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Case Report

A case report on congenital methemoglobulinemia - neonatal cyanosis

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ABSTRACT

Methemoglobin (MetHb) is a form of hemoglobin where iron is in an oxidized ferric state, impairing its oxygen-binding capacity. This condition can be hereditary or acquired, leading to methemoglobinemia when MetHb levels exceed 3%. Hereditary methemoglobinemia, although rare, presents with hypoxia and cyanosis. This case report discusses a 1-month 7-day-old female diagnosed with congenital methemoglobinemia caused by NADH-cytochrome b5 reductase deficiency, characterized by persistent cyanosis unresponsive to oxygen therapy. The patient presented with fever, loose stools, vomiting, and respiratory distress. Initial examination revealed significant findings including pallor, hyperpigmentation of the skin, tachycardia, tachypnea, and respiratory failure. Diagnosis involved ABG with co-oximetry, revealing high MetHb levels and severe metabolic acidosis. Management included methylene blue administration, packed red blood cells (PRBC) transfusion, and supportive care. Despite initial treatment challenges, the patient showed clinical improvement with normalization of methemoglobin levels. This report emphasizes the need for accurate diagnosis and careful management of congenital methemoglobinemia to prevent complications.

Keywords: Methemoglobinemia, Congenital methemoglobinemia, NADH-cytochrome b5 reductase deficiency, Cyanosis, Hereditary hypoxia, Methylene blue therapy

INTRODUCTION

Methemoglobin (MetHb) is hemoglobin in which iron is in an oxidized ferric state, making it difficult to bind with oxygen. Normally, MetHb constitutes less than 1% of hemoglobin in humans, but levels exceeding 3% lead to methemoglobinemia, which can be hereditary or acquired.[1]

Hereditary methemoglobinemia, a rare cause of hypoxia and cyanosis, has few reported cases globally.[2] It can arise from three genetic causes - CYB5R3 deficiency: the most common cause, which has two types i.e. type I (limited to erythrocytes) and type II (affecting all tissues), hemoglobin M disease, and cytochrome B5 deficiency.

CASE REPORT

Patient background

A 1-month 7-day-old female child, first born of a non-consanguineous marriage, from Jameela, Charminar, presented with a history of fever for 3 days, loose stools for 1 day, vomiting for 1 day, and difficulty in breathing for 1 day.

Symptoms and history

Fever

Fever was insidious onset, intermittent, mild to moderate, associated with chills, and unresponsive to medication.

Loose stools

Stool was watery, 5-6 times/day, non-foul smelling, non-blood tinged, without mucus.

Vomiting

Vomit was non-projectile, containing milk, occurring 30 minutes post-feeding, 4-5 episodes, non-blood tinged.

Respiratory difficulty

Increased respiratory activity with chest indrawing was observed.

No history of ear/eye discharge, excessive crying during urination, involuntary movements, abdominal distension, cyanosis, cough/cold, or similar family complaints. Antenatal history was uneventful. Birth history included full-term delivery via LSCS with a birth weight of 2940 grams, immediate crying after birth, no NICU stay, and no postnatal complications.

Table 1: Observed versus expected measurements.

Measurement	Observed	Expected
Length	51 cm	53 cm (<-3SD)
Weight	3 kg	9 kg (<-3SD)
Head circumference	34 cm	37 cm (<-3SD)
Weight for length		<-3SD

Development and immunization

Early neck holding, open hands in midline, no social smile. Immunization included only birth doses (BCG vaccine), and mixed feeding (breastfeeding and formula) with improper dilution.

Previous hospital admission

On the 22nd day of life, admitted to an outside hospital with right middle and lower zone pneumonia, metabolic acidosis, dyselectronemia, failure to thrive, and seizures (pH 6.7, HCO_3 3.3, and lactate 4). Treated with antibiotics, bicarbonate correction, midazolam, and fosphenytoin.

Examination findings

Vital signs

Pulse 180/min, BP 60/30 mmHg (<5th centile), RR 80/min, SpO_2 80% (room air), 82% (O_2 with hood at 15 l/min), afebrile.

General examination

Conjunctiva pallor, thin build, hyperpigmentation of the skin, open anterior and posterior fontanelles, no signs of vitamin deficiency, normal spine/limbs, no neurocutaneous markers, no dysmorphic facies, ophisthotonus present.

Systemic examination

Respiratory: bilateral equal air entry, no added sounds, abdominal: soft, non-tender, liver palpable 2 cm below right costal margin (firm, 5 cm span), spleen tip palpable (firm), cardiovascular: S1 S2, no murmur, and CNS: lethargic, GCS 15/15, pupils equal/reactive to light, increased tone in all limbs, power >3/5 at all joints, reflexes 2+.

Table 2: Hematological and biochemical parameters.

Date	9/12	10/12	12/12
Hb/PCV	8.5/29.1	11.1/34.7	
TC	34.46 K	24.74	
P/L/M/E	45/42/8/0	83/9.3/7.4/0.2	
Platelets	8.46 K	4.59 lakhs	
CRP	64.1		
Na/K/Cl	137/4.9/110	144/3/110	140/3.6/107
BUN/creat	12/1.08	17/1.10	
SGPT/SGOT	26/17		
CA/ALP/PO_4	15.4/281/9.2		
TP/albumin	6.6/3.6		
MeHB levels (%)	38.63 (<2)		
Cyb5R (IU/g Hb)	22.49		
pH	6.75	7.06	6.96
PCO_2	10.4	20	82
PO_2	147.8	30	292
HCO_3	1.4	5.6	15
SO_2	92.7	60	99
LAC	11.47	5.8	

Continued.

Date	9/12	10/12	12/12
PT	26.4		
INR	3	1.49	
APTT	573	31	
METHhb (%)	65	39.7	

Table 3: Hematological and biochemical parameters (continued).

Date	15/12	16/12	12AM	16/12	9PM	17/12	18/12	19/12	21/12	23/12	27/12	2/01
Hb/ PCV	8.3/ 25.7	6.6/ 20.3				6.4/ 20.8	5.7/18					
TC	21K	20K				11.4K						
P/L	45/36	51.7/ 38.7				38/44						
Platel -ets	77K	118K				174K						
Na/K/ Cl	150/1.4/ 114	149/2.6/ 117	150/3.8/ 118	146/3.3 /113		141/5.3/ 109	138/3.0/ 103	140/3/ 104	142/4.6/ 107	137/3.3/112		
BUN/ creat	/1.06	10/0.86	7/0.52									
pH	7.23	7.37	7.35	7.28	7.33	7.49	7.44	7.38	7.238	8.11		
PCO_2	35	23.8	20.6	30	25	19.8	28	23.5	8.11			
PO_2	36.1	45.9	109.5	30	48	92	71	65.5	174.3	3.5		
HCO_3	14.6	13.7	11.3	14.2	13.1	15	16.9	13.5	3.5			
SO_2	58	79.3	97.7	46.3	80/2.8	97.8	94	91.5	99.6	3		
LAC	4.3	2.45	3.08	3.2	3.54	3.23	4.61	3				

Table 4: Proximal versus distal renal tubular acidosis.

Parameters	Proximal RTA	Distal RTA	Patient
Plasma K+	Normal/low	High	3.3
Serum HCO_3	15-18	>17	13.6
Urine pH	<5.3	>5.3	6.0
Urine HCO_3	>10-15%	<5%	10.2
Urine calcium	Normal	High/normal	2.9 mmol/24 hour (normal)
Urine AG	Positive	Positive	Negative (-43)
Nephrocalcinosis	Absent	Present	Absent

Hospital course

Initially presented with fever, loose stools, vomiting, respiratory distress, and failure to thrive. Examination revealed significant pallor, hyperpigmentation, tachycardia, tachypnea, respiratory failure with shock, hypertonia (spasticity), and ophisthotonus. Differential diagnoses included acute gastroenteritis with severe dehydration, inborn errors of metabolism, and adrenal insufficiency. Treated with IV bolus, inotropes, intubation, and ventilation. ABG with co-oximetry showed high methemoglobin levels (65%) and severe metabolic acidosis. Treated with methylene blue, PRBC transfusion, and supportive care.

Diagnosis and management

High methemoglobin levels, electrolyte imbalance and persistent metabolic acidosis with polyuria suggested congenital methemoglobinemia with a possible renal tubular defect. Serial monitoring, antibiotic therapy, and supportive care led to clinical stabilization and normalization of methemoglobin levels. Further follow-up with the neurology and nephrology teams was recommended.

DISCUSSION

MetHb is hemoglobin in which iron is in an oxidized ferric state, making it difficult to bind with oxygen.[1] Normally, MetHb constitutes less than 1% of hemoglobin in humans, but levels exceeding 3% lead to methemoglobinemia, which can be hereditary or acquired.[2]

Hereditary methemoglobinemia, a rare cause of hypoxia and cyanosis, has a few reported cases globally.[3,4] It can arise from three genetic causes - CYB5R3 deficiency which is the most common cause, which has two types: type I (limited to erythrocytes) and type II (affecting all tissues), hemoglobin M disease, and cytochrome B5 deficiency.[5] A newborn presented with cyanosis shortly after birth but remained in good general health. Congenital

methemoglobinemia, an autosomal recessive disorder caused by NADH-cytochrome b5 reductase deficiency, was diagnosed, characterized by a bluish skin color that does not improve with oxygen therapy.[6] Recessive congenital methemoglobinemia (RCM) due to cytochrome b5 reductase deficiency is divided into two types - type I: cyanosis is the only symptom, and type II: cyanosis with severe mental retardation and neurological impairment.[7]

Cyanosis in newborns is challenging and often indicates severe underlying issues. Abnormal forms of hemoglobin necessitate early recognition to prevent unnecessary investigations and delays in management.[8]

Differentiation from hemoglobin M can be done using absorption spectrum analysis and electrophoresis at pH 7.1.

ABG with co-oximetry is the gold standard for diagnosis.[9]

The use of methylene blue is an option, but it should be approached with caution due to the risk of toxicity at higher doses. Notable side effects include hypertension, motor restlessness, dyspnea, nausea, vomiting, sweating, and anaphylaxis. Close monitoring during administration is essential.[10] Management includes: reducing exposure to known toxins, high-flow oxygen and nonrebreather support, administering methylene blue (1–2 mg/kg IV over 5 minutes), and considering alternatives like vitamin C or exchange transfusion for G6PD-deficient patients.[11,12]

CONCLUSION

Congenital methemoglobinemia is a rare syndrome marked by lifelong cyanosis due to either mutant hemoglobin (Hb-M) or NADH-dependent methemoglobin reductase (NADH-MR) deficiency. It requires accurate diagnosis and careful management to prevent complications. Although rare, it can occur in various populations and requires healthcare services for cytochrome b5 reductase enzymatic activity and molecular genetic testing for proper management.

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