Original Research Paper

Volume - 13 | Issue - 07 | July - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Haematology

INCIDENTALLY DETECTED METHEMOGLOBINEMIA AND RESPONSE TO ASCORBIC ACID- A CASE SERIES AND REVIEW OF LITERATURE

Rema Ganapathi	Department of Clinical Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala
Prabhakar Kedar	ICMR National Institute of Immunohematology, 13th floor, KEM Hospital Parel Mumbai-400012
Prashant Warang	ICMR National Institute of Immunohematology, 13th floor, KEM Hospital Parel Mumbai-400012
Karthik Ganesh	Department of Clinical Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala
Manoj Unni	Department of Clinical Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala
Raghuveer Prabhu	Department of Clinical Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala
Neeraj Sidharthan	Department of Clinical Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala

ABSTRACT Methemoglobinemia is a condition caused by the oxidation of iron in hemoglobin, which reduces its ability to carry oxygen and leads to tissue hypoxia. Symptoms depend upon the amount of methemoglobin in the blood. Methylene blue is the recommended treatment, but ascorbic acid has also been shown to reduce methemoglobin levels and provide symptomatic relief in some cases. A case series of 16 patients with methemoglobinemia of various etiologies are presented, all of whom showed improvement with ascorbic acid therapy. The basic pathology, clinical features, management, and approach to a case of methemoglobinemia are also discussed.

KEYWORDS : Methemoglobinemia, Ascorbic acid, Chronic, Toxin induced

INTRODUCTION

Methemoglobinemia is a rare condition with estimated prevalence of 1 in 100,000 population characterized by the presence of elevated levels of methemoglobin, a form of hemoglobin that is unable to bind oxygen effectively leading to symptoms such as cyanosis, fatigue, and shortness of breath. The condition is often underdiagnosed, particularly in patients of Indian ethnicity.

Methemoglobin levels are usually kept in check by Red blood cell(RBC) NADH-cytochrome b5 reductase, but when levels exceed this reduction capacity, symptoms can occur[1,2,3]. Congenital Methemoglobinemia may be caused by mutations in globin chains or enzyme deficiencies, whereas Acquired methemoglobinemia occurs by toxins and drugs that oxidize hemoglobin iron[4]. The classic treatment for acquired methemoglobinemia, methylene blue, activates a different reductase in RBCs that uses NADPH as a cofactor, but is contraindicated in G6PD deficient individuals[5]. Vitamin C has also been shown to be effective in treating methemoglobinemia. It is important to have a high index of suspicion for diagnosing the condition in patients presenting with symptoms of cyanosis, fatigue, and shortness of breath[6]. This study aims to provide insight into the presentation, and management of methemoglobinemia in patients of Indian ethnicity.

METHODOLOGY

This retrospective study with setting in a tertiary care Hematology unit has cases from August 2014 to August 2022. Patients who were diagnosed with methemoglobinemia during evaluation for cyanosis or asymptomatic desaturation and had levels greater than 2% by co-oximetry were included. Co-oximetry result and saturation gap was recorded in all patients. Reports of family members of patients with chronic methemoglobinemia were also screened. NADH- cytochrome B5 reductase level estimation in patients and family members wherever available was compiled.Genetic confirmation of mutations was recorded as available.Medications received by patients Vitamin C and or methemoglobin was noted.

RESULTS

Sixteen patients met the inclusion criteria and belonged to two groups: chronic and toxic/acute methemoglobinemia.

The cases of chronic methemoglobinemia included 11 patients, all of whom had asymptomatic cyanosis with pulse oximetry showing SPO2 levels less than 92%. Cardiac and respiratory causes for cyanosis were ruled out, and arterial blood gas analysis showed normal PaO2 levels. Cooximetry detected the presence of methemoglobin > 10% in all except two cases.

Five patients had toxic methemoglobinemia. Rasburicase, Primaquine and Dapsone were the offending agents identified in our cohort[7,11,12]. All patients were asymptomatic and the desaturation was incidentally detected during pulse oximetry. The methemoglobinemia confirmed by co-oximetry, reversed following the withdrawal of the offending agent in all patients.

Table 1: The Demographics And Characteristics Of The Patients.

Patient Characteristics	Patients with Chronic Methemoglobinemia	Patients with Toxic methemoglobinemia
Number of patients	11	5
Median Spo2(%)	88(73-92)	88(86-89)
Median PaO2	98(94-120)	99(94-100)
Median Methemoglobin level (%)	22(8-32)	23(13.2-26)
Median Age at diagnosis (Years)	13(8m- 36)	20(11-57)
Sex No: (%) Male Female	 8 (72) 3 (27)	 1(20) 4(80)
Cytochrome B5 reductase levels checked	7	nil
Type 1 Reductase deficiency	7	Not done
Type 2 Reductase deficiency	1	Not done
Positive family screening	8(72%)	Not done
Trigger identified	0	5(100%)

Methylene Blue	1(9%)	1(20%)
Vitamin C	11(100%)	5(100%)
Neurological involvement	1(9%)	0
Reduction in Methemoglobin levels with treatment	11(100%)	5(100%)

Males predominated the congenital methemoglobinemia cases (72%), while 80% of toxic cases were females. Out of seven patients whose NADH cytochrome B5 reductase levels were checked and identified to be low, one patient had mutations for Type 1 and Type 2 reductase deficiency while all others had type 1 deficiency. Previously asymptomatic first-degree relatives were detected to have methemoglobinemia in 72% cases of chronic methemoglobinemia when screened with co-oximetry.

In both cohorts, Methylene blue was administered only in patients with Methemoglobin level >30%, but all patients received oral Vitamin C once to 3 times daily based on the treating physician's discretion. The dose was reduced to 500 mg once daily after the initial 1-2 weeks in chronic methemoglobinemia patients. Both cohorts showed a symptomatic response and quantitative reduction in methemoglobin levels with a therapeutic trial of ascorbic acid. In patients with toxic methemoglobinemia, Vitamin C was stopped after the reversal of methemoglobinemia. There was no recurrence noted after the offending agent was withdrawn.

DISCUSSION

Methemoglobin, an abnormal hemoglobin in which the central iron ion in the heme group is oxidized to a ferric state, leads to decreased oxygen-carrying capacity and tissue hypoxia[3]. The diagnosis is challenging, clinical presentation being nonspecific and laboratory tests not readily available. Co-oximetry, Spectrophotometry and measurement of NADH methemoglobin reductase levels are the most used and reliable diagnostic methods.[8,9,10,11,12]

Occupational risk for toxic methemoglobinemia includes exposure to aniline dyes, nitro-containing pesticides, and chemicals used in the production of explosives. Appropriate protective measures should be implemented to minimize the risk of exposure in workers in these settings along with close monitoring. [4,13,14,15]Table 2 gives the list of therapeutic agents and environmental toxins known.

Table 2: Therapeutic Agents And Environmental Toxins Known To Induce Methemoglobinemia[7,11,12]

Anesthetics	Prilocaine, Cetacaine, Benzocaine, Bupivacaine hydrochloride, EMLA cream
Analgesics	Celecoxib, Acetanilide, Phenazopyridine hydrochloride
Anti-inflammatory	Sulfasalazine
Antipyretics	Phenacetin
Antibiotics	Clofazimine, Sulfonamides, Dapsone, Rifampin, Nitrofuran
Antiprotozoals	Quinine, Primaquine, Chloroquine
Antiepileptic agents	Phenytoin, Sodium Valproate
Vasodilators	Nitric oxide (Pulmonary vasculature) Nitroglycerin (systemic and coronary vasculature), nitrates
Antihypertensives	Sodium Nitroprusside, nitrites
Antacid	Bismuth subnitrate
Antiemetic	Metoclopramide hydrochloride
Antidepressant	Hydroxylamine
Nonsteroidal anti androgen	Flutamide
Cryoprotectant	DMSO
Antidote	Methylene Blue
Topical Antimicrobial	Silver Nitrate
Enzyme	Rasburicase
Chemicals in Dye industry	Alloxan, Aniline, Benzene, Ferricyanide
Semiconductor/ computer chip crystal manufacture	Arsine
Herbicides	Chlorates, paraquat
Fungicide	Chromate
Pesticide	Dinitrophenol, Naphthalene
Explosive	Trinitrotoluene
Miscellaneous	Bivalent copper, Exhaust fumes, smoke

Hereditary methemoglobinemia is more prevalent in populations such as the Navajo and Athabascan Alaskans and the Yakutsk people of Siberia. In India, there have been reports of families with NADH cytochrome b5 reductase deficiency[16,17,18]. Levels rise under conditions of oxidative stress, and cyanosis usually becomes evident at levels above 1.5%. The body normally controls methemoglobin levels through two main mechanisms: the major NADH-dependent pathway, which is responsible for 95-99% of methemoglobin removal by reduction, and the minor NADPH-dependent pathway, which utilizes glutathione and glucose-6-phosphate dehydrogenase (G6PD). The NADPH-dependent pathway is greatly activated in the presence of the redox compound methylene blue, which is why methylene blue is contraindicated in G6PD deficiency[5]. Acquired drug-induced and toxin induced causes account for the majority of cases[19,20].

Congenital methemoglobinemias may be caused by mutations in the hemoglobin molecule (HbM) or deficiencies in the enzyme cytochrome b5 reductase. Hemoglobin M ,the result of a point mutation in the globin chain stabilizes iron in the ferric state and can present as neonatal methemoglobinemia[17]. Congenital cytochrome b5 reductase deficiencies can be treated with methylene blue or ascorbic acid, and come in two types, type 1 and type 2. Type 1 is more common, and results in deficiency only in red blood cells, while type 2 is rarer and more serious, leading to neurological complications and early death[16].

Symptoms of methemoglobinemia can range from asymptomatic cyanosis to arrhythmias and seizures. Table 3 shows the clinical profile in relation to the level of methemoglobin in blood.The presence of a saturation gap, which is the difference between the oxygen saturation measured by a pulse oximeter and the actual oxygen saturation seen in a blood gas analysis, typically greater than 5% is characteristic of methemoglobinemia. Pulse oximetry reading is affected by the presence of methemoglobin, leading to inaccuracy. Co-oximetry allows for differentiation between methemoglobin, carboxyhemoglobin, oxyhemoglobin, and deoxyhemoglobin. In patients with significant methemoglobinemia accurate oxygen saturation can be measured using co-oximetry[2].

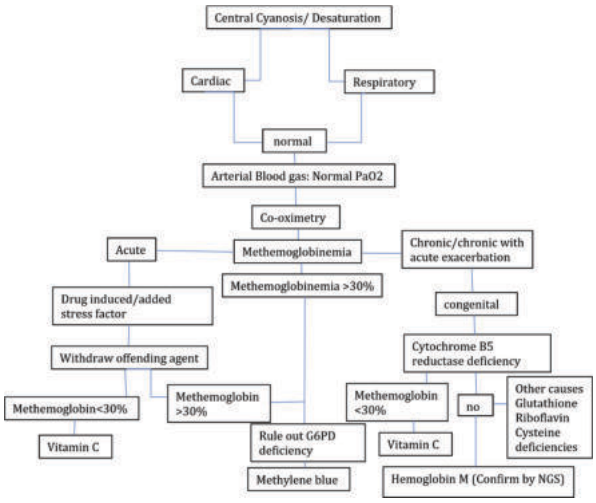
Table 3 : Blood Levels Of Methemoglobins And Clinical Profile [2]

Methemoglobin %	Symptoms
1-2	Normal
<10	No symptoms
10-20	Central cyanosis
20-30	Dyspnea on exertion
30-50	Palpitations, dizziness,tachypnea, confusion, fatigue
50-70	Acidosis ,seizures,arrhythmias,coma
>70	Fatal

Methylene blue is converted to methylene leucoblue, by an NADPH reductase, which reduces methemoglobin to hemoglobin, except in individuals with Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency. The usual dose of methylene blue is 1-2 mg/kg, administered as a 1% solution in IV saline over 3-5 minutes, and may be repeated at 1 mg/kg every 30 minutes as necessary. Care must be taken as methylene blue itself can cause methemoglobinemia at doses greater than 7 mg/kg [19,21,22,23].

Ascorbic acid or Vitamin C has been shown to reduce the ferric ion to ferrous state thereby reducing the methemoglobin levels. The mechanism of action is not well understood, but theories include it acting as an electron acceptor and antioxidant, and reducing methemoglobin in conjunction with glutathione. Studies have shown that ascorbic acid alone or in combination with Vitamin E can be effective in reducing methemoglobin levels in patients with methemoglobinemia [23,24,25,26]. However, when the concentration of methemoglobin is more than 30%, methylene blue becomes essential.

Proposed Algorithmic Approach To Methemoglobinemia [27]



CONCLUSION

Co-oximetry is an effective bedside method for diagnosis and monitoring response to therapy in methemoglobinemia. A high index of suspicion is required in patients presenting with symptoms of cyanosis, fatigue, and shortness of breath, particularly in patients of Indian ethnicity.

Drawbacks of this retrospective study are that Cytochrome b5 reductase levels was not done in patients who presented with toxic methemoglobinemia. All patients showed improvement with ascorbic acid therapy but a control group with another standard of care like Methylene blue was absent. Being a case series with only 16 patients of Indian ethnicity, it is possible that a larger cohort or in other races may yield different results

In summary, both ascorbic acid and methylene blue are effective in treating methemoglobinemia, with different mechanisms of action. Ascorbic acid is generally considered safe and has minimal side effect, making it a good first-line agent for most cases. However, methylene blue can be considered in patients unresponsive to ascorbic acid. The potential benefits and risks of each agent and individual patient factors to be taken into consideration when selecting the treatment.[28-38]

REFERENCES

1. Dana C. Matthews, Bertil Glader; Avery's Diseases of the Newborn (Ninth Edition), 2012; Methemoglobinemia
2. Khanal R, Karmacharya P, Pathak R, Poudel DR, Ghimire S, Alweis R, et al. Do all patients with acquired methemoglobinemia need treatment? A lesson learnt. J Community Hosp Intern Med Perspect 2015;5:29079.
3. Turner MD, Karlis V, Glickman RS. The recognition, physiology, and treatment of medication-induced methemoglobinemia: A case report.Anesth Prog 2007;54:115-7.
4. Dela Cruz, Maricel; Glick, Joshua; Merker, Seth H.; Vearrier, David (11 May 2018). "Survival after severe methemoglobinemia secondary to sodium nitrate ingestion". Toxicology Communications. 2: 21-23.doi:10.1080/24734306.2018.1467532
5. N.V. Bhagavan, Chung-Eun Ha, in Essentials of Medical Biochemistry (Second Edition), 2015 ;Methemoglobinemia
6. Oral Vitamin C in the treatment of congenital methemoglobinemia .R.H. Anand.Journal of Pediatric Hematology/Oncology, Vol25, pp.794-795, 2003.
7. Browning, L. A. , and Kruse J. A.. 2005. Hemolysis and methemoglobinemia secondary to rasburicase administration. Ann. Pharmacother. 39:1932–1935.
8. Curry SC, Chang D, Connor D, et al. Comparison of Co-oximetry and Spectrophotometry for the Detection of Methemoglobinemia. Journal of Medical Toxicology. 2017;13(3):241-246. doi:10.1007/s13181-017-0604-x
9. Roberts DM, Buckley NA. Diagnostic confirmation of methemoglobinemia using co-oximetry. Journal of Analytical Toxicology. 2016;40(8):636-638. doi:10.1093/jat/bkw070
10. Fernando B, Plummer V. A rapid diagnostic method for methaemoglobinaemia using NADH-dependent diaphorase activity. J Emerg Med. 2016 Feb;50(2):315-7. doi: 10.1016/j.jemermed.2015.08.004. Epub 2015 Nov 5. PMID: 26547656.
11. Tripathi M, Dubey PK, Ambesh SP, Agrawal J. Severe Methemoglobinemia: A Case Report and Review of Literature. Journal of Clinical Anesthesia. 2019;54:51-54. doi:10.1016/j.jclinane.2018.09.020
12. Kaya H, Aydinok Y, Ersöz S, et al. Methemoglobinemia due to prilocaine use during cystoscopy. Journal of Medical Case Reports. 2017;11:286. doi:10.1186/s13256-017-1465-9
13. Kalita R, et al. Prevalence of Methemoglobinemia in Workers Exposed to Aniline Dye in Textile Factory: A Cross-Sectional Study. J Occup Environ Med. 2018 Sep;60(9):e469-e473.
14. Li X, et al. Methemoglobinemia Risk among Pesticide Applicators Exposed to Nitro Compounds in China. J Occup Environ Med. 2017 Jul;59(7):e110-e115.
15. Kolli V, et al. Occupational methemoglobinemia due to exposure to nitro-containing chemicals used in explosives production. J Occup Med Toxicol. 2019 Jul 3;14:18.
16. Congenital methemoglobinemia due to NADH-methemoglobinreductase deficiency in three Indian families.Kedar PS1, Colah RB, Ghosh K, Mohanty D.).(Haematologia (Budap). 2002;32(4):543-9.
17. Edward J. BenzJr., Benjamin L. Ebert, Hemoglobin Variants Associated With Hemolytic Anemia, Altered Oxygen Affinity, and Methemoglobinemias.Chapter 43 in Hematology (Seventh Edition), 2018 p608-615. https://doi.org/10.1016/B978-0-323-35762-3.00043-3.
18. Case Reports Hemoglobin M (Milwaukee) Affects Arterial Oxygen Saturation and Makes Pulse Oximetry Unreliable.Stucke, Astrid G. M.D.*; Riess, Matthias L. M.D., Ph.D.*; Connolly, Lois A. M.D.†)(Anesthesiology:April 2006 - Volume 104 - Issue 4 - pp 887-888
19. Methemoglobinemia in a Young Man;Yasmin S. Hamirani, MD, Wayne Franklin, MD, [...], and Raymond F. Stainback, MD, FACC) (Texas Heart Institute Journal,Texas Heart Institute.Harwood-Nuss' Clinical Practice of Emergency Medicine.Allan B. Wolfson, Gregory W. Hendey, Louis J. LingPg 1485.
20. Rehman HU. Methemoglobinemia. West J Med. 2001 Sep;175(3):193-6. doi: 10.1136/ewjm.175.3.193. PMID: 11527852; PMCID: PMC1071541.
21. Marianne Boylston, Deborah Beer. Methemoglobinemia: A Case Study. Critical Care Nurse. 2002;22:50–5. [PubMed] [Google Scholar]
22. Clifton, Jack II, Leikin, Jerrold Methylene blue. American Journal of Therapeutics. 2003;10:289–91. [PubMed] [Google Scholar]
23. Methemoglobinemia:Etiology, pharmacology and management. J.R. Roberts. Journal of Emergency Medicine , Vol22,pp3-11, 2002.
24. Methemoglobinemia and ascorbate deficiency in hemoglobin E β thalassemia: metabolic and clinical implications. Angela Allen,1,2 Christopher Fisher,1 Anuja Premawardhena,3 Dayananda Bandara,4 Ashok Perera,4 Stephen Allen,2 Timothy St Pierre,5 Nancy Olivieri,6 and David Weatherall