Brief Communication

Received: August 2, 1996

Accepted: January 13, 1997

Acta Haematol 1997;98:170-171

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

M.		Romana ^a
J.P.		Diara
T.		Merghoub ^c
L.		Kéclard ^a
C.		Saint-Martin ^b
C.		Berchel ^a
G.		Mérault ^a

^aUnité de Recherche sur la Drépanocytose, INSERM U-359 et ^bCentre Intégré de la Drépanocytose, Pointe-à-Pitre, Guadeloupe, ^cUnité de Recherche sur la Pharmacologie du Développement, INSERM U-120, Paris, France

Key Words

Hemoglobinopathies

δβ fusion gene

Hb S/Hb Lepore

M. Romana, Unité de Recherche sur la Drépanocytose, INSERM U-359, Centre Hospitalier Universitaire, BP 465, F-97159 Pointe-à-Pitre Cedex, Guadeloupe (France), Tel. (590) 383 48 99, fax (590) 383 05 13

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 hemoglobins (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 proband 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 proband 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-thal-assemic-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) micro-cytic 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 $\delta\beta$ -globin gene fusion was amplified using PCR [2], and direct nucleotide sequence analysis of the PCR product established that the mutation was of the Leporewashington-Boston type. None of the family members studied carried the commonest type of α -thalassemia found in Guadeloupe ($-\alpha 3 \cdot 7$). Haplotype analysis was also conducted. The following polymorphic restriction sites, HincII-5' ϵ , XmnI-5' Gy, HindIII-Gy, HindIII-Ay, β^0/β^+ Π - $\Psi\beta$, β^0/β^+ Π -3' $\Psi\beta$, AroI- Π - β , β^0/β^+ Π -3' β , β^0/β^+ Π -3' β and β^0/β^+ Π -3' β were analyzed. The β s 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 Leporewashington-Boston chromosome. Alternatively, it may well be that the crossover between normal chromosomes leading to this Hb Lepore chromosome occurred as an independent event.

KARGER

E-Mail karger@karger.ch Fax + 41 61 306 12 34 <http://www.karger.ch>

©1997 S.Karger AG, Basel 0001-5792/97/0983-0170\$12.00/0

This article is also accessible online at: <http://BioMedNet.com/karger>

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 hepato-splenomegaly, 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.

Acknowledgements

We wish to thank the staff of the Pediatric Services of the Centre Hospitalier Universitaire of Pointe-à-Pitre and the Centre Intégré de la Drépanocytose. This work was supported by grants from INSERM, the Conseil Général de la Guadeloupe and CORDET. This paper is dedicated to Guy Mérault who initiated and conducted this study, but suddenly died.

References

- Labe D, Schroeder WA, Huisman THJ: The amino acid sequence of the δ - β chains of hemoglobin LeporeAugusta = Lepore Washington. *Biochim Biophys Acta* 1966;127:428-437. Craig JE, Barnetson RA, Prior J, Raven JL, Thein SL: Rapid detection of deletions causing $\delta\beta$ -thalassemia and hereditary persistence of fetal hemoglobin by enzymatic amplification. *Blood* 1994;83:1673-1682.
- Lanclos KD, Patterson J, Efremov GD, Wong SC, Villegas A, Ojwang PJ, Wilson JB, Kultar F, Huisman THJ: Characterization of chromosomes with hybrid genes for Hb Lepore-Washington, Hb Lepore-Baltimore, Hb P-Nullotic, and Hb Kenya. *Hum Genet* 1987;77:40-45. Fioretti G, De Angioletti M, Masciangelo F, Lacena G, Scarcello A, De Bonio C, Pagano L, Guarino E, De Rosa L, Salvati F, Careta C: Origin heterogeneity of Hb Lepore-Boston gene in Italy. *Am J Hum Genet* 1992;50:781-786. Sowards DP, Ware RE, Kinney TR: Hemoglobin sickle-Lepore: Report of two siblings and review of the literature. *Am J Hematol* 1993;44:192-195.
- Mirabile E, Testa R, Consalvo C: Association of Hb S/Hb Lepore and $\delta\beta$ -thalassemia/Hb Lepore in Sicilian patients: Review of the presence of Hb Lepore in Sicily. *Eur J Haematol* 1995;55:126-130.
- Voskariidou E, Konstantopoulos K, Kollia P, Papadakis M, Loukopoulos D: Hb Lepore (Pylos)/Hb S compounds heterozygosity in two Greek families. *Am J Hematol* 1995;49:131-134.

Hemoglobin Sickle-Lepore

Acta Haematol 1997;98:170-171