Endocrine complications

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Introduction

More than five decades ago, thalassemia major (TM) was fatal in the first decade of life. This poor prognosis changed since the survival rates started to increase progressively thanks to the implementation of continuous and significant improvement of diagnostic and therapeutic methods, consisting mainly of an intensive transfusion program combined with chelation therapy and imaging methods.[1-4]

Regular red blood cell (RBC) transfusions eliminate the complications of anemia, compensatory bone marrow expansion, bone changes and splenomegaly, restore the physiological growth throughout childhood and extend survival. The most serious disadvantage of life-saving transfusions is the inexorable accumulation of iron within tissues. Iron is physiologically stored intracellularly in the form of ferritin, a protein whose synthesis is induced upon the influx of iron. When the storage capacity of ferritin is exceeded, pathological quantities of metabolically active iron are released intracellularly in the form of hemosiderin and free iron within an expanded labile pool. This metabolically active iron catalyzes the formation of free radicals, which damage membrane lipids and other macromolecules, leading to cell death and eventually organ failure. Other factors contributing to the variability of cellular iron overload are: a) the cell surface transferrin receptors and the capacity of the cells to deploy defence mechanisms against inorganic iron; b) individual susceptibility to iron toxic effect; c) the development of organ(s) damage secondary to persisting severe iron overload in the years preceding iron chelation therapy; and d) liver disorders, chronic hypoxia and associated endocrine complications.[1-3]

Multi-transfused thalassemia major (TM) patients frequently develop severe endocrine complications mainly due to iron overload, anemia, and chronic liver disease, which require prompt diagnosis, treatment and close follow-up by specialists.[4]

Hypogonadism

The most common endocrine complication documented in TM patients is hypogonadotropic hypogonadism which increases with age and the associated comorbidities.[3] The incidence rate of hypogonadism, in both sexes, varies considerably between countries and much more between specialized centers, ranging from around 50% and may even approach 100%.[1-4]

Hormone replacement therapy with sex steroids aims to relieve symptoms and signs of androgen or estrogens deficiency, using convenient and effective formulations of testosterone or estrogen/progesterone. Despite the large number of TM patients for whom HRT is prescribed, little prospective data exist to aid clinicians in making evidence-based decisions for the optimal treatment regimens. Furthermore, no evidence-based guidelines for the management of these patients exist, and many recommendations are based on theoretical knowledge about physiology and endocrinology and extrapolated from the evidence of HRT in normal postmenopausal females. Further investigations are needed to understand whether HRT should be continued until the average age of menopause. No data are available to evaluate the impact of HRT therapy in TM patients on other risk factors associated with the disease such as liver dysfunction and impaired glucose tolerance. Long-term risks for the development of breast cancer, endometrial cancer, venous thromboembolism, and cardiovascular events are not known.[5-7]

In conclusion, long-term HRT is required for relief the symptoms of hypogonadism and to prevent long-term health sequel of testosterone or estrogen deficiency. The type of HRT, dosage, and route of administration are extremely complex in patients with thalassemia because of the chronicity of treatment and because many physical and psychological changes take place during the treatment period.Therefore, international research consortia should be established to allow investigation of these important questions, and to allow clinicians to make the best possible health care HRT treatment decisions.

Glucose abnormalities in patients with thalassemia major

Glucose tolerance abnormalities and diabetes mellitus (DM) are common complications in patients with TM. Disturbances of glucose homeostasis range from increased insulin resistance and mild glucose intolerance to overt diabetes mellitus. Patients with mild disorders are usually asymptomatic; impaired glucose tolerance (IGT) is common, occurring in up to 24.1%.[8-11] Unfortunately, this represents an additional potential risk to their cardiac function.[12]

Although iron overload induced DM shares certain characteristics with both type 1 diabetes and type 2 diabetes, it appears to be a separate entity with a unique pathophysiology. As in type 1 DM, insulin deficiency is a primary defect; however, it is usually relative rather than absolute. Similar to type 2 DM, the onset of the disease is usually gradual and insidious and insulin resistance is detected in some patients.

Pancreatic iron loading in these patients begins after the first decade of life and the incidence of complications increases with age. The rate of iron accumulation is directly related to the annual blood consumption, the delay in starting chelation and to low compliance and/or inadequate chelator doses. While glucose intolerance occurs at an early stage of adolescence, DM frequently occurs

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at later stages and is usually secondary to iron overload and subsequent chronic liver disease. Depending on the age composition of cohorts, up to 25% of patients with TM may have isolated impaired fasting plasma glucose (FPG), a condition in which the fasting blood glucose is elevated above what is considered normal, but is not high enough to be classified as DM. FPG has a good correlation with other glycemic indices such as fasting insulin, insulin resistance index and beta cell function index. Impaired FPG is considered a pre-diabetic state. However, it is not known how many patients with TM with impaired FPG progress over the years to diabetes. The prevalence of DM and impaired glucose tolerance (IGT) in adolescents and young adults with TM conventionally treated with DFO varies in different series (up to 10.5% and 24%, in different series. The considerable variation in the occurrence of glycemic abnormalities can be partially explained by the marked differences in the age composition of cohorts, their genetic background, transfusion regimens, degree of chelation and the screening method used.[13-16]

Growth hormone deficiency

The diagnosis of growth hormone deficiency (GHD) is generally straightforward in children as growth retardation is present. However, in adults the diagnosis of GHD is often challenging. GHD in adults is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance and cardiac capacity and altered lipid metabolism with increase in adiposity.[3]

In patients with chronic diseases, the clinical evaluation of GHD is difficult because signs and symptoms may be subtle and nonspecific, and universal provocative testing in all patients is difficult because the approach is cumbersome and expensive. Therefore, other markers are needed to identify adults who may have GHD and could potentially benefit from GH replacement therapy.[17]

Recent studies suggest that insulin-like growth factor-1 (IGF-1) may be used for primary screening, to avoid performing GH stimulation tests in the majority of healthy or diseased subjects, when appropriate normative sex and age-correlated ranges are available.[18] Therefore, the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) promoted a study to collect more information on IGF-1 values in young adult Italian thalassemia major (TM) patients. ICET-A concluded their survey with the following recommendations: A GH stimulation test should be indicated in presence of the following clinical and laboratory parameters: Short stature (Height standard deviation scores <−2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF-I level <−2 standard deviations. Very low IGF-1 levels, especially in those patients with childhood-onset GHD, in the presence of pituitary iron deposition and/or atrophy are highly suggestive of GHD.[19] In adult TM patients, with normal liver function, an IGF-I level <50th percentile should be taken in consideration as a cut-off level for the GH assessment.[20]

Hypothyroidism

The reported thyroid dysfunction seen in patients with TM includes primary hypothyroidism-caused abnormalities of the thyroid gland, subclinical hypothyroidism as well as secondary hypothyroidism (CH).[21-24] The frequency of hypothyroidism shows a discrepancy depending on the region, quality of management, and treatment protocols.[3,21-24] The reported frequency of thyroid dysfunctions ranges between 13% and 60% in different studies and occurs after 10 years of age regardless of difference in the rate of prevalence, largely as in the form of subclinical hypothyroidism.[21-24]

We have documented a prevalence of CH of 6% in patients with a chronological age below 21 years and 7.9% in those above 21 years.[25] Clinicians should be alert for the diagnosis of CH through accurate interpretation of thyroid function tests. We recommend L-thyroxine therapy if the level of FT4 is consistently low provided that the patient has normal cortisol levels.

Adrenal insufficiency

Accurate assessment of the hypothalamic-pituitary- adrenal (HPA) axis is essential for the management of patients with potential or suspected pituitary or hypothalamic disease that is frequent in patients with TM. [26-35] The diagnosis of AI is relatively simple when glucocorticoid secretion is profoundly depressed. [32,34] However, AI can present a difficult diagnostic challenge, especially when adrenal insufficiency is partial. This is a particularly important issue as acute crises may occur during stress periods in undiagnosed patients.[26,28,34]

Recently, several studies reported a significant prevalence of "biochemical" central adrenal insufficiency (CAI), ranging from 15% to 53.6%, [26-28] in children, adolescent and adults with TM. The pathophysiological basis of "biochemical" AI in TM has not yet been well-defined. Chronic transfusions induce iron overload in several organs, including adrenal and pituitary glands.[26,28,34] Therefore, it is possible that pituitary iron deposition might reduce ACTH secretion leading to CAI. Furthermore, the adrenal glands might also be directly affected by iron toxicity.

There are two methods to differentiate between primary and secondary AI. First is done by measuring plasma ACTH concentration in the basal fasting AM blood sample. If it is higher than normal, the patient has primary AI, whereas if it is low, the diagnosis of secondary or tertiary AI should be considered. The second method assesses the serum cortisol values in response to exogenous corticotropin (ACTH) stimulation or insulin tolerance test (ITT). The agent most commonly used is synthetic ACTH (1-24) (cosyntropin), which has the full biologic potency of native ACTH [34]. The text is useful for the diagnosis of AI but not for the differential diagnosis between peripheral and central forms. Therefore, a prolonged corticotropin administration may become helpful in the differential diagnosis. Unfortunately, this diagnostic approach has not been validated in patients with TM.[28,34]

The lack of treatment guidelines and published research often leave hematologists and internists with hesitant to approach TM patients presenting uncommon endocrine complications. Therefore, as a third step, we thought worth to prepare clinical practice recommendations for all those taking care of TM patients on current criteria for the assessment of CAI . The recommendations provide helpful information on laboratory parameters and their interpretation, as well as adrenal hormone replacement dosages and management strategies. The guidelines emphasize that clinicians need to suspect AI earlier in TM patients with risk factors, such as advanced age, severe iron overload and/or poor compliance to therapy, and with multiple endocrine complications.

Hypoparathyroidism

In the general population, hypoparathyroidism (HPT) can be transient or permanent, inherited or acquired, or caused by inabili-

ty of parathyroid gland to synthesize or secrete PTH. This may be due to abnormal development of the parathyroid gland, destruction of parathyroid tissue, or peripheral resistance to PTH.

It is a rare disease, with the leading clinical symptoms of hypocalcemia which is associated to high serum phosphorus levels, and absent or inappropriately low levels of parathyroid hormone (PTH). [36] The low extracellular ionized (Ca^{2+}) may have a profound impact on the function of a large number of tissues and organ systems including the brain, muscles, kidneys and heart.[37,38]

In adults, the most common cause of HPT is parathyroid gland injury or inadvertent removal during thyroid surgery whereas in patients with thalassemias it is mainly attributed to iron overload, secondary to multiple blood transfusions and suboptimal chelation therapy.[36, 39-41]

The prevalence of overt HPT reported in 1661 TM patients, by the Italian Working Group on Endocrine Complications in Non Endocrine Diseases, was 3.6% [39], whereas a subclinical HPT, utilizing the nocturnal measurements of serum minerals, was observed in almost 100% of 13 TM patients, with normal morning serum calcium levels.[42]

HPT requires lifelong therapy with vitamin D or metabolites. Both under- and overtreatment can lead to unintended outcomes that can be irreversible. In undertreated or late treated patients with HPT, where there is a combination of chronic hypocalcemia and hyperphosphatemia, ectopic calcifications in organs may occur. [43,44] In over treated patient the risk of kidney stones and nephrocalcinosis is markedly increased. [45]

Conclusions

In conclusion, iron overload remains a critical problem, even in countries where chelation therapy is widely available and adequately implemented recently. An early recognition and prevention of the endocrine complications, by early and regular chelation therapy, is mandatory for the improvement of the quality of life of these patients.

References

1. De Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Soliman NA, Elalaily R, Kattamis C. Endocrine profile of ß-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab. 2016;20:451-459.
2. De Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Kattamis C, Soliman NA, Elalaily R. Clinical and Biochemical Data of Adult Thalassemia Major patients (TM) with Multipzle Endocrine Complications (MEC) *versus* TM Patients with Normal Endocrine Functions: A long-term Retrospective Study (40 years) in a Tertiary Care Center in Italy. Mediterr J Hematol Infect Dis. 2016 Apr 12;8(1):e2016022.
3. De Sanctis V, Soliman AT, Candini G, Elsedfy H. The recommendation of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine for the assessment of growth hormone secretion in thalassemia. Indian J Endocrinol Metab. 2015;19:306-307.
4. Tiosano D, Hochberg Z.Endocrine complications of thalassemia. J Endocrinol Invest. 2001;24:716-723.
5. De Sanctis V, Daar S, Soliman AT, Elsedfy H, Khater D, Di Maio S. Does Testosterone Replacement Therapy Promote an Augmented Risk of Thrombotic Events in Thalassemia Major Male Patients with Hypogonadism? Indian J Endocrinol Metab. 2017;21:636-637.
6. De Sanctis V, Soliman AT, Elsedfy H, Albu A, Al Jaouni S, Anastasi S, Bisconte MG, Canatan D, Christou S, Daar S, Di Maio S, El Kholy M, Khater D, Elshinawy M, Kilinc Y, Mattei R, Mosli HH, Quota A, Roberti MG, Sobti P, Yaarubi SA, Canpisi S, Kattamis C. Review and Recommendations on Management of Adult Female Thalassemia Patients with Hypogonadism based on Literature Review and Experience of ICET-A Network Specialists.Mediterr J Hematol Infect Dis. 2017 Jan 1;9(1):e2017001.
7. De Sanctis V, Soliman AT, Elsedfy H, Di Maio S. Current practice in treating adult female thalassemia major patients with hypogonadism: An International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine survey from Italy Indian J Endocrinol Metab. 2016;20:880-881.
8. De Sanctis V, Soliman A, Yassin M. Iron overload and glucose metabolism in subjects with ß-thalassaemia major: an overview. Curr Diabetes Rev 2013;9:332-341.
9. Tzoulis P. Review of endocrine complications in adult patients with ß-thalassaemia major. Thalassemia Reports 2014; 4:51-56.
10. Hafez M, Youssry I, El-Hamed FA, Ibrahim A. Abnormal glucose tolerance in beta thalassemia: assessment of risk factors. Hemoglobin 2009;33:101-108.
11. De Sanctis V, Soliman AT, Elsedfy H, Pepe A, Kattamis C, El Kholy M, Yassin M. Diabetes and Glucose Metabolism in Thalassemia Major: An Update.Expert Rev Hematol. 2016;9:401-408.
12. Pepe A, Meloni A, Rossi G, Caruso V, Cuccia L, Spasiano A, Gerardi C, Zuccarelli A, D'Ascola DG, Grimaldi S, Santodirocco M, Campisi S, Lai ME, Piraino B, Chiodi E, Ascioti C, Gulino L, Positano V, Lombardi M, Gamberini MR. Cardiac complications and diabetes in thalassaemia major: a large historical multicentre study. Br J Haematol 2013;163:520-527.
13. Papakonstantinou O, Ladis V, Kostaridou S, Maris T, Berdousi H, Kattamis C, Gourtsoyiannis N. The pancreas in beta thalassemia major: MR imaging features and correlation with iron stores and glucose disturbances. Eur Radiol 2007;17:1535-1543.
14. Au WY, Lam WM, Chu WC, Tam S, Wong WK, Pennell DJ, Lie AK, Liang R. A magnetic resonance imaging study of iron overload in hemopoietic stem cell transplant recipients with increased ferritin levels. Transplant Proc 2007;39:3369-3374.
15. Soliman AT, Yasin M, El-Awwa A, De Sanctis V. Detection of glycemic abnormalities in adolescents with beta thalassemia using continuous glucose monitoring and oral glucose tolerance in adolescents and young adults with ß-thalassemia major: Pilot study. Indian J Endocrinol Metab 2013;17:490-495.
16. Noetzli LJ, Mittelman SD, Watanabe RM, Coates TD, Wood JC. Pancreatic iron and glucose dysregulation in thalassemia major. Am J Hematol 2012;87:155-160.
17. Soliman AT, De Sanctis V, Elalaily R, Yassin M. Insulin-like growth factor- I and factors affecting it in thalassemia major. Indian J Endocrinol Metab. 2015;19:245-51.
18. De Sanctis V, Soliman AT, Candini G, Yassin M, Raiola G, Galati MC, Elalaily R, Elsedfy H, Skordis N, Garofalo P, Anastasi S, Campisi S, Karimi M, Kattamis C, Canatan D, Kilinc Y, Sobti P, Fiscina B, El Kholy M. Insulin-like Growth Factor-1 (IGF-1): Demographic, Clinical and Laboratory Data in 120 Consecutive Adult Patients with Thalassaemia Major. Mediterr J Hematol Infect Dis. 2014 Nov 1;6(1):e2014074.
19. Soliman A, De Sanctis V, Yassin M, Abdelrahman MO. Growth hormone - insulin-like growth factor-I axis and bone mineral density in adults with thalassemia major. Indian J Endocrinol Metab. 2014;18:32-38.
20. Soliman A, De Sanctis V, Elsedfy H, Yassin M, Skordis N, Karimi M, Sobti P, Raiola G, El Kholy M. Growth hormone defi-

ciency in adults with thalassemia: an overview and the I-CET recommendations. Georgian Med News. 2013;(222):79-88.
21. Delvecchio M, Cavallo L. Growth and endocrine function in thalassemia major in childhood and adolescence.J Endocrinol Invest. 2010;33:61-68.
22. Sharma R, Seth A, Chandra J, Gohain S, Kapoor S, Singh P, Pemde H. Endocrinopathies in adolescents with thalassaemia major receiving oral iron chelation therapy. Paediatr Int Child Health. 2016;36:22-27.
23. Soliman AT, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, Yassin M, De Sanctis V. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years.Indian J Endocrinol Metab. 2013;17:1090-1095.
24. Abdel-Razek AR, Abdel-Salam A, El-Sonbaty MM, Youness ER. Study of thyroid function in Egyptian children with β-thalassemia major and β-thalassemia intermedia. J Egypt Public Health Assoc. 2013;88:148-152.
25. De Sanctis V, Soliman A, Candini G, Campisi S, Anastasi S, Iassin M. High prevalence of central hypothyroidism in adult patients with β-thalassemia major. Georgian Med News. 2013;(222):88-94.
26. Poomthavorn P, Isaradisaikul B, Chuansumrit A, Khlairit P, Sriphrapradang A, Mahachoklertwattana P. High prevalence of "biochemical" adrenal insufficiency in thalassemics: is it a matter of different testings or decreased cortisol binding globulin? J Clin Endocrinol Metab. 2010;95:4609-46015.
27. Scacchi M, Danesi L, Cattaneo A, Valassi E, Pecori Giraldi F, Radaelli P, Ambrogio A, D'Angelo E, Mirra N, Zanaboni L, Cappellini MD, Cavagnini F. The pituitary-adrenal axis in adult thalassaemic patients. Eur J Endocrinol. 2010;162:43-48.
28. Soliman AT, Yassin M, Majuid NM, Sabt A, Abdulrahman MO, De Sanctis V. Cortisol response to low dose *versus* standard dose (back-to-back) adrenocorticotrophic stimulation tests in children and young adults with thalassemia major. Indian J Endocrinol Metab. 2013;17:1046-1052.
29. Elsedfy HH, El Kholy M, Hamza RT, Hamed A, Elalfy M. Adrenal function in thalassemia major adolescents. Pediatr Endocrinol Rev. 2011;8 Suppl 2:295-299.
30. De Sanctis V, Skordis N, Galati MC, Raiola G, Giovannini M, Candini G, Kaffe K, Savvides I, Christou S. Growth hormone and adrenal response to intramuscular glucagon test and its relationship to IGF-1 production and left ventricular ejection fraction in adult B-thalassemia major patients. Pediatr Endocrinol Rev. 2011;8 Suppl 2:290-294.
31. Jaruratanasirikul S, Tanchotikul S, Wongcharnchailert M, Laosombat V, Sangsupavanich P, Leetanaporn K. A low dose adrenocorticotropin test (1 microg ACTH) for the evaluation of adrenal function in children with beta-thalassemia receiving hypertransfusion with suboptimal iron-chelating therapy. J Pediatr Endocrinol Metab. 2007;20:1183-1188.
32. Baldini M, Mancarella M, Cassinerio E, Marcon A, Ambrogio AG, Motta I. Adrenal insufficiency: An emerging challenge in thalassemia? Am J Hematol. 2017;92:E119-E121.
33. Guzelbey T, Gurses B, Ozturk E, Ozveren O, Sarsilmaz A, Karasu E. Evaluation of Iron Deposition in the Adrenal Glands of β Thalassemia Major Patients Using 3-Tesla MRI. Iran J Radiol. 2016 May 10;13(3):e36375. eCollection 2016 Jul.
34. De Sanctis V, Soliman AT, Elsedfy H, Albu A, Al Jaouni S, Yaarubi SA, Anastasi S, Canatan D, Di Maio M, Di Maio S, El Kholy M, Karimi M, Khater D, Kilinc Y, Lum SH, Skordis N, Sobti P, Stoeva I, Tzoulis P, Wali Y, Kattamis C. The ICET-A Survey on Current Criteria Used by Clinicians for the Assessment of Central Adrenal Insufficiency in Thalassemia: Analysis of Results and Recommendations.Mediterr J Hematol Infect Dis. 2016 Jul 1;8(1):e2016034. doi: 10.4084/MJHID.2016.034
35. Huang KE, Mittelman SD, Coates TD, Geffner ME, Wood JC. A significant proportion of thalassemia major patients have adrenal insufficiency detectable on provocative testing.J Pediatr Hematol Oncol. 2015;37:54-59.
36. Bilezikian JP, Khan A, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. J Clin Endocrinol Metab. 2009;94:335-339.
37. De Sanctis V, Borsari G, Brachi S, Gubellini E, Gamberini MR, Carandina G. A rare cause of heart failure in iron-overload thalassaemic patients-primary hypoparathyroidism. Georgian Med News. 2008; (156):111-113.
38. De Sanctis V, Govoni MR, Sprocati M, Marsella M, Conti E. Cardiomyopathy and pericardial effusion in a 7 year-old boy with beta-thalassaemia major, severe primary hypothyroidism and hypoparathyroidism due to iron overload. Pediatr Endocrinol Rev. 2008; 6 (Suppl 1):181-184.
39. Italian Working Group on endocrine complications in non-endocrine diseases. Multicentre study on prevalence of endocrine complications in thalassaemia major. Clin Endocrinol 1994; 42:581-586.
40. De Sanctis V, Roos M, Gasser T, Fortini M, Raiola G, Galati MC. Italian Working Group on Endocrine Complications in Non- Endocrine Diseases. Impact of long-term iron chelation therapy on growth and endocrine functions in thalassaemia. J Pediatr Endocrinol Metab. 2006;19:471-480.
41. De Sanctis V, Vullo C, Bagni B, Chiccoli L. Hypoparathyroidism in beta-thalassemia major. Clinical and laboratory observations in 24 patients. Acta Haematol. 1992; 88:105-108.
42. Even L, Bader T, Hochberg Z. Nocturnal calcium, phosphorus and parathyroid hormone in the diagnosis of concealed and subclinical hypoparathyroidism Eur J Endocrinol. 2007;156: 113-116.
43. Karimi M, Rasekhi AR, Rasekh M, Nabavizadeh SA, Assadsangabi R, Amirhakimi GH. Hypoparathyroidism and intracerebral calcification in patients with beta-thalassemia major. Eur J Radiol. 2009;70:481-484.
44. De Sanctis V, Giovannini M, Ciccone S, Karimi M. Generalized tonic-clonic seizures in a thalassemic patient with hypoparathyroidism and brain calcinosis. Pediatr Endocrinol Rev. 2011;8 (Suppl.2):334-336.
45. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med. 2008;359:391-403.