*Disorders of Erythropoiesis*

## Association of Hb Shelby with Hb S in the south of Brazil

**We, herein, report the first observation of compound heterozygosity for hemoglobin Shelby and hemoglobin S identified in the south of Brazil. The variant hemoglobin was identified by isoelectric focusing (IEF), high performance liquid chromatography (HPLC) and DNA sequence analysis.**

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Hemoglobin (Hb) Shelby [β131(H9)Gln→Lys] is a rare, mildly unstable β-globin variant. This hemoglobin was previously identified as having deletion of the glutamine residue at β131 and was named Hb Leslie or Hb Deaconess.[1] The variant was subsequently renamed by Moo-Penn *et al.*[2] and Wilson *et al.*,[3] who obtained data indicating that the glutamyl residue 131 of the β-chain is not deleted but is, instead, replaced by a lysyl residue. Compound heterozygosity for Hb S/Hb Shelby, leads to lower co-polymerization with Hb S than seen in Hb A/Hb S hybrids. Since the mean corpuscular hemoglobin concentrations of the few patients reported in literature are normal, this finding coupled with the elevated Hb $A_2$ and Hb F levels, both of which are known to inhibit polymerization of Hb S, may contribute to patients´ mild clinical presentation.[4]

We describe the first reported case of Hb Shelby, in association with Hb S, found in southern Brazil in a 9-month old boy of African descent. At neonatal screening,

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**** Beta Thal Short 01598-A ****
DATE:15/07/03      TIME:16:20:43

TECH ID#      : 1
VIAL#           8
SAMPLE ID# 00000000000000000005

ANALYTE ID        %     TIME        AREA

F               12.9     1.16      130561
P3               0.3     1.74        3032
Unknown  1      2.6     2.21       25415
Ao              4.4     2.38       42305
A2              8.6     2.71       72860
S-WINDOW       58.1     4.50      557574
Unknown  2     12.3     4.80      118430

              TOTAL AREA           949477

F          12.9%    A2           8.6%
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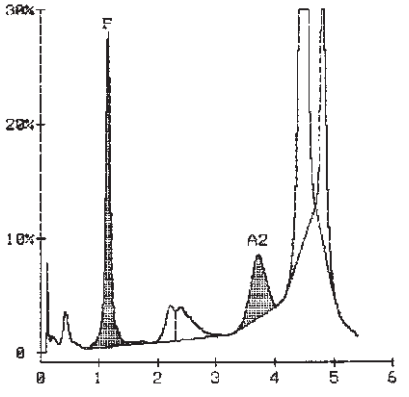


**Table 1.** Summary of hematologic data, IEF and HPLC findings, and results of iron studies and clinical investigations of the patient and his family members.

| Subject | Patient | Mother | Sister | Father |
|---|---|---|---|---|
| Age | 9 months | 20 years | 1 1/2 year | 33 years |
| RBC (×10⁶/μL) | 4.31 | 4.23 | 3.98 | 5.47 |
| Hb (g/dL) | 9.6 | 12.4 | 9.1 | 15.7 |
| Hct (%) | 29 | 37.7 | 28 | 46.1 |
| MCV (fL) | 67.3 | 89 | 69.8 | 84.3 |
| MHC (pg) | 22.3 | 29.3 | 22.9 | 28.8 |
| MCHC (%) | 33.1 | 32.9 | 32.8 | 34.1 |
| RDW (%) | 16.7 | 12.8 | 17.2 | 15.2 |
| WBC (×10³/μL) | 9.9 | 16.2 | 21.8 | 5.6 |
| Platelet (×10³/μL) | 613 | 319 | 613 | 355 |
| Iron status | ND | SI: 61 μg/dL<br>TIBC: 365 μg/dL<br>TS: 16.7 % | ND | ND |
| IEF pattern | Hb S+abnormal band co-migrating next to Hb F (P.I. 7.03) | Hb A+abnormal band co-migrating next to Hb F (P.I. 7.03) | Hb S+abnormal band co-migrating next to Hb F (P.I. 7.03) | Hb AS |
| HPLC pattern | Hb S+Hb F+ unusual peak: 12.3% (RT: 4.80) | Hb S+Hb F+ unusual peak: 24.7% (RT: 4.80) | Hb A+unusual peak: 12.4% (RT: 4.80) | Hb AS |
| β-blobin genotype | Compound heterozygous for Hb S (codon 6 GAG→GTG) and Hb Shelby (codon 131 CAG→AAG) | Likely heterozygous for Hb Shelby (codon 131 CAG→AAG) | Compound heterozygous for Hb S (codon 6 GAG→GTG) and Hb Shelby (codon 131 CAG→AAG) | Likely heterozygous for Hb S (codon 6 GAG→GTG) |
| α-globin genotype | No (-α$^{3.7}$) | No (-α$^{3.7}$) | No (-α$^{3.7}$) | No (-α$^{3.7}$) |
| Clinical symtoms (fever, anemia, pneumonia) | Yes | No | Yes | No |

*RBC: red blood cells; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: MCH concentration; RDW: red cell distribution width; SI: serum iron; TIBC: total iron binding capacity; TS: transferrin saturation; ND: not determined.*

HPLC analysis showed a pattern of Hb S (10.9%) and an unusual peak at RT 1.49 (1.8%). At 9 months of age the hemoglobin pattern was re-evaluated. A summary of the patient´s and relatives' hematologic data, IEF (Perkin Elmer) and HPLC (Variant-Biorad) findings, results of iron studies and clinical information is presented in Table 1. The patient's HPLC trace is shown in Figure 1.

Samples were sent to the Hemoglobin Diagnostic Reference Laboratory, Boston University, for DNA sequencing. The analysis indicated that the case was a compound heterozygote for Hb S and Hb Shelby without (-α$^{3.7}$) thalassemia. His father was identified as a carrier of Hb AS and his mother as a carrier of Hb Shelby. The same clinical, hematologic and hemoglobin pattern was found

**Figure 1 (Left).** HPLC (Variant™, Biorad) showing Hb F, Hb $A_2$, Hb S and Hb Shelby.

in the patient´s sister. The patient and his sister are symptomatic, with abnormal development, no history of transfusions, recurrent fever and infectious diseases.

A previous study showed that the interaction of Hb Shelby with Hb S resulted in mild clinical symptoms,[5] in contrast to the symptoms of these children. Thus, more studies regarding these associations are required to explain the basis for the different clinical presentations.

Finally, from an analytical point of view, the importance of also carrying out IEF and HPLC, in addition to DNA-based diagnostics, should be considered when investigating neonatally-screened individuals to avoid data misinterpretation and a false diagnosis of sickle cell disease.

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