A case of beta thalassaemia trait of unusual severity due to co-inheritance of triple alpha mutation

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Introduction
The -3.7 mutation is the commonest alpha thalassaemia mutation in Sri Lanka1,2 as well as worldwide1 and it occurs due to unequal cross-over between homologous sequences of the α2 and α1 genes during meiosis1. The reciprocal allele (anti -3.7) is the triple alpha mutation which is uncommon in Sri Lanka2 and triplicated or quadruplicated α globin genes were found in 4% of the population3. Triple alpha mutation is phenotypically silent at both homozygous and heterozygous states whereas when co-inherited with heterozygous beta thalassaemia which is usually asymptomatic1, contributes for globin chain imbalance and subsequent thalassaemia intermedia phenotype. Some patients who are heterozygous for both beta thalassaemia and triple alpha mutation are clinically asymptomatic4. We report a case of beta thalassaemia trait with co-inheritance of heterozygous triple alpha mutation who became transfusion dependent at the age of three years.

Case report
A 3 year old girl, born to non-consanguineous parents, without any perinatal complications, presented with jaundice of one year duration and recent onset of dark coloured urine, pale stools and intermittent abdominal pain for 3 weeks. She was apparently well up to the age of 2 years when she developed progressive jaundice. She had been given 6 blood transfusions by 3 years of age and following each transfusion, has had transient improvement of the jaundice. She has no symptoms of cholecystitis, malabsorption or chronic liver cell disease. There is no clinically significant family history of transfusion dependent anaemia or jaundice. She was developmentally normal and had been vaccinated appropriately including with Hepatitis B.

On examination, she had subtle dysmorphic features and was pale, deeply icteric, and afebrile with moderate hepatosplenomegaly. There was no lymphadenopathy, no features of cholecystitis, chronic liver cell disease or Wilson disease. Her growth and development was age appropriate.

Her investigations revealed evidence of Coomb negative haemolytic anaemia with normal white cells and platelet count, blood picture evidence of haemoglobinopathy (hypochromic microcytic red cells, partially haemoglobinized cells, polychromatic cells, and nucleated red cells), normal serum ferritin, and HPLC of beta thalassaemia trait. Deletional alpha thalassaemia genes were not detected. Urine haemosiderin, urinary haemoglobin, and heat stability test for unstable haemoglobins, were also negative. Her HEMPAS test was negative and the bone marrow aspiration and trephine biopsy were unremarkable except for erythroid hyperplasia with few dysplastic features. Her father’s HPLC revealed beta thalassaemia carrier state and her mother’s HPLC was normal.

She was further investigated to identify the aetiology of the cholestasis. The 24 hour urinary copper excretion and HIDA scan were normal. Hepatitis A & C IgM antibodies, Hepatitis B surface antigen, and antinuclear antibodies were also negative.

This 3 year old child who is heterozygous for beta thalassaemia had haemolysis of unusual severity (gallstones, biliary sludge) and transfusion dependency. We considered co-existing other haemolytic processes such as G6PD deficiency or...
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autoimmune haemolytic anaemia, unstable haemoglobins, dominant beta thalassaemia, coexisting excess alpha chains, congenital dyserythropoietic anaemia and Wilson disease to explain the unusual severity.

Dominant beta thalassaemia was considered unlikely as father was asymptomatic and with the above investigations we could exclude all other possibilities except the presence of excess alpha chains. Therefore we performed genetic analysis and the presence of triple alpha gene (anti 3.7) in both mother and the child were detected by GAP PCR for which the father was negative.

Therefore we diagnosed thalassaemia intermedia in this child due to heterozygosity for both beta thalassaemia and triple alpha gene mutation (anti-3.7).

Discussion
In beta thalassaemia clinical manifestations are due to excess alpha chains which deposit on erythroid precursors causing ineffective erythropoiesis. Heterozygous beta thalassaemia is asymptomatic as the globin chain imbalance is minimal. Homozygosity or heterozygosity for triple alpha/quadruple alpha also is asymptomatic in the absence of beta thalassaemia gene since alpha chain excess is minimal. Triple alpha mutation when co inherited with beta thalassaemia trait even in the heterozygous state contributes for thalassaemia intermedia phenotype. Patients develop clinically significant anaemia requiring transfusion and excessive haemolysis causing biliary sludge and gallstones as in our case.

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