

Short Report

Thalassemia Intermedia Caused by a Combination of a Globin Gene Triplication with Heterozygosity for β^0 Thalassemia: A Case ReportKonstantinos Manganas ¹, Sophia Delicou ^{1,*}, Aikaterini Xydaki ¹, Zoi Pallantza ²

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Received: May 19, 2019**Accepted:** September 9, 2019**Published:** September 17, 2019**Abstract**

Thalassemia syndromes are a group of hemoglobinopathies characterized by gene defects that disrupt normal hemoglobin production. Thalassemia intermedia (TI) is referred to as a group of disorders with a less severe form of the disease compared to thalassemia major. We present a case of a 60-year-old woman who was referred to a hematologist for chronic anemia and splenomegaly.

KeywordsThalassemia; α chain; anemia**1. Introduction**

Earlier studies focused on patients with thalassemia syndromes have identified numerous causative mutations in the globin genes, the upstream or downstream untranslated regions and



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the regulatory regions that control the expression of the α - and β -globin genes and synthesis of the tetrameric hemoglobin molecule [1].

β -thalassemia results from the reduced (β^+ -thalassemia intermedia) or no (β^0 -thalassemia major) production of structurally normal β -globin chains, as a consequent to the point mutations concerning the β -globin genes. In β -thalassemia, the production of normal α globin chains from the unaffected α globin genes continues normally, which results in the accumulation of excess unbound α globin chains within the erythroid precursors. Since free α globin chains are not able to form stable tetramers, they precipitate in the red cell precursors, forming inclusion bodies [2]. α -thalassemia has been reported to be resulting from the deletion of entire α genes, rather than point mutations in the genes. The disease is classified broadly into α^0 -thalassemias, in which no α -chains are produced, and α^+ -thalassemias, in which there is reduced synthesis of α -chains. The normal genotype is represented as aa/aa , while the homozygous and heterozygous states of the deletion forms are represented as $-a/-a$ and $-a/aa$, respectively. Similarly, the non-deletion forms of α^+ -thalassemia are represented as aT^a/aT^a and aT^a/aa , respectively [3]. The $-\alpha$ 3.7 rightward deletion has been most frequently reported worldwide among the α -globin deletions, while the frequency of the $\alpha\alpha\alpha$ anti 3.7 triplication has not yet clearly described. The carriers of the $\alpha\alpha\alpha$ anti 3.7 triplication do not show any clinical signs or changes in their hematological profile but the co-existence of this triplication with β -thalassemia worsens the clinical and hematological features of the patients suffering from homozygous β -thalassemia and the ones that have the β -thalassemia trait [4].

2. Case Presentation

A 60-year-old Greek female patient presented with severe hypochromic microcytic anemia (baseline Hb:7.5 g/dL, MCV:78 MCH:23.5 MCHC:30.1) and her blood film showed markedly hypochromic and microcytic red cells. Iron was 210 μ g/dL, ferritin was 230 ng/dL, TIBC was 480 μ g/dL, and transferrin saturation was found to be 43.75%. The physical examination showed hepatosplenomegaly, jaundice, and a heart murmur. After excluding the possibility of iron deficiency, it was decided to screen for myelodysplasia or dyserythropoiesis. The bone marrow examination revealed a hyperplastic erythroid series with normoblastic maturation and severe dyserythropoietic morphology. The analysis of hemoglobin pattern with high-performance liquid chromatography (HPLC) for hypochromic and microcytic red cells showed borderline raised Hb A2:6% (range: 3.5%–5.5%) and Hb F:2.6% (range<2%), but no Hb Bart's or HbH inclusion bodies were seen. The genotype analysis revealed the diagnosis of concurrent $\alpha\alpha\alpha$ anti 3.7 triplication and heterozygous β^0 -thalassemia (IVSI-1G>A). An investigation of family showed that the patient's son had concurrent $\alpha\alpha\alpha$ anti 3.7 triplication and heterozygous β^0 -thalassemia (IVSI-1G>A) and a daughter had α -thalassemia trait $\alpha\alpha\alpha$ anti 3.7 triplication. The patient was requiring monthly blood transfusions (an average of 3 units per month) and she was on iron chelation therapy due to increased ferritin levels. Her son was clinically asymptomatic with microcytic anemia without other laboratory abnormalities.

3. Discussion

α -thalassemia is characterized by the reduced production of the α -globin chains of the hemoglobin tetramer. Individuals with a mutation affecting α -globin genes only on a single

chromosome, with the other one being unaffected, usually have mild anemia without any clinical signs or symptoms. In this case, the syndrome is characterized as “silent” α -thalassemia (if the mutation involves one gene) or α -thalassemia trait (if two genes are involved) [1]. Compound heterozygotes or homozygotes, i.e., individuals with α -globin gene mutations that affect both chromosomes, express moderate to severe hemolysis and anemia, a syndrome known as HbH disease [1]. The excess of β globin chains results in the formation of non-functional β chain tetramers called HbH (β_4 tetramers) in adults and γ chain tetramers called Hb Bart's (γ_4 tetramers) in the prenatal period [1]. The most severe and generally fatal clinical phenotype of α -thalassemia is Hb Bart's Hydrops Fetalis Syndrome, a form of α -thalassemia with no expression of α -genes [1].

The triplication of the α -globin gene results from an unequal crossover between misaligned homologous segments in the α -globin gene cluster during meiosis. Triplication exists in two forms, $\alpha\alpha\alpha$ -anti37 configuration or $\alpha\alpha\alpha$ -anti 42 configuration. Alpha gene triplication ($\alpha\alpha\alpha$ -anti 3.7) is a rare numerical change in the α -gene that in co-existence with β -thalassemia minor worsens its phenotype and makes differential phenotypes [5]. A few patients with heterozygosity for β /?-thalassemia and an unexpectedly severe clinical picture were reported in the early 1970s [6]. The researchers were considering an interacting triplicated α -locus to explain the clinical course of these cases. Since then, many cases have been reported where individuals with β -thalassemia heterozygosity in combination with a triplicated α -globin gene manifest worsened clinical and hematological features compared to the individuals with β -thalassemia minor. Further, in the latter case, the clinical syndrome has been described as mild to moderate β -thalassemia intermedia [5]. In our case, the age of the patient initially led us to investigate other causes of anemia. The differentiation of bone marrow aspiration included myelodysplasia and/or dyserythropoiesis, but no blasts or other findings were noted. The analysis of the hemoglobin molecule with electrophoretic methods is an important laboratory test, which sometimes offers a definite diagnosis of the thalassemia syndrome and the Hb variants. However, further information is needed in order to interpret the test, which includes age, ethnicity, medical history, the onset of anemia, and family history [7]. Our patient mentioned that she was prenatally screened and aware of being a β -thalassemia carrier.

HPLC is used worldwide and a library of Hb variants to assist the diagnosis of thalassemia syndromes and Hb variants is available. However, the test cannot accurately detect and quantify the percentages of Hb Bart's and HbH, which are both important in the diagnosis of α -thalassemia syndromes [7]. The molecular analysis of DNA sequences is the most accurate diagnostic test for these conditions. Mutation-specific detection makes the use of the information from any ethnic population regarding their common profiles of both α -globin and β -globin mutations (deletions, point mutations or gene rearrangements) to generate a panel of mutations for detection, and uses different polymerase chain reaction (PCR)-based methods to identify these known mutations [7].

According to the age of onset and transfusion requirements, the clinical severity of the thalassemia intermedia syndrome varies from mild to moderate in most patients. Moreover, in patients, presented at adulthood and showing normal growth and fertility, anemia may worsen with age [5].

In conclusion, in elderly patients with anemia that cannot be attributed to any other cause related to their age, with a history of known beta-thalassemia trait and in patients presented with the phenotype of β -thalassemia intermedia, the genotype of triplicated α -globin gene in combination with heterozygosity for β^0 -thalassemia should always be considered as a cause. The

presence of triplicated α -globin genes should also be looked for in individuals with β -thalassemia minor who are more anemic or symptomatic than expected and in those affected by β -thalassemia intermedia but with only one parent showing positivity for β -thalassemia on hemoglobin analysis. The detailed knowledge of the incidence of α -thalassemia (including carrier status) and its genetic diversity is crucial for defining strategies oriented at decreasing the long-term health burden of hemoglobinopathies and encouraging accurate diagnosis. This will avoid incorrect and costly treatment.

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Author Contributions

All authors have contributed equally to the work.

Competing Interests

The authors have declared that no competing interests exist.

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