Hemoglobin H Disease with Hemoglobin J-Korat: Report of Two Cases

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Abstract: Hemoglobin J-Korat or J-Bangkok ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$) has been occasionally reported in Thailand in the forms of trait or double or triple heterozygotes. Here we report 2 unrelated cases of triple heterozygotes of Hb H, alpha(0)- and alpha(+)-thalassemias with Hb J-Korat traits. They are 55- and 50-year-old Thai patients having moderate pallor, spleen enlargement 2-3 cm below left costal margin, no hepatomegaly. Their Hb concentrations ranges between Hb 8.7-9.6 g%, Hct 27.6-33.3 %, MCV 54.0-93.6 fL, MCH 15.7-29.5 pg, MCHC 28.9-31.5 g%, RDW 15.5-25.1 %, comparable to Hb 8.1 g%, Hct 29.5%, MCV 63.0 fL, MCH 17.3 pg with mild jaundice, mild hepato-splenomegaly of naïve Hb H disease. The diagnosis of this entity depends on the Hbelectrophoresis that demonstrates the band of Hb J-Korat as well as Hb A and it could be confirmed by the genotype study. It seems that the patients with the triple heterozygous Hb H with Hb J-Korat trait have the clinical and hematological manifestations which are not different from that of Hb H disease per se. Furthermore, Hb H disease with Hb J-Korat trait still has acute hemolytic crisis during the exposure to the oxidative stress, the important characteristic of Hb H disease per se.

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Hemoglobin J-Korat หรือ J-Bangkok ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$) พบได้เป็นครั้งคราวในประเทศไทย ทั้งในรูปภาวะแฝง หรือภาวะ double หรือ triple heterozygote ในรายงานนี้มีผู้ป่วย 2 ราย ที่ไม่เกี่ยวข้องกันเป็น triple heterozygotes ระหว่าง Hb H disease ที่เป็น alpha (0)- และ alpha (+)-thalassemias แฝงร่วมกับภาวะแฝงของ Hb J-Korat ผู้ป่วยทั้งสองราย อายุ 55 ปี และ 50 ปี มีภาวะซีดปานกลาง ม้ามโตประมาณ 2-3 เซนติเมตรต่ำกว่าใต้ชายโครงซ้าย ไม่พบว่าตับโตความเข้มข้น Hb ระหว่าง 8.7-9.6 กรัม%, Hct 27.6-33.3 %, MCV 54.0-93.6 เฟมโตลิตร, MCH 15.7-29.5 พิโครกรัม, MCHC 28.9-31.5 g%, RDW 15.5-25.1 %, เทียบกับ Hb 8.1 กรัม%, Hct 29.5%, MCV 63.0 เฟมโตลิตร, MCH 17.3 พิโครกรัม ร่วมกับภาวะดีซ่านเล็กน้อย ตับม้ามโตเล็กน้อย ของโรค Hb H ธรรมดาการวินิจฉัยโรคนี้ ทำได้ด้วยการตรวจ Hbelectrophoresis พบ band ของ Hb J-Korat ร่วมกับ Hb A และอาจจะยืนยันด้วยการตรวจ genotype ในผู้ป่วยทั้งสองราย ดูเหมือนว่าการมี Hb J-Korat แฝงร่วมไปในโรค Hb H ไม่ได้ทำให้ผู้ป่วยมีอาการแสดงทางคลินิกหรือผลการตรวจทางโลหิตแตกต่างไปจากผู้ที่เป็นโรค Hb H เพียงอย่างเดียวยิ่งกว่านั้นผู้ป่วยโรค Hb H with Hb J-Korat แฝง ยังคงมีการแตกของเม็ดเลือดแดงอย่างรุนแรงในช่วงที่ต้องเผชิญกับ oxidative stress, ซึ่งนับเป็นคุณสมบัติที่สำคัญของผู้ป่วยโรค Hb H ธรรมดานั่นเอง

Introduction

Hemoglobin (Hb) H disease is a clinically common alpha-thalassemic disease. It is resulted from the double heterozygosity of alpha(0)-thalassemia due to the deletion of both linked alpha-globin genes on chromosome 16, and alpha(+)-thalassemia from the single alpha-globin gene deletion (--/-alpha) or non-deletional alpha-thalassemia genes such as Hb Constant-Spring (CS). Its main manifestation is microcytic chronic hemolytic anemia, Hb concentration rangesfrom 9 to 10 g%, occasionally complicated by acute hemolytic crisis when exposes to high fever leading to unavoidable blood transfusion[1].

Hb H disease can be co-incidentally transmitted with beta thalassemia or beta hemoglobinopathy, such as Hb H disease with Hb E ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$) traitor HbAEBart disease, Hb H with Hb Pyrgos ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$)[2], Hb H-CS with Hb J-Bangkok (or J-Korat)[3].

Hb J-Korat (J-Bangkok or J-Meinung) is resulted from the combination of 2 normal alpha globin chains and 2 abnormal beta globin chains whose glycine at the 56th position is substituted by aspartic acid ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$). It was firstly recognized in 1956 in an American Negro woman[4] and then it has been sporadically reported in Indonesian[5], Gujerati Indian[6], French Canadian, Swedish American, Caucasians, Algerian, Hakkanese in Taiwan and Thais[7]. Its heterozygote is clinically and hematolo-gicallynormal[8] while its homozygote has slight normocytic anemia[9]. When it combines with Hb S, these double heterozygosities have still clinical syndrome similar to naïve Hb S trait[10]. Hb J-Korat in the form of triple heterozygosities with alpha(0)-thalassemia with Hb CS trait[3], it does not add any clinical defect to the victim, the clinical manifestations are all confined within that of Hb H disease per se, ie., moderate hypochromic microcytic anemia, mild hepato-splenomegaly. And herein, we report two unrelated cases of Hb H disease with Hb J-Korat, the new triple heterozygosities.

Case Report

Case 1: A 55-year old Thai man had had chronic anemia since childhood with spleen enlargement 3 cm. below left costal margin, no jaundice.

CBC: RBC 6.22x106/mm^3, Hb 9.6 g%, Hct 33.3 %, MCV 54.0 fL, MCH 15.7 pg, MCHC 28.9 g%, RDW 25.1 %, WBC 2,700/mm^3, platelet 220,000/mm^3 micro 1+ poikilo 3+, schistocyte 2+, hypo 2+

Serum direct bilirubin 0.8 mg%, total bilirubin 2.1 mg%, AST 13 IU, ALT 11 IU, alkaline phosphatase 43 IU, cholesterol 101 mg%, triglyceride 90 mg%, creatinine 0.7 mg%.

BM biopsy showed normocellularity 40%, M: E 3: 1, adequate megakaryocyte, blast less than 1% and the flow cytometry showed no PNH clone.

Total iron binding capacity (TIBC) 228 ug/dl, SI 83 ug/dL, ferritin 59.4 ng/mL.

Direct and indirect Coombs' tests and ANA were all negative.

Hb electrophoresis: Hb J-Bangkok, Hb F 2.1%, A2 1.6%. The PCR for alpha(0)-thalassemia (Southeast Asian deletion type) and alpha(+)-thalassemia genes were shown positive.

Case 2: A 50-year-old woman had acute onset of fever with hemolytic crisis. The physical examination revealed pallor with jaundice, no hepatomegaly but spleen 2 cm enlargement.

CBC: Hb 5.6 g%, Hct 17.9 %, MCV 94.7 fL, MCH 29.6 pg, MCHC 31.3 g%, RDW 15.5 % and at the steady state: Hb 8.7 g%, Hct 27.6 %, MCV 93.6 fL, MCH 29.5 pg, MCHC 31.5 g% RDW 15.5 %.

Hb electrophoresis: Hb J 29.4 %, Hb A 66.6 %, Hb A2 2.2 %, Hb F 1.6 %, the direct and indirect Coombs's tests were negative, creatinine 0.9 mg%, ALT 34 IU/L. Genotype analysis revealed Hb H disease, alpha(0)-thalassemia (SEA deletion type) and alpha(+)-thalassemia genes were shown positive.

Discussion

When Hb H disease with Hb J-Korat is compared with deletional Hb H and non-deletional Hb H disease such as Hb H-CS disease without Hb E heterozygote, the degree of anemia in our case is not different from both, viz. the Hb concentration is 8.7-9.6 vs. 8.6±1.2 vs. 7.1±2.3 g%, MCV 62.8±5.84 vs 71.8±7.01 fL, and MCH 19.8±1.73 vs 21.2±2.52 pg, respectively[11].

Hb J-Korat looks similar to Hb E in the aspect that it is resulted from the single amino acid substitution in beta globin chain, glycine at the 56^{th} position substituted by aspartic acid in the former and glutamic acid at the 26^{th} position substituted by lysine in the latter. If Hb H disease with Hb J-Korat is compared with Hb H disease with Hb E trait (HbAEBart disease), and Hb H-CS with Hb E trait (HbAEBart-CS) the Hb concentration is 8.7-9.6 vs. 9.1±1.1 vs. 8.0±0.9 g%, respectively[12].

The Hb concentration of the patients with Hb H disease is less anemic as compared with that of Hb H-CS disease. This fact is still persistent in the cases of Hb H and Hb H-CS diseases with Hb J-Bangkok ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$), the Hb concentration of the former is less anemic than the latter (8.7-9.6 g% vs. 8.1 g%).

When Hb H disease is coincidentally transmitted with beta thalassemia or beta hemoglobinopathy, the fraction of Hb H may not be demonstrated probably because of the instability of Hb H itself as well as the too small amount of the fraction from the decreased imbalance between the alpha and the slightly excessive beta globin chains as seen in case of Hb H with Hb

Hope or Hb H with Hb Tak[13] or Hb H with beta thalassemia trait[14]. To diagnose these triple heterozygosities, it needs the polymerase chain reaction (PCR) method for detecting the alpha(0)-thalassemia and alpha (+)-thalassemia genotyping following the Hb electrophoresis which may show only slightly increased Hb A_2 .

Because Hb J-Korat with or without other thalassemias or hemoglobinopathies[15,16] seemingly does not aggravate any clinically or hematologically-deleterious effect to the victims, it can be simply overlooked and its true prevalence may be underestimated. It is always found by chance on the Hb electrophoresis as in our cases.

Conclusion

Two cases of Hb H disease with Hb J-Korat ($\alpha^{A}_{2}\beta^{56gly\rightarrow asp}_{2}$)[2] are reported. Hb J-Korat seemingly does not add any clinically or hematologically deleterious effect to naïve Hb H, the splenomegaly 2-3 cm below left costal margin, Hb level 8.7-9.6 g%, and one patient still expresses the hemolytic crisis during fever. The band of Hb J-Korat can be recognized on Hb electrophoresis but the band of Hb H may be missed. Its confirmation needs the genotype analysis.

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