International Journal of Research in Medical Sciences
Rao BVN et al. Int J Res Med Sci. 2017 Oct;5(10):4632-4635
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20174610

Case Report

Healthy blue man: congenital methemoglobinemia

B. V. Nagabhushana Rao[1]*, S. C. Sinha[2], S. Modi[3], S. Sunita[4]

[1]Department of Medicine, Queen's NRI Hospital, Gurudwara Lane, Seethammadhara, Visakhapatnam - 530013, Andhra Pradesh, India
[2]Department of Cardiology, Queen's NRI Hospital, Gurudwara Lane, Seethammadhara, Visakhapatnam - 530013, Andhra Pradesh, India
[3]Department of Neurology, Queen's NRI Hospital, Gurudwara Lane, Seethammadhara, Visakhapatnam - 530013, Andhra Pradesh, India
[4]Department of Pathology, Queen's NRI Hospital, Gurudwara Lane, Seethammadhara, Visakhapatnam - 530013, Andhra Pradesh, India

Received: 23 July 2017
Accepted: 21 August 2017

***Correspondence:**
Dr. B. V. Nagabhushana Rao,
E-mail: bhavanavnrao@gmail.com

ABSTRACT

Congenital methemoglobinemia, though often discussed in medical teachings is rarely encountered in clinical practice as the condition is asymptomatic. Here we present such a case and discuss in detail the clinical presentation of both congenital and acquired methemoglobinemia. We also outlined the management of the conditions. One should suspect methemoglobinemia when cyanosis is not being corrected by supplementing oxygen and and when the oxygen saturation is low by pulse oximetry and normal by arterial blood gas analysis. Treatment modalities for congenital methemoglobinemia is of cosmetic purpose, but timely intervention in acquired methemoglobinemia could be lifesaving. Methylene blue, Ascorbic acid and Riboflavin are drugs of choice.

Keywords: Congenital methemoglobinemia, Cyanosis, Healthy blue man, Methylene blue, Pulse oximeter

INTRODUCTION

Methemoglobinemia may be congenital or acquired. Congenital methemoglobinemia is often seen in certain ethnic groups where consanguineous marriages are common. Most cases of methemoglobinemia are acquired and often due to exposure to toxins, drugs or poisons. Methemoglobinemia is an abnormal state of hemoglobin where in the usual ferrous form of iron is oxidized to ferric form which cannot reversibly bind to oxygen. Ferric hemoglobin also increases the affinity of the remaining ferrous molecules for oxygen and shifts the oxygen dissociation curve to left, hence prevents easy release of oxygen to the tissue.[1] The net result is functional anemia. In normal individuals' oxidation of hemoglobin occurs spontaneously converting 0.5 to 3% of hemoglobin to methemoglobin daily. This auto oxidation is reverted by internal mechanisms resulting in maintaining a steady state of methemoglobin approximately around 1%. There are two pathways, the major one being NADH dependant Cytochrome b5 reductase mediated, and the other one NADPH dependent G6PD mediated. Second one is active only in the presence of externally administered electron acceptors like methylene blue or riboflavin. Congenital causes are due to cytochrome b5 reductase deficiency or hemoglobin M disease. Rarely it can be due to cytochrome reductase deficiency. Acquired methemoglobinemia is often due to drugs or toxins.[2] Drugs given in usual doses also can increase methemoglobin concentration. Individuals with partial

cytochrome b5 reductase deficiency and children whose enzyme activity is half the normal are vulnerable. Dapsone is the most common drug implicated as well as local anesthetic agents. Inhaled nitric oxide, aniline dyes and other related products may be involved. Methemoglobinemia precipitated by heroin, cocaine and other street drugs may be a diagnostic difficulty.

CASE HISTORY

A forty-year-old male patient was referred from Primary Hospital to our hospital for immediate admission and management on 27 May 2016. He was a healthy heavy vehicle driver who had never been hospitalised earlier. He attended Primary hospital for cough, cold and mild breathlessness on exertion. As the doctor found him having clubbing, cyanosis and high hemoglobin and low oxygen saturation by pulse oximetry he was urgently referred to our hospital. He was healthy and except for recent respiratory complaints, he had never been to hospital. He is known to have bluish discoloration of hands, feet and tongue since childhood.

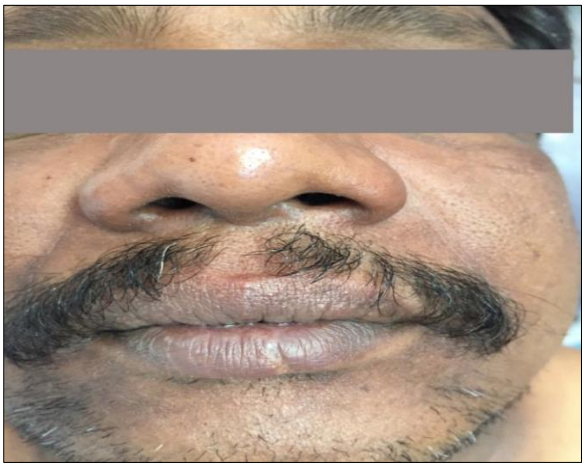


Figure 1: Cyanosed lips.

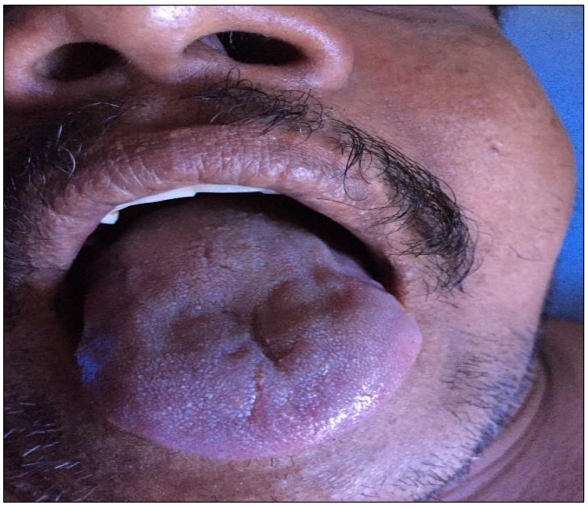


Figure 2: Cyanosed tongue.

Abnormal shape of nails was pointed out by his classmates in primary school. None of his family members or ancestors had similar illness. On clinical examination, he has gross finger clubbing and cyanosis, both central and peripheral. Blood pressure was 120/80mmHg, Pulse 72/minute, weight 76kg, height 5feet 6 inches and body mass index of 27. Respiratory system was normal on examination. Heart sounds were normal and no murmur was heard. Abdominal examination revealed no organomegaly. Neurological examination was normal. His lips (Figure 1), tongue (Figure 2) and hands (Figure 3) were discolored. Nails show clubbing and cyanosis (Figure 4).

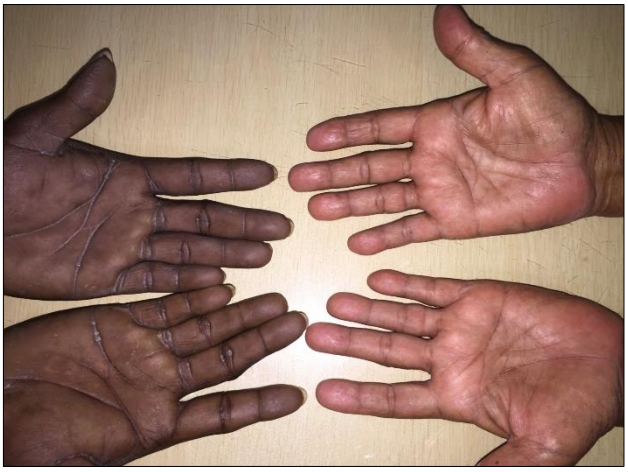


Figure 3: Cyanosed hands.

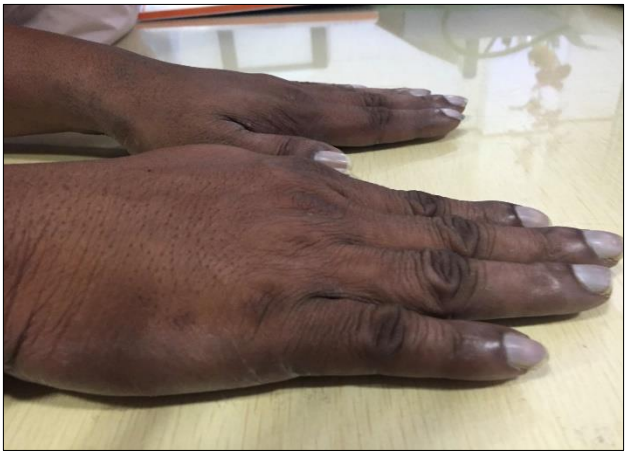


Figure 4: Clubbing and cyanosis.

Investigations

Hemoglobin

18.5grams (13.0-18.0), platelets: 180000 (150000-400000) and total white cell count: 4,800 (4000-11000). Random blood sugar, creatinine, liver function tests, thyroid function test, serum electrolytes, lactate dehydrogenase (LDH), chest x-ray, ECG, echocardiography and ultrasound examination of the

abdomen were normal. Peripheral smear examination showed polycythaemia but did not show abnormal cells.

Hemoglobin electrophoresis was normal. Oxygen saturation by pulse oximetry had shown saturation of 85% (Figure 5) whereas by arterial blood gas analyser saturation was 97.6% (Figure 6).

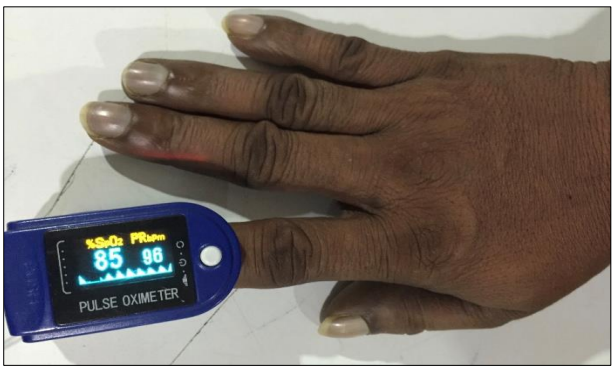
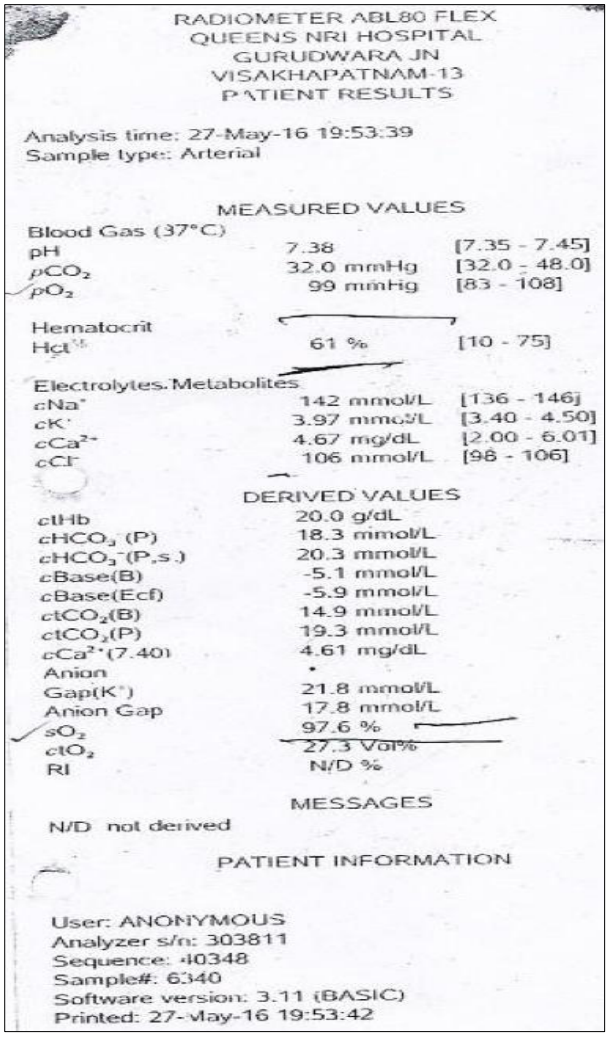


Figure 5: Pulse oximetry.


RADIOMETER ABL80 FLEX
QUEENS NRI HOSPITAL
GURUDWARA JN
VISAKHAPATNAM-13
PATIENT RESULTS

Analysis time: 27-May-16 19:53:39
Sample type: Arterial

MEASURED VALUES

Blood Gas (37°C)		
pH	7.38	[7.35 - 7.45]
pCO_2	32.0 mmHg	[32.0 - 48.0]
pO_2	99 mmHg	[83 - 108]
Hematocrit		
Hct	61 %	[10 - 75]
Electrolytes,Metabolites		
cNa^+	142 mmol/L	[136 - 146]
cK^+	3.97 mmol/L	[3.40 - 4.50]
cCa^{2+}	4.67 mg/dL	[2.00 - 6.01]
cCl^-	106 mmol/L	[98 - 106]

DERIVED VALUES

ctHb	20.0 g/dL
$cHCO_3$ (P)	18.3 mmol/L
$cHCO_3^-$(P,s.)	20.3 mmol/L
cBase(B)	-5.1 mmol/L
cBase(Ecf)	-5.9 mmol/L
$ctCO_2$(B)	14.9 mmol/L
$ctCO_2$(P)	19.3 mmol/L
cCa^{2+}(7.40)	4.61 mg/dL
Anion Gap(K+)	21.8 mmol/L
Anion Gap	17.8 mmol/L
sO_2	97.6 %
ctO_2	27.3 Vol%
RI	N/D %

MESSAGES

N/D not derived

PATIENT INFORMATION

User: ANONYMOUS
Analyzer s/n: 303811
Sequence: 40348
Sample#: 6340
Software version: 3.11 (BASIC)
Printed: 27-May-16 19:53:42

Figure 6: Arterial blood gas.

Phlebotomist found that blood was abnormally colored, dark brown instead of the usual red (Figure 7). Methemoglobin estimated by spectrophotometer was 38% (1-2% normal).

Figure 7: Dark brown coloured blood.

DISCUSSION

Congenital methemoglobinemia is often discovered accidentally. Our patient attended the clinic for trivial respiratory symptoms and further investigated for the presence of cyanosis. Except for a headache and fatigability, individuals with congenital methemoglobinemia with chronically elevated methemoglobin levels up to 40% can be asymptomatic.[3] Acute rise in methemoglobin due to exposure to drugs or toxins may make them symptomatic. Life expectancy will be normal. Polycythaemia may be the only hematological abnormality one may find, as in our patient.[4] This condition has to be suspected when clinical symptoms are associated with normal saturation by ABG and low saturation by pulse oximetry i.e. mismatch of oxygen saturation between and ABG and Pulse oximeter.[5] Rad 57 pulse oximeter uses eight wavelengths may pick up methemoglobin but may be inaccurate at low saturations.[6] Cyanosis in generations suggest autosomal dominant Hemoglobin M disease, affected siblings and healthy parents suggest autosomal recessive cytochrome b5R deficient congenital methemoglobinemia. Hemoglobin electrophoresis distinguishes Hemoglobin M disease. Measurement of cytochrome b5R and cytochrome b5 is possible in specialty laboratory. All the other causes of deoxygenation of Hemoglobin, which can cause cyanosis should be excluded. Sulfhemoglobin if exceeding 0.5mg/dl can cause cyanosis and to be differentiated.

Treatment for congenital methemoglobinemia is for cosmetic purpose only as often sufferers are asymptomatic. Nevertheless, they should be advised to avoid exposure to agents that may induce methemoglobinemia. Treatment options include Methylene blue 100 to 300mg orally daily or Ascorbic acid 300 to 1000mg orally daily. Riboflavin 20 to 30mg daily is also an alternative.[7] In contrast to congenital methemoglobinemia acquired methemoglobinemia is symptomatic and symptoms depends on the speed at which methemoglobin is formed and its percentage. Early symptoms include cyanosis, light headedness, fatigue, dyspnoea, lethargy and tachycardia. At higher concentration of methemoglobin respiratory depression, coma, seizure and death may occur. Pre-existing anemia, heart and lung diseases may make the individual vulnerable to the toxic effects of methemoglobinemia. Treatment starts with immediate stopping of the offending drug or toxin. That may suffice if the methemoglobin level is less than 20%. Severe degree of methemoglobinemia has to be managed in intensive care and may require mechanical ventilation. If the individual is symptomatic and methemoglobin level is more than 20% specific therapy with Methylene blue or Ascorbic acid is warranted. Methylene blue shouldn't be given to G6PD deficient people or in excessive doses as it may precipitate hemolysis.[8] Ascorbic acid orally 300 to 1000mg in divided doses is alternative where Methylene blue cannot be given or not available. High dose of Ascorbic Acid (10 grams six hourly intravenously) was also successfully tried in patients of Dapsone induced methemoglobinemia with normal renal function.[9]

CONCLUSION

Congenital methemoglobinemia is rare and one requires a high index of suspicion as these individuals are asymptomatic. An asymptotic cyanosed patient, whose oxygen saturation is not improving with oxygen supplementation and has a mismatch of oxygen saturation by pulse oximetry and ABG is a candidate for methemoglobin estimation.

ACKNOWLEDGEMENTS

Authors would like to thank Mr. Shyam Prasad Parvathaneni, Manager, Print and Media, Queens NRI Hospital, Visakhapatnam, India for his photography services.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Rao BVN, Sinha SC, Modi S, Sunita S. Healthy blue man: congenital methemoglobinemia. Int J Res Med Sci 2017;5:4632-5.