The curious case of hemoglobin DC disease masquerading as sickle cell anemia

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Abstract

Hemoglobin D is a relatively rare disease first reported in 1951. We present the first reported case of Hemoglobin DC disease. This is a case of a Hemoglobinopathy with DC disease in a woman with a previous diagnosis of Hemoglobin SC disease. A 19-year-old woman presented to the Adult Hematology clinic at a tertiary care hospital in Northwest Louisiana for transition of care from Pediatric Hematology for a diagnosis of Hemoglobin SC disease diagnosed at the age 4. Historical data suggested no avascular necrosis, acute chest syndrome, and very few episodes of pain crisis. She has never taken hydroxyurea. Laboratory work showed persistently normal hemoglobin and white blood cell counts. All sickle cell preparations in the past were negative. Computerized tomography scan of the abdomen was reviewed and showed a spleen grossly normal in size and appearance. Given the incongruent clinical picture for sickle cell disease, repeat hemoglobinopathy evaluation with Capillary electrophoresis and confirmatory acid electrophoresis (to differentiate hemoglobins that co-migrate with Hemoglobin S) showed a probable double heterozygote for Hemoglobin D and C with suspected coexistent alpha thalassemia minor based on red blood cell indices. This case confirms the importance of the required confirmatory method to ensure a correct diagnosis since a misdiagnosis can lead to numerous adverse clinical or psychological effects for patients.

Introduction

Hemoglobin D disease is a rare condition compared to Sickle cell anemia which is a relatively common hemoglobinopathy. We present a rare case of Hemoglobin DC disease. There is some literature about Hemoglobin D disease; however, we found no cases with a DC combination. Given the rarity of the disease, prevalence is unknown. Hemoglobin D itself is phenotypically silent.[1] However, Sickle cell disease has many genotypic and phenotypic variants depending on the hemoglobin variant.[2] Gel electrophoresis is a commonly used method to diagnosis of Sickle cell disease, Sickle trait and other sickling hemoglobin variants.[3,4] Cellulose acetate electrophoresis at pH 8.4 is a standard method of separating hemoglobin S (HbS) from other Hemoglobin variants. However, it does not differentiate between Hemoglobin S, G, and D. Once the presence of Hemoglobin S like variant is confirmed on cellulose acetate electrophoresis, a confirmatory acid electrophoresis on citrate agar is used to separate HB S from HB D and G disease since they co-migrate on alkaline ph given common net negative charge. The reason to differentiate between these hemoglobinopathies is because of the marked difference in disease course and prognosis.[5,6] We present a case of 19-year-old female who was misdiagnosed with HB SC disease due to inadequate diagnostic testing.

Case Report

A 19-year-old female presented for transition of care from Pediatric Hematology to Adult Hematology. She was diagnosed with Hemoglobin SC disease with coexistent α thalassemia at the age 4 on cellulose acetate hemoglobin electrophoresis. She reported two episodes of possible vaso-occlusive pain crisis in the past, with no history of any sickle cell anemia complications including acute chest syndrome, splenic sequestration, and avascular necrosis. She denied any history of blood or exchange transfusion or frequent infections. She did not have any family members with sickle cell disease. She denied any alcohol or illicit drug use. She denied having any current sexual partner. Physical exam showed normal vital signs. Skin showed no pallor or jaundice. Remainder of the physical exam was unremarkable. Lab workup was obtained for further evaluation. Initial blood count showed microcytic picture with normal Hemoglobin and low mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). Retic count was 2.2% (0.2-1.8%). A table of the patient's complete blood counts from 2015 to 2017 is below (Table 1).

A peripheral blood smear found occasional target cells but no sickle cells (Figure 1). Lactate dehydrogenase was 145 U/L (normal range 81- 234 U/l). A comprehensive metabolic panel showed sodium of 139 mmol/L (reference value 136-145 mmol/L) and potassium of 3.9 mmol/L (3.5-5.1mmol/L) with normal renal function. Other significant labs on presentation included alanine aminotransferase (ALT) of 35 U/L (12-78 U/L), aspartate aminotransferase (AST) of 18U/L (15-37 U/L), alkaline phosphatase (ALP) of 73 U/L (45-117 U/L), and total bilirubin of 0.4 mg/dL (0.2-1.0 mg/dL). Stool for occult blood was negative. Chest X-ray showed no acute cardiopulmonary abnormality. Computerized tomography scan of the abdomen and pelvis with intravenous contrast was performed and showed an intact spleen. In our patient, the lack of complications associated with sickle cell

disease such as acute chest syndrome and pain crisis, presence of intact spleen, and normal hemoglobin was what made the original diagnosis of sickle cell anemia questionable. Given the high discrepancy in lab values compared to other sickle cell disease patients, a hemoglobinopathy evaluation was performed. The result showed Hemoglobin DC disease rather than diagnosis of Hemoglobin SC disease (Figures 2 and 3). Sickle cell disease is associated with significant morbidity and mortality early in life. An incorrect diagnosis can result in significant psychological effects that can be avoided by making the correct diagnosis prior to psychological priming of a patient. This case highlights the need for complete hemoglobinopathy evaluation for correct diagnosis.
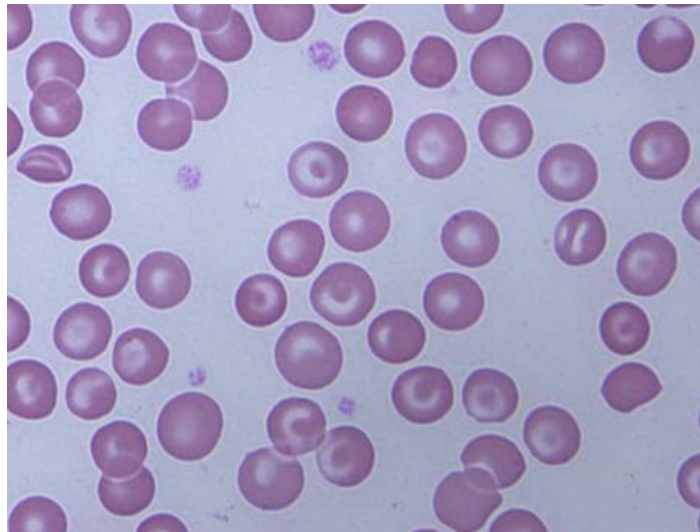
Discussion

The first reported case of Hemoglobin D disease was reported in 1951 by Itano *et al.*[7] Since then, it remains poorly studied compared to Hemoglobin S, C and Beta thalassemia.[8] It has been popularly reported as Hemoglobin D Punjab (given high prevalence in the Punjab region of Northwestern Indian) and Hemoglobin D Los Angeles (as this was first studied in Los Angeles by Itano).[7,8] Hemoglobin D disease usually does not have a specific phenotypic presentation. The first reported case from Punjab was an asymptomatic male with an incidental diagnosis of hemoglobinopathy.[9] Both Hemoglobin D trait and Hemoglobin DD disease are typically clinically and hematologically silent or may present with mild hemolytic anemia. As a result, these patients do not seek medical attention.[8]

However, Hemoglobin D acquires clinical significance when it occurs in combination with either β thalassemia or Hemoglobin S.[10] Sickle cell disease has many variants of which Hemoglobin SS disease compromises 60% cases in the United States.[2] It is important to note there is not much data on the prevalence of other hemoglobinopathies. The most common clinically seen manifestations of sickle cell disease include anemia, vaso-occlusive events, splenic sequestration, and acute chest syndrome.[11] Other life-threatening complications include bacterial sepsis, stroke, and chronic organ damage including cerebral infarction, end stage renal disease, sickle chronic lung disease, leg ulcers and osteonecrosis.[12-14] It is important to differentiate these hemoglobinopathies since there is a marked difference in disease course and prognosis.[5,6] Given the clinical risks,

Figure 1. This the microscopic view of peripheral smear. Target cells seen. No sickle RBC identified.
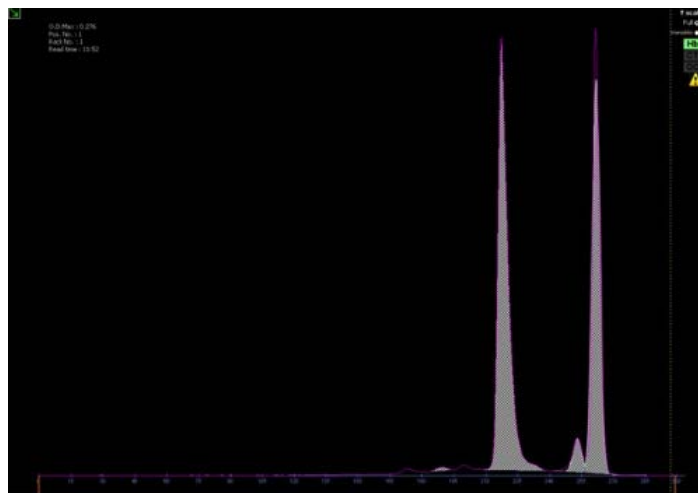

Figure 2. Capillary zone electrophoresis with two predominant peaks in HB D and HB C zone.
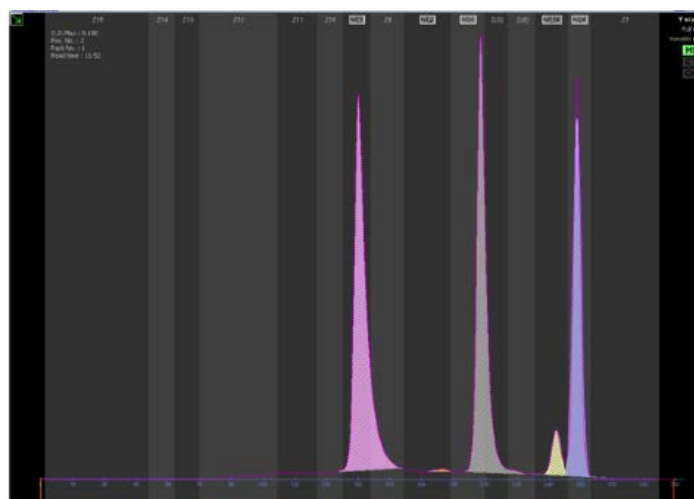

Figure 3. Capillary zone electrophoresis adjustment (addition of normal hemoglobin A allows identification of abnormal peaks).

Table 1. A table of the patient's complete blood count from 2015 to 2017.

Component (Latest Ref Range & Units)	3/3/2017	8/4/2016	2/19/2015
WBC (4.5-12.5 K/uL)	8.14	17.25 (H)	8.00
RBC (4.1-5.1 M/uL)	5.84 (H)	5.71 (H)	5.66 (H)
Hemoglobin (12.0-16.0 G/dL)	13.4	13.2	13.3
Hematocrit (36-46%)	39.0	37.4	40.3
MCV (78-98 fL)	66.8 (L)	65.5 (L)	71.3 (L)
MCH (25-33 pg)	23.0 (L)	23.2 (L)	23.5 (L)
MCHC (31-37 G/dL)	34.4	35.3	32.9
RDW (12.3-17.0 %)	14.8	15.1	14.4
Platelet (159-386 K/uL)	218	209	263
MPV (7.5-11.2 fL)	10.1	9.2	8.2

Ref: Reference,(H): High, (L): Low, K/uL: thousands per cubic milliliter, M/uL: million per microliter, G/dL: Gram/decilitre, fL: femtoliters, pg: picograms.

high mortality, and psychological effects of sickle cell disease, it is important to make the correct diagnosis.

Gel electrophoresis is one of the most commonly used and heavily relied upon tests for diagnosis of sickle cell disease vs sickle cell trait.[3,4] Cellulose acetate agar runs at an alkaline pH 8.4 is often one the first tests used by in the lab given the ease of handling and minimal preparative work. Alternatively, labs can use other methods such as capillary electrophoresis to separate hemoglobin variants, a semi-automated method which is used in our laboratory. Since both methods can't be used to confirm hemoglobins that co-migrate or co-ellute on screening, a confirmatory method must be used to accurate separate hemoglobins such as hemoglobin S from hemoglobins D and G. Therefore, the diagnosis is confirmed, often by acidic electrophoresis (pH 6.0 to 6.2) with citric agar to differentiate the hemoglobin variants.[3-5] At this pH, hemoglobin varieties that co-migrate on alkaline pH can be easily delineated. This method is commonly used to diagnose sickle cell disease at birth when there is a high concentration of hemoglobin F.[15] In our patient, Globin chain analysis will be used for confirmation. Other diagnostic tests used include separation of different hemoglobins according to their isoelectric point by isoelectric focusing (IEF), High Performance Liquid Chromatography (HPLC) and Reversed Phase High performance liquid chromatography HPLC.[16-18] In difficult cases, methods such as structural characterization of the hemoglobin polypeptide chain are used when initial tests are inconclusive.[15,19,20]

Conclusions

The goal is to emphasize the requirement for confirmatory tests when a diagnosis of Hemoglobin S disease is made to differentiate it from other hemoglobinopathies such as Hemoglobin D disease since the clinical presentation, management, course of disease and complications differ significantly. Also, complete hemoglobinopathy evaluation is important if the clinical picture is inconsistent with the previous diagnosis as occurred in our patient. Given the high prevalence of Hemoglobin S disease, it is possible that many patients with Hemoglobin D or G variants remain undiagnosed or misdiagnosed as Hemoglobin S disease. Hence, we suggest dual electrophoresis diagnosis for every patient with a preliminary diagnosis of Hemoglobin S disease. Once the presence of Hemoglobin S is confirmed on cellulose acetate electrophoresis it should be run on citrate agar to separate Hemoglobin S from D and G. The reason for the need for differentiation of these hemoglobinopathy is marked difference in disease course and prognosis.[5,6]

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