



Sudden Onset of Life-Threatening Methaemoglobinaemia After Intake of Inappropriately Stored Vegetable (Collard Greens) Meal in a 2.5-Year-Old Child

İki Buçuk Yaşındaki Bir Çocukta Uygunsuz Şartlarda Saklanmış Sebze (Kara Lahana) Tüketimi Sonrasında Yaşamı Tehdit Eden Methemoglobinemi

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ABSTRACT

Acquired methaemoglobinaemia most commonly occurs due to intake of or contact to certain drugs, such as local anesthetics. However, intake of certain vegetables which are essential for a healthy diet may also cause methaemoglobinaemia due to their high nitrate or nitrite content, and prolonged and inappropriate storage after preparation of vegetable meals increases the risk. We present a 2.5-year-old girl with Down's syndrome who presented with central cyanosis due to severe methaemoglobinemia with a methaemoglobin level of 62% after intake of collard greens (*Brassica oleracea* var. *acephala*) soup. Although development of methaemoglobinaemia after food intake has been reported rarely before, recognition of this potentially life-threatening condition early in its course may be life-saving.

Key words: Methaemoglobinaemia, vegetable intake, nitrate, nitrite

ÖZET

Edinsel methemoglobinemi en sık olarak, lokal anestetik ilaçlar gibi belirli ajanların alımından ya da belirli ajanlarla temastan sonra görülmektedir. Ancak, sağlıklı bir beslenme için gerekli olan belirli sebzelerin alımından sonra da methemoglobinemi gelişebildiği bilinmektedir. Bu durum, özellikle yeşil yapraklı sebzelerle hazırlanan yemekler, uzun süreli olarak uygunsuz koşullarda saklanırsa ortaya çıkabilir. Sebzelerin yüksek nitrat ve nitrit içeriği, methemoglobinemi geliştirme potansiyellerinden sorumlu tutulmaktadır. Burada, kara lahana çorbası tüketiminden sonra ortaya çıkan methemoglobinemiye (methemoglobin oranı: %62) ikincil santral siyanoz gelişen 2,5 yaşındaki Down sendromlu bir kız çocuğunu sunmak istedik. Besin alımı sonrasında methemoglobinemi gelişimi nadir olarak bildirilmiş olmasına rağmen, yaşamı tehdit eden bu durumun erken dönemde tanınması ve tedavi edilmesi önemlidir.

Anahtar kelimeler: Methemoglobinemi, sebze tüketimi, nitrat, nitrit

INTRODUCTION

Methaemoglobinaemia is among the most common causes of central cyanosis developing in the absence of any cardiac or pulmonary disorder. Methaemoglobin (MetHb) is an altered form of haemoglobin in which the iron in haeme molecule is oxidized from its ferrous (Fe^{2+}) to ferric (Fe^{3+})

state. It has very high affinity to the bound oxygen, hence, oxygen delivery to tissues is impaired. An increase in MetHb concentration which should normally be lower than 1% of total haemoglobin may cause tissue hypoxia, lactic acidosis and even death^{1,2}.

As MetHb is a dark-colored pigment, patients with methaemoglobinaemia often have bluish skin discoloration, and their tongue and lips may look cyanotic. In addition, the blood has characteristically a chocolate-brown color. The severity of the clinical signs and symptoms depend on the MetHb level in blood, individual factors and accompanying disorders. Symptoms develop secondary to tissue hypoxia in all the cases^{1,2}.

Acquired methaemoglobinaemia usually develops secondary to some medications^{2,3}. Methaemoglobinaemia after food intake has been reported less commonly⁴⁻⁶. We present here a 2.5-year-old girl with Down's syndrome who developed severe methaemoglobinaemia after intake of collard greens soup.

CASE

The 2.5-year-old female patient was admitted to the emergency service with the complaints of bluish discoloration on the lips, tongue, nail beds and fingertips, vomiting and dizziness about one hour after food intake. There was no history of aspiration or any drug intake. The child was fed with collard greens soup cooked 3 days ago and stored in the refrigerator (+4 °C), and it was kept at room temperature for a few hours on the last day before use. No other family member ate the soup, and none developed any complaints. The mother noted perioral cyanosis in the absence of coughing or wheezing. Thereafter, the patient vomited once, and responded weakly to external stimuli.

In the emergency service, 100% oxygen through a non-rebreather mask was administered to the centrally cyanotic and apathic patient, however, oxygen saturation by pulse oxymetry did not exceed 75-80%. She was noted to be tachycardic with a heart rate of 145/min. Venous blood samples taken for laboratory investigations were noted to be chocolate-brown in colour. In the laboratory examination, the patient had mild normocytic anemia (haemoglobin 10.7 g/dL), leukocytosis (leukocyte count $19.83 \times 10^9/L$), and serum glucose level was elevated (228 mg/dL).

Serum electrolytes, C-reactive protein, chest X-ray, electro- and echocardiography were all normal. Blood gas analysis revealed metabolic acidosis and severe methaemoglobinemia (pH 7.19 nmol/L, HCO_3^- 14 mmol/L, pCO₂ 38 mmHg, MetHb 62%, lactate 9.7 nmol/L).

Oxygen supplementation was continued, and intravenous hydration was started. As methylene blue was unavailable, intravenous ascorbic acid infusion (300 mg/d) was administered. Four hours after therapy, the oxygen saturation of the patient raised to 95%, and lactic acidosis resolved completely. MetHb percentage in blood decreased to 22.7%. Ascorbic acid infusion was continued for a total of 24 hours. Besides, serum glucose level which was found to be elevated due to stress at admission declined to normal range. As the patient's symptoms disappeared completely, and MetHb level in blood was found 1.8% at the 14th hour of therapy, she was discharged after the completion of ascorbic acid infusion.

DISCUSSION

Methaemoglobinemia may be either congenital or acquired. Acquired methaemoglobinaemia is more common, and it may occur after intake of or contact with certain oxidizing agents. Local anesthetics, dapsone, aniline and phenacetin have been found to be associated with methaemoglobinaemia^{2,3,7,8}. Diarrheal disease may also cause this disorder by altering the intestinal flora and thus causing increased conversion of nitrates to nitrites which are absorbed into the bloodstream and are strong oxidants of ferrohaemoglobin.⁹ Besides, the disorder can occur after intake of nitrate-rich well water and vegetables, particularly leafy green vegetables such as borage and chard.^{4-6,10} Owing to the immaturity of their enzymatic systems, elevated levels of readily oxidized fetal haemoglobin and lower stomach acidity which promotes growth of microorganisms, infants younger than 3 months are particularly susceptible

to methaemoglobinaemia, although older infants and children are also at risk^{4,6}.

Methaemoglobin which is the oxidized form of haemoglobin has increased affinity to oxygen, and causes hypoxemia by shifting the oxygen-dissociation curve to the left which means that oxygen delivery to tissues is impaired, thus, cyanosis, dizziness, malaise, and with higher MetHb concentrations, even stupor, coma, metabolic acidosis and death from cardiovascular failure may be seen in methaemoglobinaemia^{1,2,7}. At her admission, our patient was cyanotic and apathic, had metabolic acidosis and MetHb percentage was severely elevated (62%).

The disorder presented here occurred for the first time in the 2.5-year-old case. There was no history of any drug use or diarrheal disease, and the water supply was from a modern urban system. Signs and symptoms of methaemoglobinaemia developed about one hour after food intake. Therefore, we thought acquired methaemoglobinaemia secondary to vegetable intake to be the diagnosis. The collard greens soup was cooked 3 days ago, and it was kept at room temperature for a few hours on the last day before the child ate it. In fresh and undamaged vegetables, nitrite concentrations are usually very low, whereas under inappropriate post-harvest storage and food processing, nitrite concentrations may reach toxic levels capable of inducing methaemoglobinaemia as a result of bacterial contamination and endogenous nitrate reductase action⁶.

We summarized the main characteristics of vegetable-born childhood methaemoglobinaemia cases reported so far in the literature. For this purpose, a Pubmed search using the terms "methaemoglobinaemia" and "vegetable" was conducted. The main characteristics of the cases including the vegetable(s) consumed are summarized in Table 1^{4,5,11-15}.

In their study including 78 cases of diet-induced methaemoglobinaemia aged 4-18 months with MetHb percentages between 8.7% and

61.3%, it was found that the time elapsed from puree preparation to intake of vegetable meals (>24 h) and site of storage (room temperature) to be significantly associated with occurrence of methaemoglobinaemia.⁴ This may be explained by the promotion of conversion of nitrates in vegetables to nitrites in case the interval between preparation and consumption is prolonged, and the product is stored at room temperature. On the contrary, nitrite accumulation in frozen vegetables is inhibited, as endogenous nitrate reductase becomes inactivated.⁶ Furthermore, infantile cases of methaemoglobinaemia (MetHb percentages between 10% and 58.2%) secondary to vegetable puree consumption that was kept refrigerated for 12-72 hours have been reported before in the literature.⁵ Centre for Food Safety (CFS) recommends immediate use of infant food prepared in vegetable puree form, and states that this type of infant food should be kept frozen when the consumption is to be delayed, as keeping vegetables in cold (refrigerated) is not safe enough (detailed information available at www.cfs.gov.hk).

In acquired methaemoglobinaemia, intravenous methylene blue which activates NADPH MetHb reductase is the preferred pharmacological treatment after securing the airway and maintaining high-flow oxygen, and glucose-6-phosphate-dehydrogenase deficiency should be excluded before its administration^{1,2}. In our hospital, methylene blue was not available, so, we used intravenous ascorbic acid (300 mg/d). It is also effective by reducing ferrihaemoglobin to ferrohaemoglobin, although the response is slower than with methylene blue².

In conclusion, when a child presents with cyanosis responding inadequately to oxygen administration, methaemoglobinaemia should always be considered. Certain types of vegetables such as collard greens which is consumed quite often in Northern Turkey may cause methaemoglobinaemia through their high nitrate or nitrite content, and use of them early after

preparation and storage in appropriate conditions may diminish this risk.

Table 1. Literature review of childhood cases of vegetable-born methaemoglobinaemia

Author, year	No of cases (age)	MetHb level (%)	Vegetable consumed
Martinez, 2012	78 (4-18 mo)	31.7-61.3	Borage, chard
Savino, 2006	2 (1 mo; 2 mo)	30.4; 27	Courgette
Murone, 2005	4 (7-9.5 mo)	37-65	Fennel
Bryk, 2003	1 (6 mo)	25	Mixed vegetable puree (made from potatoes, carrots, squash and celery)
Sanchez-Echaniz, 2001	7 (7-13 mo)	10-58.2	Silver beets, carrots, pumpkin, green beans
Geffner, 1981	2 (1 mo; 6 wk)	No data; 35	Spinach water; gerber pureed spinach, beets and carrots
Keating, 1973	1 (2 wk)	No data	Carrot

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