CASE REPORT
Korean J Clin Lab Sci. 2017;49(4):495-497
https://doi.org/10.15324/kjcls.2017.49.4.495
pISSN 1738-3544 eISSN 2288-1662

KJCLS

Multiple Endocrinologic Complications in Thalassemia Major

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Thalassemia major is a genetic disorder with a defective synthesis of either the alpha or the beta chain of hemoglobin A. Blood transfusion is crucial for the survival in these patients. Unfortunately, endocrine dysfunction is a very common complication in these patients and is principally due to excessive iron overload as a result of frequent blood transfusions. Although regular blood transfusion may increase life expectancy, disturbances in growth and pubertal development, abnormal gonadal functions, impaired thyroid, parathyroid and adrenal functions, diabetes, and disorderly bone growth are common side effects. We hereby present a case of a 23-year-old, unmarried woman with beta thalassemia major presenting with primary amenorrhea, poor development of secondary sexual character, and short stature. Thorough history, clinical examination, and laboratory investigation, including dynamic function test (insulin tolerance test) were conducted. These tests confirmed that she had multiple endocrinopathies, including hypogonadotropic hypogonadism, growth hormone deficiency, and subclinical adrenal insufficiency, which were caused by iron overload. She required hormone replacement therapy. Early recognition of possible deficiencies in hypothalamo-pituitary-end organ hormones caused by iron overload in thalassemia patients that undergo frequent blood transfusion procedures is essential. Appropriate treatments, including transfusion regimen and chelation therapy, as well as specific treatment of each complication are the crucial for the successful management and improvement of quality of life these patients.

Key words: Thalassemia, Regular blood transfusions, Endocrine dysfunction

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Received: July 17, 2017
Revised 1st: September 5, 2017
Revised 2nd: September 25, 2017
Accepted: September 25, 2017

INTRODUCTION

Thalassemia major is a hereditary disorder of haemoglobin chain synthesis and the homozygous state results in severe anaemia. The combination of transfusion and chelation therapy has dramatically increased the life expectancy of thalassemic patients. However, frequent blood transfusion in turn can lead to iron overload resulting in a high incidence of endocrine abnormalities in children, adolescents and young adults [1]. Excessive iron is deposited in most tissues primarily in the liver, heart and the endocrine glands [2]. Disorders of growth, sexual development & fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypoadrenalism are the main endocrine complications found in thalassemic patients [3]. Endocrine abnormalities should be monitored carefully and a thorough endocrine evaluation should be carried out yearly in every thalassemic patient.

CASE

A 23-year-old unmarried woman, known case of beta thalassemia major, reported to the endocrinology outpatient department with primary amenorrhea, poor development of secondary sexual character and short stature. She had history of regular blood transfusion with

Table 1. Insulin tolerance test result

Time	Test		
	Glucose (mmol/L)	Cortisol (nmol/L)	Growth hormone (μg/L)
0 min (basal)	7.3	443.1	0.913
30 min	5.6	312.2	4.29
90 min	3.3	252.3	3.42
120 min	2.2	307.6	1.07
150 min	4.9	362.6	2.42

the Haemoglobin range from 6~11 g/dL and was on subcutaneous Derferrioxamine 1500 mg 5 times a week. She had splenectomy at the age of 16. On examination, she was of thin built with height 141 cm and weight 41 kg. She had thalassemic facies. Her breast development was prepubertal (Tanner Stage I) and absent pubic and axillary hair. She had a splenectomy scar at the left hypochondrium. Her liver was enlarged. Laboratory investigations on serum ferritin and endocrinology profile were carried out. She had high serum ferritin of 14,288 ng/mL (reference range: 14.5~87.6 ng/mL). She had hypogonadotrophic hypogonadism with serum FSH 0.2 IU/L (reference range : 1.7~7.7 IU/L), serum LH 0.2 IU/L (reference range : 1.0~11.4 IU/L), and serum estradiol <18.35 pmol/L (reference range : 45~854 pmol/L). Her thyroid function test result was normal. Her initial 8 am serum growth hormone was 1.07 μg/L (reference range : <9.88 μg/L) and serum cortisol was 278.5 nmol/L (reference range : 166~507 nmol/L). Insulin tolerance test was then carried out to assess her growth hormone and ACTH/cortisol reserve and the result (Table 1) showed she had inadequacy in both growth hormone and cortisol response. However her serum ACTH was normal, 3.02 pmol/L (reference range : 1.6~13.9 pmol/L).

DISCUSSION

In this present case, the 23 years old female patient was suffering from iron-overload due to repeated blood transfusion, as reflected by her serum ferritin status which was many folds higher than the upper limit of norm. It has already been established that the iron overload is the prime cause of endocrinopathy in thalassemia [3]. And hypogonadism is the most common endocrine complication in such patient [4]. There is evidence that hypogonadism can be due to primary gonadal failure as a result of iron overload in the gonads, but more commonly results from haemosiderosis of the gonadotroph cells in the pituitary gland leading to hypogonadotropic hypogonadism [5]. Hypogonadism is clinically diagnosed in a female by the presence of primary or secondary amenorrhea with absent or poor development of secondary sexual characteristics. The history and clinical findings of our patient were substantiated by the laboratory investigations which showed her circulating gonadotropins were inappropriately low and the estradiol level was extremely lower than the normal value (hypogonadotropic hypogonadism). She should be started on hormone replacement therapy with sex steroids. Our patient's short stature and insulin tolerance test showed she had growth hormone deficiency. However, growth failure in thalassemia is not solely due to growth hormone deficiency, but is multifactorial. The fundamental problem is the free iron and hemosiderosis-induced endocrinopathies (growth hormone deficiency, hypogonadism, delayed puberty, hypothyroidism, disturbance in calcium homeostasis and bone disease). Additional factors may contribute to the aetiology of growth delay including chronic anaemia and hypoxia, chronic liver disease, zinc and folic acid and nutritional deficiencies, toxicity of iron chelating agents particularly desferrioxamine, emotional factors, and dysregulation of the GH-IGF-1 axis. Delayed or arrested puberty is also an important contributing factor to growth failure in adolescent, who do not exhibit a normal growth spurt [3,6,7]. Growth hormone deficiency is not a rare occurrence in adult thalassemic patients [8]. Supplementation of growth hormone requires analysis of many factors, including the effect of treatment on cardiac functions, metabolic parameters and psychosocial functioning, along with financial cost considerations. Prevalence of adrenal insufficiency is variable in thalassemia patients, it is important to identify because adrenal insufficiency is a potentially life-threatening

co-morbidity for which preventative treatment is readily available and can be life-saving. The pathophysiological basis of adrenal insufficiency in thalassemia major has not been well-defined. Pituitary iron deposition might reduce ACTH secretion producing secondary adrenal insufficiency. Adrenal glands might also be directly affected by iron toxicity producing primary adrenal insufficiency [9-11]. Our patient had normal basal cortisol level and basal ACTH level, however from insulin tolerance test, she was diagnosed to have subclinical adrenal insufficiency. Patient with subclinical disease may benefit from glucocorticoid coverage during stressful condition [12]. Prolongation of survival in thalassemia brought many thalassemic patients to endocrinology clinics as endocrine organs are vulnerable to damage from iron overload. Patients should be carefully evaluated for possible deficiencies in hypothalamo-pituitary-end organ hormones. Early recognition of these complications, institution of appropriate treatment including transfusion regimen and chelation therapy, and specific treatment of each complication are the keys to successful management and improvement of quality of life.

Acknowledgements: None
Funding: None
Conflict of interest: None

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