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Hypocalcemia in thalassemia major patients requires an extra-careful approach

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Abstract

Thalassemia is a hematological disorder caused by a gene mutation that leads to defective synthesis of hemoglobin complex. One of the complications of thalassemia is hypocalcemia which is presented with paresthesia, muscle spasm, low-serum calcium, and intracranial calcification. Hypocalcemia can affect thalassemic patients via various mechanisms. Blood transfusion-related and transfusion-independent iron overload, drug side effects, vitamin D3 deficiency, and genetic disorders and polymorphisms are among the etiologies of hypocalcemia in major thalassemia. A careful approach to the differential etiology of this phenomenon is crucial for a resultful treatment.

Keywords: Hematological disorders, Thalassemia treatment, Resistant hypocalcemia, Vitamin D, Laboratory tests

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To Editor,

Thalassemia is a genetic disorder caused by multiple mutations on chromosome 11 that disrupt the synthesis of the globin chains. This inherited disorder is characterized by impaired hemoglobin synthesis and decreased production or absence of one or more globin chains. Therefore, patients with thalassemia develop anemia ranging from mild to severe and even to the point of blood transfusion-dependency. Hypothetically thalassemic patients are at risk of hypocalcemia in various ways.

Hypocalcemia is a less-studied yet frequently reported complication in thalassemia major. The prevalence of hypocalcemia is reported up to 49% in thalassemic patients (1). Gender, frequency of blood transfusion, drug regimen, vitamin D deficiency, and genetic polymorphisms are among the risk factors of presenting hypocalcemia (2). In thalassemic patients, there's a combination of these factors. The treatment of thalassemia includes blood transfusion to maintain the hemoglobin level to an optimal level, sufficient to curb the extramedullary and inefficient hematopoiesis and low enough to minimize the risk of iron overload. Nevertheless, frequent blood transfusion is still the main cause of hemochromatosis in thalassemic patients (3). The median rate of iron excretion in healthy adults are 1.18 mg/d for men, 1.58 mg/d for menstruating women, and 0.99 mg/d for post-menopausal women (4). Whereas one unit of blood transfusion contains 200-250

mg of iron (3). Patients with thalassemia may develop iron overload not only via blood transfusion but also as a result of increased intestinal absorption. Transfusion independent iron overload is mediated by an increased level of erythropoietin and decreased hepcidin that leads to overexpression of ferroportin in intestinal epithelium and thus, more duodenal iron absorption (5). The excessive iron gradually deposits in various tissues and organs (siderosis), such as parathyroid, thyroid, and pituitary glands which take part in calcium metabolism (6). Hypoparathyroidism secondary to iron overload in patients with thalassemia was first diagnosed by Gabriele in 1971. However, all patients with thalassemia do not develop hypoparathyroidism. Case reports suggest that hypoparathyroidism in thalassemic patients is a less prevalent condition compared to other endocrine abnormalities, but ironically hypocalcemia have appeared to be three-fold more common in the same studies (7). Hence, all the other possible mechanisms should be considered distinctly in a thalassemic patient. Thalassemia major patients receive a variety of drugs based on the outcome of the disease. Hypocalcemia is the side effect of some of these drugs. To this date, deferoxamine and deferasirox by renal damage, amphotericin B by hypomagnesemia, and deferiprone by an unknown cause, are among the drug that are reported to lead to hypocalcemia in thalassemic patients (7-9). Apart from

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■ Implication for health policy/practice/research/medical education

Thalassemia can lead to hypocalcemia through various mechanisms. Healthcare policies should prioritize screening, while healthcare professionals need to conduct a careful differential evaluation to treat the condition effectively. Likewise, medical education and research can focus on prevention, diagnosis, and treatment strategies.

physiological and ethno-racial reasons and drugs side effect, vitamin D deficiency in thalassemia major patients can be an outcome of cardiac iron loading (5). This phenomenon is another etiology of hypocalcemia. By ruling aforementioned risk factors out, genetic disorders and polymorphisms remain as the last differential-diagnosis. Some people are intrinsically more prone to hypocalcemia. This is mostly due to altered activity or lower expression of calcium, magnesium, or phosphorus metabolism components, vitamin D regulators, and parathyroid indexes (10). Genetic factors might result a treatment-resistant type of hypocalcemia.

Diagnosis of symptomatic hypocalcemia is usually straightforward. The patients present paresthesia, tetany, muscle spasms, and circumoral insensibility. Electrocardiography shows results similar to myocardial infarction. Corrected calcium level of serum falls below 2.12 mmol/L. And in some patients, it is presented with widespread intracranial calcification which is detectable by brain CT scan (11). However, prevention and managing hypocalcemia in thalassemia major patients can be challenging. This is because these patients are exposed to more risk factors than healthy individuals that can stymie the treatment. Hence, a thorough approach to differential etiology of the discussed occurrence is crucial.

Authors' contribution

Conceptualization: MB, BK, EA.

Validation: BK.

Investigation: MB, EA.

Supervision: MD, NNGF.

Project administration: EA.

Writing—original draft: PG.

Writing—review and editing: MB, EA.

Conflicts of interest

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