Case Report

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Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_42_22

Addison's disease in a lady with hemoglobin H disease

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Abstract:

Hemoglobin H (HbH) disease is alpha (α)-thalassemia characterized by the inactivation of three of four α-globin genes due to deletions with or without nondeletional α-thalassemia. HbH disease is not necessarily a benign disorder as has been generally thought. Here, we report a 33-year-old female who has a lifelong history of anemia without blood transfusions. but when she got married, during pregnancies developed symptomatic moderate-to-severe anemia necessitating infrequent blood transfusions. Later due to symptomatic anemias and increasing the frequency of blood transfusions, she underwent splenectomy, 3 years from splenectomy she developed a gradual dark skin discoloration with frequent hypotension and was diagnosed with Addison's disease which is a rare endocrine complication of thalassemia-induced iron overload.

Keywords:

Addison's disease, hemoglobin H disease, hypotension, pregnancy

Introduction

Hemoglobin H (HbH) disease occurs due to defects in three of the four alpha (α) genes found in healthy people. HbH (--/-α) is compatible with life and usually has a similar presentation to that of thalassemia intermedia.[1] However, clinical signs vary among patients, and while some patients may need intermittent or frequent transfusions, others do not. This group of disorders is sometimes known as deletional HbH disease. In Southeast Asia, the deletion of two α-globin genes, plus the inactivation of the third α-globins gene by a nondeletional mutation are present in approximately 20% of patients with HbH disease (--|αTα or --|ααT). The disease is not always benign, especially during the neonatal period, in infancy, and during pregnancy and it has been associated with hydrops fetalis.[2,3]

Several complications linked to chronic anemia and ineffective erythropoiesis including iron overload, endocrinopathies, especially diabetes mellitus, extramedullary hematopoiesis, chronic leg ulcer, pulmonary hypertension, and thrombosis, and so forth have long been observed in patients with thalassemia syndromes.[4] Secondary iron overload occurs due to different mechanisms depending on the underlying medical condition. In the context of hematological diseases, iron most commonly deposits in the body due to chronic blood transfusion as seen in patients with β-thalassemia major. In the case of nontransfusion-dependent thalassemias (NTDT) such as β-thalassemia intermedia and HbH disease, iron overload can develop due to ineffective erythropoiesis, leading to an inappropriately low hepcidin level and subsequently to an increase in the absorption of iron from the gastrointestinal tract (GIT).[5] Addison's disease is a rare endocrine disease,[6] it has an incidence of 0.8 per million and a prevalence of 40-110 per million in the USA and European countries.[7] Addison's disease or primary hypoadrenalism is caused by a total or

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Submission: 08-08-2022
Revised: 07-09-2022
Accepted: 10-09-2022
Published: 09-11-2022

How to cite this article: Rashid NG. Addison's disease in a lady with hemoglobin H disease. Iraqi J Hematol 2022;11:182-5.

near-total destruction or dysfunction of one or both adrenal cortices. This results in decreased secretion of the adrenal cortical hormones – cortisol, aldosterone, and androgens. The disease is characterized by weight loss, muscle weakness, fatigue, low blood pressure, and sometimes darkening of the skin in both exposed and nonexposed parts of the body. It can mimic a gastrointestinal disorder or a psychiatric disease, especially depression.[8] A deficiency of adrenocorticotrophic hormone (ACTH) can also produce hypocortisolism, but this is known as secondary adrenal insufficiency. Addison's disease is a term restricted to primary adrenocortical insufficiency. Addison's disease secondary to iron overload due to HbH disease is an extremely rare condition in comparison with other endocrinopathies in thalassemia syndromes such as diabetes mellitus or hypogonadism, that is why we consider that here we report a very rare case of Addison's disease secondary to HbH disease.

Case Report

The history of this 33-year-old young female with gravida 3, para 2, abortion 0, and a positive blood group dates back to 2008 when she got her first pregnancy, at that time she got pallor, tiredness, shortness of breath, and easy fatigability with moderate-to-severe anemia. She was managed by her district doctors and received multiple blood transfusions until the delivery of her first baby and was without blood transfusion thereafter.

In 2012, she got her second pregnancy and again was symptomatically anemic and she received multiple blood transfusions from the local doctors of her district. In 2013, she was referred to our center (Hiwa Hemato-Oncology Hospital) in Slemani-Kurdistan region-Iraq. A full hematologic workup was arranged, the patient had anemia Hb 6.58 gm/dl, low MCV and MCH, normal RDW, normal retic count, negative Coombs test, negative viral screen, normal renal and hepatic functions. Ferritin of 350 ng/dl, positive HbH preparation, and normal Hb-electrophoresis for B-thalassemia with TSH of 11 mIU/L. Abdominal ultrasonography showed huge splenomegaly of 20 cm; echocardiography repeatedly was normal. Hence, we diagnosed the patient as a case of HbH disease with hypothyroidism.

The patient was put on regular follow-up with folic acid and thyroxin tablets orally with occasional blood transfusions. However, unfortunately, she intentionally lost from our follow-up for more than 1 year when she returned back she was tired with severe anemia, spleen size around 22 cm with dizziness, she also complains of abdominal heaviness, and early satiety due to huge splenomegaly. She received infrequent blood transfusions with regular follow-up, but due to progressive splenomegaly and anemia, we discussed the patient's option of splenectomy, the patient consented to splenectomy, and after presplenectomy vaccinations, she underwent a splenectomy in 2018 with postoperative penicillin V and aspirin prophylaxis.

After splenectomy, she was stable with acceptable Hb 9.5-10g/dl for nearly 2 years with a high ferritin level of >1000 ng/dl and was sent to the thalassemia center for iron chelation therapy but unfortunately, her complaints were not good due to unavailability of drugs during certain periods and the patient was at a rural area which obstacles her attendance to thalassemia center.

From the end of 2020, she got black discoloration of her body starting from her lower limb and then abdomen [Figure 1] with frequent bouts of nausea and hypotension. We were suspicious about the possibility of concomitant hemochromatosis, molecular studies for C282Y, and HEF 21 genes were negative.

Finally, she got her third pregnancy with progressive hypotension with black discoloration all over the body including the oral mucosa. Lastly we sent the lady to an endocrinologist to exclude the possibility of Addison's disease, the diagnosis was a primary adrenal failure with elevated plasma ACTH level >2000 pg/ml and serum cortisol level 12.3 mcg/dl at evening.The treatment was started with hydrocortisone tablet with fludrocortisone tablet with skincare and regular follow up. Now, the patient is stable with improvement in general well-being with improved hypotension and tolerable Hb of 89 gm/dl and her third pregnancy is now near term, although she is still not complaining with her iron chelation regularly despite that we explained that high ferritin level is very dangerous for deterioration of her disease and she may get diabetes or heart failure in future.

Discussion

The clinical manifestations of thalassemia intermedia result from ineffective erythropoiesis, chronic anemia, and iron overload. HbH which is a form of NTDT has a diverse phenotypic presentation depending on the degree of α-globin chain deficiency which in turn relates to the underlying α-thalassemia mutations with hemolysis being the dominant clinical symptom.[9]

Scrutinizing α-thalassemia is not as easy as β-thalassemia due to the lower carrier rate in our region, and the difficulty in confirming the diagnosis of α-thalassemia carriers through routine Hb electrophoresis.

The carrier rate of α-thalassemia in Iraq is estimated at <1%, but no study has yet rectified the exact carrier

rate in this region. So far, a couple of small studies by Al-Allawi *et al*. have described the spectrum of α-globin gene mutations among carriers in the provinces of Dohuk and Slemani.[10,11]

It has been previously documented that HbH patients with deletion/deletion and HbH disease genotype are of the least severe phenotype, followed by deletion/nondeletion arrangement, and the nondeletion/nondeletion genotype which is supposed to be the most severe.[1,12]

A cohort study of β-thalassemia intermedia patients has shown terrifying evidence that these patients representing NTDT had a much higher incidence of several thalassemia-related complications compared to transfusion-dependent β-thalassemia who were well-treated.[13,14]

Despite our extensive search to find complications related to HbH patients, we got very little data, one of them was a case study about a 32-year-old splenectomized Greek woman, para 1, at the 22nd weeks of gestation, who was referred to the A and Es with a 1-week history of abdominal discomfort and persistent vomiting, who was found to have hepatic and venous thrombosis.[15]

Regarding our case with HbH disease, she gave us a history of symptomatic anemia since 2008 [Table 1] when she got pregnant with her first pregnancy and she mostly received blood transfusions during her pregnancies when she became symptomatic.

This lady has had hypothyroidism since 2012, we do not know really that this hypothyroidism is related to her thalassemia intermedia and chronic abnormally high iron level or not and we do not think that this hypothyroidism has any relation with autoimmune hypoadrenalism as our patient a decade ago did not complain of Addison's disease and even currently she has no hypoglycemia or hyponatremia with a negative autoimmune screen.

In 2018 as she developed mechanical symptoms of splenomegaly with features of anemia, splenectomy was done; she was good and stable for nearly 2 years postsplenectomy, and then she developed gradual hyperpigmentation of skin with weakness, nausea, and hypotension; we thought that this lady might have concomitant hemochromatosis which was excluded through genetic tests for HFE gene with C282Y mutation. However, with the persistence of symptoms, we thought the patient probably got Addison's disease due to excessive iron deposition through infrequent blood transfusions or excessive GIT iron absorption [Table 2] due to the downregulation of hepcidin.

After her diagnosis with Addison's disease, she started on combined steroids with mineralocorticoids by the endocrinologist and her condition is improving meanwhile she got her third pregnancy. In this case study, we found that very scanty data available about HbH disease and its complications in comparison to what is available about complications of β-thalassemia patients.

Actually, we did not find any data about the incidence of Addison's disease in HbH patients, so we think for the first time we report a patient with primary adrenal insufficiency in HbH patient, probably this patient got this condition because she did not complain about her iron chelation therapy despite her referral for thalassemia center several times.

Table 1: Mean hemoglobin level for each year of follow-up

Hb (g/dl)	Years
7.5	2013
7.3	2014
7	2015
7.2	2017
9.5	2018
10.5	2019
10	2020
9.6	2021
9	2022

Hb=Hemoglobin

Table 2: Mean ferritin level for each year of follow-up

Ferritin level (ng/ml)	Years
573	2014
775	2015
603	2017
950	2018
2100	2019
1490	2020
805	2021
830	2022

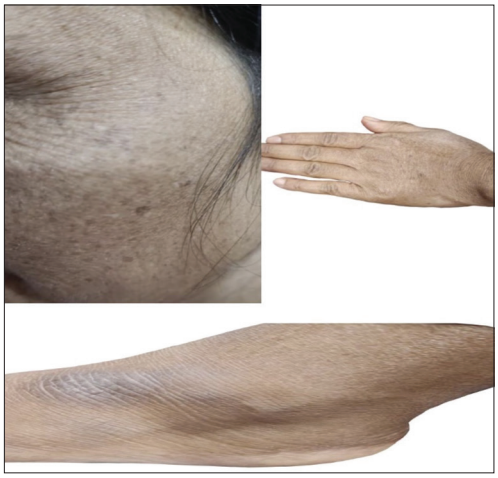

Figure 1: Hyperpigmented skin lesions

Conclusion

It was thought that iron overload-related complications were more frequent in transfusion-dependent β-thalassemia major, but now due to implementing good management and follow-up plan for those groups of patients, their complications are decreasing everywhere. Meanwhile we are facing a lot of complications of NTDT patients including HbH cases due to absence of solid guidelines for their management and the belief that the latter group of patients has less problems. Finally, here, we report a very rare complication of HbH disease which we did not find it anywhere.

Patient consent

The author certifies that he obtained the patient's consent for disclosing her medical information with the images.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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