Clinical Case Report

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Hemoglobin Hornchurch [β43 (CD2) Glu > Lys; HBB: c.130G > A] in a Chinese boy complicated with thrombocytopenia

A case report and literature review

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Abstract

Rationale: Hemoglobin Hornchurch is regarded as an asymptomatic hemoglobinopathy with no obvious hematological or clinical abnormalities. Recently, we identified hemoglobin Hornchurch in a 13-year-old Chinese boy complicated with thrombocytopenia, which displayed instability in isopropanol precipitation test.

Patient concerns: In this case report, we reported a Chinese boy with hemoglobin Hornchurch complicated by thrombocytopenia. The patients have been misdiagnosed as aplastic anemia and myelodysplastic syndrome before.

Diagnoses: Hemolysis tests, high-performance liquid chromatography, and *HBB* gene sequencing identified the E44K (G>A) mutation. Isopropanol precipitation test showed instability in hemoglobin Hornchurch.

Interventions: The patient was given immunosuppressive therapy for 3 months.

Outcomes: His general conditions have improved along with the recovery of the hemogram index.

Lessons: Further research is needed to clarify the relation between structural abnormality and functional properties of hemoglobin Hornchurch. This second case of hemoglobin Hornchurch indicates that there might be more hemoglobin variants or their carriers in the Chinese population.

Abbreviations: CBC = complete blood count, Hb = hemoglobin, MAIPA = monoclonal antibody specific immobilization of platelet antigens, MCV = mean corpuscular volume, PAIgG = platelet-associated immunoglobulin G, RBC = red blood cell, RDW = red cell distribution width, WBC = white blood cell.

Keywords: Chinese, hemoglobinopathy, thrombocytopenia

1. Introduction

Inherited hemoglobinopathy contains numbers of structurally abnormal hemoglobin. There are 897 variants of the β-globin chain included in Human Hemoglobin Variant database (HbVar) (http://globin.cse.psu.edu), among which 115 are proved to be unstable hemoglobins.[1] Hemoglobin Hornchurch (Hb Hornchurch), caused by the GAG>AAG substitution at codon 43 in β-globin gene, is regarded as an asymptomatic hemoglobinopathy with no obvious hematological or clinical abnormalities. Only 4 cases have been reported so far, 3 Caucasian and 1 Chinese. Recently, we identified Hb Hornchurch in a 13-year-old Chinese boy complicated with thrombocytopenia. Moreover, unlike previous reports,[2–5] we discovered instability in this Hb variant.

2. Case report

A 13-year-old Chinese boy of Han nationality was referred to our hospital with complaints of long-term thrombocytopenia. The onset of the disease in 2013 manifested as purpura and fever. Complete blood count (CBC) revealed pancytopenia [Hb: 108 g/L, platelet: 23×10^9/L, white blood cell (WBC): 1.4×10^9/L, neutrophil: 0.5×10^9/L]. The patient was given anti-infective therapy as well as intravenous infusion of gamma globulin and dexamethasone. He took oral prednisone for 20 mg/day after being discharged. Similar situations occurred half a year later, Hb fell to 46 g/L, platelet to 11×10^9/L, WBC to 2.22×10^9/L, and neutrophil to 0.3×10^9/L. Reticulocyte count was 24.3×10^9/L. Bone marrow analysis revealed erythroid hyperplasia, megaloblastic change, occasional nuclear malformation, and reduced megakaryocytes and platelets. This patient also developed

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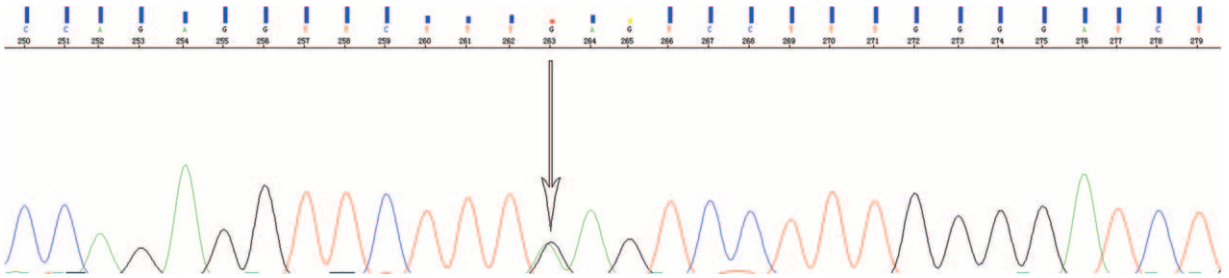

Figure 1. Sequence analysis of the *HBB* gene identifying the heterozygous G>A mutation at codon 43, corresponding to the Glu→Lys substitution of Hb Hornchurch in the patient.

jaundice. Aplastic anemia and myelodysplastic syndrome were suspected. He was given anti-infective therapy in combination with infusion of red blood cells (RBCs) and platelets. This patient underwent bone marrow analysis for 5 times in all. All revealed bone marrow active hyperplasia and rare platelets. The latter 4 bone marrow analyses also showed decreased myeloid erythroid ratio (0.16:1, 0.4:1, 1.22:1, 0.71:1). Cytogenetic analysis of bone marrow cells was normal. Autoantibodies were negative. CD55+ and CD59+ cells were among normal ranges. During the course of disease, the highest platelet count achieved was 126×10^9/L.

In January 2017, this patient came to our department. Physical examinations revealed Cushing face. CBC showed Hb 118 g/L, reticulocyte count 36×10^9/L, MCV (mean corpuscular volume), 94.2 fL, red cell distribution width (RDW) 13.5%, and platelet

Table 1

Timeline.

Dates	Relevant past medical history and interventions
June 2013–January 2017	The onset of the disease manifested as purpura and fever. CBC revealed pancytopenia. The patient was given anti-infective therapy as well as intravenous infusion of gamma globulin and dexamethasone. He took oral prednisone for 20 mg/d after being discharged. More severe pancytopenia occurred half a year later. Bone marrow analysis revealed erythroid hyperplasia, megaloblastic change, occasional nuclear malformation, and reduced megakaryocytes and platelets. Aplastic anemia and myelodysplastic syndrome were suspected. He was given anti-infective therapy in combination with infusion of RBCs and platelets. During the course of disease, the highest platelet count achieved was 126 × 109/L.

Dates	Summaries from initial and follow-up visits	Diagnostic testing (including dates)	Interventions
January 2017	A 13-year-old Chinese boy of Han nationality was referred to our hospital with complaints of long-term thrombocytopenia. CBC, liver function, MAIPA, and hemolysis tests were carried out.	CBC showed Hb 118 g/L, reticulocyte count 36×10^9/L, MCV 94.2 fL, RDW13.5%, and platelet count 62×10^9/L. WBC count was within the normal range. Liver function showed that levels of total bilirubin, direct bilirubin, and indirect bilirubin were normal. Hemolysis tests revealed positive isopropanol precipitation test. Hb F and Hb A2 were 7.3% (normal range 0.2–1.2%) and 3.6% (normal range 2.3–3.3%), respectively. Direct Coombs test, erythrocyte osmotic fragility test, G-6-PD fluorescence spot test, Ham test, and sucrose hemolysis test were all negative. High-performance liquid chromatography indicated the variant Hb eluted in S window, with a percentage of 43.1. His reticulate platelet percentage and PAIgG were 9.8% (normal range 12.5 ± 4.15%) and 43.4% (normal range 35.6 ± 7.4%), respectively. MAIPA showed that antibodies to GPIIb were positive. (January 2017)	Prevention of trauma and bleeding was the main concern before any diagnosis was reached.
February 2017	According to the hemolysis test results, *HBB* gene sequencing was carried out. This patient was diagnosed to have abnormal hemoglobinopathy (Hb Hornchurch) complicated with thrombocytopenia.	*HBB* gene sequencing identified E44K (G>A) mutation. (February 2017)	He was given cyclosporin A (75 mg, bid), leucogen (20 mg, tid), and levamisole (25 mg, tid, 3d/w) for 3 mo.
April 2017	No bleeding occurred during the treatment. His Hb level and platelet count have returned to 124 g/L and 66×10^9/L by the end of April 2017.	—	He was followed up.

bid = bis in die, CBC = complete blood count, Hb = hemoglobin, MAIPA: monoclonal antibody-specific immobilization of platelet antigens, MCV = mean corpuscular volume, PAIgG = platelet-associated immunoglobulin G, RBC = red blood cell, RDW = red cell distribution width, tid = ter in die, WBC = white blood cell.

count 62×10^9/L. WBC count was within the normal range. Liver function showed that levels of total bilirubin, direct bilirubin, and indirect bilirubin were normal. Hemolysis tests revealed positive isopropanol precipitation test. HbF and HbA2 were 7.3% (normal range 0.2–1.2%) and 3.6% (normal range 2.3–3.3%), respectively. Direct Coombs test, erythrocyte osmotic fragility test, G-6-PD fluorescence spot test, Ham test, and sucrose hemolysis test were all negative. High-performance liquid chromatography indicated the variant Hb eluted in S window, with a percentage of 43.1%. *HBB* gene sequencing identified E44K (G>A) mutation (Fig. 1). On the contrary, tests for his thrombocytopenia were carried out. His reticulate platelet percentage and platelet-associated immunoglobulin G (PAIgG) were 9.8% (normal range $12.5 \pm 4.15\%$) and 43.4% (normal range $35.6 \pm 7.4\%$), respectively. Monoclonal antibody-specific immobilization of platelet antigens (MAIPA) showed that antibodies to GPIIb were positive. Therefore, this patient was diagnosed to have abnormal hemoglobinopathy (Hb Hornchurch) complicated with thrombocytopenia. He was given cyclosporin A (75 mg, bis in die), leucogen (20 mg, ter in die (tid)), and levamisole (25 mg, tid, 3d/w) for 3 months. No bleeding occurred during the treatment. His Hb level and platelet count have returned to 124 g/L and 66×10^9/L by the end of April 2017 (Table 1).

3. Discussion

The mutation site of Hb Hornchurch is external and is an $\alpha 2\beta 1$ contact.[6] There are 4 other variants at β43 (CD2) Glu, Hb G-Galveston, Hb Hoshida, Hb Haringey, Hb Hornchurch, and a nonsense mutation. None of the 3 missense mutations were reported to be unstable.[1] According to previous reports,[2–5] there were no clinical or hematological abnormalities in patients with Hb Hornchurch, and this variant possessed no instabilities or functional defects. However, our case exhibited positive isopropanol precipitation test, with evaluated HbF and HbA2 levels. Further research is needed to clarify the relation between structural abnormality and functional properties of Hb Hornchurch. On the contrary, this second case of Hb Hornchurch indicates that there might be more Hb variants or their carriers in the Chinese population.

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