Compound heterozygosity for Unstable Haemoglobin Genova and β⁰-thalassaemia associated with early onset of Thalassaemia Major Syndrome

We described the case of an infant with compound heterozygozity for a β⁰-thalassaemic mutation and Haemoglobin (Hb) Genova, an unstable Hb variant. He has required regular transfusions as early as the second month of life and since then, behaves like a thalassemia major patient. This association leads to the most severe clinical course involving an unstable variant, reported so far.

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We report the case of a child compound heterozygous for a β⁰-Thalassaemia mutation and Haemoglobin (Hb) Genova, who developed a thalassaemia major syndrome in the first weeks of life. The mother, who presented with a β-thalassaemia trait was of Italian origin and received genetic counselling late in pregnancy. The father, who was of French North European origin, had a history of chronic haemolytic anaemia of unknown origin starting in early infancy, had several blood transfusions and was splenectomized at age 10. A complete haematological study of both parents was performed in the in the 9th month of the pregnancy using standard methods (Wajcman *et al,* 2001). The mother was found carrier of the IVS-II -1(G→A) β⁰-thalassaemia mutation. In the father, examination of the blood smear revealed many red blood cells (RBC) containing numerous Heinz bodies, target cells and many reticulocytes. Red cell enzyme activities were within the normal range. Haemoglobin electrophoresis and chromatography failed to reveal any abnormal component. HbF and HbA2 levels were high (3% and 4.7%, respectively), but no microcytosis was present. The isopropanol haemoglobin instability test was found positive after a 10-minute incubation, suggesting the presence of an unstable variant DNA Sequencing of the father's ,-genes revealed the presence of the cd 28 (CTG→CCG) mutation in heterozygous form changing a Leu into a Pro to give Hb Genova (Sansone *et al.,* 1969), an unstable variant leading to chronic haemolysis with Heinz bodies and hypersplenism. (Labie *et al.,* 1972). It is likely that the mutation has occurred as a *de novo* event in the father since none of the grand parents have any history of chronic anemia.

Unfortunately the defects were diagnosed too late for a prenatal diagnosis which would have been a problem anyway, even if the molecular characterization would have been performed earlier. Although one could expect a severe phenotype from combinations of unstable hemoglobins and β⁰-thalassemia (the parents were informed on the potential consequences of the association of the 2 defects), the phenotype resulting from the association Hb Genova and β-thalassemia had never been described before. The child was born at full term with 100% HbF, and was slightly anaemic (Hb 142 g/L). Molecular analyses revealed that he had inherited both ,-globin gene abnormalities from his parents. The child's Hb value decreased progressively, reaching 95g/l at the age of one month and 64 g/L three weeks later, when a first blood transfusion was required . Since the Hb value dropped below 70 g/L again three to four weeks after the first transfusion, a standard transfusion program was set up. By the age of 1 year, the child had received 8 transfusions. At the age of 15 months, an unsuccessful attempt was made to increase the time between the transfusions. The ferritin value is now 900 mg/L, and a treatment for iron chelating is to begin within a few weeks. Haematological data of the family are shown in Table 1.

Hb Genova is a highly unstable Hb variant present in reduced amounts in the peripheral blood. Being electrophoretically neutral, this variant is difficult to detect by conventional procedures and should be distinguished from other type of hyperunstable Hbs which are completely destroyed in the RBC precursors and lead to a semi-dominant β-thalassaemia phenotype in the heterozygotes (Thein, 2004).

Associations of heterozygous β-thalassemia with unstable Hb variants have been reported requiring occasional transfusions (Wajcman and Galacteros, 2002).

Being protected by HbF synthesis in the first months of their life, most Thalassaemia Major patients become transfusion-dependent between the ages of 6 and 18 months. In the present case, despite a high level of HbF at birth, the first transfusion was required as early as the second month of life. This is due to the combination of two pathophysiological mechanisms: firstly, globin chain imbalance and dyserythropoïesis with intramedullary premature destruction of erythroid precursors and secondly, peripheral haemolysis due precipitated dimers or tetramers containing β-Genova globin chains. The present case represents one of the most severe clinical presentations reported so far in cases where unstable haemoglobins are associated with a β-thalassaemia trait.

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Table 1. Red Cell indices and haemoglobin analysis for the father, the mother and their child at different ages

	Father	*Mother*	*Child at birth*	*Child (7 weeks)[1]*	*Child (3 months)[2]*	*Child (16 months)[3]*
Red cell count (T/L)	4.92	5.11	4.45	2.42	3.08	3.20
Hemoglobin (g/L)	136	112	14.2	64	77	86
MCV (fL)	91.6	69.4	97.1	79.8	75.8	80.7
Reticulocytes (G/L)	861 (17%)				338 (11%)	32 (1%)
Heinz Bodies	+++					+++
Instability	++	-				
HbF and HbA2 (%)	3 and 4.7	3.4 and 5.4	100%HbF			9.7 and 2.6

[1]: Before the first transfusion; [2]: 1 month after the first transfusion, [3]: 3 weeks after the last transfusion (for a total of 12 transfusions).

References

1. Thein SL. Genetic insights into the clinical diversity of beta thalassaemia. Br J Haematol. 2004 24:264-74.
2. Sansone G, Carrell RW, Lehmann H. Haemoglobin Genova: beta-28 (B10) leucine replaced by proline. Nature 1967;214:877-9.
3. Solal MC, Labie D. A new case of hemoglobin Genova , 28(B10) Leu leads to Pro. Further studies on the mechanism of instability and defective synthesis. Biochim Biophys Acta. 1973;295:67-76.
4. Wajcman H, Prehu C, Bardakdjian-Michau J, Prome D, Riou J, Godart C, Mathis M, Hurtrel D, Galacteros F. Abnormal hemoglobins: laboratory methods. Hemoglobin. 2001;25:169-81.
5. Wajcman H, Galacteros F. The unstable hemoglobins: some genetic aspects. BJMG 2002;5: 3-10.