An Unusual Case of Heterozygous Hemoglobin S/Hemoglobin Fannin-Lubbock Misidentified by Capillary Hemoglobin Electrophoresis

Kerry J. Welsh and Yu Bai

Department of Pathology and Laboratory Medicine, University of Texas at Houston, Houston, TX, USA

Abstract. A 58-year-old Hispanic man under treatment for a gangrenous toe was found to have chronic microcytic anemia and a positive sickle cell screen. High-performance liquid chromatography and isoelectric focusing electrophoresis showed that the patient is double heterozygous for hemoglobin S and hemoglobin Fannin-Lubbock. The patient does not have any manifestations of a sickling disorder. Capillary hemoglobin electrophoresis initially misclassified this unusual combination of hemoglobin variants.

Introduction

Disorders of hemoglobin (Hb) synthesis can be due to either reduced synthesis of a globin chain or structural defects. More than one thousand Hb variants have been reported, the majority of which are clinically insignificant [1]. However, certain mutations may result in sickling disorders, hemolytic anemia, cyanosis, or erythrocytosis. Most Hb variants result from point mutations, but some cases may involve fusion proteins, tetramers, or multiple mutations. Double heterozygosity occurs when two variant hemoglobins are inherited, some combinations of which may lead to clinical disease such as heterozygous Hb S and Hb C. We report the second case of a patient with heterozygous Hb S and Hb Fannin-Lubbock and provide additional evidence that this is not a sickling disorder. This case was initially misidentified by capillary Hb electrophoresis.

Case report

The patient is a 58-year-old Hispanic man with a past medical history significant for poorly controlled diabetes and hypertension who first presented with a gangrenous right toe. He was initially treated with intravenous antibiotics and hyperbaric oxygen therapy, but later underwent amputation of the right great toe. The patient presented again with comprised stump and was treated with additional antibiotic therapy and hyperbaric oxygen. A hemoglobin electrophoresis was ordered for evaluation of chronic microcytic, hypochromic anemia. His hematological lab results were as follows: red blood cell count, 4.59x10^6 M/CMM; Hb, 11.5 g/dL; hematocrit, 36.2%; mean corpuscular volume, 78.7 fl; mean corpuscular hemoglobin, 25.0 pg; mean corpuscular hemoglobin concentration, 31.7 g/dL; red cell distribution width, 16.9%; platelets, 185x10^5/mm^3. Iron studies are not available and a sickle cell screen was positive. The patient's Hb A1c was 8.5%. The patient has a family history of diabetes and cancer of unknown type, but no known history of hemoglobinopathy.

Capillary Hb electrophoresis performed on this patient initially showed a peak in zone 9 (44.8%) and a peak in zone 3 (51.3%) (Figure 1), raising the possibility of O-Arab trait. However, high-performance liquid chromatography (HPLC) did not show hemoglobin A (Figure 2) and instead showed peaks in the S window (retention time, 4.42 minutes) and a second abnormal peak showing a retention time of 1.79 minutes. A second specimen drawn from the patient on a different occasion showed similar results on capillary electrophoresis (not shown). Isoelectric focusing electrophoresis showed 46.4% Hb S and 48.9% of a hemoglobin variant with similar migration to Fannin-Lubbock or Malmo (Figure 3). The discrepancy was resolved when the patient’s sample was diluted 50% with a normal sample followed by repeat performance of the capillary electrophoresis, resulting in correct alignment of the Hb zones (Figure...
4). The diluted specimen showed abnormal peaks in zone 11 and zone 5, the internal standard Hb A in zone 9, and Hb A2 appropriately in zone 3. Combining the data from the corrected capillary hemoglobin electrophoresis, HPLC, and isoelectric focusing electrophoresis, the Hb peak in zone 11 is consistent with Hb Fannin-Lubbock and the peak in zone 5 is Hb S.

This patient thus has two abnormal Hbs that consist of Hb S and Hb Fannin-Lubbock. Of significance, this patient is an adult without any clinical or hematological suspicion for a sickling disorder. The patient has a normal chest x-ray without the bony abnormalities typically seen in a sickling disorder. Furthermore, his presentation with a gangrenous toe is clinically attributed to his uncontrolled diabetes and a lower arterial duplex study showed significant peripheral vascular disease.

Discussion

Capillary Hb electrophoresis provides accurate identification of numerous hemoglobinopathies with easy-to-read patterns [2]. The fraction of Hb A is normally identified automatically, with adjustment of the zone patterns based on the Hb A fraction. To our knowledge, this is the first report of Hb Fannin-Lubbock misidentification as Hb A by the capillary hemoglobin electrophoresis system. This issue can be overcome by dilution of the patient sample 1:1 with a normal sample to create an internal standard for Hb A. This case also highlights the importance of a multi-tool strategy in the diagnosis of hemoglobinopathies, as the HPLC and isoelectric focusing did not show the presence of hemoglobin A. Furthermore, the peak in zone 9 of less than 50% on the initial capillary electrophoresis may have provided an indication that this peak was not hemoglobin A.
Hemoglobin Fannin-Lubbock trait has been described in several Hispanic families. It is a beta-chain variant with a glycine to aspartate substitution at position 119 (GGC→GAC) and a valine to leucine substitution at position 111 (GTC→CTC); this trait causes mild hemoglobin instability and is clinically insignificant [3,4]. A case of homozygous Hb Fannin-Lubbock in a child from Mexico had only the mutation on the beta chain 119Gly→Asp; this patient had mild anemia positive for Heinz bodies [5]. One case of heterozygous hemoglobin S/hemoglobin Fannin-Lubbock is reported in the literature of a three-month-old male with normal hemoglobin levels and without signs of a sickling disorder [6]. However, this previously reported case was a young child with limited follow-up available. The case presented here - of an adult with no symptoms attributable to anemia - provides further evidence that heterozygous Hb S/Fannin-Lubbock is a clinically benign entity.

References