Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Rare occurrence of hemoglobin Lepore variant in a Palestinian patient: a case report and brief literature review

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Introduction: In hemoglobinopathies, a basic lesion alters the rate of globin synthesis or the structure of the globin in healthy hemoglobin (Hb). Genetic instructions are used to synthesize the polypeptide chains that make up globin chains. The kind and extent of the structural aberration of the Hb molecule are closely related to the clinical features. Hematologically, the heterozygous form of the Lepore syndrome has a pattern resembling minor thalassemia, and electrophoretically, it is characterized by aberrant Hb Lepore fractions at a rate of 5–15% and a decreased percentage of HbA and mildly increased HbF. Clinically speaking, Hb Lepore heterozygotes patients are asymptomatic and resemble the clinical picture of patients with mild thalassemia.

Case Presentation: A 28-year-old female came to our attention for assessment of generalized weakness and fatigue for a 4-month duration. Laboratory evaluation, including complete blood count, showed mild microcytic hypochromic anemia with parameters resembling the thalassemia trait. Iron profile studies were normal. Abdominal ultrasound showed mild splenomegaly. Hb electrophoresis was performed and showed an abnormal high-performance liquid chromatography pattern with an abnormal Hb band, mild elevated HbF, and mild reduction in HbA. The interpretation of the Hb electrophoresis curve suggested heterozygosity for beta chain variant Hb Lepore.

Discussion and Conclusion: Hb Lepore is one of the structural Hb variants with a characteristic fusion gene between the delta and beta chains. Hematologically, the heterozygous form of the Lepore syndrome has a pattern resembling the thalassemia trait. In Palestine, the prevalence of Hb Lepore, either homozygous or homozygous state, is unknown.

Keywords: hemoglobinopathy, heterozygous, high-performance liquid chromatography, Lepore hemoglobin

Introduction

Hemoglobin (Hb) Lepore is one of the structural Hb variants that occur due to unequal crossing over between the δ and β globin genes. This leads to the formation of an abnormal globin chain that is a hybrid or fused globin chain between the N-terminal and C-terminal amino acid sequences of δ and β globin chain, respectively[1]. The new hybrid fusion gene leads to a 7.4 kb deletion between the delta and beta-globin genes[1,2]. There are currently three distinct Lepore Hb known, each of which exhibits a unique delta-to-beta sequence transition at the fusion junction[1–3]. These are Hb Lepore Washington Boston (δ87/β116), Hb Lepore Hollandia (δ22/β50), and Hb Lepore Baltimore (δ50/β86). Worldwide, Hb Lepore Washington Boston is the most prevalent subtype[1,2]. From a clinical point of view, patients with homozygous Hb Lepore exhibit a clinical picture of hemolytic anemia with splenomegaly and marked reduction or absence of HbA and HbA2 and an increase in HbF and Lepore variant. In the case of a heterozygous form of Hb Lepore, the clinical picture is asymptomatic with features resembling the thalassemia trait with a mild reduction in HbA and a mild increase in HbF and Hb Lepore. The hematological workup that is important for the characterization of Hb variant includes complete blood count (CBC), iron profile, Hb electrophoresis, hemolytic markers, blood film, and molecular testing. The presence of a unique Hb Lepore band on cellulose acetate electrophoresis or quantification in high-performance liquid chromatography (HPLC) can distinguish Hb Lepore from another variant, mostly thalassemia[4]. This case report has been reported in line with the SCARE 2020 Criteria[5].

HIGHLIGHTS

- Hemoglobin (Hb) Lepore is one of the structural Hb variants that occur due to unequal crossing over between the δ and β globin genes.
- Clinically speaking, Hb Lepore heterozygotes resemble those with mild thalassemia.
- Given that Hb electrophoresis is inconclusive in the first year of life, it is recommended to repeat the test after 1 year in addition to focusing on the family history.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2023) 85:5219–5222

Received 4 July 2023; Accepted 12 August 2023

Published online 1 September 2023

http://dx.doi.org/10.1097/MS9.0000000000001212

Case presentation

Our patient is a 28-year-old female who came to our attention for assessment of generalized weakness and fatigue for a 4-month duration. The chief complaint of the patient was associated with generalized weakness and abdominal pain. The patient reported no personal and/or family history of cancer; any acute, repeat, or discontinued medications; any allergies; or any genetic or psychosocial issues. A thorough review of past medical and surgical histories revealed no record of diseases, surgical procedures, or any prior hospitalization. Physical assessment of the patient was entirely normal except for pallor of the face. Laboratory evaluation, including CBC, showed mild microcytic hypochromic anemia with parameters resembling the thalassemia trait (Fig.1). Iron profile studies were normal. Abdominal ultrasound showed mild splenomegaly. Hb electrophoresis was performed and showed an abnormal pattern with mild elevation in HbF, mild reduction in HbA, and high HbA2, suggesting a heterozygosity for the beta chain variant of Hb Lepore (Figs 2–4).

Discussion

Hb Lepore is a hybrid gene product (produced by uneven crossing over between the globin genes) with a loss of 7.4 kb between the delta and beta-globin genes. It consists of a delta–beta hybrid or fused globin chain[1,2]. The three forms of Hb Lepore that have been found so far are caused by variations in the transitions from the delta to the beta sequences at fusion functions[1–3]. They are Hb Lepore Baltimore, Hb Lepore Hollandia, and Hb Lepore Washington Boston, with Hb Lepore Washington Boston being the most prevalent and occurring globally[1,2]. The formation of excess – chains causes the clinical symptoms of – thalassemia because of ineffective erythropoiesis and shorter red cell survival

Complete Blood Count, (CBC)		
RBC INDICES		
Haemoglobin	10.1 g/dL	(12 -16)
Haematocrit	32.5 %	37- 47
RBC	4.82 10^12/L	4.2 - 5.4
RDW	15.8 %	11.5 - 14.5
MCV	67 fl	76 - 99
MCH	20.95 pg	27.0 - 31.0
MCHC	31.09 %	32.0 - 36.0
LEUCOCYTES	7.70 10^9/L	4.5 - 10.00
DIFFERANTIAL		
% NEUTROPHILS	72 %	50.0 - 75.0
% LYMPHOCYTES	18 %	25.0 - 40.0
% MONOCYTES	7 %	3.0 - 7.0
Haemoglobin Electrophoresis		
Haemoglobin A	80.0	> 94 %
Haemoglobin A2	3.5	1.3 - 3.7 %
Haemoglobin F	2.5	< 2.0 %

Figure 1. Complete blood count: the results showed low Hb, low MCV, low MCH, and low MCHC. MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell count.

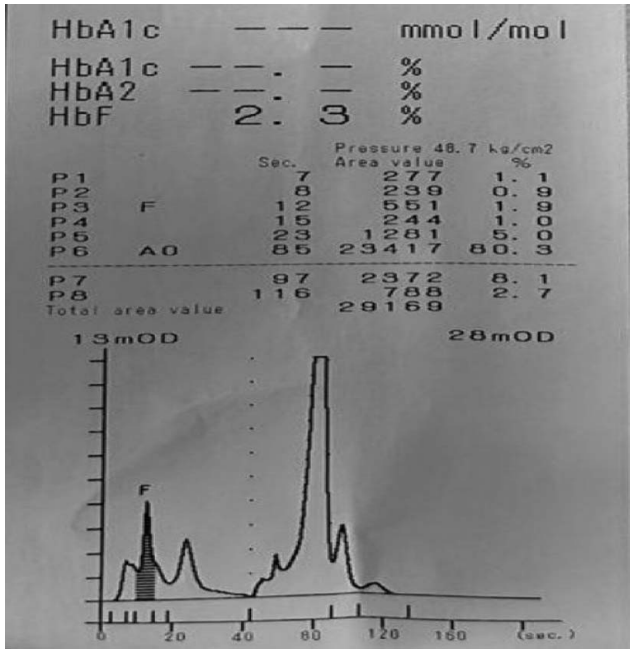

Figure 2. High-performance liquid chromatography result shows an abnormal histogram with a mild increase in HbF and an abnormal histogram shape with a band between 90 and 120 s, suggesting a heterozygous Lepore picture (Performed by ARKRAY analyzer).

in all of these variations, which results in an imbalance in the globin protein[4].

Hb Lepore heterozygotes are mostly asymptomatic, but some Greek and Yugoslavian heterozygotes showed mild splenomegaly, according to a large Italian series[6]. Heterozygotes typically have normal Hb levels and noticeable microcytosis and hypochromia in addition to being healthy[3]. Clinical manifestations in homozygotes range from a transfusion-dependent – Thalassemia major-like course to Thalassemia intermedia[3]. The degree of imbalance between globin chains and those that do not include them may be secondary to this variability[3]. Several blood count/red cell indices and Hb tests are part of the multidimensional method for the presumptive detection of Hb variants. This method makes Hb Lepore easy to find[4]. When using HPLC variant Hb testing system, Hb Lepore has the same retention time value as HbA2[2]. Values higher than 10% are indicative of another Hb variant eluted at the same time as HbA2. According to the literature, the most common variants that are eluted with HbA are Hb Lepore and HbE. Molecular testing and globin chain analysis are needed to determine the specific kind of Hb Lepore, which supports and confirms the diagnosis of variant Hb[4].

There is a general decrease in non-globin chains in all Hb Lepore variations because the synthesis of the hybrid chain is much less than that of the chain[7]. The phenotype of Hb Lepore carriers exhibits microcytosis and hypochromia and mimic thalassemia trait patient. HPLC technique for heterozygous Hb Lepore reveals 5–15% of Hb Lepore and elevated HbF levels, which are typically under 5%. In Hb Lepore homozygote patients, severe clinical symptoms resembling thalassemia major have been noted.

In this case, the HPLC results of different machine configurations showed conflicting results. Some Hb electrophoresis

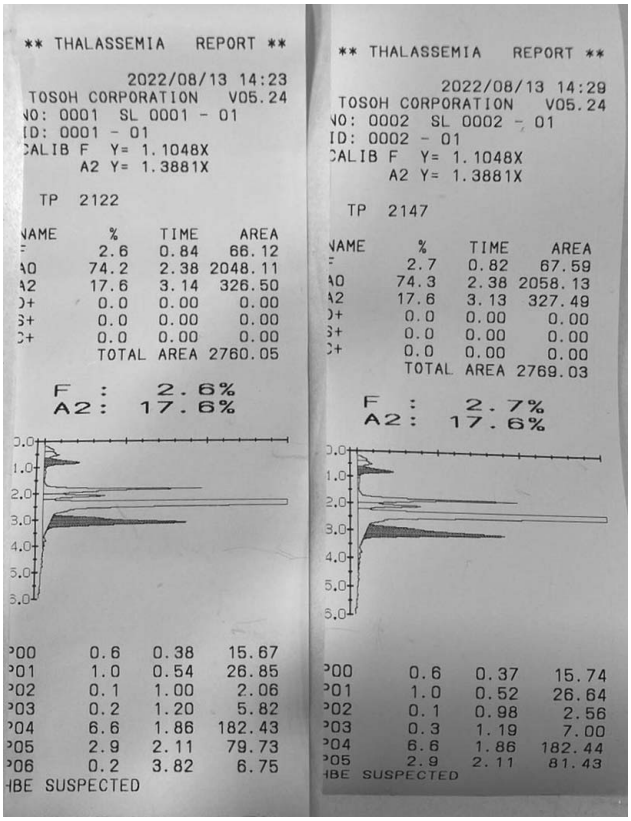

Figure 3. The sample was further analyzed by using another high-performance liquid chromatography device, TOSOH, which revealed an increase in HbA2 result (17.6%), which indicates the presence of another band eluted at the same with HbA2 band.

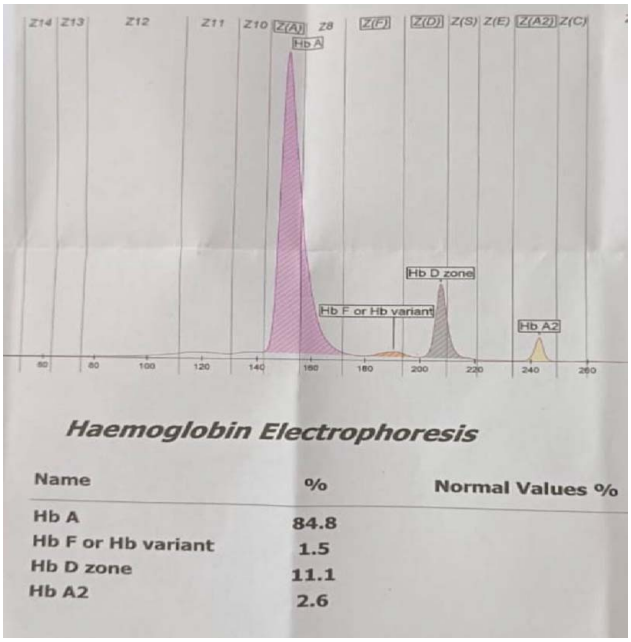

Figure 4. The same sample was also tested with other methods based on the capillary electrophoresis technique, and the result showed the abnormal band as HbD.

techniques identified the variant as HbD, and others gave the pattern of Lepore variants. In this case, the family history, clinical correlation, CBC result, iron profile, and HPLC result should be interpreted together to give an appropriate diagnosis. Some HPLC techniques give patterns and pictures reliable enough to make a diagnosis. In Palestine, which is a developing country, we depend more on biochemical analysis and HPLC result to detect the different type of Hb variants. Unfortunately, in some cases and some types of Hb variants, the definite diagnosis needs more studies, such as the molecular testing of globin chains.

Depending on the degree of globin imbalance and compensatory HbF production, the coinheritance of Hb Lepore abnormalities with thalassemic variants results in varied clinical severity and may reach transfusion-dependent thalassemia phenotype. Patients from Yugoslavia were the most severely impacted, with skeletal deformities, hepatosplenomegaly, hemolytic anemia, and dyserythropoietic[8]. Additionally, compound heterozygotes for Hbs S, C, and E with Hb Lepore also documented. Although the clinical presentations of these disorders are incredibly varied, they generally approximate the compound states of Hbs S, C, or E/thalassemia[3,7,9].

Conclusion

Hematologically, the heterozygous form of Hb Lepore is asymptomatic and has a pattern resembling minor thalassemia, and electrophoretically, it is characterized by aberrant Hb Lepore fractions at a rate of 5–10% and a decreased percentage of HbA. Hb Lepore makes up 10–20% of the electrophoresed Hb in homozygous forms, with the remaining HbF, while HbA and HbA2 are completely missing. Clinically speaking, Hb Lepore heterozygotes resemble those with mild thalassemia. Given that Hb electrophoresis is inconclusive in the first year of life, it is recommended to repeat the test after 1 year in addition to focusing on the family history. Although it is rare, it is important not to forget the Hb Lepore in similar scenarios.

Ethical approval

Our institution has exempted this study from ethical review.

Consent

Written informed consent was obtained from the patient for the publication of this case report. A copy of the informed consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

The authors declare that writing and publishing this manuscript was not funded by any organization.

Author contribution

O.N.S. and A.W.M.J.: writing the manuscript; M.Y.A. and A.S.A.: imaging description; M.Y.A.: reviewing and editing the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Oadi N. Shrateh.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The dataset is available upon reasonable request.

Acknowledgements

None.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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