

Diagnosis of concurrent hemoglobin H disease and heterozygous β -thalassemia

Definitive diagnosis of concurrent hemoglobin (Hb) H disease and heterozygous β -thalassemia cannot be made from Hb analysis alone, but necessitates genotype analysis and family study. Interactions between α - and β -thalassemia must be considered when investigating moderate to severe hypochromic microcytic anemia of uncertain cause in adult patients from areas with a high prevalence of globin gene mutations.

The co-inheritance of both α - and β -thalassemia occurs in areas with a high prevalence of globin gene mutations.¹ A rare combination is concurrent Hb H disease and heterozygous β -thalassemia,²⁻⁸ and these patients reportedly show anemia with markedly hypochromic and microcytic red cells, variable levels of Hb A₂, and significant globin chain imbalance. Hb H inclusion bodies may not be present at all, although in a few cases a trace amount of Hb Bart's is detected. Based on published prevalence figures,⁹ the expected population frequency of this combination in Hong Kong is 0.0007%, and two such patients (Table 1) are described in this report.

Case #1. The patient presented with anemic symptoms at the age of 32. Physical examination showed no hepatosplenomegaly. A hemoglobin pattern analysis for hypochromic and microcytic red cells showed borderline raised Hb A₂, normal Hb F and no Hb Bart's or Hb H inclusion bodies. The patient's bilirubin level was normal. Repeated bone marrow examinations showed hyperplastic erythroid series with micronormoblastic maturation and moderate dyserythropoietic morphology, and cytogenetic study showed a normal male karyotype. Genotype analysis revealed a diagnosis of concurrent Hb H disease and heterozygous β -thalassemia. The lowest Hb recorded was 5.9 g/dL. The patient required blood transfusion at monthly intervals and iron chelation therapy for an increased ferritin level of 5,575 pmol/L (normal range for males: 115-884 pmol/L). His phenotype was unusually severe and remained to be fully explained.

Case #2. The patient presented at the age of 33 with anemia discovered during pregnancy. Her blood film showed markedly hypochromic and microcytic red cells. The co-inheritance of α - and β -thalassemia determinants was suspected from the Hb pattern analysis that showed slightly raised Hb A₂ and occasional Hb H inclusion bodies, and was supported by family study showing three daughters with α -thalassemia trait and a son with β -thalassemia trait. No Hb Bart's or Hb H band was detectable on electrophoresis. The patient's bilirubin level was normal. A bone marrow examination performed to investigate alternative explanations of anemia showed only erythroid hyperplasia. Genotype analysis revealed a diagnosis of concurrent Hb Quong Sze (QS)-Hb H disease and heterozygous β -thalassemia. The patient's steady state Hb was around 7 g/dL and the lowest Hb recorded was 5.2 g/dL at the age of 35. She required only

infrequent blood transfusions, an average of six units a year, and was on iron chelation therapy for an increased ferritin level of 7,650 pmol/L (normal range for females: 15-331 pmol/L). Latest follow-up showed a splenomegaly of 6 cm below the left costal margin.

This report highlights the diagnostic difficulty encountered in concurrent Hb H disease and heterozygous β -thalassemia. In our two patients, who showed a significant degree of anemia, the Hb A₂ level was only slightly increased while the Hb F level was normal. There was also absence of the Hb H band that characterizes Hb H disease, and Hb H inclusion bodies were totally absent in the first case. Only the patient with Hb QS-Hb H disease had occasionally detected Hb H inclusion bodies, which in conjunction with more pronounced red cell microcytosis and hypochromia, was consistent with a more profound α/β chain imbalance and hence more severe clinical phenotype¹⁰ in non-deletional α -globin gene mutation than three α -globin gene deletion. Moreover, the late onset in our two cases suggests that anemia may worsen with age. Genotype analysis therefore serves as an important diagnostic tool in our locality to investigate adult patients with unexplained moderate to severe hypochromic microcytic anemia, without which the definitive diagnosis may be considerably delayed and unnecessary investigations for other causes of anemia may have been undertaken. Finally, a family study is also useful in these cases.

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Table 1. Clinical, hematologic and genotypic findings in concurrent Hb H disease and heterozygous β -thalassemia.

Case	Sex	Age (yrs)	Hb (g/dL)	MCV (fL)	MCH (pg)	Retic (%)	HbF (%)	HbA ₂ (%)	HbH bodies	α -genotype	β -genotype
1	M	38	7.3	72.0	22.9	<1	0.9	3.6	neg	α ^{3.7} / α -SEA	β ^{MSH-654(C\rightarrowT)} / β ^A
2	F	63	7.9	56.2	14.8	0.8	<0.3	4.0	occ	α ^{OS} / α -SEA	β ^{codon17(A\rightarrowT)} / β ^A

Normal ranges: Hb, 13-18 g/dL (males), 11.5-16.5 g/dL (females); MCV, 82-97 fL; MCH, 27-32 pg; retic, 0.2-2%; HbF, <0.9%; HbA₂, 2.3-3%.

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