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Iron deficiency anemia masking hemoglobin H disease: A case report

Somchai Insiripong*

Watcharin Yingsitsiri* Juree Boondumrongsagul*

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Hemoglobin H disease (Hb H) in adult patients can be diagnosed by identifying the band of Hb H with or without Hb Bart on Hb electrophoresis, and probably confirmed by genotyping study. However, Hb H may be suppressed by some acquired factors including iron deficiency anemia. Herein, we report a case of a 55-year-old woman was recognized as having chronic anemia since childhood. She was treated with occasional transfusions, one or two units a year. Her first Hb electrophoresis showed: HbA_2A, HbA_2 2.1%, while her Hb was 5.1 d/dL, her ferritin 6.2 ng/mL, and transferrin saturation 13.2%. She was diagnosed as having iron deficiency anemia and treated with iron compound. The causes of iron deficiency could not be definitely concluded. Two months later, her Hb level and ferritin were 8.8 g/dL and 110.7 ng/mL, respectively. Her new Hb electrophoresis showed: $HbA_2ABartH$, HbA_2 1.7 %, and HbF 0.8%. The diagnosis of Hb H disease was therefore added. In spite of the rarity of iron deficiency anemia superimposing over Hb H, if the patients with Hb H disease with unusually severe anemia were encountered, iron deficiency should be considered as one of the contributing factors. On the contrary, when iron was adequately supplemented in case of iron deficiency anemia, the Hb level could not access the normal range; Hb H disease should therefore be excluded because iron deficiency could completely suppress Hb H band.

Keywords: *Iron deficiency anemia, Hb H disease.*

Reprint request: Insiripong S, Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

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*Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

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การวินิจฉัยโรค Hemoglobin H (Hb H) ในผู้ป่วยวัยผู้ใหญ่ ทำได้ด้วยการตรวจ Hb electrophoresis แล้วพบแบนด์ของ Hb H โดยอาจจะมีหรือไม่มี Hb Bart ก็ได้ และอาจจะตรวจยืนยันด้วยการตรวจยีนส์อย่างไรก็ตาม Hb H อาจจะถูกบดบังด้วยปัจจัยต่าง ๆ ที่เกิดในภายหลัง ซึ่งรวมทั้งภาวะโลหิตจางจากการขาดเหล็กก็ได้ ในรายงานนี้เป็นการศึกษาผู้ป่วยหญิงอายุ 55 ปี ซึ่งได้รับการสังเกตว่าโลหิตจางมาตั้งแต่เด็ก และได้รับการเติมเลือดเป็นครั้งคราวประมาณ 1 หรือ 2 หน่วยต่อปี ตรวจ Hb electrophoresis ครั้งแรกพบ Hb A_2A, Hb A_2 2.1%, F 0.0% ขณะที่ความเข้มข้น Hb 5.1 g/dL และ ระดับ ferritin 6.2 ng/mL, transferrin saturation 13.2% ให้การวินิจฉัยว่าเป็นโลหิตจางจากการขาดเหล็ก และให้การรักษาด้วยยาเข้าเหล็ก สาเหตุของการขาดเหล็กในผู้ป่วยรายนี้ไม่ทราบแน่ชัด อีก 2 เดือนถัดมา Hbและ ferritin เพิ่มเป็น 8.8 g/dL และ 110.7 ng/mL ตามลำดับ ตรวจ Hb electrophoresis อีกครั้งก็พบ $HbA_2ABartH$, HbA_2 1.7 %, HbF 0.8% จึงวินิจฉัยเพิ่มว่าเป็นโรค Hb H ด้วยแม้ว่าโลหิตจางจากการขาดเหล็กในผู้ป่วยโรค Hb H จะพบน้อยมากก็ตาม เมื่อพบผู้ป่วยโรคHb H ที่มีโลหิตจางมาก ๆ อาจจะต้องคิดว่าผู้ป่วยอาจมีโลหิตจางจากการขาดเหล็กร่วมด้วย และในทางตรงข้ามในผู้ป่วยโลหิตจางจากการขาดเหล็กเมื่อได้รับการรักษาด้วยเหล็กพอแล้ว ความเข้มข้นเลือดไม่กลับขึ้นถึงขั้นปกติ อาจจะต้องหาโรค Hb H ด้วย เพราะโรคโลหิตจางจากการขาดเหล็กสามารถลดแบนด์ของ Hb H ไว้จนไม่สามารถตรวจพบได้

คำสำคัญ: *โลหิตจางจากการขาดเหล็ก, โรค Hemoglobin H.*

Hemoglobin H disease (Hb H) is one of the clinically significant alpha-thalassemia diseases, resulted from the marked decrease of alpha globin chains, leading to the formation of the tetramer (β_4 or Hb H) by the excess beta globin chain itself. Its main clinical manifestation is microcytic anemia due to the ineffective erythropoiesis and chronic hemolysis, the Hb level actually ranges between 5.7 - 11.1 g%[1] and the patients with Hb H disease usually do not need blood transfusion, except for occasional episodes of acute hemolytic crisis after exposure to oxidative stress. It could be diagnosed by the finding of the band of Hb H with or without Hb Bart on the Hb electrophoresis and could be definitely confirmed by genotyping study. Although it is a genetic disease but the amount of Hb H may be suppressed by some genetic factors as seen in the co-inheritance of Hb H disease and sickle cell trait,[2] or by acquired factors such as iron deficiency anemia.[3] Herein we report an additional case of a 55-year-old woman who was firstly diagnosed as having iron deficiency anemia but later it turned out she had Hb H that was firstly masked by the iron deficiency anemia.

Case Report

A 55-year-old Thai woman was referred to a hematologist because of severe chronic anemia since childhood. She was occasionally treated with blood transfusions, one or two units a year, and irregular oral iron supplements at the district hospital. She was not a vegetarian. There were no family members who had anemia like her. She always had hypomenorrhea and oligomenorrha and she was never pregnant. On the physical examination, she was pallor, without jaundice, and no hepatosplenomegaly. Her blood tests included: Hb 3.6 g/dL, Hct 12.1 %, MCV 50.8 fL, MCH 15.4 pg, MCHC 30.2 g%, RDW 31.9%, target cell+1, microcyte +1, poikilocyte +1, no nucleated red blood cell, WBC 7,000/mm^3, platelet 477,000/mm^3, ferritin 6.2 ng/mL, transferrin 267.9 ug/dL (normal 200 - 360), serum iron 50 ug/dL (normal 35 - 165), transferrin saturation 13.2 % (normal 4.1 - 13.8), Hb electrophoresis (by using VARIANT II, Bio-Rad®, high performance liquid chromatography): Hb A_2A, Hb A_2 2.1%, Hb F 0.0%, normal liver, kidney, and thyroid function tests. She was diagnosed as having iron deficiency anemia and was treated with Ferro-B-Cal 3 tablets (each tablet containing elementary iron 66 mg) a day. To find the cause of iron deficiency gastroscopy, colonoscopy, vaginal examination, stool examination and urinalysis were performed and they were unremarkable.

After three-month treatment: Hb 7.2 g/dL, Hct 24.7 %, MCV 61.6 fL, MCH 18.0 pg, MCHC 29.2 g%, RDW 17.9%, ferritin 35.4 ng/mL, serum iron 144.0 ug/dL, TIBC 302 ug/dL (259 - 388), Hb electrophoresis: HbA_2ABartH, Hb A_2 1.4%, and Hb F 0.2%. She was additionally diagnosed as having Hb H disease; thus, Ferro-B-Cal was decreased to one tablet a day as well as folic acid was added.

After nine-months of treatment: Hb 8.3g/dL, Hct 28.9 %, MCV 62.9fL, MCH 18.0 pg, MCHC 28.6 g%, RDW 24.8 %, and ferritin 156.4 ng/mL; Hb electrophoresis: HbA_2ABartH, Hb A_2 1.7%, and Hb F 0.8%. The genotype study revealed presence of alpha-thalassemia-1 (SEA type) and alpha-thalassemia-2 genes (3.7 kb).

Discussion

Actually the basic pathogenesis of Hb H disease is chronic hemolysis with ineffective erythropoiesis and iron absorption is usually increased in thalassemia, therefore the serum ferritin level should be expectedly normal[4] or increased[5] even without blood transfusion. Therefore, iron deficiency anemia superimposing over Hb H disease has still rarely been reported.[3]

Hb H is in fact unstable[6] and has variably accounts for 1.4 - 40 %[7] in the patients with Hb H disease. When the severity of anemia in Hb H disease is aggravated by iron deficiency, the band of Hb H on Hb electrophoresis will be possibly lessened or even absent whereas the inclusion body in the peripheral blood is also absent.[3] Therefore, in case of iron deficiency anemia, when the iron is adequately supplemented while the underlying causes of iron deficiency are found and solved if the Hb level cannot access the normal range; Hb H disease should be the one that needs to be firstly excluded.

When Hb H disease is co-inherited with beta hemoglobinopathy such as sickle cell trait, only Hb Bart, A and S can be found, no Hb H.[2] Likewise, Hb H disease in combination with Hb E[8], HbTak, Hb Hope or beta (0)-thalassemia trait, Hb H as well as inclusion body will be minimally found or absent[9] for life. However, the absence of Hb H due to iron deficiency can be rescued after the iron supplement is adequate.

The ratios of Hct / Hb before and after iron therapy were 12.1/3.6 and 28.9/8.3 = 3.36 and 3.48, respectively; this was consistent with that of 3.5 ± 0.2 of Hb H disease.[10] Therefore, when the patients with iron deficiency anemia are encountered, the Hct / Hb ratio close to 3.5 ± 0.2 may be used as one of the valid hints for early investigation of Hb H disease.

Conclusion

A 55-year-old woman with severe chronic anemia since childhood was firstly diagnosed as iron deficiency anemia and treated with oral iron tablets. Later, she was proved to have Hb H disease because her Hb electrophoresis showed band of Hb H which used to be absent while iron was deficient. This suggests that iron deficiency can mask Hb H band on Hb electrophoresis in case of Hb H disease.

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