Hemoglobin sickle D Punjab—a case report

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HbD Punjab also known as HbD Los Angeles is a β-chain variant and is characterized by a Glu→Gln substitution at codon 121 with a GAA→CAA change at the DNA level and the electrophoretic mobility at alkaline pH is similar to HbS (β6, Glu→Val). HbD has been described in both the heterozygous and homozygous states as well as in combination with HbS or β-thalassemia. Simple heterozygous and homozygous individuals with HbD are asymptomatic, whereas association with HbS is characterized by a mild to moderate hemolytic anemia. HbD-β-thalassemia is also generally a very mild condition. However, HbSD disease may manifest with variable clinical features. HbS and HbD are one of the commonly encountered Hb variants worldwide. In India, the prevalence of HbS gene varies from 0 – 34% in different tribal and some scheduled caste groups whereas the average gene frequency of HbD has been observed to be 0.86% with a higher frequency of 3.6% seen in Punjab followed by Jammu and Kashmir (3.3%) and Uttar Pradesh (2.3%). We describe a case of sickle cell hemoglobin D (HbSD) Punjab disease.

Case History

A 10 year old female child from Nagpur was referred to us with severe hemolytic anemia, occasional episodes of pains (predominantly bones and abdomen) associated with fever. She had also received three units of blood. Physical examination revealed short stature (weight 12.5 kg and height 105 cm), pallor, hepatosplenomegaly (2 cm) and splenomegaly (3 cm) below the right and left costal margins respectively. Cardiovascular, respiratory and nervous systems were normal.

Investigations

Her Hb was 5.9 g/dl and the reticulocyte count was 3.3%. Solubility test was positive. Hence, it was presumed that this patient is a case of sickle cell trait/anemia. HPLC analysis revealed the presence of both HbS and HbD (HbS-52.3%, HbD-40.8% and HbF-4.2%). The parents of the proband were also investigated. The father was found to be HbD trait while the mother was sickle cell trait. The β6 and β0 mutations were confirmed by PCR followed by restriction enzyme digestion with Ddel and EcoR1 respectively. Haplo-type analysis was done using eight restriction enzymes: XmnI (5'Gγ), HindIII (Gγ), HindIII (Aγ'), HincII (υβ), HincII (3'υβ), Rsal (5'β), Avall (β) and Hinfl (3'β) of the β-globin gene cluster by PCR and Southern blot hybridization. The β6 gene was linked to the Arab-Indian haplotype (#31) [+ + + + + + + -] whereas β0 mutation was associated with haplotype 1 [- - - - - + + +]. α-genotyping by Southern blot hybridization showed four normal α-gene (αα/αα).
Discussion

There are several variants of hemoglobin D such as HbD Punjab (Los Angeles), HbD Iran, HbD Ibadan. Of these variants, HbD Punjab only interacts with HbS, however, the nature of this interaction is not known. HbD has also been reported with other hemoglobinopathies like β-thalassemia without any additional clinical or hematological abnormalities. Earlier studies from Pakistan, Iran, UAE and Mexico have shown that the clinical presentation of HbSD disease cases is similar to that of patients with the severe form of sickle cell anemia. On the other hand, reports from India have shown variable clinical manifestations of HbSD disease.

In HbSD disease, HbD does not take part in the sickling process, as patients homozygous for HbD do not sickle. However, an earlier study has indicated that although HbD itself does not polymerize, it facilitates the polymerization of HbS, thus enhancing the severity of the disease. At the same time, the co-inheritance of α-thalassemia and enhanced HbF levels also have an inhibitory effect on the clinical expression of sickle cell disease. Earlier, it has been observed that the inheritance of α-thalassemia with sickle cell anemia and high HbF levels often results in milder clinical manifestations. On the other hand, normal or excess α-globin genes could increase the severity of sickle cell disease. Our patient had a normal α-genotype (αα/αα) along with low HbF levels which could be the possible explanation for the severity in this case.

The Arab-Indian haplotype observed in our patient have been shown to be linked to the βS gene in India. Haplotype1, linked to the βD chromosome has been reported to be the most common one in Mediterraneans as well as in all populations studied worldwide so far. Earlier studies also revealed the same haplotype1 to be associated with β0 chromosome in different population groups which probably indicates the unicentric origin of the β0 mutation. Since, there are very few studies on haplotype linkege of β0 chromosome and haplotype1 is the most frequently observed one in world populations, more intensive studies are required to determine the true origin of the β0 mutation in the world populations.

References