WebLog Journal of Hematology

Case Report
Published: 02 Mar, 2026

Hb M- Hyde Park - Rare Hemoglobinopathy in Tamil Nadu

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WebLog Open Access Publications
Article ID : wjh.2026.c0204
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Abstract

Cyanosis is most often due to cardiac or pulmonary disease, but genetic and acquired disorders of hemoglobin can result in significant arterial desaturation. Disorders such as methemoglobinemia, sulfhemoglobinemia, Hemoglobin M, Low oxygen affinity hemoglobin are the differential diagnosis once cardiopulmonary causes were excluded [1]. Acquired disorders are more common whereas long standing symptoms or symptoms in siblings is suggestive of hereditary causes. A 23-year-old female patient from Tamil nadu was admitted for mild respiratory distress with unexpected low oxygen saturation on pulse oximeter- 47%. Her arterial blood gas analysis was normal. History and medical evaluation were not suggestive of cardiopulmonary causes. No drugs or toxins exposure. She had icterus and mild splenomegaly. Her total bilirubin was elevated more of indirect bilirubin. Methemoglobin estimation by spectrometry was high 13.7%. HPLC analysis showed unknown peak in the retention in of 4.47 min. Hb A2 values was elevated -4.5%. On DNA sequencing of beta globin gene shown heterozygous point mutation leads to substitution of tyrosine in place of histidine at the codon 93 of Hb B gene. Hence diagnosed as a case of Hb M Hyde Park /HB M akita/Hb M Milwaukee [2]. Her parents and siblings showed no signs of cyanosis and normal HPLC studies. This has been the second case of Hb M HYDE PARK as fresh mutation reported in INDIA [20].

Keywords: Cyanosis; Methemoglobinl Hemoglobin M; Hb M Hyde Park

Introduction

The M hemoglobins are one of the rare causes of methemoglobinemia in which the globin gene mutation favours haeme iron oxidation. It is the rare hemoglobinopathies in which replacement of proximal or distal histidine by tyrosine in the alpha, beta or gamma subunit has rendered altered spectral and ligand binding properties. The major clinical feature of this disorder is cyanosis. The misdiagnosis of other causes of cyanosis and unneeded treatment are the major hazards of these disorders. We diagnosed the case of HB M MILWAUKEE 2/HB M HYDE PARK/HB M AKITA as a DE Nova mutation different from its usual autosomal dominant inheritance. So far only few cases of HB M were reported in India, as the advanced genetic studies and HPLC techniques made us possible to diagnose this undiagnosed cyanotic hemoglobinopathy.

Case Summary

A 23-year-old female patient presented Emergency department with complaints of giddiness for one day for which she was taken to private hospital Saturation SpO_2 measured 47% and then Referred to GRH, Madurai. On history taking, there is a dusky blue discoloration of persistent character skin from child hood, no aggravating or relieving factors. No symptoms of fatigue and exertion dyspnoea. She was the first child born from the non-consanguineous marriage of the parents. Family history was not significant. Past history was unremarkable. She is unmarried and had regular menstrual cycle. On examination patient had mild Icterus and cyanosis present over palms and tongue, Warm peripheries. No clubbing. No organomegaly. Vital parameters were within normal limit. Other system examination was unremarkable.

On evaluation mild anaemic, persistently increased Total bilirubin concentration. (Indirect > direct), high MCV 101 fL, increased reticulocyte index -3.0%. Direct Coombs negative. Peripheral smear revealed macrocytic/normochromic anaemia. Hemoglobin electrophoresis revealed abnormal hemoglobin as an unknown peak – 20% in 4. 47 minutes retention window time, elevated HbA_2. Ultrasonography showed mild splenomegaly. Echocardiography and CT pulmonary angiogram were normal. ABG analysis revealed discordant hypoxemia (high SaO_2). Patient actual A-a gradient was higher than the expected A-a gradient and high saturation gap i.e. SpO_2<SaO_2 [4]. Therefore, we suspect methemoglobinemia, sulfhemoglobinemia. High methemoglobin was detected in spectrometric analysis. We administer injection methylene blue IV 1mg/kg over 60

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Received Date: *27 Jan 2026*
Accepted Date: *28 Feb 2026*
Published Date: *02 Mar 2026*

Citation:
Noorul Ameen A. Hb M- Hyde Park - Rare Hemoglobinopathy in Tamil Nadu. WebLog J Hematol. wjh.2026. c0204. https://doi.org/10.5281/zenodo.19034736

Figure 1: Patients (top) hand compared to mother hand (bottom).

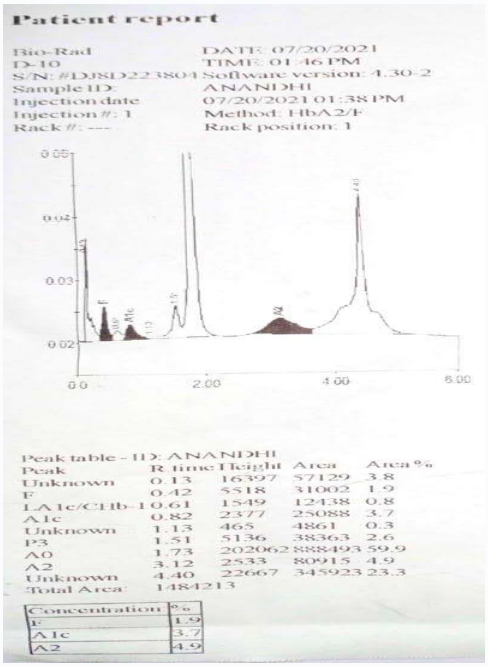


Figure 2: HPLC Report of the Patient.

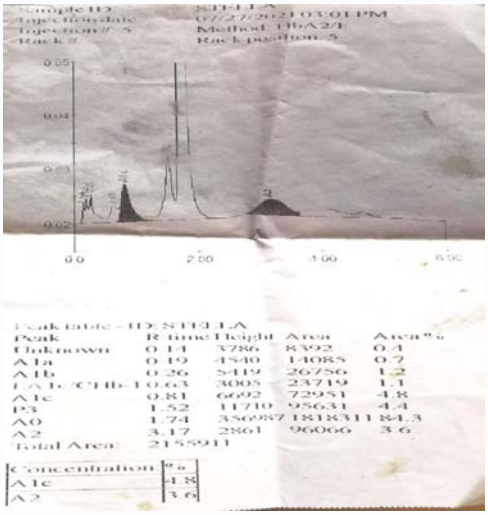


Figure 3: HPLC Report of the Sibling.

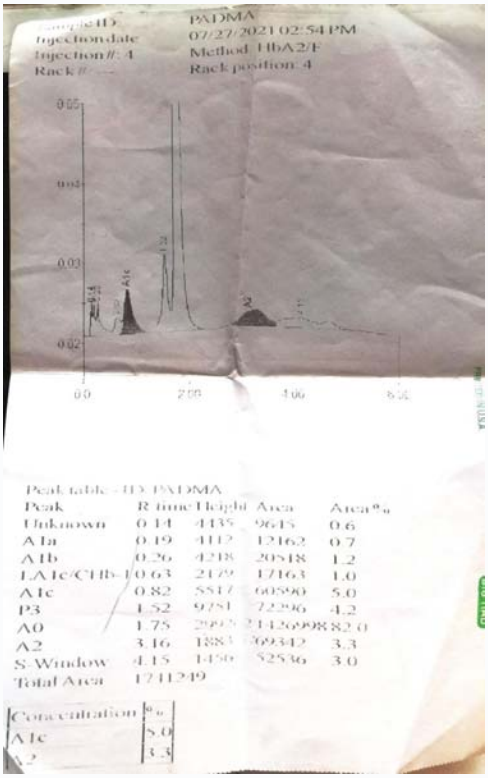


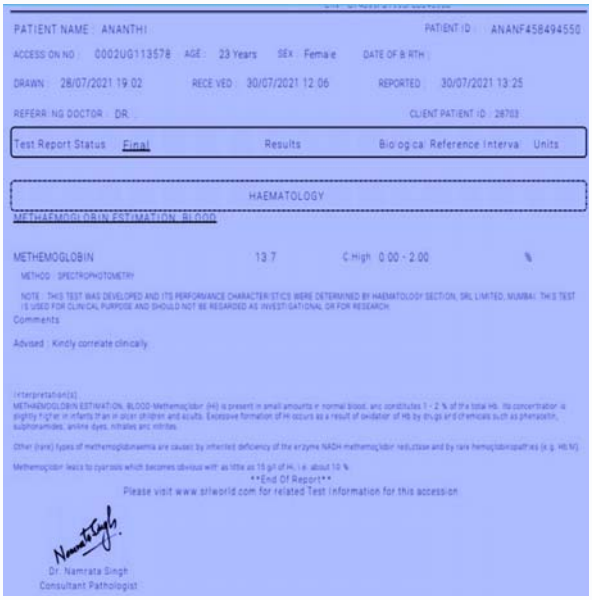
Figure 4: HPLC Report of the Mother.

minutes, no improvement in cyanosis. We tested the patient blood sample by mixing with potassium cyanide by 1 in 10 dilutions, there was no change in colour. With unknown hemoglobin peak in HPLC in the background of resistant methemoglobinemia we did a DNA gene sequencing On HBB which showed Heterozygous missense variant C 277 C>T. 93 codon of HBB gene substitution of tyrosine in place of histidine was identified [21]. Hence diagnosed as Hb M Milwaukee 2/ Hb M akita/ Hb M Hyde Park (Figures 1-6).

This patient had discordant hypoxemia, cyanosis due to methemoglobinemia from abnormal hemoglobin. Patient's mother and younger sister were examined. There were no signs of cyanosis, jaundice and normal hemoglobin electrophoretic studies. Hence this is the second case of Hb M Milwaukee 2/Hb M akita/Hb M Hyde Park arising as fresh mutation in India.

Discussion

We describe the rare cause of cyanosis in this discussion. The cyanosis unresponsive to hundred percent oxygen supply and without the cardiopulmonary etiology, recent and sudden onset favours acquired cause such as methemoglobinemia, sulfhemoglobinemia, etc. while the long-standing symptoms and family history suggest the four causes Hereditary methemoglobinemia, hemoglobin M, Low oxygen affinity hemoglobin, unstable hemoglobin [1]. The last three causes were due to structurally defective hemoglobins [13]. Hereditary methemoglobinemia is due to cytochrome b5 reductase enzyme deficiency and is inherited as autosomal recessive trait, clinical disease is not expected in parents. In hemoglobin M stabilisation of haeme iron in the ferric state by the formation of ionic bonds between the iron atom and the abnormal amino acid residue. Unstable hemoglobin disease is characterised by the disturbances in the tertiary structure of the haeme pocket produce increased


PATIENT NAME : ANANTHI PATIENT ID : ANANF458494550

ACCESS ON NO : 0002UG113578 AGE : 23 Years SEX : Female DATE OF B RTH :

DRAWN : 28/07/2021 19:02 RECE VED : 30/07/2021 12:06 REPORTED : 30/07/2021 13:25

REFERR NG DOCTOR : DR. CLIENT PATIENT ID : 26703

Test Report Status Final Results Biolog cal Reference Interva Units

HAEMATOLOGY

METHAEMOGLOBIN ESTIMATION, BLOOD

METHEMOGLOBIN 13.7 C High 0.00 - 2.00 %

METHOD : SPECTROPHOTOMETRY

NOTE : THIS TEST WAS DEVELOPED AND ITS PERFORMANCE CHARACTERISTICS WERE DETERMINED BY HAEMATOLOGY SECTION, SRL LIMITED, MUMBAI. THIS TEST IS USED FOR CLINICAL PURPOSE AND SHOULD NOT BE REGARDED AS INVESTIGATIONAL OR FOR RESEARCH

Comments

Advised : Kindly correlate clinically

Interpretation(s)

METHAEMOGLOBIN ESTIMATION, BLOOD Methemoglobin (Hi) is present in small amounts in normal blood, and constitutes 1 - 2 % of the total Hb. Its concentration is slightly higher in infants than in older children and adults. Excessive formation of Hi occurs as a result of oxidation of Hb by drugs and chemicals such as phenacetin, sulphonamides, aniline dyes, nitrates and nitrites.

Other (rare) types of methemoglobinaemia are caused by inherited deficiency of the enzyme NADH methemoglobin reductase and by rare hemoglobinopathies (e.g. Hb M).

Methemoglobin leads to cyanosis which becomes obvious with as little as 15 g/l of Hi, i.e. about 10 %

End Of Report

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Dr. Namrata Singh
Consultant Pathologist

Figure 5: Serum Methemoglobin Estimation.

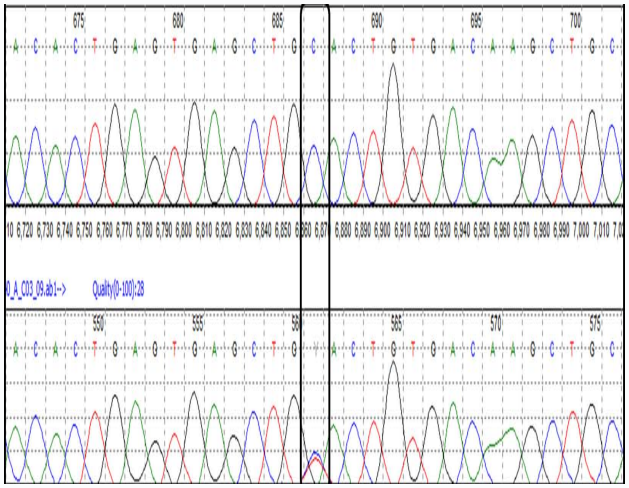

Figure 6: Sanger`s Genome Sequence of the Patient Showed HBB Gene Muation.

methemoglobin production but with oxidative tendency, so it is relatively uncommon to develop significant cyanosis. The last type low oxygen affinity hemoglobin such as Hb Kansas with its decreased oxygen affinity develops cyanosis due to increased levels of deoxy hemoglobin in the blood [8].

Normally small amounts of hemoglobin are continually being oxidised by endogenous agents including oxygen itself (auto oxidation). When oxygen reacts with deoxygenated hemoglobin to produce oxyhemoglobin, one electron from haeme iron ferrous is transferred to the bound oxygen, thereby forming a ferric superoxide anion complex. Subsequently, when hemoglobin is deoxygenated most oxygen released as O_2 but small amount leaves as superoxide anion O_2-. The partially transferred electron is not returned to iron, leaving the haeme as Fe_3+ i.e. methemoglobin. Usually methemoglobin levels are less than 1% of the total hemoglobin, because erythrocytes have cytochrome B5 reductase enzyme that catalyse its reduction. Genetically determined methemoglobinemia are either due to deficiency of cytochrome B5 reductase enzyme deficiency or globin gene mutated Hemoglobin M. While the latter is autosomal dominant usually have positive family history.

Hemoglobin M exhibit abnormal visible absorption spectrum that helps to distinguishes it from methemoglobin. On spectrophotometric recording they do not have an absorbance peak at 630-635 nm which is typical of methemoglobin [5]. Clinically skin and mucus membrane are brownish or slate coloured not like true cyanosis. Therefore, called pseudo cyanosis and it is not associated with severe dyspnoea or clubbing. Abnormal haeme in Hb M have increase tendency to oxidation and low redox potential with variable degree of reduction capacity. Proportion of abnormal haeme in genetically determined and fixed, so that decreased oxygen delivery is problematical only when superimposed on underlying anaemia [1].

Hb M variants are described of which 4 are β-globin variants (Hb Chile, Hb M-Saskatoon, Hb M-Milwaukee-1, Hb M-Milwaukee-2), 4 is α1 or α2 globin variants (Hb M-Boston, Hb Auckland, Hb M-Iwate, Hb M-Yantai) and 2 are γ globin variants (Hb F-M-Osaka, Hb F-M-Fort Ripley) [18, 21]. Most common mutation is the substitution of the proximal or distal histidine residues with tyrosine. Amino acid substitutions at these critical haeme binding sites result in irreversible or prolonged oxidation of iron from ferrous (Fe_2+) to ferric (Fe_3+) state. The amino acid substitution as well as the ferric iron alters the physicochemical properties of the variant hemoglobins like oxygen affinity (P50), Bohr effect, electrophoretic migration, chromatographic affinities and absorption spectra [3].

Hb-M Hyde Park was first reported in 1966 by Heller et al. in black patient in the USA. In 1968, Shibata et al. a family with hereditary cyanosis in the Akita province of Japan were diagnosed to have a new variant of Hb-M and it was named as Hb-M Akita. Later found to have the same primary hemoglobin structure as in Hb-M Hyde Park. Hutt et al. 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.

So far five cases of Hb M have been reported in India so far. The first case was reported in a Muslim family, where the Hb M variant was similar to Hb M Boston by Balaji RT, et al. [6], and the second case was reported in a Punjabi family by Amritsar Das KC, et al. [7]. The third case was of a 11-year-old girl with history of cyanosis and methemoglobin levels of 39.3%, later identified as a Hb M variant – Hb M Ratnagiri (b-63 CAT->TAT) which is similar to Hb M Saskatoon [10]. The fourth case was a three-year-old Punjabi girl from chhimba community diagnosed as Hb M Iwate by Ganesh Kumar V, et al. [18]. The fifth case was a 26-year-old male from Ananthapur, district of Andhra Pradesh diagnosed as case Hb M Hyde Park by D Upadhey, et al. [14]. All the reported variants have autosomal dominant inheritance pattern. Then the sixth case of a 2-year-old girl from Gurugram diagnosed as case of Hb M Hyde Park arising from de nova mutation reported by Loveena, et al. 2020 [20]. Similarly, two cases of Hb M Hyde Park as fresh mutation has been documented Stamatoyannopoulas et al. 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 [11]. Another case occurred in a 6-year-old girl who was diagnosed with Hb-M Hyde Park in 1992. Rotoli et al. reported that neither the parents nor the sibling showed any abnormalities [12].

In our patients, once cardiopulmonary causes were excluded by A-a gradient, CT chest imaging, echocardiography and CT pulmonary angiography. Low SpO_2 levels in pulse oximeter with normal arterial blood gas analysis gives the clue to abnormal hemoglobin [4]. Serum methemoglobin was elevated. But it is not responding to reducing agents such as injection methylene blue and in vitro potassium cyanide mixing studies. We did HPLC studies as there was mild haemolytic anaemia which revealed an unknown peak in the pattern. As the exact hemoglobin variants were not clear and so the DNA gene sequencing proceeded. Results showed the mutation beta globin gene suggestive of Hb M Hyde Park. Therefore this has been the seventh case of Hb M to be reported in India.

Patients siblings and parents were examined, but her father died few months due to cardiac arrest. Mother and sister history were unremarkable. No signs of cyanosis, jaundice and organomegaly. Hemoglobin, bilirubin and HPLC studies were within normal limits. Hence to the best of our knowledge this is the second case of Hb M Hyde Park as denova mutation in India.

Conclusion

Hemoglobinopathy M is the rare cause of cyanosis often misdiagnosed for its childhood central cyanotic presentation. Treatment is neither necessary nor possible. Premarital genetic counselling and general anaesthetic precaution.

Hence correct diagnosis is important because that will forestall therapeutic and diagnostic misadventures.

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