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Case Report

Time to think beyond sickle cell screening and haemoglobin electrophoresis: a case report and review of literature of sickle cell D-Punjab falsely labelled as sickle cell SS from central India

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ABSTRACT

Sickle cell haemoglobin D disease (D-Punjab) is a rare variant of sickle cell disease (SCD) reported from central India. Exact incidence of pulmonary thrombosis in patients with HbSD is unknown. Pulmonary thrombosis is known complication of SCD but rare in case of HbSD pattern. We reported a case of 34-year-old male patient with HbSD (D-Punjab) with acute chest syndrome (ACS). CT pulmonary angiogram revealed near complete thrombosis of right middle lobe segmental and subsegmental branches with pulmonary infarct. Our patient responded to anticoagulant therapy. This case report is a reminder that HPLC should be done in all patients with sickle cell disease along with solubility test and hemoglobin electrophoresis to detect exact incidence of hemoglobin D disease in central India.

Keywords: Sickle cell disease, Pulmonary thrombosis, Acute chest syndrome, D-Punjab, CT pulmonary angiogram, High performance liquid chromatography

INTRODUCTION

Hemoglobin variants usually are the consequence of single amino acid substitutions caused by point mutations in genes encoding globin chains, resulting in a tetramer with different physicochemical characteristics. Hb D-Punjab is a variant, which was described in 1950 by Itano, derived from a point mutation in the beta-globin gene (HBB) in the first base of the 121 codons (GAA→CAA) with the substitution of glutamine for glutamic acid (Glu>Gln) in the beta globin chain.

Hb D-Punjab is one of the most common hemoglobin variants worldwide, after Hb S and Hb C. It is prevalent in Northwest India especially in Punjab and Gujarat region, with an estimated frequency of 2.0% due to prevalence of consanguineous marriages. In western India, more specifically in the Gujarat region, its frequency drops by one half. The exact incidence of heterozygous Hb S/D is not available from central India.[1,2]

It can be inherited heterozygously with normal HbA or thalassemia or with sickle cell disease (Hb S) or rarely as homozygously with Hb DD.

Hb D-Punjab when associated to Hb S, the double heterozygous Hb S or D, the result is moderate to severe clinical manifestations; this association can be clinically similar to homozygous Hb SS. Pain, due to vaso-occlusive events, is one of the most common complications. Furthermore, stroke and acute chest syndrome can occur in carriers of this genotype acute chest syndrome (ACS) is one of the leading causes of morbidity and mortality in sickle cell disease (SCD).

This report presents a case of heterozygous Hb S or D, a rare variant of SCD, with ACS complicated by pulmonary thrombosis who was treated with anticoagulants.

CASE REPORT

34-year-old male, presented to general medicine casualty with complaints of sudden onset chestpain breathlessness for 1 day. The patient's previous Hb electrophoresis reports revealed sickle cell pattern with SS pattern. On examination, he was febrile with temperature of 38°C, icteric and pale with a pulse rate of 122 beats/min and blood pressure of 120/70 mmHg. The patient was tachypneic, with an oxygen saturation of 85% on room air. So patient was given supplemental oxygen and was then maintaining saturation of 96% on 8 l of O_2. His chest auscultation revealed fine crepitations in right chest. ECG revealed incomplete right bundle branch block with sinus tachycardia. Chest X-ray (CXR) showed a right middle lobe (RML) density. Patient's complete hemogram revealed Hb 8.1 g/dl, WBC 17.7×10^3/µl, and platelets 139×10^3/µl. He was given IV antibiotics, maintenance intravenous (IV) fluids. On day 2 of hospitalization Despite supplemental oxygen patient was not maintaining saturation hence D-Dimer was done which found to be 7500 ng/ml (normal<500 ng/ml) and hence CTPA was done which revealed near complete thrombosis of right middle lobe segmental and subsegmental branches of right interlobar artery and focal partial obstruction of right lower lobe segmental branch of interlobar artery (Figure 1).

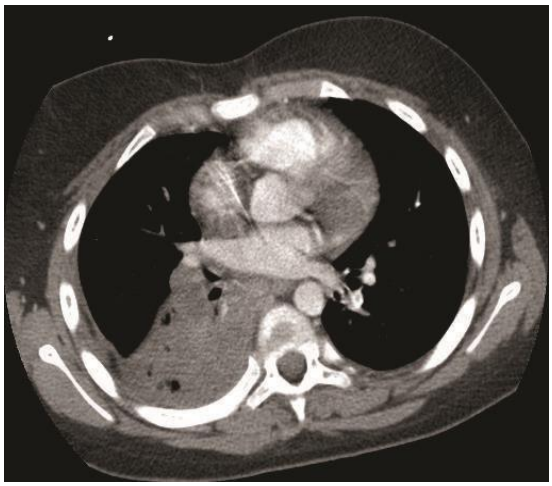

Figure 1: CT chest with pulmonary angiogram. Near complete thrombosis of right middle lobe segmental and subsegmental branches of right interlobar artery and focal partial obstruction of right lower lobe segmental branch of interlobar artery.

Repeated CBC showed WBC 11.8×10^3/µl and Hb 7.5 g/dl. One units of packed RBCs were transfused and his Hb increased to 9.5 g/dl. Hb electrophoresis was repeated again and showed ss pattern. HPLC was also done which revealed a pattern of compound heterozygous for hemoglobin S and hemoglobin D.

Thrombophilia work up for protein C and S; antithrombin III and factor V Leiden were negative. Heparin drip was started after obtaining baseline coagulation studies at the rate of 1000 ml/hr for 24 hr. Effect of anticoagulation was monitored with a PTT every 6 hours.

The dose of heparin then adjusted to 5000IU QID. When the therapeutic level was reached, on day 6, heparin was tapered, and subcutaneous LMWH was initiated at 0.6 cc SC BD. On day 10, patient shifted to rivaroxaban 15 mg BD and adviced to continue for 21 days followed by 20 mg OD to be continued. Patient symptomatically improved. He was weaned of oxygen, and repeated CXR showed improvement. Repeated CBC showed Hb 10.4 g/dl and WBC 9.5×10^3/µl. The patient improved symptomatically and was discharged on day 14 of admission.

DISCUSSION

There are several variants of hemoglobin D such as HbD Punjab (Los Angeles), HbD Iran, HbD Ibadan. Among which most common is most common is HbD Punjab.[3] Hb D-Punjab, uncommon structural hemoglobin variant mainly in few Asian individuals belonging to India, Pakistan, Iran, Iraq, and other parts of the world.[4,5] It is derived from a point mutation in the beta-globin gene (HBB: c.364G>C; rs33946267) prevalent in the Punjab region, North western Indian. Hemoglobin D-Punjab can be inherited in heterozygosis with hemoglobin Acausing no clinical or hematological alterations, or in homozygosis, the rarest form of inheritance, a condition that is commonly not related to clinical symptomatology. Moreover,this variant can exist in association with other hemoglobinopathies, such as thalassemias; the most noticeable clinical alterations occur when hemoglobin D-Punjab is associated hemoglobin S.

Among double heterozygotes are clinically benign except Hb SD.[6] It can have diversity of clinical presentations, ranging from asymptomatic to severe anemia. Their prognosis is better than that of patients with Hb S/S, and the unpredictability of presentation is affected by the Hb F level, α-thalassemia, HBB haplotype, age and environmental factors. 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.[3]

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, substituted glutamine residue in hemoglobin D facilitates the polymerization of HbS, thus enhancing the severity of the disease.[7]

While the gold standard test for diagnosis of haemoglobinopathies is molecular studies, most cases in this region are diagnosed based on High-performance

liquid chromatography (HPLC) and Capillary electrophoresis (CE) which are more affordable in this low income population. The principle of HPLC and CE is based on the difference in electrophoretic mobility of different HB variants. Normally, under alkaline pH, electrophoretic mobility of haemoglobin D-Punjab is same as haemoglobin S; however, in acidic pH, its mobility is similar to haemoglobin A. our patient was initially labelled as sickle cell SS and was treated as sickle cell SS .This case report warrants that there could be a likelyhood of many other similar cases which coluld be falsely labelled as sickle cell disease

According to Srinivas et al HPLC (cation exchange) has the advantage of not only detecting these abnormal hemoglobin rapidly but also helps in quantifying them accurately. It also has an additional advantage over electrophoresis in detecting a double heterozygous (HbS/D) state.[8] HbDP syndromes are not uncommon and are relatively under diagnosed. So HPLC should be recommended in regions with high prevalence of hemoglobinopathies. Similar study by Sachdev et al concluded that cation exchange HPLC is emerging as one of the best methods for screening and detection of various hemoglobinopathies with rapid, reproducible and precise results.[9] It can be used for early detection and management of hemoglobinopathies and variants.[7] Findings must be supplemented by hemogram findings, family/sibling studies, hemoglobin electrophoresis, other confirmatory techniques and molecular studies based on HPLC findings and on a case-to-case basis.

CONCLUSION

Hemoglobin D-Punjab variant is a rare entity seen mostly in the North-Western part of India. But it should also be considered in patients of Central India, especially in Vidarbha region with high prevalence of hemoglobinopathies like sickle cell disease and thalassemia. This vital differential should always be kept in the mind of physicians, who deal with several alleged hemoglobinopathies. Inclusion of HPLC to detect prevalence of hemoglobin D-Punjab in routine investigation in regions with high prevalence of sickle cell disease.

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