AN UNUSUAL CAUSE FOR CYANOSIS

K H Mak, A T H Tan, E Jacob, L F Chio

ABSTRACT

Cyanosis is a common physical sign in clinical medicine. Cardiac or respiratory conditions are the usual causes. We report a patient with an unusual cause for cyanosis and highlight the salient clues that lead to the diagnosis.

Keywords: Autosomal recessive, Congenital heart disease, Methaemoglobinaemia, Methaemoglobin reductase, Polycythemia

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INTRODUCTION

Cyanosis is a blue colour that is due to an increased amount of deoxygenated haemoglobin in the subpapillary venous plexus of the skin[1]. The visual perception of "blueness" varies greatly amongst physicians; the average physician does not perceive cyanosis with certainty until oxygen saturation falls to about 85%, and some not until 75%. It is common to describe cyanosis as peripheral when the "blueness" is most marked at the distal regions such as the hands, the feet or the tip of the nose. It is central when both the distal areas and mucous membranes are involved. The common causes of central cyanosis are usually cardiac or respiratory in origin (Table I)[2]. Abnormal haemoglobins, methaemoglobinaemia (congenital or acquired) and sulphaemoglobinaemia are the rarer causes. We describe a patient with an unusual cause for cyanosis.

CASE REPORT

The patient, a 41-year-old asymptomatic man, was told that the colour of his appearance was blue since birth. When he was a child he had frequent febrile illness and was seen by a paediatrician who told his parents that he was suffering from a heart problem. Subsequently, he was followed up by a doctor in another hospital for the heart problem. However, his general practitioner noted this peculiar skin discolouration and referred him to our department for further investigations. He was not on any long term medications nor did he take any traditional herbs on a regular basis. There was no other significant medical history of note except that he had an allergic reaction to penicillin.

On examination, he was well-built and comfortable. There was no dysmorphic features. His lips, tongue and nail beds were deeply cyanosed. There was no clubbing or any skin or oral lesions. The jugular venous pulse was not elevated. Blood pressure was 110/80 mmHg. The apex beat was not displaced and the heart sounds were normal. There was a soft ejection systolic murmur at the left lower sternal edge. The lungs were clear. There was no hepatosplenomegaly and the kidneys were not palpable. Neurologically, he was normal.

Haemoglobin was 19.1g/dl with a haematocrit of 59.0%. The white cell and platelet counts were normal. Blood urea, electrolytes, creatinine and sugar levels were also normal. Arterial blood pH was 7.325, partial pressure of carbon dioxide was 38.8 mmHg and oxygen was 101.6 mmHg and oxygen saturation was 97.0%. Electrocardiogram and chest radiograph were normal. Echocardiogram showed a normal anatomical heart with normal function. Cardiac catheterisation did not demonstrate any shunt or arterio-venous or pulmonary fistula. Haemoglobin electrophoresis was normal. His blood was negative for cyanide or lignocaine. Assay for methaemoglobin was elevated and the enzyme methaemoglobin reductase was absent. All these pointed to the diagnosis of methaemoglobinaemia. The family members of the patients were subsequently studied and it confirmed that the patient was indeed suffering from congenital methaemoglobinaemia (Fig 1, Table II).

Table I – Causes for Central Cyanosis

Decreased arterial oxygen saturation
a) decreased atmosphere pressure (high altitude)
b) impaired pulmonary function
– alveolar hypoventilation
– uneven pulmonary ventilation and perfusion
– impaired oxygen diffusion
c) anatomic shunts
– certain types of congenital hearts (eg septal defects)
– pulmonary arterio-venous fistula
– multiple small intrapulmonary shunts
d) haemoglobin with low affinity for oxygen

Table II – Results of the assays of methaemoglobin and the enzyme methaemoglobin reductase

Subject	Methaemoglobin (μmol/l)	Methaemoglobin reductase (U/g Hb)
Reference	< 174	4.7 – 8.6
IIA	3775	4.3
IIB	5968	0
IIC	–	–
IID	3819	3.2
IIE	3788	5.4
IIF	–	–
IIG	3788	4.3
IIIA	495	5.2
IIIB	366	3.4
IIIC	536	4.2

Department of Cardiology
Singapore General Hospital
Outram Road
Singapore 0316

K H Mak, MRCP(UK)
Medical Officer (Specialist)

A T H Tan, FRACP
Head and Senior Consultant

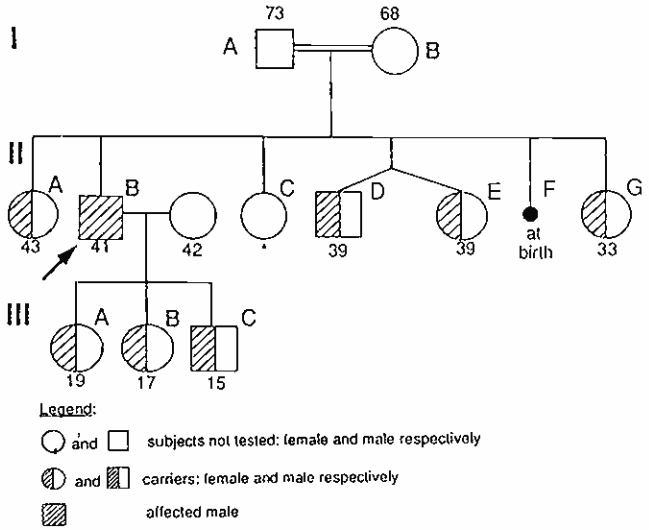
Clinical Biochemistry Laboratories
Department of Pathology
Singapore General Hospital

E Jacob, PhD
Head

L F Chio, PhD
Biochemist

Correspondence to: Dr K H Mak

Fig 1 – Family tree of the patient



* subject was a blue baby and was given away as an infant

DISCUSSION

The first patient with congenital type I methaemoglobinaemia (metHb) in South-east Asia was described by Kueh et al[3]. The patient was from East Malaysia. We report the first Singaporean with the condition and the phenotype of his relations.

Patients with metHb may present with symptoms of hypoxia - easy fatiguability, intermittent headaches and exertional dyspnoea. This is because methaemoglobin cannot bind oxygen well as the iron is in the ferric state. However, majority of the patients are asymptomatic. The clue to this condition is that of a very blue patient who is not sick.

MetHb is a rare condition and more common cardiac or respiratory conditions have to be ruled out. It is unlikely that the patient had a cardiac or respiratory condition that could have resulted in cyanosis because of the absence of clinical symptoms, normal physical examination (except of cyanosis), morphological and doppler echocardiogram, colour flow imaging, angiogram and partial pressure of oxygen of arterial blood (in air).

The diagnosis of metHb was suggested by the high levels of methaemoglobin in the blood. The differential diagnosis of chronic metHb[4,5] includes (a) chronic ingestion of oxidant drugs (eg phenacetin), (b) congenital deficiency of one of the methaemoglobin reductase, (c) presence of one the abnormal haemoglobin M. (Table III)

Table III – Differential Diagnosis for Chronic Methaemoglobinaemia

	Drug Cause	Enzyme Deficiency	Haemoglobin M
Blood Film	Heinz body	normal	normal
Electrophoresis	normal	normal	Hb M
Enzyme assay	normal	absent	normal

The normal peripheral blood film, absence of a history of chronic drug ingestion, presence of abnormal skin discolouration since young, normal haemoglobin electrophoresis and absence of the enzyme methaemoglobin reductase confirmed the diagnosis.

The patient was a son of a consanguinous marriage. This probably gave a clue to the diagnosis as the condition is inherited in an autosomal recessive manner. In our study of his family members we found some of them to be carriers (Fig 1). On the other hand, haemoglobin Ms have a dominant mode of inheritance[6].

Polycythemia was reported to be usually mild in these patients[4]. Both our patient and the patient from East Malaysia[3] had high haemoglobin level. This was not unexpected because methaemoglobin has poor oxygen carrying capacity. The chronic hypoxic state therefore resulted in compensatory polycythemia.

Treatment is indicated for patients with symptoms or for comestic reasons. Vitamin C, methylene blue and riboflavin have been used successfully. In the East Malaysian patient, vitamin C reduced both the haemoglobin and methaemoglobin levels[3]. Methylene blue can be administered intravenously (1 mg of 1% methylene blue/kg body weight in five minutes) or orally (60 mg three to four times a day)[6]. Patients with severe symptoms from hyperviscosity and not responding to treatment could be venesected. On the other hand, for patients with acute metHb and vascular collapse, haemodialysis and exchange transfusion are the treatments of choice[6].

These patients usually have a normal lifespan[7]. However, they may give rise to problems with the measurement of oxygen saturation by pulse oximetry[8]. Operators must be informed of the patient's condition. Extra care must also be exercised for this group of patients when using oxidant drugs.

CONCLUSION

MetHb is an uncommon clinical condition. Patients present with an abnormal skin discolouration frequently described as cyanosis. The outstanding feature of this group of patients is that they are well in spite of the marked cyanosis. Nonetheless, cardiac, respiratory and abnormal haemoglobins have to be excluded first. The diagnosis is made by a high level of methaemoglobin in the blood and the lack of the enzyme methaemoglobin reductase. Drugs can induce metHb too, but the discolouration is usually transient and resolves upon withdrawal of the offending drug. To make the diagnosis of congenital metHb, the family members are studied. As this is a relatively benign condition, the patient and relatives are given reassurance. Reducing agents like vitamin C improve the colour of the patient and reduce the methaemoglobin levels in the blood.

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