Endocrinopathies in thalassemia major patient

D A Lubis\textsuperscript{1,2*} and E M Yunir\textsuperscript{1}

\textsuperscript{1}Division of Endocrinology, Diabetes and Metabolic, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
\textsuperscript{2}Division of Endocrinology, Diabetes and Metabolic, Department of Internal Medicine, Faculty of Medicine, University of Sumatera Utara, Medan, North Sumatera, Indonesia

*Correspondence mail to: dianindita@hotmail.com

Abstract. Advanced in chelation therapy and regular blood transfusion have marked improvements in the life expectancy of patients with thalassemia major, however these patients still have to deal with several complications. We report a 19-year-old male, presented with multiple endocrine complication-related thalassemia; hypogonadism, short stature, osteoporosis with history of fracture, and subclinical hypothyroid.

1. Introduction
Thalassemia major is a hereditary disorder of hemoglobin synthesis that requires a regular blood transfusion. The combination of chelation therapy and blood transfusion in these patients has dramatically extended the life expectancy. However, the repetition of blood transfusions leads to the accumulation of iron in several organs such as liver, heart, and the endocrine glands, resulting in a high incidence of endocrine dysfunctions in children, adolescents, and young adults. The main endocrine complications in thalassemia patients are disorders of growth, sexual development and fertility, diabetes mellitus, hypothyroidism, abnormal bone mineralization and insufficiency adrenal.\cite{1} This manuscript aimed to review endocrine complications of thalassemia by presenting a case with multiple endocrinopathies.

2. Case Presentation
A 15-year-old male who had been diagnosed with major $\beta$-thalassemia at the age of 1, was referred to the clinic of endocrinology for evaluation of his height. The patient underwent intermittent whole blood transfusions every 14 days. Subcutaneous Deferoxamine injection also started at age 1. He has had good compliance with blood transfusion and chelation therapy. On examination, he was uncivilized, height 137 cm (mid-parental height was 161.5 ± 5 cm) and body mass index was 13.3 kg/m\textsuperscript{2}, with pubertal testes (4 mL bilaterally). Biochemical testing revealed hypogonadotropic hypogonadism. He initiated treatment with testosterone (150 mg monthly IM) for six months each cycle, followed by hormonal reassessment, resulting not significant development of secondary sexual characteristics. Testosterone therapy was then stopped, after three cycles.

At 16 years of age, he admitted to the emergency department with a history of trivial fall at home. Following the fall, he was unable to bear weight on right hand and foot. Radiographs were taken, which revealed pathological fractures of femur and radial. He also performed a bone mineral density (BMD) 2 site test which revealed low bone density for chronological age, with Z score for lumbar
vertebra -3.7. The patient, who had sustained immobilization due to multiple fractures and feared to fall, was subjected to a rehabilitation program and was given Zoledronic acid, combined with vitamin D and calcium supplementation. The patient was full weight-bearing and good function with a fully healed femur after a year of treatment.

At the age of 18, the patient was to internal medicine department as a continuation of evaluation of hypogonadism and a view of short stature. The presentation of his secondary sexual characteristic has not appeared yet. He had a prepubertal penis, testis volume 6 mL bilaterally, markedly short stature, and a low BMI of 14.9 kg/m². Laboratory investigations were low normal testosterone levels (2.97 ng/mL), high level of luteinizing hormone (LH) (14.98 mIU/mL), normal follicle-stimulating hormone (FSH) levels (10.7 mIU/mL), normal blood glucose levels (81 mg/dL), normal IGF-1 levels (206 ng/mL), high TSHs levels (8.040 uIU/mL) with normal FT4 levels (1.300 mg/dL). He had no signs and symptoms of hypothyroidism; fatigue, cold intolerance, consistent weight gain, nor memory problems. He had no enlargement of the thyroid glands and no edema. His diagnosed was with subclinical hypothyroid and Euthyrox was given.

At this age, he repeated the bone age test which showed a mentally disabled boy, bone morphology suited thalassemia patients, the ephyseal fusion of the proximal phalanges, the radius ossifies, and the ulna has not finished. With the approximate of total PRC transfusion around 172,800 cc, we would like to observe the hemosiderosis in related organs. He then performed T2* MRI. The result was normal T2* of the heart, while T2* of the liver was severe hemosiderosis, and the pancreas was moderate hemosiderosis. A regular transfusion and chelator therapy continued. Testosterone therapy was no longer given based on the latest testosterone level. The patient achieved clinical improvements and was recommended to continue the treatment with annually follow up of complications-related thalassemia.

3. Discussion

Thalassemia is the most common hereditary cause of anemia. Before the introduction of regular blood transfusion, thalassemia patients died within the first few years. Transfusion and chelating therapy have improved the quality of life and longer life expectancies of these patients.[2,3] However, due to repeated transfusion, iron overload and deposition of iron in vital organs may cause morbidity in patients with thalassemia β–major. The iron deposition involves endocrine glands and the hypothalamic-pituitary axis. Most of the endocrine abnormalities in developed countries were after ten years of age. In developing countries, nonetheless, it is possible to have a high prevalence of endocrine complications at an early age due to suboptimal of transfusions and chelation therapy.[4]

Primary and secondary characteristics of sexual development are usually in thalassemia patients. Primary gonadal failure results from gonadal iron deposition. While secondary hypogonadism due to iron deposition on gonadotrophic cells of the pituitary gland as revealed by poor response of LH and FSH to GnRH stimulation or a combination of both primary and secondary hypogonadism. Some studies have reported the incidence rate of failure of onset of puberty reaching 50% and may approach even 100%. Leptin is a polypeptide hormone produced by adipose cells that acts as a permissive signal to initiate puberty. Impaired in Leptin synthesis has been stated caused by iron toxicity on adipose tissue which delays a sexual maturation. Manifestations of low gonadotropin levels are adelayed onset of menarche, oligomenorrhea, secondary amenorrhea, reduced testicular size and breast size. These manifestations usually occur in significantly elevated serum iron and ferritin levels.[1]

Another common endocrine dysfunction was short stature. Around 20%-30% patients with thalassemia major were reported to have growth hormone (GH) deficiency. The remaining 70%-80% had provocative tests such as clonidine or glucagon stimulation tests have revealed a lower peak of GH levels compared to those found in patients with short constitutional stature. The yearly growth velocity is either decreased or completely absent in thalassemia patients. Factors that potentially caused growth failure include iron overload, Deferoxamine toxicity, free radical toxicity, anemia, zinc deficiency, delayed puberty, liver cirrhosis, primary hypothyroidism and defect in Growth Hormone-
Insulin-like Growth Factor-1 (GH-IGF-1) axis.[1] Low serum insulin-like growth factor-1 with normal growth hormone reserve in short thalassemia patients indicate that a state of relative growth hormone resistance exists.[2] Skeletal maturation, on the other hand, occurs under the primary control of hormones from the adrenal, thyroid and sex glands.[5] This patient showed normal IGF-1 levels, suggesting that the short stature was not secondary to decreased IGF-1 by the liver.

Thyroid dysfunction was a complication in 3-27% of thalassemia patients, but its severity is related to the degree of iron overload. Autoimmune has no role in the pathogenesis of hypothyroid in thalassemia patients. Most of thalassemia patients have subclinical compensated hypothyroidism with high TSH but normal T4 and T3 levels. Only 5% of thalassemia patient develop overt clinical hypothyroidism that requires treatment. The pathogenesis is remained unclear but thought to relate to lipid peroxidation, oxidative stress, and free radical release. Thyroid antibodies are negative, the thyroid glands are impalpable, and clinical features of disease are not present.[1,4]

Abnormal carbohydrate metabolism is another major endocrine abnormality found in thalassemia patients. During the second decade of life, glucose intolerance usually develops in these patients. Prevalence of impaired fasting glucose and impaired glucose tolerance was 28.6 and 7.1%, respectively.[2] The prevalence of diabetes is varying up to 21% in patients with thalassemia. Several etiologies have been assumed to contribute to the development of diabetes-related thalassemia. Overload of transfusion iron is the main factor damaging pancreatic β-cells and causing diabetes. Risk factors for developing glucose intolerance in thalassemia include advanced age at onset of chelation therapy, poor compliance with chelation therapy, altered β-cell insulin secretion, insulin resistance following liver disease, autoimmunity, and Hepatitis C virus infection affecting glucose metabolism.[6] One study revealed that diabetes risk could be reduced with serum ferritin of less than 2500 ug/L.[4]

Hypoparathyroidism related to thalassemia is a rare complication that usually found in males and evident after ten years of age. Most of the patients are asymptomatic while a few have mild symptoms. The first evidence is a loss of diurnal variation in parathyroid hormone (PTH) levels; patients have low PTH, calcium, vitamin D levels and high phosphate levels. Overt hypoparathyroidism caused by iron toxicity is seen in 3%-4% thalassemia patients while preclinical hypoparathyroidism reported occurring in almost 100% of thalassemia patients.[1]

Adrenal insufficiency affected 13% to 46% of thalassemia patients and was far more common in males. The prevalence is increased with greater transfusion burden, wasting, and poor linear growth. The pathophysiology of adrenal insufficiency in thalassemia major remains uncertain. It is maybe primary of adrenal insufficiency is due to iron deposits in the adrenal cortex, which are mainly restricted to the zona glomerulosa with rare involvement of the fascicularis zone. While secondary adrenal insufficiency in thalassemia patients with pituitary iron deposition that might reduce Adrenocorticotropic hormone (ACTH).[1,7] In this case, the patient did not reveal symptoms of adrenal insufficiency, so we did not perform cortisol level.

Thalassemia correlates to osteopenia with cortical thickening, marrow expansion, trabecular coarsening and bone deformity. Low bone mass is in 40-60% of thalassemia patients.[4] Hypogonadism, diabetes mellitus, hypoparathyroidism, hypothyroidism, iron overload and its treatment are factors that made osteopenia in thalassemia patients. Other contributory factors are malnutrition, inadequate exercise and absence of gonadal hormones during puberty and adrenal sex hormones during adrenarche. Pathological fractures are encountered in more than 20% of cases due to significant reduction in cortical and trabecular bone mineral density.[1]

Early studies have shown little impact on the course of progressive endocrine dysfunction in patients with chelation therapy, Deferoxamine. Only aggressive chelation therapy with a combination of Deferoxamine and Deferiprone has achieved improved outcomes of endocrine complications. However, intensive chelation was normally in emergency and for a short period, as it could impact the therapy compliance negatively and drug-related adverse events.[8]
4. Conclusion
High prevalence of endocrine disorders demonstrating that these abnormalities were related to iron overload. These findings highlight the importance of iron overload in development of endocrine abnormalities. This patient has hypogonadism, short stature, osteoporosis with ahistory of fracture, and subclinical hypothyroid, as his endocrine complication-related thalassemia. Endocrine evaluation in these patients must be regularly, and it is recommended to start chelating therapy during the first years of life in patients who have iron overload. Treatment for endocrine abnormalities needs to continue to optimize the quality of life of the patient.

References
[1] De P, Mistry R, Wright C, Pancham S, Burbridge W, Gangopadhayay K, Pang T and Das G A review of endocrine disorders in thalassemia 2014 Open J. Endocr. Metab. Dis. 4 25–34
[2] Najafipour F 2008 Evaluation of endocrine disorders in patients with thalassemia major Int. J. Endocrinol. Metab. 2 104–13
[3] Safizadeh H, Farahmandinia Z, Nejad S S, Pourdamghan N and Araste M 2012 Quality of life in patients with thalassemia major and intermedia in kerman-iran (I.R.) Mediterr. J. Hematol. Infect. Dis. 4 1
[4] Joshi R and Phatarpekar A 2013 Endocrine abnormalities in children with Beta thalassaemia major Sri Lanka J. Child Health 42 81–6
[5] Rimoin D L, Borochowitz Z and Horton W A 1986 Short stature: Physiology and pathology West J. Med. 144 710–21
[6] Barnard M and Tzoulis P 2013 Diabetes and thalassemia Thalass. Reports 3 49–53
[7] Huang K E, Mittelman S D, Coates T D, Geffner M E and Wood J C 2015 A significant proportion of thalassemia major patients have adrenal insufficiency detectable on provocative testing J. Pediatr. Hematol. Oncol. 37 54–9
[8] Casale M, Citarella S, Filosa A, De Michele E, Palmieri F, Ragozzino A, Amendola G, Pugliese U, Tartaglione I, Rocca F D, et al. 2014 Endocrine function and bone disease during long-term chelation therapy with deferasirox in patients with beta-thalassemia major Am. J. Hematol. 89 1102–6