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Hb-M Hyde Park: a rare cause of cyanosis arising from a de novo mutation

TO THE EDITOR: Cyanosis is an abnormal bluish discoloration of the skin and mucous membranes. It is most commonly seen in conditions associated with cardiovascular and respiratory insufficiency that lead to hypoxemia. A rare cause of lifelong cyanosis is methemoglobinemia occurring due to either an enzymatic deficiency or the presence of abnormal hemoglobin variants known as hemoglobin M (Hb-M) [1]. Herein, we report the case of a 2-year-old child who was found to have a rare Hb-M variant resulting from a de novo mutation.

The proband was a 2-year-old girl who presented at the pediatric hematology clinic with anemia and a bluish discoloration of the lips. Her parents indicated a history of fever and respiratory infection dating to three months ago and she was found to have pallor and cyanosis. All these findings were ascribed to the respiratory tract infection, and she was treated accordingly. The infection subsided; however, cyanosis continued for several weeks. The child had no history of fatigue or exertional dyspnea and no significant history of any recent drug intake. She was the first child born from the non-consanguineous marriage of the parents, had a birth weight of 3 kg, and had an uneventful neonatal period. The family history was unremarkable. Clinically, the child was active and playful but had pallor; her lips and nails showed bluish discoloration due to cyanosis (Fig. 1A). However, no clubbing or organomegaly was found. Her vital parameters were within normal limits. Echocardiogram revealed normal parameters. Other systems were also unremarkable.

A peripheral blood sample was sent for routine hematological and biochemical investigation. Complete blood count showed the following findings: hemoglobin (Hb), 10.1 g/dL; red blood cell count, 4.14×10^6/μL; hematocrit, 32.0%; mean corpuscular volume, 77.3 fL; mean corpuscular hemoglobin (MCH), 24.4 pg; MCH concentration (MCHC), 31.6 g/dL; red cell distribution width, 16.9%; total leucocyte count, 13.2×10^3/μL; platelets, 496×10^3/μL; reticulocyte count, 1.1%. Biochemical tests such as serum iron profile, liver function test, and G6PD assay showed normal results. Oxygen saturation measured by pulse oximetry was 57%, while SaO_2 was 98.1%. However, the methemoglobin level was high at 6.7% (normal, $<1\%$). The blood sample also showed

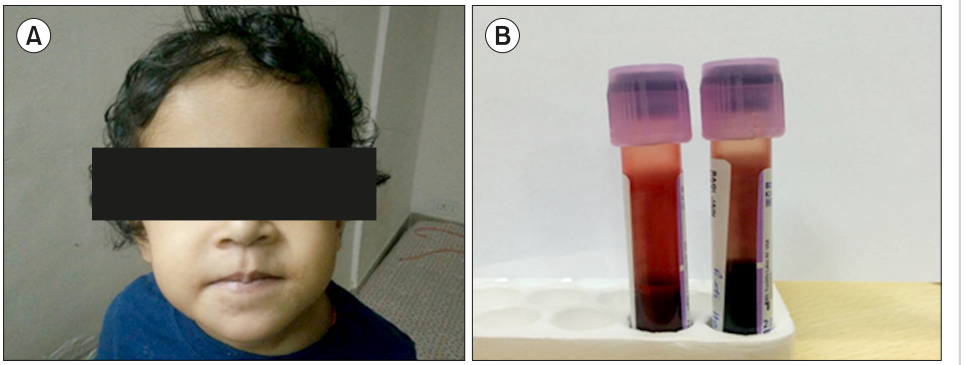
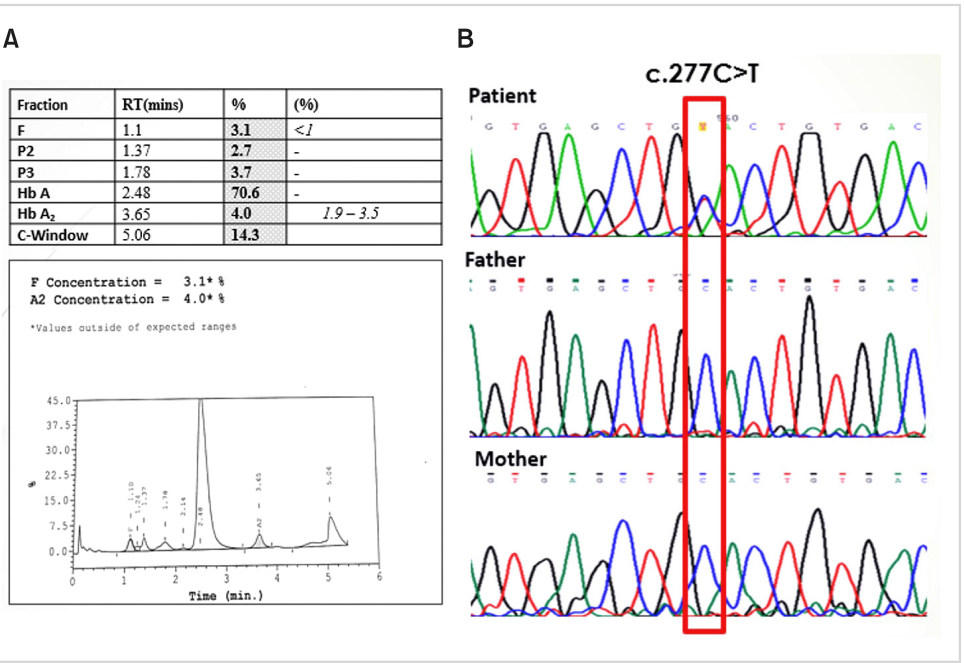


Fig. 1. **(A)** Photograph of the child showing bluish discoloration of lips. **(B)** Anti coagulated venous blood sample of patient (**B**, right) shows distinct brown color as compared to the normal blood sample (**B**, left).



Fraction	RT(mins)	%	(%)
F	1.1	3.1	<1
P2	1.37	2.7	-
P3	1.78	3.7	-
Hb A	2.48	70.6	-
Hb A_2	3.65	4.0	1.9 – 3.5
C-Window	5.06	14.3	

Fig. 2. **(A)** HPLC showing an abnormal hemoglobin peak at C-window and retention time 5.06 mins. **(B)** Chromatogram of HBB gene by Sanger sequencing showing patient being heterozygous for HBB:c.277 C>T [beta92(F8) His>Tyr] and both parents negative, indicating de novo origin in child.

a distinct dark brown color (Fig. 1B).

To investigate the possibility of anemia, high-performance liquid chromatography (HPLC) was performed; the results revealed an unknown Hb peak of 14.3% in the C-window at a retention time (RT) of 5.06 min with increased Hb F levels (3.1%; normal, 0.1–1.2%) and elevated Hb A2 (4.0%; normal, 2.0–3.3%) (Fig. 2A). Considering the levels of Hb A2, Hb F, and abnormal hemoglobin, HPLC was carried out in samples collected from the parents, which showed normal levels. Thus, gene sequencing of the child and her parents was performed. Automated DNA sequence analysis of the beta globin gene in the patient showed a C>T substitution at codon 92 (Fig. 2B). This heterozygous point mutation leads to the substitution of histidine (CAC) by tyrosine (TAC) at the b 92 position, which is seen in Hb-M Hyde Park (also known as Hb Milwaukee 2). However, parent gene sequencing analysis showed normal results. Moreover, no other mutations for beta thalassemia trait were seen in both the child and her parents.

Considering the negative family history for cyanosis and the normal parental HPLC and DNA mutational analysis, the patient was diagnosed with Hb-M Hyde Park due to a de novo mutation.

Methemoglobinemia is a disorder in which there are increased levels of methemoglobin (MetHb) in the circulation. The iron in MetHb is present in the ferric state, which is much more stable than the ferrous state, and thus, it has a decreased ability to bind to O_2 [1]. The most common cause of methemoglobinemia is the intake of certain drugs and chemical agents including local anesthetic agents such as lidocaine, procaine, and benzocaine; aniline dyes, nitrates, sulfonamides, primaquine, dapsone, and acetaminophen, among others. Some inherited conditions such as cytochrome B5 reductase deficiency and NADPH-methemoglobin reductase deficiency can also lead to this disorder [1, 2]. Methemoglobinemia may arise due to mutations in globin chains—alpha, beta, or gamma—leading to the formation of abnormal hemoglobin, Hb-M [1-3]. Hb-M displays

an autosomal dominant inheritance pattern. It is a rare hemoglobinopathy in which the proximal or distal histidine in the alpha, beta, or gamma subunit is replaced by a tyrosine residue [1].

Hb-M Hyde Park/Hb-M Milwaukee2/Hb-M Akita is a rare beta globin chain variant of hemoglobin M wherein the mutation is present at codon 92 by C>T substitution leading to the replacement of histidine by tyrosine (His> Tyr) [1]. Patients with Hb-M Hyde Park are usually asymptomatic but present with cyanosis. This is an unstable hemoglobin resulting in a mild hemolytic picture with anemia and reticulocytosis. Owing to the prominent cyanosis, patients are frequently misdiagnosed for cyanotic heart disease [1].

The first case of Hb-M Hyde Park was reported in 1966 by Heller *et al.* [4] in black patient in the USA. Since then, very few cases have been reported worldwide. In 1968, Shibata *et al.* discovered a new variant of Hb-M in a family with hereditary cyanosis in the Akita province of Japan. It was named as Hb-M Akita but was later found to have the same primary hemoglobin structure as in Hb-M Hyde Park [5, 6]. Hutt *et al.* [7] in 1998 found Hb-M Milwaukee 2 in a patient with Hb E trait. They also found that the mutation in this case was identical to Hb-M Akita and Hb-M Hyde Park.

Most of these reported cases had a hereditary pattern in which the patient's parents, siblings, or both had similar symptoms and were found to have Hb-M Hyde Park. However, only two cases of Hb-M Hyde Park arising from a de novo mutation have been described thus far. Stamatoyannopoulas *et al.* [8] in 1976 reported a case of a 10-year-old child who had cyanosis and Hb-M Hyde Park. However, none of the parents showed any symptoms or positivity for this Hb variant. Another case occurred in a 6-year-old girl who was diagnosed with Hb-M Hyde Park in 1992. Rotoli *et al.* [9] reported that neither the parents nor the sibling showed any abnormalities.

In India, only few cases of Hb-M have been reported, which includes Hb-M Iwate, Hb-M Ratnagiri, and Hb-M Boston [10-12]. However, only a single case of hereditary Hb-M Hyde Park has been reported in India to date. Upadhye *et al.* [12], in 2014, reported the case of a 26-year-old man who was incidentally found to have low oxygen saturation and cyanosis. On further investigation, he was found to have elevated methemoglobin levels. HPLC and DNA sequence analysis confirmed a diagnosis of Hb-M Hyde Park. Subsequently, his mother was also found to have similar complaints [12].

Therefore, to the best of our knowledge, this study is the first to report a case of Hb-M Hyde Park arising due to a de novo mutation in India. The patient in our case presented with the classical history of anemia with cyanosis: dark colored blood and elevated methemoglobin levels. HPLC and DNA sequencing results were indicative of Hb-M Hyde Park. Our patient showed elevated levels of HbF and HbA2, which was also observed by Loong *et al.* [13]. Although elevated levels of HbF and HbA2 are found in individuals with the beta thalassemia trait, our patient and her parents did not show any such mutation in their DNA sequencing. The cause of the elevated HbF and HbA2 in this patient remains unknown and needs further study. Hb-M Hyde Park patients are usually asymptomatic and thus require no further treatment. However, because Hb-M shows greatly decreased oxygen affinity compared to normal hemoglobin and this affects the oxygen saturation, its significance increases under general anesthesia [14].

To conclude, Hb-M Hyde Park is a rare hemoglobinopathy and should be considered as the underlying cause of cyanosis, especially when the search for other common causes has been unproductive. However, the importance of HPLC and DNA gene sequencing in the identification of abnormal hemoglobin variants is indispensable. Generally, the clinical course of such patients is unremarkable. However, owing to low oxygen affinity of hemoglobin M, these patients require special attention by an anesthetist when undergoing any surgery.

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Nuances in the management of acquired hemophilia A in an elderly patient with large granular lymphocytic leukemia

TO THE EDITOR: Acquired hemophilia A (AHA) is a rare (1–4 cases/million/yr) often underdiagnosed bleeding diathesis caused by polyclonal neutralizing immunoglobulins (IgG1 and IgG4) that block the interaction of factor VIII (FVIII) with factor IX, phospholipids and von Willebrand factor. Although it could be idiopathic, it has been described in association with various autoimmune disorders, pregnancy, blood and solid organ malignancies, and certain drugs. Lack of clear treatment guidelines and poor prognosis (mortality, 8–22%) makes AHA an object of concern for clinicians [1]. We discuss the case of a patient with large granular lymphocytic leukemia (LGLL) who presented with acute onset of bleeding and was diagnosed with AHA. To our knowledge, this association has only been reported once in the literature [2]. The nuances in managing AHA with the available hemostatic products and immunosuppressive therapies are also explored.

An 82-year-old man diagnosed with LGLL two years earlier for which he was being observed, presented with extensive non-traumatic bruising of both hips and the left side of the chest wall. His hemoglobin on admission was 9.9 g/dL which progressively decreased to 7.4 g/dL. The platelet count (184,000/μL) and absolute neutrophil count (5.5×10^9/L) were normal. Hemoglobin level briskly fell to 6.5 g/dL after a single bout of rectal bleed despite performing one-unit blood transfusion. The patient had a history of multiple vascular comorbidities, such as coronary artery disease, bilateral iliac artery occlusions, and left partial carotid artery occlusion, which were corrected by percutaneous cutaneous intervention, aortoiliac vascular graft, and endarterectomy, respectively. Aspirin and clopidogrel started for these vascular comorbidities were discontinued. The activated partial thromboplastin time (aPTT) was elevated (80 s) and was not corrected on 1:1 mixing study with normal plasma. The prothrombin time was normal while circulating FVIII inhibitor level was 15 Bethesda Units (BU), suggestive of AHA. Lupus anticoagulant, Coombs test, and disseminated intravascular coagulation workup were negative; however, FVIII levels were found to be markedly reduced (less than 2%) leading to a diagnosis of AHA. Due to the patient's age and vascular comorbidities, the use of bypassing agents such as rFVII or FVIII inhibitor bypass activity for hemostasis was avoided as there were concerns for thrombotic risk. Initially, the patient was administered 6,000 units of porcine FVIII to achieve 30% of plasma FVIII activity. Further, the dose was titrated to 200 units/kg to achieve 50% activity. He was simultaneously treated with immunosuppressive therapy using prednisone (1 mg/kg/d), cyclophosphamide (100 mg/d), and rituximab (375 mg/m^2/wk for 4 wk) to reverse the inhibitor. When he visited our outpatient clinic for the last dose of rituximab, FVIII was up to 19% and FVIII inhibitor had reduced to 4 BU (down from 15 BU). He did not have any clinically overt bleeding at that time, suggesting partial remission.

AHA typically presents with acute onset of bleeding without any prior history of coagulopathy in a bimodal age distribution of 20–30 years and 60–80 years, respectively. Nearly half of the cases are idiopathic while the rest are associated with autoimmune conditions, malignancies, and drugs. It has also been described in pregnancy, particularly in the postpartum setting. Clinically, 80% of cases with FVIII antibodies present with skin, soft tissue, and mucosal bleeds. This is different from congenital FVIII deficiency which typically presents with hemarthroses [1]. Although the spectrum of bleeding in AHA ranges from minor superficial to gastrointestinal, urological bleeding, and retroperitoneal hematomas, in 90% of cases, it strongly tends towards the latter life-threatening type of bleeding [1]. AHA diagnosis requires a sound history corroborated with lab findings, a prolonged aPTT not corrected on mixing with normal plasma, FVIII assay, and a circulating inhibitor of FVIII [3, 4].