Hemoglobin-M Disease

R.T. Bajaj, R.M. Malik, Meena Desai and P.K. Sukumaran*

Abstract

Hemoglobin-M disease in a Muslim (Khoja) family involving 5 members is reported. Clinical, hematological and genetic data on the family are described.

Introduction

Hemoglobin-M diseases include dominantly transmitted forms of methemoglobinemias. The situation here in analogous to that of other hemoglobinopathies with abnormal substitution of an aminoacid residue in the globin chain. It is a rare condition in which presence of cyanosis is not associated with any disability, and cardiac or respiratory distress are conspicuously absent.

Litarczek et al[1] in 1930 described an adult with cyanosis from childhood and entertained the possibility of a metabolic disorder. The familial nature of the disease was pointed out by Hitzenberger et al[2] and Bensely et al.[3] Horle n and Weber[4] were the first to study a family with dominantly inherited methemoglobinemia with no defect in methaemoglobin reducing capacity. The defect, they said, could be due to an abnormal hemoglobin.

The Hemoglobin-M diseases are extremely rare, but they occur sporadically in virtually every part of the world. Their rarity in deeply pigmented races appears to be due to the fact that cyanosis, the presenting feature, would be more difficult to recognize.

In this country Hemoglobin-M disease has been reported only once before.[5]

Case Report

M., a Muslim (Khoja) male infant, 5 months, born of a non-consanguineous marriage, was admitted in the hospital on 25-5-1972 for high fever and not accepting feeds for 2 days.

The child was the youngest of 5 children. Birth history was normal and there was no history of illness prior to this hospital admission.

On examination he was poorly built and nourished with a length of 24" and weight 10.3 Lbs. Temperature, on admission was 100°F, pulse 148/min. and respiratory rate 30/min. The child appeared dazed and tremulous. The anterior fontanelle was tense and neck stiffness was present.

He had severe cyanosis and skin, lips, tongue and nails had a peculiar slate-grey colour. Cyanosis had been noted from birth.

Examination of the cardiovascular and respiratory systems was normal. Liver was just palpable. Spleen was not palpable.

The father of the patient was cyanosed and the grandfather, now deceased, also was reported to have had cyanosis from birth. The patient's mother was normal. The paternal uncles of the child were unaffected. The father was a well grown man, who gave no history of breathlessness or easy fatiguability or diminished exercise tolerance.

All the three siblings of the patient had cyanosis, but their built and nutrition was normal and systemic examination revealed nothing abnormal. (Fig. 1).

Investigations : Hemoglobin 10.8 g per 100 ml, RBC. count 3.87 millions/cumm; hematocrit 34%; WBC count; 19200/cumm; P=58%, E=3%, L=34% and M=5%; CSF turbid, cell count 5,120/cumm; P=85%, L=15%; proteins 2,500 mg per 100 ml globulin++; sugar 12 mg per 100 ml, chlorides 530 mg per 100 ml Smear of CSF showed pneumococci. CSF

t Bai Jerbai Wadia Hospital for Children & Institute of Child Health, Parel, Bombay, 12 and Cancer Research Institute, Tata Memorial Centre, Bombay, 12.

and blood cultures were negative. X-ray of chest and ECG were norinal.

The blood collected for investigations was chocolate coloured.

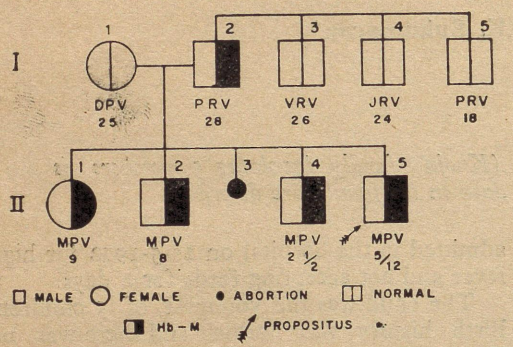

Fig. 1. Pedigree of the family. Ages are shown by numbers under the initials.

Since the family history suggested a dominant inheritance studies for Hemoglobin-M were carried out on the patient's and other family member's blood. The concentrations of Hemoglobin-M are shown in Table. I.

TABLE I

Subject	Age	% Hb. M.
Father	28 yrs.	40.0 %
Sister	9 yrs.	34.6 %
Brother	7 yrs.	39.4 %
Brother	2½ yrs.	42.7 %
Patient	5/12 yr.	36.7 %

Spectroscopic examination of the blood of the patient did not show any absorption band in the red region.

Cyanotic manifestations from birth in the patient and other members of the family indicated that the Hemoglobin-M in them could be due to abnormality in the alpha chain. Possibility of this being Hemoglobin-M Boston cannot be ruled out. Characterization of this hemoglobin is being carried out and will be reported elsewhere.

Discussion

Methemoglobin is the oxidised derivative of hemoglobin in which the iron of the four heme groups is changed from the usual ferrous to the ferric state. As a consequence the iron is no longer able to combine with oxygen. Methemoglobin is accordingly unable to serve as a respiratory pigment.

Methemoglobin in these individuals comprises 20-50% of the total hemoglobin. Each individual has his peculiar maximum level of of methemoglobin.

The disease is will tolerated and respiratory and cardiac distress are conspicuously absent. Compensatory polycythemia and associated reticulocytosis are occasionally observed.

The blood in these individuals is chocolate coloured.

Blood of normal persons contains methemoglobin, but the intraerythrocytic methemoglobin reducing system reduces methemoglobin as fast as it is formed and only very small amounts of less than 2%[6] occur in normal blood. An equilibrium exists between these two competing processes.

Two definitive causes of hereditary methemoglobinemia have been described :

I. Congenital absence of an enzyme which reduces methemoglobin. In this condition which is of autosomal recessive inheritance, the enzyme DPNH diaphorase is completely lacking.

II. The Hemoglobin-M diseases:

The Hemoglobins-M are now known to belong to the general category of the abnormal hemoglobins.

They differ from Hemoglobin-A by a single amino-acid substitution occurring in the alpha or beta chains in the vicinity of a heme group.

Five different Hemoglobin-M pigmetns have been indentified.[7] These are listed in Table II.

Unlike the enzyme deficiency methemoglobin the Hemoglobin-M methemoglobnis have anamolous spectroscopic properties. The usual quantitative tests by the method of Evelyn and Malloy[8] and even qualitative tests for identification give erronous values.

The Hemoglobins-M like most of the abnormal hemoglobins are therefore detected by electrophoresis. Separation of these

abnormal fractions can be accomplished by converting the samples into methemoglobin which is run at a suitable pH. At this pH

TABLE II

Hb-M	Substitution at	Change
Hb-M Boston	α-58	Histidene ⟶ tyrosine
Hb-M Iwate	α-87	Histidene ⟶ tyrosine
Hb-M Saskatoon	β-63	Histidene ⟶ tyrosine
Hb-M Milwaukee	β-67	Valine ⟶ Glutamic acid
Hb-M Hyde-Park	β-92	Histidene ⟶ Tyrosine

Hemoglobin-A separates from Hemoglobin-M giving the abnormal pigment the characteristic brown colour on paper and cellulose acetate (Fig. 2.).

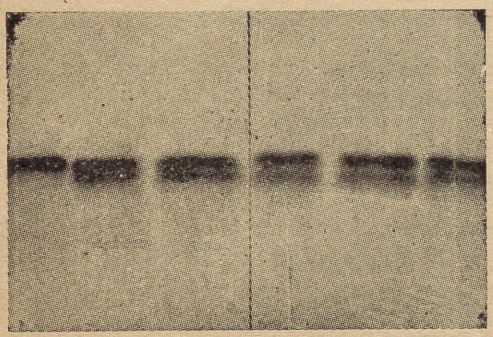

Fig. 2. Cellulose acetate electrophoresis in Phosphate buffer, pH 7.1 of haemoglobin (treated with ferricyanide). From left—Mother (DPV): Propositus (MPV); Father (PRV); Sister (MPV); Brother (MPV) and Brother (MPV). All except mother show haemoglobin A+M.

Final identification, as to the exact amino-acid substitution involved, requires "fingerprinting" of the tryptic digest of the isolated globin followed by amino-acid sequence determination.

In the Haemoglobin-M diseases, studies performed to date have failed to demonstrate any abnormality of the RBC enzyme systems. RBC life span is also normal.

The Hemoglobins-M are transmitted as a dominant character with no predilection for either sex.[9] In the present case one sibling of the patient was an affected female and two others were affected males.

Some types of Hemoglobin-M disease do not respond at all to ascorbic acid and methylene blue, while members of some pedigrees do, to 'a variable extent.'[10],[11] Our patient was given ascorbic acid in doses of 500 mg. daily with no alleviation of cyanosis.

The methemoglobinemias are not reported to predispose to increased susceptibility to infection and the pyogenic meningitis occurring in this patient was probably coincidental.

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