoparathyroidism is calcium and calcitriol (9).

Osteopenia and osteoporosis

Osteoporosis in thalassemia is a multifactorial process. The basic mechanism is increased bone resorption (25,26). Iron toxicity, GH insufficiency and hypogonadotropic hypogonadism are supposed to be important factors for bone loss(27).

In a longitudinal follow-up study of 277 thalassemia patients, fractures were confirmed in 11,6% of cases. Hemoglobin levels were inversely correlated with bone loss and the decline in bone mass was more pronounced in male thalassemia patients (28). Another study from Turkey found the prevalence of osteoporosis to be 13,6% in a group of 388 thalassemia patients including 246 patients with thalassemia major (29).

Bisphosphonates which are potent inhibitors of osteoclastic bone resorption (30) are the treatments of choice in osteoporosis associated with thalassemia. Morabito et al reported a 2,6% increase in lumbar and 5,6% increase in femur neck bone mass in one year with alendronate treatment in thalassemia patients (31). Voskaridou et al, found better results with zolendronic acid (15,2% and 11,3 % in lumbar and femoral neck respectively, when zolendronic acid is given every three months) (32). The median follow-up period of both studies was one year and data is insufficient to evaluate the fracture outcome. But significant improvement in bone mineral density supports the use of bisphosphonates as first-line agents in thalassemia associated osteoporosis (33). Supplemental calcium 500-1000 mg/day should be started at the age of 12. Vitamin D 400-800 IU/day is suggested for thalassemia patients according to the vitamin D status (11).

Diabetes

About 20-30% of adult thalassemia patients have diabetes (34.35). Iron-induced beta-cell damage has traditionally been implied in the pathogenesis but recent studies demonstrated that insulin resistance precedes diabetes in thalassemia patients (36,37). Impaired glucose tolerance can be reversed with the intensification of chelation therapy (38,39). Annual oral glucose tolerance test is suggested in the follow-up of thalassemia patients who are 16 years of age or older(11). At present there is no clinical trial on the use of metformin in thalassemia patients. Insulin may be given when other measures fail (11). Diabetic thalassemia patients who are insulin dependent differ from type 1 diabetes in some aspects: they are less prone to ketosis and to the development of chronic vascular complications and their renal glucose threshold is higher (40). In the follow-up; HbA1c is not a reliable marker since its measurement is affected by hemoglobinopathies (41). Instead, fructosamine may be used (11).

Hypogonadism

Hypogonadism is the most common endocrine complication in thalassemia (29,42,43). Pituitary iron overload begins in the first decade of life prior to the liver and cardiac iron deposition (44). The association between pituitary iron overload and hypogonadism is well established (44,45). Pituitary iron overload and iron-induced oxidative stress result in secondary hypogonadism in thalassemia patients (46). Patients suffer from delayed puberty, primary or secondary amenorrhea (9). For boys, beginning treatment with intramuscular depot testosterone and continuing either with intramuscular form or with testosterone gel is suggested. For girls, combination of ethynil estradiol and norethisterone or medroxyprogesterone acetate provides pubertal development and regular menses (11).

Ovarian function in females is preserved and females with thalassemia are able to conceive either spontaneously or after the induction of ovulation (47). Pregnant women with thalassemia major should be followed up very closely by obstetrician, hematologist and cardiologist (11).

Since chronic anemia may lead to fetal hypoxia and unwanted obstetric outcomes such as intrauterine growth retardation and fetal death (48), hemoglobin of the mother should be kept above 10 g/dL (11). An Italian center reported that 91% of pregnancies in women with thalassemia major proceeded successfully to live births (47). Iron chelators are not used during pregnancy due to their possible teratogenic effects. Actually, pregnancy is assumed to be an iron chelation state by itself, due to hemodilution and fetal iron consumption (48).

For males, the induction of spermatogenesis with human chorionic gonadotropin and human menopausal gonadotropin injections and cryopreservation of the obtained sperm is suggested (49).

Adrenal Insufficiency

Although the clinical adrenal insufficiency is rare, it is difficult to assume the exact prevalence of biochemical adrenal insufficiency in thalassemia, since variable diagnostic tests are used to report variable rates in the literature (50,52). Adrenal insufficiency may appear at hypothalamic, pituitary or adrenal levels (50).

ACTH stimulation test is a practical alternative to the gold standard test; insulin tolerance test to diagnose adrenal insufficiency (50,51). Low dose-1 mcg low dose -1 mcg tetracosactide (Synacthen®) (LD)test is thought to detect more cases of adrenal insufficiency than standard dose -250 mcg (SD) test. In a study conducted on 98 adult beta thalassemia patients, ACTH was found to be elevated in 15,3% of the cases and subnormal cortisol response to LD test was detected in 32.1% of the patients (53).

Thalassemia patients are suggested to be screened by basal serum cortisol and ACTH stimulation test when necessary. Using any of the two tests, a peak cortisol level of 18 µg/dL 30-60 min after ACTH stimulation is abnormal. Patients with subclinical disease may be given glucocorticoid coverage only for stressful conditions. (11).

Table 1: Summary of management of endocrinological complications in adult thalassemia patients

Hypogonadism	For females: ethynil estradiol and norethisterone or medroxyprogesterone acetate For males: intramuscular depot testosterone or testosterone gel *Fertility:* For females: close follow-up during pregnancy For males: hCG or HMG +cryopreservation of sperms
Growth hormone deficiency	No exact guideline- studies needed
Hypothyroidism	Primary hypothyroidism is common L- thyroxine replacement
Diabetes mellitus	Metformin (questionable)/ insulin Intensification of chelation therapy reverses glucose intolerance
Hypoparathyroidism	Calcium and calcitriol
Osteopenia/osteporosis	Bisphosphonates, calcium and vitamin D
Adrenal insufficiency	Clinically rare/ steroid replacement recommended in stressful conditions if the patient has subclinical disease

CLINICAL CASE

A 34-year-old male patient was consulted by hematologist for the evaluation of hypogonadism and osteoporosis. He had been diagnosed with thalassemia major when he was 6 months old and had been receiving blood transfusions monthly since then. He has undergone splenectomy at the age of five. He said he entered puberty at the age of 15. For the last few years he was suffering from decreased libido and erectile impotence. On physical examination he had a dark skin color, frontal bossing and prominent facial bones. He had normal external genitalia and scarce body hair (Tanner stage IV) but had no facial hair. He declared he had not been compliant with the testosterone treatment given. He had been given active vitamin D tablets for osteoporosis. He had no history of fractures. Laboratory examination revealed overt diabetes, growth hormone deficiency, low testosteron with low follicle stimulating and luteinizing hormone levels. Bone mineral density showed osteoporosis with a T score of -4,5 at spine.

DISCUSSION

The man described in the case had several endocrinological problems complicating thalassemia major. Treatment with testosterone gel or intramuscular testosterone may be given for hypogonadism and the patient may be consulted for spermiogram and cryopreservation for fertility, if desired. Osteoporosis should be treated either with alendronate or zolendronic acid together with vitamin D and calcium supplements. Metformin may be tried to control blood glucose and may be switched to insulin if fails. HbA1c is not a proper marker for a follow-up of diabetes so serial blood glucose measurements are needed to evaluate the success of the treatment. There is no evidence-based approach for the management of growth hormone deficiency in this patient. Adrenal assessment does not seem to be necessary since there is no clinical evidence for hypocortisolism in this case.

CONCLUSION

Prolongation of survival in thalassemia brought many thalassemia patients to adult endocrinology clinics. Starting from the pituitary, endocrine organs are vulnerable to damage from iron overload. Patients should be carefully evaluated for possible deficiencies in hypothalamo-pituitary –end organ hormones as well as for dysglycemia and bone loss. Appropriate management of endocrine problems in thalassemia may help to prevent related morbidities and improve the quality of life of these patients.

Conflict of Interest
No conflict of interest was declared by the authors.

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