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Four globin gene defects in a healthy child

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During neonatal screening for Sickle Cell Disease, other haemoglobin (Hb) abnormalities can be detected. The most frequent defects encountered are Hb C, Hb E, Hb Bart's and less often, the absence of Hb A signalling a beta-thalassaemia. We report the case of a newborn that presents at birth, an undetectable Hb A fraction and a fraction of Hb Bart's (isoelectrofocusing from a dry blood sample). Using HPLC (Variant, Bio-rad, Hercules, CA, USA, Sickle Cell Program) on the same sample, we found a weak peak of Hb A (2,9%) and Hb Bart's. As the baby was born at 39 weeks of gestation, we asked for a control on peripheral blood for the newborn and a family study. The control was performed at the age of 3,5 month and showed a HbA-like and HbF level of 39 % and 57 % respectively (Variant, Bio-rad, b-thal Short Program). The mother presented a b-thalassaemia trait with Hb A_2 level of 5,8% and HbF level of 2,6% whereas the HPLC analysis for the father sample revealed an abnormal Hb fraction with mobility close to the Hb A (retention times 2.21 and 2. 38 respectively). Finally, for the baby, performing chains separation on HPLC (Shimadzu, Kyoto, Japan), only an abnormal b-globin chain, the one transmitted by her father, was demonstrated. Molecular analysis of the child's DNA revealed a compound heterozygosity for a mutation in codon 124 CCA->CAA resulting in the substitution of a Proline by a Glutamine (Hb Ty Gard) and a b-thalassaemia mutation IVS 2-654 T->C. As we found Hb Bart's at birth and the mother being of Indonesian origin, we look for a deletional a-thalassaemia by southern blot and found the a^{SEA} deletion heterozygous in the mother's and the child's samples. We tested also an elder brother of the baby who presented no elevated HbA_2, marked microcytosis and polycythemia (due to a-thalassaemia) but also 2,6% of HbF, suggesting a possible hereditary persistence of foetal haemoglobin (HPFH). All results of haemoglobin studies and red cells values are summarized in table 1.The child was seen for the last time at the age of 2 years and presents 23.5 % Hb F suggesting that she, as her elder brother, has inherited, from her mother, a HPFH which has not been investigated at the molecular level.

Hb Ty Gard, first reported in 1978 in a heterozygous patient by Burseaux et al (1), is a high affinity variant. The substituted residue is invariant in all the human a and non-a-chains except the z-chain (replaced by Ile). The prediction for such a modification at the a_1b_1 contact should be an instability rather than a modification of oxygen affinity. Surprisingly, even in association with b-thalassaemia, there is only mild instability and the single physiological consequence observed is a moderate increase of the erythrocyte mass in elder patients, due to high O_2 affinity.

The child is now 2 year old and is symptom free. The ratio between functional b and a-genes is normal (1:2) because of both heterozygous b-thalassaemia and a-thalassaemia type 1. The presence of high Hb F level may prevent the potential effect of Hb Ty Gard instability. There is no sign of hemolysis either clinically (no splenomegaly) nor haematologically (Bilirubin: 5mmol/L, Haptoglobin 0.47g/L, Reticulocytes count: $55.4x10^9$/L). The red cells count being already 6.12 $x10^{12}$/L, the tendency to have an increased erythrocyte mass, conferred by Hb Ty Gard and majored by the beta-thalassaemia trait, should be checked in the future.

References

1. Bursaux E, Blouquit Y, Poyart C, Rosa J. Hemoglobin Ty Gard ($a_2b_2$124(H2) Pro->Gln): A stable high O2 affinity variant at the a_1b_1 contact. FEBS Letters 1978; 88(1): 155-9.