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A Case of Compound Heterozygous HbS and HbD Disease in Premarital Screening

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Abstract **Case Report**

Introduction: Among the inherited disorders of blood, haemoglobinopathy and thalassaemia constitute a major bulk of non-communicable genetic diseases in India. They cause a high degree of morbidity in affected individuals. Moderate to severe haemolytic anaemia among vulnerable segments of the society like infants and children, adolescent girls, pregnant women, etc. may result in many deaths in India. Hemoglobinopathies are a vast group of inherited disorders of hemoglobin production and function. Compound heterozygous HbSD-Punjab is an uncommon hemoglobinopathy encountered in Indians. In premarital screening, molecular testing is mostly inconvenient and diagnosis often relies on the abnormal hemoglobin analysis, family studies and epidemiological facts. We present the clinical and laboratory characteristics of hemoglobin D-Punjab with sickle cell disease found on premarital screening. ***Case Report:*** Blood sample of a 22 year old patient for high-performance liquid chromatography was received. A complete blood count (CBC) showed mild anemia with Hb of 8.3 g/dl with mild microcytic hypochromic red cell indices.The HPLC showed HbD and S-window on BIO RAD D10 machine. The high-performance liquid chromatography showed normal hemoglobin Hb F and Hb A2, which indicates presence of a Compound heterozygous for HbSD-Punjab. ***Conclusion*:** Compound heterozygous state for HbD-Punjab with S-window is a rare disorder. HbSD-Punjab has a heterogeneous clinical presentation. Anemia and sickle crises are quite common. The data obtained from the clinical findings, blood picture and electrophoresis or HPLC will help in diagnosis. Genetic counseling is advisable in patients with presence of a Compound heterozygous HbSD-Punjab.

Keywords: Compound heterozygous HbSD-Punjab, HPLC, Premarital screening.

INTRODUCTION

Hemoglobinopathies are a group of clinical disorders caused by genetic defects that cause either an abnormal structure of hemoglobin or insufficient production.

Hemoglobinopathy can be broadly classified as disorders that result from structurally altered haemoglobin molecules (e.g. Sickle cell anemia) or disorders that arise from numerical imbalance of otherwise normal globin chain synthesis (β Thalassemia) [1]. Haemoglobinopathies may be due to deletion, insertion or substitution in the amino acid sequence in either alpha or beta globin chains leading to the formation of structurally defective haemoglobin (Hb). The first hemoglobinopathy, HbS, was discovered by Pauling *et al*., [2].

Many different mutations cause β Thalassemia and related disorders [3]. These mutations can affect every step in the pathway of globin gene expression: transcription, processing of the messenger ribonucleic acid (mRNA), precursor, and translation of mature mRNA and preservation of post translational integrity of β chain. More than 400 mutations have been described [4].

Hemoglobin D (Hb D) has more than a dozen variants among which Hb D-Punjab is most common [5]. Rarely, a compound heterozygous state for HbD-Punjab with S-window has been described. The variants differ at molecular level, but genetic tests are often unfeasable in premarital screening. In practice, the diagnosis and marriage guidance often rely on the results of abnormal hemoglobin analysis, family studies and epidemiological knowledge.

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) [6]. HbD-Punjab is an uncommon structural Hb variant seen in Punjabis and a higher frequency in Muslims in consanguineous marriages [7].

Compound heterozygosity for βS/βD results in a severe hemolytic anemia and a clinical syndrome similar to that of sickle cell disease. Here, we report a case of HbSD Punjab disease.

CASE REPORT

A twenty two years old male, resident of Surat (Gujarat) had taken up Abnormal haemoglobin studies test by high-performance liquid chromatography (HPLC) as a part of his premarital screening test. He was diagnosed as HbSD disease during routine Premartial screening tests, which included various tests ranging from complete blood counts to abnormal haemoglobin studies.

On performing serum electrophoresis for abnormal haemoglobin studies on this patient, patient was found to be carrying both HbD and HbS hemoglobins.

The patient was advised parental screening for abnormal haemoglobin and DNA analysis for definitive diagnosis.

Investigations:

This patient was diagnosed by Hb electrophoresis done on D10 Biorad by High performance liquid chromatography (HPLC), sickling and solubility tests.

Patient's Hb was 8.3 g/dl and his reticulocyte count was 3.0%.Sickling and Solubility test were found to be positive.

HPLC analysis revealed the presence of both HbS and HbD (HbS-39.5%, HbD-45.5% and HbF-2.7%). The parents of the patient were also investigated. The father was found to be HbD trait while the mother was sickle cell trait.

Haematological tests including haemoglobin, hematocrit, and cell indices are as below (Table I).

Table 1: Showing Hematological Parameters of Patient Investigation

	Result	Unit	Reference Range
Haemoglobin	8.3	g/dl	11.5-14.5
RBC	3.16	10^{*6} /uL	4.0-5.3
Packed Cells Volume	25.2	%	33-43
Total Leucocyte Count	18.8	10^{*3} /uL	4000-12000
MCV	79.7	fl	76-90
MCH	26.4	pg	25-31
MCHC	33.1	g/dl	32-36
Platelet	73	10^{*3} /uL	140-440
RDW-CV	23.9	%	11.5-15.0

High performance liquid chromatography (HPLC) was done for screening this patient for hemoglobinopathies. It was performed on the Bio Rad D10 using beta thalassemia extended program. It showed two abnormal Hb peaks, one within the D-window (as unknown) with a retention time (RT) of 3.88 min comprising 45.5 % of the total Hb and the other peak within S-window with a RT of 4.12 min comprising 39.5% of the total Hb. As per Bio Rad Library of Abnormal Hemoglobin version 2, the abnormal Hb in D window is possibly HbD-Punjab and the peak within the S-window is most likely due to HbS (Figure 1).

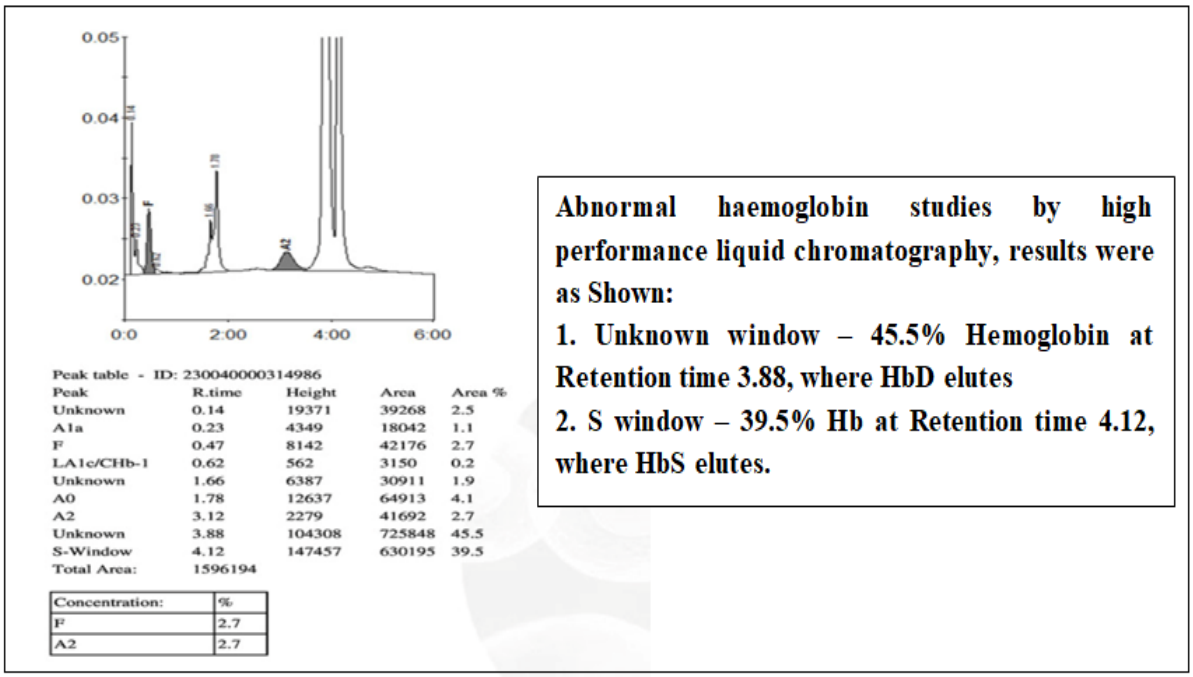

Figure 1: As shown above, HbD elutes as unknown window at 3.88min (45.5%) and HbS elutes at 4.12 min window (39.5%)

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 [8].

In our patient, this HbDS variant of haemoglobin is clinically benign, causing no signs or symptoms, hence the diagnosis was made only on screening for haemoglobin.

The patients with Hb D-Punjab/S genotype/phenotype have diversity of clinical presentations, ranging from asymptomatic to severe anemia [8-10]. The prognosis of HbDS is better than that of patient with Hb S/S(Sickle disease). HbD Punjab itself does not cause polymerisation but enhances the polymerisation of HbS by β^{121} glutamine residue thereby increasing the severity of disease [11].

Serum electrophoresis by HPLC (High performance liquid chromatography) by BioRad D10 can be used as screening test for determining the presence of various normal and abnormal variant hemoglobin, especially in the area with high incidence of HbD genotype, rather than gel electrophoresis. This is a fairly accurate method for the diagnosis, yet the confirmation should be done after HPLC by DNA analysis from peripheral blood sample.

CONCLUSION

Hemoglobinopathies are inherited conditions, some of which carry considerable clinical and genetic implications. So it is of utmost importance that all individuals should undergo premariatal screening for abnormal hemoglobins and precise documentation and record keeping of the same is of paramount importance.

All Hb D-Punjab double heterozygotes are clinically benign, except HbSD-Punjab. HbSD-Punjab has a heterogeneous clinical presentation. Anemia and sickle crises are quite common.

Because the inheritance of a haemoglobinopathy per se has genetic implications, it is important that genetic counseling is available for these patients.

Automated HPLC has largely replaced haemoglobin gel electrophoresis as the intial investigative procedure in laboratories analyzing large number of samples.

Laboratory investigation of a suspected hemoglobinoparthy should follow a defined protocol, which should be devised to suit individual local requirements. The data obtained from the clinical findings, blood picture and electrophoresis or HPLC will usually indicate in which direction to proceed.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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