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Methemoglobinemia: Clinical Perspective, Managements and Cases review

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Abstract

Methemoglobinemia is rare disorder caused by the oxidation of hemoglobin's iron from ferrous (fe2+) to ferric (fe3+),impairing oxygen transport and causing hypoxia. It is classified as heredietary or acquired. Hereditary forms result from NADH-cytochrome b5 reductase deficiencies or Hemoglobin M disease, while acquired cases are due to oxidizing agents,drugs or toxins.Symptoms ranges from mild cyanosis (1-10% methemoglobin) to life threatening effects (>70%).

Diagnosis has advanced with tools like multiwavelength pulse oximetry,arterial bood gas analysis, and genetic testing.Treatment varies with severity including methylene blue,ascorbic acid and discontinuation of causative agent.Infants are particularly at risk due to immature enzyme systems.This review highlights the pathophysiology,risk factors,advanced diagnosticand management strategies of methemoglobinemia,along with a case demonstrating successful intervension.

Keywords: Methemoglobinemia, Hypoxia, Cyanosis, Methylene blue

INTRODUCTION

In the blood, hemoglobin (Hgb) is a tetrameric molecule having subunit of heme which consist of 2 alphaand 2 beta chains. Iron is present within the heme molecule in ferrous state. When the ferrous (Fe2+) state converts into ferric (Fe3+) state due to oxidation of iron during oxygenation and deoxygenation of hemoglobin then it becomes incapable to make bond and carry the oxygen molecule. This condition is called as" Methemoglobinemia",leads to various disorders in the body. This changed hemoglobin due to ferric state is called as "Methenoglobin".

Methemoglobinemia is categorized as acquired and hereditary methemoglobinemia. Acquired methemoglobinemia is most common form occurs due to the drugs and toxins which are responsible for oxidizing ferrous into ferric state. Hereditay methemoglobinemia is caused by M or NADH reductase deficiency and it is get suspected by the oxygen saturation in body.

Mwthemoglobinemia is rare and it shows the symptoms with respect to % methenoglobin present in the patient. The normal hemoglobin (Hb) range for adult male is 14.0 – 17.5 g/dl, while for adult females, it is 12.3 -15.3 g/dl. Consequently, the normal range of methenoglobin (MetHb) levels in adults would be less than approximately 0.14 – 0.175g/dl for males and 0.12 – 0.153 g/dl for females. The amount of MetHb is determine by dividing the concentration of MetHb but total Hb present in body. When there is 1% of methenoglobin is in blood then it is start of this disorder, when it ranges more than 10% then

patient may have more symptoms at lower level. 30%-35% of the methenoglobin range in blood leads to weakness, confusion, trachycardia, chest pain, headache, anxiety etc. when it reaches to 70% thenpatient usually cannot survive against methemoglobinemia. Methemoglobinemia is commonly represents the lack of hemoglobin in blood which is responsible to shortage of oxygen & carbon dioxide to the tissues. This shortage leads the signs like blue colour occurance to the skin which is described with cyanosis and due to external physical occurance of the skin, methemoglobinemia is also called as 'Blue Baby Syndrome'. In infants, the risk pf methemoglobinemia for long period of time is more as compare to adults because infants have lowers NADH and Cytochrome-b-5-reductase (cb5r) activity which is responsible to convert the methenoglobin in hemoglobin means recovery. For prevent the risk of methemoglobinemia, oxidizing drugs should not be preferred for the childrens under the 6 months old and for the above aged, oxidizing drugs such as benzocaine and prilocaine should be at limited composition as 2.5mg/kg of the person.

RISK FACTORS

There are two categories of Methemoglobinemia, Acquired and Congenital (hereditary). Acquired Methemoglobinemia is occurs due to the chemicals and medications. Other causing factors of acquired Methemoglobinemia are nitrate rich vegitables, additives in foods and overdoses of drugs etc. The cases have been identified in increasing number in Los Angeles from last few years. Signs and symptoms of this type starts to occur around half an hour after administration or after application of chemical substance. There are two machanisms of acquired methemoglobinemia, first one is rare and includes direct oxidation due to chlorates, hexavalents chromates & cobalts etc. But second complex mechanism of oxidation occurs indirectly and usually which includes both oxygen and iron which produces superoxide and hydrogen paroxides when oxygen accepts electrons from ferrous iron which bound to hemoglobin. Due to the lack of oxygen supplement Cyanosis and Tissue Ischemia may be led by acquires methemoglobinemia. Heriditary methemoglobinemia is rare genetic condition caused by biallelic mutations in the CYB5R3 gene, leading to NADH cytochrome b5 reductase deficiencies. It is classified into two subtypes; Type 1, with enzyme deficiency limited to red blood cells (RBCs), causing cyanosis and mild symptoms.Type 2 involves systemis deficiency which leads to severe neurological involvement and high morbidity. Over 80 CYB5R3 varients have been reported, with genotype-phenotype correlations observed. Hemoglobin M disease os rare in which autosomal dominant conditions caused by mutations in HBA1, HBA2, HBG1 or HBG2 which leads to cyanosis due to structural abnormalities in hemoglobin. These mutations cause iron in heme to resist reduction to its functional state, with at least 13 HbM variants reported, including HbM Bostom, Saskatoon, lwate and Hyde Park. Symptoms vary by globin chain affected with alfa- globin variants evident at birth and beta-globin variants manifesting after 6-9 months. Methemoglobinemia is more likely in people with heart or lungs diseases, anemia or those who are very young or old, especially during surgery. Treatment is needed if methemoglobin levels are 10% with risk factors or 30% or more level of methemoglobin for anyone. Common causes include drugs like lidocaine, dapson and nitric oxide. A rare condition called Hemoglobin M does not respond to usual treatments but may improved with a blood exchange. Adding dextrose helps the body during treatment of it.

Sr. No.	Class of Drugs	Examples
1.	Nitrites/nitrates	Amyl nitrite, Sodium nitrate,

		Nitro-glycerine, Nitroprusside, Nitric oxide
2.	Antineoplastics	Cyclophosphamide, Ifosfamide, Flutamide
3.	Local Anaesthetics	Benzocaine, Lidocaine, Prilocaine
4.	Sulphonamide	Sulphasalazine, Sulphanilamide, Sulphapyridine
5.	Antimalerial Drugs	Chroquine, Primaquine
6.	Antibiotics	Dapson, Sulphamethoxazole
7.	Others	Metoclopramide, Sodium valproate, Phenytoin

Table 1: Drugs that causes methemoglobinemia

MACHANISM INVOLVE

Methemoglobinemia is rare and it may cause due to poisoning and overdoses of medications due to improper selection or prescription for the patient needed. In some cases deficiency of cytochrome b-5 reductase also responsible as we have seen earlier. Mutations in gene also be reported as causing factor in the patient having cyanosis and dysphea(Difficulty in breathing) by DNA analysis. Due to the use of nitrogenous fertilizers, the level of nitrate is increased in underground water that's why vegitables and living food sources uptake it through root hairs. After the ingestion of this nitrate containing products by animals especially humans,nitrates is taken as food which converts inti nitrites into the living system which forms methemoglobinemia. And infants readily oxidized it in methemoglobinemia. Signs and symptoms of this may be get delayed with respect to actual cause of it with respect to amount of risk factor uptaken and then methemoglobinemia may be acute and chronic depending on period as well as characteristics of it.

Sodium nitrite(NaNO3 : molecular weight is 84.99g/mol) is commonly used as a preservatives and antimicrobial agent in foods and meat products which causes severe methemoglobinemia which impair the ability of blood to carry the oxygen molecule. Methyelene blue is the primary antidote for treating this danger condition. A 28 year old man presented with transient loss of consciousness, cyanosis and severe methemoglobinemia (methenoglobin 92.5%) after ingesting appropriately 15g of sodium nitrate. He was treated with 100% oxyegen, gastric lavage and a single 150mg dose of intravenous methylene blue which resolved cyanosis and reduced methenoglobin to 19% within 60 minutes. On the second day, the patient reported intentional sodium nitrite ingestion. Despite persistent sodium nitrite in his system, no rebound methemoglobinemia occurred. MRI showed symmetrical hyperintense, lesion in the globus pallidus. The patient recovered without neurological impairment and was discharged on day 7.

MODERN DIAGNOSIS

By studying the cases, we got know the diagnosis based on the physical characteristics like headache, blue colouration,dyspnea etc. But the mechanical diagnosis of methemoglobinemia results the accuracy in reading of symptoms.

Blood test is one of them to diagnose it which includes:

1) Pulse Oximetry : To diagnosis of methemoglobinemia pulse oximeter is used which measures the oxygen level in blood but nowadays The Masimo Rad-57 multiwavelength pulse oximeter is introduced which effectively detected and monitored methemoglobinemia in a surgical patient which providing continuous, eal-time methenoglobin readings, unlike convensional pulse oximeters. It's allow to tinely diagnosis and treatment with its values closely matching laboratory CO-oxymetry results which demonstrating its clinical utility in managing dyshemoglobinemia.
2) Arterial Blood Gas Analysis : Arterial Blood Gas (ABG) analysis is a valuable tool in diagnosing methemoglobinemia, especially in cases of cyanosis with a structurally normal heart. Elevated methenoglobin levels, often overlooked in routine ABG interpretation, can be present as low oxygen saturation by pulse oximetry despite normal PO2 levels. ABG machines equipped to measure methemoglobin levels can aid in prompt recognition and management of the condition, emphasizing the need for careful evaluation in undiagnosed cyanosis cases. Some other tests are also conducted to diagnosis with respect to amount, capability and form of hemoglobin such as:
3) Enzyme (CYB5R) activity was measured using standard methods alongwith routine haematological investigations. Molecular analysis involved PCR, DNA sequencing and structural interpretation using DEEP VIEW SWISS-PDB VIEWER and Pymol.

There was case in which methemoglonemia was rare cause of cyanosis and dyspnea unrelated to cardiopulmonary conditionsistypically asymptomatic even with methemoglobin levels up to 40% of total hemoglobin. In this case, the diagnosis was missed despite extensive cardiopulmonary investigations and was ultimately identified through physical examination and arterial blood gas analysis. Subsequent DNA analysis revealed a novel mutation in the cytochrome b5 reductase gene as the cause of the methemoglobinemia .

MANAGEMENT

Methemoglobinemia is formed by the exposure of oxidants include drugs, dietary oxidants, toxical oxidants etc. This oxidants leading methemoglobinemia is reversible because the incapability to carry oxygen responsible for hypoxia which can recovered by methenoglobin reduction systems. There are also some cofactors such as methylene blue and ascorbic acid which are controlled by the systems against methemoglobinemia. Cytochrome b5 MetHb reductase pathway reduces MetHb to hemoglobin in presence of Nicotinamide adenine dinucleotide (NADH) while Nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase also function as second pathway in which glucose-6-phosphate dehydrogenase (G6PD) is necessary to this recovery conversion.

Management with repective condition:

1) Severe Methemoglobinemia; this is life threatening condition which is managed by preferring emergency therapy.
2) Acute Acquired Methemoglobinemia; this condition caused by the exposure of inducing agents which is managed by discontinuation of inducing drugs and initiating emergency therapy.
3) Chronic Mild Methemoglobinemia; this condition present with cyanosis and may be asymptomatic which is managed by specific therapies.
4) Chronic Methemoglobinemia; this condition becomes descriptive with persistent cyanosis and it is treated by using methylene blue, citric acid and oxygen supplementary.

Drugs used widely for treatment
1.Methylene blue 2.Ascorbic acid 3.Cimetidine
Therapies: 1.Hyoerbaric oxygen Therapy 2.exchange transfusion

Table 2: Drugs used for manage Methemoglobinemia

OBJECTIVE

The main objective of this study to emphasize the negligence of instructions, components and side effects of drugs as well as genetic transmission especially mutations and enzyme deficiencies which may lead to life threatening condition called 'Methemoglobinemia' by analysing the global cases to know the characteristics and physiology with different age groups to aware the society for the better healthcare and avoiding irritating and threatening symptoms.

RESEARCH METHODOLOGY

For my review work on the topic Methemoglobinemia, I have used reading the comprehension and analysing the questionnaire as key methodologies.The literature review was composed and prepared by findings from various resources, while questionnaires have gathered insights from medical proffesionals to enhanced understanding of diagnostic challenges and treatment strategies. This methods have provides a comprehensive overview of the topic and highlight areas for the researched and composition of it.

CONCLUSION

Methemoglobinemia is the rare disorder having limited treatment options and it growing widely due to exposure of nitrates in foods or drugs.To getting known about machanism help significantly to find out the intensity of methemoglobinemia.This paper concludes the importance of key findings of treatment and risk factors of methemoglobinemia.

In pharmaceutical sectors and medical technology methemoglobinemia is one of the critical topic to research about curing perspective.All the findings are potent in all the fields of clinical pharmacy for development and controlling the methemoglobinemia.

By using the modern analytical techniques of blood, hemoglobin and other body fluids, analysis of this disorder can be easy in research segment.The understanding it's pathophysiology, early diagnosis and appropriate treatment strategies are crucial to manage it.By leading the advancement of knowledge in this area of review will increase the patient care and preventing strategies which ultimately decrease the burden of methemoglobinemia.

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