Review Article

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Thalassemia intermedia; folic acid and vitamin B12 supplementation. What we know and what is needed?

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Abstract

This study presented a mini review on folic acid deficiency and recommendations for its supplementation in thalassemia intermedia (TI). TI is a clinical condition which lies between thalassemia major and thalassemia minor. Although TI patients may not need regular blood transfusion, precise diagnosis and management are critical for the prevention of clinical complications and quality of life improvement. Blood transfusion, iron chelation, and modulation of HbF are the main management strategies used for TI patients. High red blood cells turnover and nutritional deficiency in thalassemic patients lead to some vitamins and minerals deficiency as well as folic acid deficiency. Folic acid deficiency is more prevalent in TI patients compared with thalassemia major because of fewer blood transfusion which leads to higher red cells turnover. Therefore, Daily folic acid supplementation (1 mg/day) is recommended in these patients but the annual evaluation of vitamin B12 deficiency is also recommended in these patients for the prevention of its deficiency and complications.

Key words: Complication, Deficiency, Folic acid, Thalassemia intermedia

Introduction

Beta thalassemia is a common genetic disorder which results from beta globin chain synthesis defect. Based on clinical complications, beta thalassemia is divided into three main subgroups; thalassemia minor, thalassemia intermedia (TI), and thalassemia major (TM). TM is a severe clinical form of disease which is presents with severe hemolytic anemia and ineffective erythropoiesis. These patients need lifelong blood transfusion which leads to iron overload. As such, regular blood transfusion as well as appropriate iron chelation therapy is the main treatment strategy in this group of patients (1, 2). Dietary requirements such as folic acid in thalassemia intermedia are challenging issues so that this mini review is an attempt to address this issue in TI patients.

General presentation on thalassemia intermedia

TI is a clinical condition which is lies between TM and thalassemia minor (3). Thalassemia intermedia was first described in 1955. Regarding its genetic diversities, it has wide clinical spectrum manifestations from mild to severe hemolytic anemia. Unlike TM, its clinical presentations usually manifest after ages 2-6 years old (4). In TI patients, the hemoglobin level is usually maintained between 7-11 g/dl and these patients are transfusion independent or rarely require blood transfusions. Thalassemia intermedia presents with pallor, jaundice, anemia and splenomegaly. They might have skeletal deformities or growth retardation during puberty or later if transfusions, occasional or persistent, and

appropriate management are not conducted timely (3, 5, and 6). Diagnosis of B-TI is mainly based on clinical decision. Thalassemia intermedia and TM have some clinical and lab data overlap, so that definite differential diagnosis between them is essential for precise management. In fact, the treatment strategies are different and precise diagnosis of TI from TM is crucial for the prevention of their later complications. The first step in the management of TM is regular blood transfusion and optimal iron chelation but TI belongs to non-transfusion dependent thalassemia (NTDT) group that does not require regular transfusion as the first treatment approach. Chronic hemolytic anemia, ineffective erythropoiesis, and iron overload are three main pathophysiologic features involved in TI patients. Erythroid marrow hyperplasia, skeletal deformities, and extramedullary hematopoiesis (EMH) are major clinical consequences of poor controlled TI due to ineffective erythropoiesis. Hemolytic anemia is commonly associated with splenomegaly, jaundice, and cholelithiasis induced by hyperbilirubinemia. Hypercoagulable state and pulmonary hypertension (PHT) are two important complications render life threatening consequences in patients with TI. Cardiac dysfunction and endocrine complications including diabetic mellitus, hypogonadism, infertility, and hypoparathyroidism are less common in TI compared to TM which arises from iron overload and its organ depositions. Leg ulcer is also a major complication in TI patients, occurring in almost one third of patients with poorly controlled disease. Cachexia and hyperuricemia due to the hypercatabolism of erythroid hyperplastic tissue are other metabolic complications which are more prevalent in TI than TM patients. (3, 7-12). Lifelong management of TI is essential for the prevention of clinical complications and quality of life health improvement. The main management strategies for TI are transfusion therapy, iron chelation, splenectomy, modulation of gamma-globulin chain production, stem cell transplantation, and recently experimental clinical trial on Minihepcidin Peptide or similar drugs (ACE-536, ACE-011) which enhance differentiation or maturation of developing red blood cells in the bone marrow are also new hopeful treatment option in improving anemia and Iron overload in TI patients (3, 13-16). Although transfusion is not regularly needed in TI patients, it is an essential treatment option in some situations (17, 18). Occasionally, blood transfusion in addition to increased intestinal iron absorption due to chronic hemolytic anemia leads to iron overload in some patients, which requires iron chelation therapy for the prevention of iron deposition in critical organs (19). Enhanced HbF production by hydroxyurea is also well-studied in decreasing clinical complications in TI patients (20-21). Splenectomy is also indicated in some situations including hypersplenism leading to worsening anemia, leucopenia or thrombocytopenia (3, 22).

Nutrition in TI

The nutrition is important in supportive care of thalassemic patients. Furthermore, the growth failure observed in these patients may be partially related to ineffective nutrition. Thalassemic patients must encourage avoiding high iron containing foods and vegetables for prevention of higher iron absorption and accumulation in the body. It is also recommended that these patients encourage drinking tea and coffee for decreasing foods iron absorption from the diets. Ineffective erythropoiesis in thalassemia patients leads to increase red cells turnover which results to increased nutrients and energy to maintain normal erythropoiesis. Also it is showed that thalassemia patients are in risk of deficiency of vitamins and minerals including vitamins A, B groups, C, D and E in addition to minerals like zinc and

calcium. So, other supportive management strategies including prescription of vitamin C, vitamin D and calcium for prevention of osteoporosis, Growth hormone for prevention of growth retardation and other mineral supplementations are also recommended in TI patients (3, 17). From these nutritional factors folic acid deficiency appears to be more common in these individuals (25, 26).

Folic acid in general

Folic acid is a group of water-soluble vitamin B which is the oxidized and the most stable form of folate (27). Folic acid is the synthetic oxidised monoglutamyl form of folate that is widely used in vitamin supplements and in the fortification of foods. Folic acid is a co-enzyme for many cellular pathways and biological reactions including synthesis of purines, pyrimidines and nucleoproteins (involved in DNA and RNA synthesis), cell replication, intracellular signaling, and gene programming through methylation (28, 29). The recommended daily allowance of folic acid is 65–300 μg/d for infants and children and 400 μg/d for adults. This need is increased during pregnancy and breast feeding in women.

Inadequate dietary intake, digestive disorders (such as celiac or crohn's diseases) which prevent folic acid from being well absorbed in the gastrointestinal system, over the needs of the body, like in pregnancy and during breast feeding are some causes of folic acid deficiency.

Folic acid is also important in red blood cells (RBCs) production and the main known RBC disorder in folic acid deficiency is megaloblastic anemia. Hemolytic anemia like sickle cell disease and thalassemia are well documented as causes of folic acid deficiency (30, 31). Increased erythropoiesis and high cell turnover lead to increased folic acid utilization which causes folic acid deficiency during these disorders.

Present literature data on folate deficiency in thalassemia

Although the importance of folic acid supplementation in sickle cell disease is well documented in literatures (30, 31, and 33), its importance in thalassemia major and intermedia has not been well evaluated. In a study by Mojtahedzadeh, et al in Iran, 28 TM patients were evaluated for folic acid supplementation and it was found that 29-68% of patients were folic acid deficient (34). It is clear that folic acid supplementation is much more important in non-transfused B-TI than TM due to more severe hemolysis. In fact, in TI patients who have not received regular blood transfusion, the rate of red cell turnover may be higher compared to TM. Therefore, folic acid supplementation is more crucial in this group of patients due to an increased demand for folic acid from ineffective erythropoiesis and also, low dietary intake. In addition, there is a particular concern in pregnant TI patients because of high risk of neural tube defects, such as spina bifida, in the growing fetus.

Final recommendations

Daily supplementation with 1 to 5 mg folic acid together with high folic acid diet such as fruits and vegetables are recommended for thalassemic patients, especially in TI. One of the controversial effects of folic acid supplementation which is documented in sickle cell disease is its potential to mask findings of vitamin B12 deficiency which could be associated with neuropsychiatric dysfunction (35-37). This situation may be seen in thalassemia patients on daily supplementation of folic acid. As such, at least an annual evaluation of vitamin B12 level in thalassemia patients who are on daily supplementation of folic acid is recommended for prevention of vitamin B12 deficiency and its complications. So, vitamin B12 supplementation is also recommended in thalassemic subjects with vitamin B12 deficiency.

In conclusion, folic acid supplementation can be much more effective in TI than TM. On the other hand, TM patients who are on regular blood transfusion and maintain hemoglobin levels of 12 gr/dl are not required to take folic acid supplementation but in non-transfused β-TI with lifelong persistent hemolysis and anemia, folic acid supplementation is mandatory to decrease severity of anemia and improve clinical status.

Conflict of interest

The authors declare that there is no conflict of interest.

Refernces

1. Li CK. New trend in the epidemiology of thalassaemia. Best Pract Res Clin Obstet Gynaecol. 2016; 26. Pii: S1521-6934(16)30121-3.
2. Rund D, Rachmilewitz E. β-Thalassemia. N Engl J Med. 2005; 353: 1135-46.
3. Karimi M, Cohan N, De Sanctis V, Mallat NS, Taher A. Guidelines for diagnosis and management of Beta-thalassemia intermedia. Pediatr Hematol Oncol. 2014; 31(7): 583-96.
4. Haddad A, Tyan P, Radwan A, Mallat N, Taher A. β-Thalassemia Intermedia: A Bird's-Eye View. Turk J Haematol. 2014; 31(1): 5-16.
5. El Rassi F, Cappellini MD, Inati A, Taher A. Beta-thalassemia Intermedia: An Overview. Pediatric Annals. 2008; 37(5): 322-328.
6. Taher A, Isma'eel H, Cappellini MD. Thalassemia intermedia: Revisited. Blood Cells Mol Dis. 2006; 37: 12-20.
7. Rachid Haidar, Hani Mhaidli, Ali T. Taher. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. Eur Spine J. 2010; 19(6): 871–878.
8. Karimi M, Cohan N, Bagheri MH, Lotfi M, Omidvari SH, Geramizadeh B. A lump on the head. Lancet. 2008; 372: 1436.
9. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Splenectomy and thrombosis: the case of thalassemia intermedia. J Thromb Haemost. 2010;8(10):2152-8.
10. Karimi M, Bagheri H, Rastgu F, Rachmilewitz E. Magnetic resonance imaging to determine the incidence of brain ischaemia in patients with β-thalassaemia intermedia. Thromb Haemost. 2010; 103: 989–993.
11. Amoozgar H, Farhani N, Karimi M. Risk factors for pulmonary hypertension in patients with thalassemia intermedia. Eur J Haematol. 2011; 85: 549-551.
12. Matta BN, Abbas O, Maakaron JE, Koussa S, Daderian RH, Taher AT. Leg ulcers in patients with β-thalassaemia intermedia: a single centre's experience. J Eur Acad Dermatol Venereol. 2014; 28(9): 1245-50.
13. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. Blood. 2010; 115(10): 1886-1892.
14. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept (ACE-536) Reduces Disease Burden, Including Anemia, Iron Overload, and Leg Ulcers, in Adults with Beta-Thalassemia: Results from a Phase 2 Study. Blood. 2015; 126:752.
15. Carrancio S1, Markovics J, Wong P, Leisten J, Castiglioni P, Groza MC, et al. An activin receptor IIA ligand trap promotes erythropoiesis resulting in a rapid induction of red blood cells and haemoglobin. Br J Haematol. 2014; 165(6):870-82.
16. Suragani RN1, Cadena SM2, Cawley SM2, Sako D1, Mitchell D1, Li R1, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014; 20(4):408-14.
17. Taher A, Musallam K, Cappellini MD, Weatherall DJ. Optimal management of β

thalassaemia intermedia. Br J Haematol. 2011; 152: 512–523.
18. El Rassi F, Cappellini MD, Inati A, Taher A. Beta-thalassemia Intermedia: An Overview. Pediatric Annals. 2008; 37(5): 322-328.
19. Taher AT, Porter JB, Viprakasit V, Kattamis A, Chuncharunee S, Sutcharitchan P, et al. Deferasirox effectively reduces iron overload in non-transfusion-dependent thalassemia (NTDT) patients: 1-year extension results from the THALASSA study. Ann Hematol. 2013; 92(11): 1485-93.
20. Karimi M1, Darzi H, Yavarian M. Hematologic and clinical responses of thalassemia intermedia patients to hydroxyurea during 6 years of therapy in Iran. J Pediatr Hematol Oncol. 2005 Jul; 27(7):380-5.
21. Karimi M, Mohammadi F, Behmanesh F, Samani S M, Borzouee M, Amoozgar H, Haghpanah S. Effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia. Eur J Haematol. 2010; 84: 52–58.
22. Karimi M, Haghpanah S, Farhadi A, Yavarian M. Genotype-phenotype relationship of patients with β-thalassemia taking hydroxyurea: a 13-year experience in Iran. Int J Hematol. 2012; 95(1): 51-6.
23. Dixit A, Chatterjee T C, Mishra P, Choudhry D R, Mahapatra M, Tyagi S, et al. Hydroxyurea in thalassemia intermedia–a promising therapy. Ann Hematol. 2005; 84: 441–446.
24. Taher AT, Musallam KM, Karimi M, Cappellini MD. Contemporary approaches to treatment of beta-thalassemia intermedia. Blood Rev. 2012; 26 (Suppl1):S24-7.
25. Borgna-Pignatti C. Modern treatment of thalassemia intermedia. GJH. 2007; 138:291-304.
26. Claster S, Wood JC, Noetzil L, et al. Nutritional deficiencies in iron overloaded patients with hemoglobinopathies. Am J Hematol. 2009; 84:344-8.
27. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Molecular Genetics and Metabolism. 2000; 71(1-2): 121–138.
28. Mantovani E, Filippini F, Bortolus R, Franchi M. Folic acid supplementation and preterm birth: results from observational studies. Biomed Res Int. 2014; 2014: 481914.
29. Patel KR, Sobczyńska-Malefora A. The adverse effects of an excessive folic acid intake. Eur J Clin Nutr. 2016; 12. Doi: 10.1038/ejcn.2016.194. [Epub ahead of print]
30. Ndefo UA, Maxwell AE, Nguyen H, Chiobi TL. Pharmacological management of sickle cell disease. P T. 2008; 33(4): 238-43.
31. Borgna-Pignatti C. Modern treatment of thalassaemia intermedia. Br J Haematol. 2007; 138(3): 291-304.
32. van der Dijs FP, Fokkema MR, Dijck-Brouwer DA, Niessink B, van der Wal TI, Schnog JJ, et al. Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease. Am J Hematol. 2002; 69(4): 239-46.
33. Al-Yassin A, Osei A, Rees D. Folic acid supplementation in children with sickle cell disease. Arch Dis Child. 2012; 97: A91-A92.
34. Mojtahedzadeh F, Kosaryan M, Mahdavi MR, Akbari J. The effect of folic acid supplementation in beta-thalassemia major: a randomized placebo-controlled clinical trial. Arch Iranian Med. 2006; 9 (3): 266-268.
35. Dhar M1, Bellevue R, Carmel R. Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anemia treated with folate supplementation. N Engl J Med. 2003 May 29; 348(22):2204-7.
36. Hoffer LJ. Folate supplementation in sickle cell anemia. N Engl J Med. 2003 21; 349(8): 813.
37. Ballas SK, Baxter JK, Riddick G. Folate supplementation and twinning in

patients with sickle cell disease. Am J Hematol. 2006; 81(4): 296-7.