Endocrinopathies in patients with thalassemias

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ABSTRACT

Thalassemia major is a hereditary disorder of hemoglobin synthesis resulting in severe anemia. Treatment consists of multiple blood transfusions, a complication of which is iron overload. Excessive iron is then deposited in almost all tissues but primarily in the liver, heart and the endocrine glands. Lately, desferrioxamine has been used as a chelating agent in an attempt to prevent the complications of tissue damage by iron deposition. Early introduction of the chelating agent to combat iron overload in vulnerable organs leads to improved life expectancy. However, these patients often present with multiple endocrine dysfunction such as growth failure, hypogonadism, abnormalities in glucose metabolism, hypothyroidism, hypoparathyroidism and less frequently hypoadrenalism. We briefly review the current status of endocrine gland abnormalities in patients with thalassemia major.

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ß-thalassemia is an inherited defect in the ß-globin chain of hemoglobin characterized by severe anemia, splenomegaly, and skeletal changes. The inability to produce ß-globin chains result in accumulation of α-globin chains that precipitate within erythroid precursors in the bone marrow.[1] Programmed chronic transfusions, with chelation of iron, to control symptoms of anemia, stunting of growth, hypersplenism and iron overload, is the logical therapy for thalassemic patients.[2] With adequate care, these patients may achieve a life expectancy beyond the second, third or even fourth decade of life. In addition to growth failure, delay in onset of puberty is a common problem in these patients. Other endocrinopathies including hypogonadism, abnormality in glucose metabolism, hypoparathyroidism, hypothyroidism, and rarely hypoadrenalism occurs mainly in older patients who tend to have high serum ferritin levels.[3] Iron intoxication affects the functions of nearly all the endocrine glands, more commonly the pituitary, gonads and the pancreas and less frequently thyroid, parathyroid and adrenal glands.

Endocrine dysfunction is a frequent complication in thalassemic patients who are on regular transfusions. In some reports, up to 66% have at least a single endocrine disorder and 40% have multiple endocrinopathies.[4] The precise mechanism of iron toxicity to endocrine glands is not well elucidated. However, reduced nicotinamide adenine dinucleotide phosphate-induced lipid peroxidation, cytochrome P450 inactivation, free radicals production and damage to glands are thought to be the etiology.[5] Chelation therapy has been shown to result in postponing or even preventing the endocrine disorders. Obviously, early institution of chelation therapy with the aim of preventing iron overload results in normal sexual development in 90% versus less than 40% in those in whom initiation of chelation therapy starts after development of advanced hemosiderosis.[6] Intensive chelation therapy with desferrioxamine is effective not only in delaying but, in some cases, even reversing organ damage caused by transfusional iron overload.[7] The quality of life and the cost of treatment of these patients are a heavy burden on the

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health services. There should be a heightened awareness of the anticipated complications of the disease and its treatment.

Growth failure. The heterogeneity of ß-thalassemia mutations ($ß^0$ versus $ß^+$) and the coexistence of other thalassemias (α or δß thalassemias) account for the variability in the degree of anemia, tissue hypoxia, bone expansion and subsequently growth impairment.[8,9] In addition, the type and level of hemoglobin, the pattern of growth retardation, and degree of bone changes are used to sub-classify the clinical phenotypes of thalassemia major.[8] Possible etiologies for growth retardation include pituitary iron overload with impairment of somatotroph function or defect at hepatic growth hormone (GH) receptors,[10] in addition to toxic effect of desferrioxamine on long bone growth, bone disorders with abnormal body proportions (truncal shortening), zinc deficit, low hemoglobin levels and development of other endocrinopathies.[3] The pituitary iron overload is best detected by magnetic resonance imaging (MRI).[11]

Untreated patients with thalassemia major do not attain height and weight greater than the third percentile in their first few years of life when compared with non-thalassemic peers. Hypertransfusion programs along with chelation regimens have been proved to have a radical beneficial impact on growth and bone disorders in patients with thalassemia.[12,13] The recommended and adapted regimen is to maintain the hemoglobin at a level of 10-11g/dL by regular transfusion, aside from early introduction of chelating therapy. This has been shown to have a positive physical impact on normal growth and exercise tolerance equivalent to non-thalassemic peers. There is also preservation or improvement of growth hormone secretion.[14] With improving survival rate, a substantial number of patients with thalassemia attain the age of puberty, and a large percentage (44%),[15] develop growth retardation, short stature and pubertal failure. It is evident from published data that thalassemic patients who commence treatment before 10 years of age can achieve normal growth, while a number of those who start therapy after 10 years of age have a delay in their growth.[16,17] This is more pronounced in males.[16,17]

Growth disturbances are more marked in older patients, as two thirds of males and one third of females over 14 years of age are 2 standard deviations (2 SD) below the normal mean, and more than 80% of males and 75% of females have delayed skeletal maturation.[17] The pubertal growth spurt is often delayed or absent. However, these patients continue to grow into their early twenties, at slower rate, and they have a tendency to attain normal height after 20 years of age.[16,17] As mentioned earlier it is important to prevent growth retardation in thalassemic patients by establishing a hyper-transfusion program and early initiation of chelating agents. If these patients present with growth retardation then detailed clinical evaluation is mandatory, bearing in mind the fact of delayed growth in such patients. In the presence of GH deficiency, long term administration of recombinant human growth hormone (rhGH) therapy is safe and promising. Furthermore, a low dose of long acting sex steroid treatment in boys with delayed bone age and without GH deficiency is safe and can produce similar results to those obtained with rhGH therapy.[18]

Hypogonadism. Absent or delayed pubertal development secondary to hypogonadism is a well-recognized complication in thalassemic patients. The iron-toxicity damages pituitary, gonads or both, which subsequently leads to the hypogonadism.[19] Gonadotropin deficiency or gonadal failure is manifested in males by delayed or arrested puberty and in females by absence of menarche or discontinuation of regular menstruation and even secondary amenorrhea.[20] On the other hand, desferrioxamine toxicity may reduce sperm mobility.[21] Pituitary-gonadal axis is very sensitive and even a modest amount of iron deposition within the anterior pituitary can interfere with its function. The pituitary damage leading to secondary hypogonadism is rarely reversible even with the most intensive iron chelation. Thus, prevention with early institution of chelating agents is the standard care. Other possible causes of hypogonadism in beta-thalassemia major include liver disorders, chronic hypoxia, diabetes mellitus and zinc deficiency.[22]

Hypogonadism is found in more than 40% of thalassemic patients,[23] with delayed emergence of gonadal functions. It is recommended that these patients should have suitable hormone substitutes. However, the age of initiation and dosage is controversial. The proponents of early hormonal-replacement are base on the psychological benefits and improvement of growth velocity and final height, while opponents claim that hypogonadism in thalassemia is characteristically expressed by delayed sexual maturation and thus they advocate postponement of hormonal therapy to a time when arrested sexual maturation is easily identified.[24] However, due to inconsistency of hypogonadism among thalassemic patients, individualization in hormonal replacement is the appropriate decision by the hematologist and the endocrinologist, taking into consideration the coexistence of impairment of other organs, particularly heart, liver and endocrine system. Additionally, bone age and racial age of maturation must be considered prior to initiation of hormonal replacement therapy.

After clinical and laboratory evaluation and documentation of hypogonadism, there are several regimens for treating such patients. One alternative is to administer in males, testosterone enanthate on a monthly basis starting at 50mg and increasing it up to 200mg intramuscularly (IM) every 3-4 weeks. Periodical assessment by an experienced endocrinologist is essential in such cases. In females, conjugated estrogens and progesterone starting with a low estrogen dose (0.3 mg orally [PO], once a day [QD]) and increasing it to 1.25 mg PO QD over 6 months to one year until breakthrough bleeding occurs. This is then followed by cyclic therapy with estrogens for the first 21 days of each cycle along with medroxyprogesterone (5-10 mg PO QD) in the last 10 days. The primary aim of the foregoing treatment is to induce pubertal development. However, since the treatment is a long term, it is essential to differentiate primary from secondary hypogonadism before initiation of therapy. In patients with secondary hypogonadism, pulsatile luteinizing hormone-releasing hormone (LHRH) or human gonadotropin (chorionic or menopausal) therapy is an option to stimulate ovulation in females and enhance male fertility.[25] Successful pregnancy following gonadotropin therapy in young females with hypogonadotropic hypogonadism secondary to iron overload has been reported.[26,27]

Disturbances of glucose metabolism. Recently, a positive association between ferritin level and diabetes mellitus has been found in the general population,[28] even without significant iron overload. In thalassemic patients, iron overload affecting glucose regulation is thought to be due to several mechanisms, including liver dysfunction and insulin resistance, aside from the consequence of the damage inflicted by iron overload on the pancreatic beta-cell leading to pancreatic dysfunction. The suggested risk factors include age, increased amount of blood transfusion, serum ferritin level, non-compliance with iron chelation therapy, family history of diabetes mellitus, viral hepatitis and pubertal status.[29] The effect of iron overload manifests after the first decade of life and the incidence increases with age. Studies have shown that 21% of thalassemic patients have an abnormal oral glucose tolerance test (OGTT), 51% have impaired insulin secretion, 32% have increased insulin secretion, and 19% have delayed insulin secretion.[30] These conditions are believed to precede the clinical expression of diabetes mellitus. The prevalence of diabetes mellitus has been reported to range from 2.3-24%.[31]

There are unique features of diabetes mellitus and glucose disturbances in thalassemic patients. First, these patients have a high renal glucose threshold, and thus glucosuria appears at blood glucose levels above 200-350 mg/dl compared to 180mg/dL in normal individuals. Secondly, there are absence of islet cell antibodies, lack of human leukocyte antigen association, and rarity of development of ketoacidosis which characterizes type 1 diabetes mellitus.[32] Thirdly, diabetes mellitus can be prevented or reversed by early and intensive chelation therapy with subsequent reduction of insulin dose or even cessation of it in patients who are already diabetic.[33] Fourthly, oral hypoglycemic agents are found to be effective in these patients in spite of the direct iron effect on islet cells. The fifth and the last feature of diabetes mellitus in these patients is early development and accelerated course of diabetic nephropathy, which may be attributed to high oxidative stress.[34] It is advisable to periodically check glucose level from early years of life using OGTT and to treat patients accordingly using diet, exercise, oral hypoglycemic agents or insulin. Additionally, intensive intravenous desferrioxamine, 150 mg/kg/day, is recommended in thalassemic patients, who develop diabetes mellitus.[35]

Hypothyroidism. Hypothyroidism resulting from hemosiderosis has been observed. Its prevalence and severity vary in different cohorts, ranging from 2.7% to 19.4%, and its natural history is poorly described.[36-38] Usually, it presents just after 10 years of age and both sexes are equally affected. Hemosiderotic hypothyroidism manifests mainly by increased thyroid stimulating hormone (TSH) along with normal or low thyroxin (T_4) and tri-iodothyronine (T_3), consistent with mild primary hypothyroidism. In this group of patients, the thyroid pituitary axis is less sensitive to iron-induced damage than the gonadal and GH axis, and the thyroid gland appears to fail before the central components of the axis. The abnormal thyroid function may be reversible in the early stages by intensive iron chelation. Its progression is variable and it may take years to progress from normal to preclinical or mild hypothyroidism. Characteristically, the thyroid gland is not enlarged, thyroid antibodies are absent and thyroid Technetium 99 (Tc^{99}) scan shows absent or irregular radioactive uptake. L-thyroxin supplement should be cautiously initiated in these patients, especially in the presence of hemosiderotic cardiomyopathy.[39]

Hypoparathyroidism and disturbance of calcium hemostasis. Physiologically, calcium is controlled within a narrow range by vitamin D (Vit D) and parathormone. Calcium absorption is amplified by Vit D, while hypocalcemia stimulates parathormone secretion, which enhances calcium mobilization from the bones in addition to stimulation of 1-α-hydroxylation of Vit D in the kidney, and enhancement of calcium reabsorption from kidneys. Hypocalcemia is not rare in thalassemic patients and the etiology is multi-factorial. The most common causes are hypoparathyroidism, Vit D deficiency, and chronic liver disease preventing

25-hydroxylation of Vit D, bone marrow expansion, and reduction of bone mass and mineral content. Hypoparathyroidism in transfusion-dependent patients with ß-thalassemia seems to be accompanied by other endocrinopathies. It is usually a late complication and occurs after the age of 16 years. The incidence of hypoparathyroidism in thalassemic patients with iron overload varies from 3.6%[35] to 4.5%[40] and the prevalence of hypoparathyroidism is reported to be 10.7%.[41] Periodic measurement of serum calcium, magnesium, phosphorus and alkaline phosphatase along with 25-hydroxy-Vit D level is recommended. Hypoparathyroidism is manifested by hypocalcemia, hyperphosphatemia, normal or low alkaline phosphatase and normal level of Vit D.[42] Maintenance of normal calcium is of vital importance in thalassemic patients due to the possibility of the coexistence of hemosiderotic cardiomyopathy, which predisposes to cardiac arrhythmias. Therapy of hypocalcemia related to hypoparathyroidism should include Vit D and calcium supplement. However, control of plasma calcium may be difficult, usually, requiring high doses of Vit D. Vitamin D 4000 IU can be used as prophylaxis to prevent development of true hypocalcemia.

Hypoadrenalism. Iron overload in thalassemic patients affect the adrenocorticotrophic hormone (ACTH) reserve or adrenal function very rarely. Iron deposit mainly occurs in the zona glomerulosa of adrenal gland and when it is severe it can interfere with its function.[43] Stimulation test for pituitary adrenal axis reserve is needed only if there is clinical suspicion, especially in patients with multiple hormone deficiencies. Once hypoadrenalism is documented, therapy with glucocorticoids or glucocorticoid plus mineralocorticoids should be initiated.

In conclusion, programmed chronic blood transfusion with early institution of chelating agents is the logical therapy for thalassemic patients. Delay in starting desferrioxamine treatment can lead to development of multiple organ damage including the endocrine glands. Growth failure, delayed puberty and hypogonadism are the most common endocrine abnormalities. Diabetes mellitus in thalassemic patients has several unique features compared to that in the general population. The natural history of hypothyroidism is poorly described in these patients, but it is usually mild and may be reversible by intensive iron chelation. Control of plasma calcium is difficult and 10% develop hypoparathyroidism. Iron overload rarely leads to hypoadrenalism. A number of these complications of thalassemia can be prevented by early institution of chelating agents.

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