Hemoglobin **Sickle-Lepore**: An Unusual Case of Sickle Cell Disease

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Hemoglobin Lepore Washington-Boston is a β-globin structural variant, produced in a reduced amount and formed from the fusion of N-terminus δ-chains (residues 1-87) and C-terminus β-chains (residues 116-146) [1]. The double heterozygous condition for sickle and Lepore hemoglobin (Hb S/Hb Lepore) gives rise to a sickle hemoglobinopathy rarely described in the literature. In this report, we describe a family from Guadeloupe (French West Indies) in which one child is a compound heterozygote for Hb S and Hb Lepore Washington-Boston.

The propositus is a 10-year-old male born in Guadeloupe. He was noted at birth to have an FS pattern on isoelectrofocusing and HPLC. At the age of 6 months, a family study was performed. Peripheral blood parameters were determined on an automatic analyzer and hemoglobin electrophoresis was carried out by standard methods. The F cells were assayed by a microscopic immunofluorescent method using a monoclonal antibody raised against human γ-globin chain.

The hemoglobin phenotype of the father was typical for sickle cell trait. The pattern of the mother of the propositus was AA on citrate agar but showed an A'SA.2 pattern on isoelectrofocusing. The hemoglobin in the S position accounted for approximately 10% of the total hemoglobin. She had a modest fetal hemoglobin level with 4.6% and a heterocellular distribution of F cells (18.3%), in agreement with the β-thalassemic-like condition of the Hb Lepore gene. Moreover, she presented slight microcytosis (MCV = 78.0 fl) and hypochromia (MCH = 26.3 pg). At the age of 9 years, the proband had mild hypochromic (MCH = 23.8 pg) microcytic anemia (Hb =...
10.9 g/dl, MCV = 73.8 fl), an Hb Lepore level of 14.1% with an Hb F level of 15.6% and 55.5% F cells.

The deletion junction of the δβ-globin gene fusion was amplified using PCR [2], and direct nucleotide sequence analysis of the PCR product established that the mutation was of the Lepore Washington-Boston type. None of the family members studied carried the commonest type of α-thalassemia found in Guadeloupe (–α3·7). Haplotype analysis was also conducted. The following polymorphic restriction sites, HincII-5'ε, XmnI-5'γc, HindIII-α and HindIII-γ were analyzed. The β chromosome was characterized as Bantu (#20) type whereas the Hb Lepore mutation was associated with the haplotype [– + – ++ – +] which was different from previously described haplotypes associated with this mutation in other populations [3, 4]. This different haplotype could be explained by an unequal recombination event between a normal and a Hb Lepore Washington-Boston chromosome. Alternatively, it may well be that the crossover between normal chromosomes leading to this Hb Lepore chromosome occurred as an independent event.

The patient was lost to follow-up for 4 years. During this time, he reportedly had no clinical expression of the disease. At the age of 4 years and 6 months, the patient presented to the Emergency Room for treatment of a pneumonia with fever complicated by a painful event and disability. After treatment, he was included in the follow-up program of the Centre Intégré de la Drépanocytose (sickle cell center). Over the following 5 years, he was treated six times with intravenous hydration, nonsteroidal anti-inflammatory drugs and antibiotics (when fever occurred) for painful, disabling events on each occasion. These hospitalizations lasted from 2 to 8 days with an average of 3.5 days. His spleen and liver were never palpable. Hemoglobin concentration has been stable and he has required no transfusion. Until to date, his growth has been normal.

The clinical condition of this new Hb S/Hb Lepore case is comparable to the other cases already reported in the literature. To date, 16 cases of compound heterozygote Hb S/Hb Lepore have been reported. They are characterized by marked hematological as well as clinical heterogeneity [5-7]. Most of the patients had mild microcytic hemolytic anemia. The expression of Hb F was highly variable, ranging from 3.5 to 25%. Clinical expression of Hb S/Hb Lepore disease varied from an asymptomatic 76-year-old woman who had uneventful pregnancies, to patients with moderately severe anemia with hepatosplenomegaly, spontaneous abortions, pneumonia, bone pain, retinopathy and avascular necrosis of the hip. Except for the first manifestation of the disease, our patient exhibited almost exclusively vaso-occlusive events which were easily treated. This moderate clinical expression could be related to the Hb F level (15%) as well as to the percentage of F cells (55.5%). Indeed, as for sickle cell anemia, a relationship of the clinical severity of Hb S/Hb Lepore syndromes to the level of Hb F could be observed [5]. However, it seems that the clinical presentation of this disease does not fully correspond to the Hb F levels [7] and further work is needed to understand the great variability of the clinical presentation of Hb S/Hb Lepore.

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References


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