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ORIGINAL ARTICLE

Clinical consequences of alpha-thalassemia in the Basque Country, Spain. Impact of neonatal screening☆,☆☆

A. Aristizabal[a,*], S. Merino[b], E. Catediano[a], M. Sasieta[b], P. Aragües[c], A. Navajas[a]

[a] *Servicio de Pediatría, Hospital Universitario de Cruces, Barakaldo, Vizcaya, Spain*
[b] *Servicio de Hematología, Hospital Universitario de Cruces, Barakaldo, Vizcaya, Spain*
[c] *Servicio de Bioquímica, Hospital Universitario de Cruces, Barakaldo, Vizcaya, Spain*

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KEYWORDS
Alpha;
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Abstract
Introduction: Alpha-thalassemia is the most common hemoglobinopathy with a variable clinical manifestation depending on the number of allele mutations (asymptomatic/mild anemia if 1–2 allele mutations, severe disease if 3–4 allele mutations). A study was conducted from May 2011 on hemoglobinopathies found in the neonatal screening in the autonomous community of the Basque Country (CAPV).
Objectives: To analyze the impact of alpha-thalassemia in this area and the effectiveness of its neonatal screening.
Methods: A review was made of patients with a positive gene study for alpha-thalassemia over a 2-year period (2012–2013) and an analysis was made of the age at diagnosis, ethnic group, analytical result, and treatment.
Results: The genetic study was performed on 107 patients, of which 61 had some mutation, with 62% having one allele mutation and 38% with two alleles. The mean age at diagnosis was 31 years, with 28% being younger than eighteen years old. Most of the patients were European with a significant number of Africans (26%) and Arabs (13%). All patients were asymptomatic, and 28% had mild anemia. Two patients were diagnosed by neonatal screening. Most of them did not need any treatment or only required iron therapy.

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☆☆ Previous presentation: The results of this study were presented as an oral communication titled ''Repercusión clínica de alfa-talasemia en nuestro medio'' at the III Memorial Profesor Juan Rodríguez Soriano scientific meeting of the Sociedad Vasco-Navarra de Pediatría; November 8, 2013; Bilbao, Spain.

* Corresponding author.
E-mail address: amaia.aristizabalsegarra@osakidetza.net (A. Aristizabal).

Conclusions: The detection of one or two alpha gene mutations has no clinical impact, but allows genetic counseling. No patient was found with 3–4 mutations or severe symptoms in our region. Contrary to the diagnosis of other diseases, our results do not support that routine neonatal screening for alpha-thalassemia has any clinical impact in our community.

PALABRAS CLAVE
Alfa;
Talasemia;
Screening;
Neonatal

Repercusión clínica de la alfa-talasemia en nuestro medio. Impacto del *screening* neonatal

Resumen
Introducción: La alfa-talasemia es la hemoglobinopatía más frecuente de expresión clínica variable en función del número de alelos mutados (1–2 alelos mutados: asintomático/anemia leve, 3–4 alelos mutados: enfermedad grave). Desde mayo de 2011 se ha añadido el estudio de hemoglobinopatías al *screening* neonatal en la Comunidad Autónoma del País Vasco (CAPV).
Objetivos: Valorar el impacto de la alfa-talasemia en nuestro medio y la utilidad del *screening* neonatal en su detección.
Método: Revisión de pacientes con estudio genético positivo para alfa-talasemia durante 2 años (2012–2013) y estudio de la edad al diagnóstico, etnia, resultados analíticos y tratamiento.
Resultados: Se realizó un estudio genético de alfa-talasemia a 107 pacientes, de los cuales 61 presentaron alguna mutación. El 62% tenía un alelo mutado y el 38%, 2 alelos. La edad media al diagnóstico fue de 31 años, con un 28% menores de 18 años. La mayoría eran de procedencia europea con un porcentaje no desdeñable de africanos (26%) y árabes (13%). Todos los pacientes estudiados estaban asintomáticos con anemia leve en el 28%. Dos pacientes fueron diagnosticados por *screening* neonatal. La mayoría de pacientes no requirió tratamiento o precisó ferroterapia.
Conclusiones: La presencia de una o 2 mutaciones en los genes alfa carece de repercusión clínica, y el único interés de su estudio es que permite el consejo genético. En nuestro entorno no hemos encontrado pacientes con 3–4 mutaciones ni con sintomatología grave. A diferencia de lo que ocurre con otras enfermedades, nuestros resultados no apoyan que el *screening* neonatal de alfa-talasemia tenga un impacto significativo en nuestro entorno.

Introduction

Thalassaemias are inherited disorders of hemoglobin synthesis. The most common type of hemoglobin at birth is hemoglobin A, which is composed of four polypeptide chains, two alpha (α) chains and two beta (β) chains. In alpha-thalassaemia, there is reduced or absent production of the alpha chain, and consequently a relative excess of beta chains (gamma chains in the newborn). Excess beta chains can form soluble tetramers (HbH), but these are unstable and precipitate, giving rise to symptoms (peripheral haemolysis and, to a lesser degree, ineffective erythropoiesis).[1,2]

Each copy of chromosome 16 has two pairs of genes that encode the alpha chain, so the normal genotype is $\alpha\alpha/\alpha\alpha$. The main mechanism leading to alpha-thalassaemias is the partial or total deletion of a gene.[3] At least 128 different genetic defects that may cause alpha-thalassaemia have been identified to date.[4,5] We also know of at least seven forms of alpha-thalassaemia that are due to nondeletional mutations, which usually carry more severe symptoms. The most frequent deletion in Spain involves 3.7 kb of DNA ($-\alpha^{3.7}$), which through homologous recombination leaves a single functional alpha gene in the affected chromosome[4,6,7]:

- Loss of the 4 alleles (-/-) leads to a total absence of alpha chains, which is incompatible with life (Hb Bart syndrome).
- Deletion of 3 alleles (α-/-) is also known as hemoglobin H disease (HbH) because it leads to the formation of tetramers of excess beta chains and causes moderate to severe haemolytic anemia, ineffective erythropoiesis, splenomegaly and bone changes.
- Deletions of 1 ($\alpha\alpha/\alpha$-) or 2 ($\alpha\alpha$/- or α-/α-) alleles are known as silent alpha-thalassaemia and alpha-thalassaemia trait, respectively. Patients are usually asymptomatic, but may have mild microcytic and hypochromic anemia. These forms are more prevalent in individuals of Asian or African descent.[1–4]