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Case Report

An unusual presentation of hemoglobin SD Punjab in a Saudi Arabian adult

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ABSTRACT

HbDPunjab is an uncommon variant hemoglobin that does not result in significant pathology when inherited as a homozygous disorder. When inherited with other hemoglobinopathies, it may result in varying disease phenotypes. HbSDPunjab has been rarely reported in Saudi Arabia, coexisting with alpha or beta thalassemia. In this report, we discuss the case of a 39 years old male who presented with severe anemia and renal injury and was later diagnosed with HbSDPunjab through electropheresis and genetic testing.

Keywords: Hemoglobin D, Sickle cell anemia

INTRODUCTION

Hemoglobin S (HbS) is a variant hemoglobin which results from substitution of the amino acid valine for glutamic acid at the sixth position of the β-globin chain. Inheritance of homozygous HbS (HbSS) results in a severe form of sickle cell disease (SCD) and patients typically experience a multitude of clinical complications, including acute and chronic pain, stroke, end organ dysfunction, and increased risk of mortality. The most common underlying genotypes are HbSS and HbSβ thalassemia. Less common genotypes include HbSC, $HbSO^{Arab}$, and $HbSD^{Punjab}$.

Co-inheritance of HbD^{Punjab} with α- or B-thalassemia have been previously reported in Saudi families, but there have been no published reports of Saudi patients with $HbSD^{Punjab}$.[1,2] In this case we discuss a Saudi patient with $HbSD^{Punjab}$ who was first diagnosed in the 4th decade of life with severe anemia and renal disease. This case illustrates the variable presentations that patients with this genotype may manifest.

CASE REPORT

A 39-year-old Saudi man, of indigenous Arab ethnicity, presented to the hematology clinic with a history of anemia. He initially presented to the general practitioner, complaining of fatigue, dizziness, and intermittent headache of 5 months' duration. Upon investigation, he was found to be severely anemic and subsequently received transfusion on two occasions. He was then referred to the hematology clinic for further assessment.

The patient denied shortness of breath, palpitations, or chest pain. There was no history of abdominal pain or change in bowel habits. He denied yellow discoloration of the eyes, or change in color of urine or stools. He complained of mild left flank pain, not associated with dysuria or urinary symptoms. There was no history of

loss of weight, fever, or night sweats. There was no history of bleeding from any site, and no history of body ache or bone pain. Review of other systems was unremarkable.

The patient reported history of anemia at the age of 8, for which he received blood transfusion once at that age. He was taking folic acid and iron supplements, and had no known allergies. He is married with two healthy daughters, and he has six siblings, one with sickle cell trait, and 5 were never tested. He denied smoking and illicit drug use. Physical examination revealed pallor but was otherwise unremarkable. There was no lymphadenopathy or organomegaly.

Investigations showed a hemoglobin of 3.3 g/dL, hematocrit 10%, MCV 82 fL, MCH 27 g/dL, MCHC33%, reticulocytes 4.6%, WBC 7.05 K/µL. His blood group was A+ with negative antibody screening and negative direct Coombs test. Blood film showed many nucleated red blood cells and sickle cells. Sickle cell solubility test was positive, and G6PD level was 13.7u/g Hb (normal range=4.6-13.5). Other investigations revealed the following: urea 13.1 mmol/L, creatinine (218 umol/L), albumin 32 g/L, GGT 159 U/L, LDH 601 U/L, total bilirubin 24 umol/L, direct bilirubin 6 umol/L and serum ferritin of 1797 ng/mL.

The patient was admitted to the hospital where he received blood transfusion and intravenous fluids. Hemoglobin electrophoresis (capillary electrophoresis in alkaline pH) showed Hb A 4.8%, Hb F 3.5%, Hb S 88.8%, Hb A2 2.9% (Figure 1). Upon review of the electrophoresis result, two types of hemoglobin were discerned at the Hb S position, together accounting for 88% of the patient's hemoglobin. The second peak was identified as hemoglobin D. Subsequently, molecular sequencing of the β globin gene confirmed double heterozygosity for hemoglobin S [c.20A>T (p.Glu7Val)], and Hb D-Punjab [c.364G>C (p.Glu122Gln)]. He was thus diagnosed with HbSD-Punjab disease.

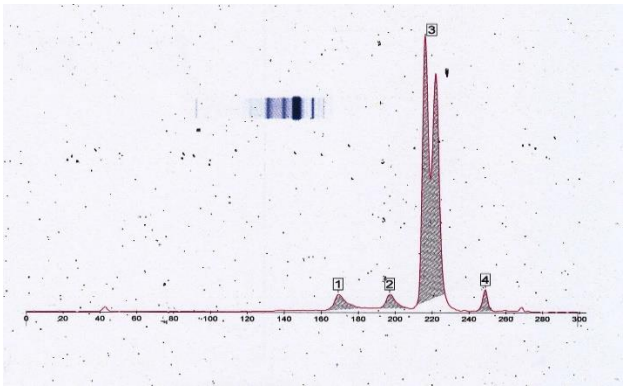

Figure 1: Hemoglobin electrophoresis in alkaline pH. 1 (HbA), 2 (Hb F), 3 (Hb S/ Hb D), 4 (Hb A2).

Results of further evaluation for renal disease showed 24-hour urine protein was 5.1 grams, and renal ultrasound showed multiple renal echogenic foci. A small, calcified spleen was noted on abdominal imaging, and an echocardiogram showed mild mitral regurgitation and an ejection fraction of 58%. The patient was started on hydroxyurea and folic acid, and was subsequently discharged in a stable condition. Serum ferritin was persistently elevated so he was started on oral iron chelation, and planned for T2* assessment of tissue iron in the heart and the liver.

The patient continues to be followed up in clinic, requiring blood transfusions every 2-3 months. He has not developed any other SCD related complications including; vaso-occlusive crisis, acute chest syndrome, pulmonary hypertension or priapism. Upon investigation, one of his siblings was confirmed to have Hb S trait, and another was found to be heterozygous for HbD-Punjab. The remaining siblings could not be reached for screening.

DISCUSSION

Hemoglobin D (Hb D) is a rare inherited hemoglobinopathy affecting the β-globin chain. It has several subtypes including HbD Punjab (HBB: c.364G>C; p.Glu122Gln) also named HbLos-Angeles reported in Pakistan and the North Western region of India. It is the most prevalent subtype world-wide.[3-5] Hb D Iran (HBB:c.67G>C; p.Glu22Gln)is another subtype mostly prevalent in the Middle East.[6-8] While homozygous HbD disease is mostly clinically asymptomatic, double heterozygosity for Hb D with hemoglobin S (Hb S), and β-thalassemia has a variable phenotype, depending on the interaction of HbD with other hemoglobinopathy genes.[8-10]

Recurrent pain and organ damage are the hallmarks of sickle cell disease (SCD), caused by polymerization of deoxygenated hemoglobin S, triggering a host of physiological and vaso-occlusive crises.[11-13] Depending on geographical regions and genetic origins, SCD has different haplotypes including Central African Republic (CAR), Benin (BEN), Senegal (SEN), Cameroon (CAM), and Arab/Indian (ARAB), prevalent in Saudi Arabia. The Arab phenotype is associated with a higher level of Hb F and less severe clinical disease. However, genetic and environmental factors can affect the clinical presentation of SCD. A recent study in France showed that extreme heat and cold weather conditions could be associated with an increase in the frequency of hospitalization due to acute pain, and acute chest syndrome.[14] Moreover, socioeconomic factors such as poor living conditions and lack of access to health care increase disease related complications including recurrent infections.[15] Evidence has shown that exercise and physical exertion can trigger the symptoms of the disease due to metabolic changes such as hypoxia, lactic acidosis, and dehydration.[16,17]

In this case, the patient presented for the first time with renal disease. Around one half of SCD patients develop

renal disease by the fourth decade of life.[18] Renal papillary infarction can result in painless hematuria that is gross in proportion, frequently reported among SCD patients and individuals with sickle cell trait.[19] Renal tubular acidosis can occur as a result of disturbances in the medullary blood flow that can lead to improper maintenance of the electrochemical gradients in the collecting ducts. These disturbances are often mild and asymptomatic but occasionally progress to severe clinical manifestations in case of rhabdomyolysis or volume depletion resulting in hyperkalemia and acidosis.[20] Acute kidney injury (AKI) in sickle cell disease correlates with different potential causes. These causes include: sepsis, rhabdomyolysis, renal vein thrombosis, and hepatorenal syndrome. There is an increased risk of urinary tract infection (UTI) in SCD patients due to autosplenectomy, and increased susceptibility to encapsulated organisms. Moreover, blood clots within the urinary tract can cause obstruction and gross hematuria.[21,22] In patients with nephropathy caused by SCD, the glomerular filtration rate (GFR) is higher than normal in young patients, and declines steadily after the age of 30, to reach end-stage renal disease levels.[23,24] Acute and progressive decline in GFR can be associated with glomerular injury and progressive proteinuria, but the pattern of progression is less severe compared to the acute causes of nephrotic syndrome.[25] Membrano-proliferative glomerulo-nephritis has been shown to be associated with hepatitis C infection possibly transmitted by blood transfusions in SCD.[26] Various phenomena, linked to SCD, can mask pre-existing hypertension via hypotensive mechanisms as a compensation for microcirculatory blood flow disturbances, including; systemic vasodilatation and increased production of prostaglandins, all of which have been proposed to be the reason for hypertensive SCD patients to appear, relatively, "normotensive".[27]

We report on a case of SCD with a rare genotype of Hb SD-Punjab. To our knowledge, it is the first reported case of HbSD-Punjab in a patient from indigenous Saudi tribes. Hemoglobin D- Punjab is rare in the Middle East, where Hemoglobin D Iran is more common. Despite evidence that HbSD-Punjab disease is clinically as severe as homozygous HbSS disease, this patient had an unremarkable medical history.[28,29] Moreover, he was diagnosed for the first time at the age of 39 upon presenting to our hospital. Among 9 children with HbSD-Punjab from the United Arab Emirates, 7 experienced pain crisis, recurrent infections, and splenic sequestration while 2 were asymptomatic apart from anemia.[30] In India, 25 out of 42 patients with HbSD-Punjab, had severe disease as reflected by 3 or more pain crisis per year.[29] Patients with severe disease in this study received hydroxyurea with a favourable outcome.

CONCLUSION

In conclusion, this is an uncommon case of HbSD-Punjab disease presenting in a patient from the Saudi indigenous tribes. Contrary to previous reports, his disease ran a benign clinical course and he was diagnosed in his late thirties. Further studies on genotype-phenotype associations of SCD in Saudi Arabia are needed.

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REFERENCES

1. Alotaibi ST, Ahmed MA. Hemoglobin D trait with alpha thalassemia in a Saudi family. Ann Saudi Med. 2000;20(3-4):251-2.
2. Owaidah TM, Al-Saleh MM, Al-Hellani AM. Hemoglobin D/beta-thalassemia and beta-thalassemia major in a Saudi family. Saudi Med J. 2005;26(4):674-7.
3. Schnee J, Aulehla-Scholz C, Eigel A, Horst J. Hb D Los Angeles (D-Punjab) and Hb Presbyterian: analysis of the defect at the DNA level. Human Genetics. 1990;84(4):365-7.
4. Itano HA. A Third abnormal hemoglobin associated with hereditary hemolytic anemia. Proc Natl Acad Sci U S A. 1951;37(12):775-84.
5. Yavarian M, Karimi M, Paran F, Neven C, Harteveld CL, Giordano PC. Multi centric origin of Hb D-Punjab [beta121(GH4)Glu-->Gln, GAA>CAA]. Hemoglobin. 2009;33(6):399-405.
6. Rahbar S. Haemoglobin D Iran: 2 22 glutamic acid leads to glutamine (B4). Br J Haematol. 1973;24(1):31-5.
7. Rohe RA, Sharma V, Ranney HM. Hemoglobin D Iran alpha A2 beta 22 2-Glu leads to Gln in association with thalassemia. Blood. 1973;42(3):455-62.
8. Sturgeon P, Itano HA, Bergren WR. Clinical manifestations of inherited abnormal hemoglobins. I. The interaction of hemoglobin-S with hemoglobin-D. Blood. 1955;10(5):389-404.
9. Adachi K, Kim J, Ballas S, Surrey S, Asakura T. Facilitation of Hb S polymerization by the substitution of Glu for Gln at beta 121. J Biol Chem. 1988;263(12):5607-10.
10. Kelleher JF Jr., Park JO, Kim HC, Schroeder WA. Life-threatening complications in a child with hemoglobin SD-Los Angeles disease. Hemoglobin. 1984;8(3):203-13.
11. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376(9757):2018-31.
12. Inati A, Koussa S, Taher A, Perrine S. Sickle cell disease: new insights into pathophysiology and treatment. Pediatr Ann. 2008;37(5):311-21.
13. Brousse V, Makani J, Rees DC. Management of sickle cell disease in the community. BMJ. 2014;348:g1765.
14. Mekontso Dessap A, Contou D, Dandine-Roulland C. Environmental influences on daily emergency admissions in sickle-cell disease patients. Medicine (Baltimore). 2014;93(29):e280.

15. Marmot M. Social determinants of health inequalities. Lancet. 2005;365(9464):1099-104.
16. Halphen I, Elie C, Brousse V. Severe nocturnal and postexercise hypoxia in children and adolescents with sickle cell disease. PloS one. 2014;9(5):e97462.
17. Faes C, Balayssac-Siransy E, Connes P. Moderate endurance exercise in patients with sickle cell anaemia: effects on oxidative stress and endothelial activation. Br J Haematol. 2014;164(1):124-30.
18. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006;17(8):2228-35.
19. Lumerman JH, Hom D, Eiley D, Smith AD. Heightened suspicion and rapid evaluation with CT for early diagnosis of partial renal infarction. J Endourol. 1999;13(3):209-14.
20. Allon M. Renal abnormalities in sickle cell disease. Arch Intern Med. 1990;150(3):501-4.
21. Sklar AH, Perez JC, Harp RJ, Caruana RJ. Acute renal failure in sickle cell anemia. Int J Artif Organs. 1990;13(6):347-51.
22. Audard V, Homs S, Habibi A. Acute kidney injury in sickle patients with painful crisis or acute chest syndrome and its relation to pulmonary hypertension. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association- European Renal Association. 2010;25(8):2524-9.
23. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. New England J Med. 1992;326(14):910-5.
24. Bhathena DB, Sondheimer JH. The glomerulopathy of homozygous sickle hemoglobin (SS) disease: morphology and pathogenesis. Journal of the American Society of Nephrology: JASN. 1991;1(11):1241-52.
25. Nasr SH, Markowitz GS, Sentman RL, D'Agati VD. Sickle cell disease, nephrotic syndrome, and renal failure. Kidney Int. 2006;69(7):1276-80.
26. Bruno D, Wigfall DR, Zimmerman SA, Rosoff PM, Wiener JS. Genitourinary complications of sickle cell disease. J Urol. 2001;166(3):803-11.
27. Hatch FE, Crowe LR, Miles DE, Young JP, Portner ME. Altered vascular reactivity in sickle hemoglobinopathy. A possible protective factor from hypertension. Am J Hypertens. 1989;2(1):2-8.
28. Oberoi SS, Marya CM, Sharma N, Mohanty V, Marwah M, Oberoi A. Knowledge and attitude of Indian clinical dental students towards the dental treatment of patients with human immunodeficiency virus (HIV)/acquired immune-deficiency syndrome (AIDS). Int Dent J. 2014;64(6):324-32.
29. Patel S, Purohit P, Mashon RS. The effect of hydroxyurea on compound heterozygotes for sickle cell-hemoglobin D-Punjab--a single centre experience in eastern India. Pediatr Blood Cancer. 2014;61(8):1341-6.
30. El-Kalla S, Mathews AR. Hb D-Punjab in the United Arab Emirates. Hemoglobin. 1997;21(4):369-75.

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