HK J Paediatr (new series) 2019;**24**:231-234

Case Report

An Infant with Diarrhoea and Cyanosis: A Case Report of Methaemoglobinaemia

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Abstract We report a young infant with diarrhoea and associated methaemoglobinaemia, who presented acutely with shock and cyanosis. The baby was subsequently diagnosed to have cow's milk protein intolerance. The clinical features, pathogenesis, aetiology and management of the condition were reviewed. We would like to highlight that methaemoglobinaemia is a medical emergency, and prompt treatment with methylene blue is life-saving and usually results in good outcome.

Key words Children; Cow's milk protein allergy; Diarrhoea; Methaemoglobinaemia; Nitrate

Case Report

A 31-day-old Chinese baby girl presented to the Accident and Emergency Department with two weeks history of diarrhoea and poor feeding. She was the second child of a non-consanguineous Chinese couple with no significant family history. Her perinatal course was uneventful. Feeding by cow's milk-based formula was introduced on day 1 of life and tolerated. On day 19, she started to have diarrhoea. Feeding was changed to soy-based formula as suggested by a family doctor. Promethazine, lacteol, and kaolin pectin were prescribed. Diarrhoea then improved. One week later, mother noticed that baby's face became blue and pale. She visited another doctor who performed electrocardiogram and chest X-ray with normal findings. Feeding with cow's milk-based formula was resumed. Diarrhoea then worsened and baby developed vomiting and refused to eat. At presentation, she was lethargic, tachycardic and tachypnoeic with central cyanosis (Figure 1). The circulation was poor with skin mottling and delayed capillary refill. Blood pressure was not measurable. Oxygen saturation (SpO2) was 89-90% in room air by pulse oximetry. Her body weight was measured to be similar to her birth weight. She was afebrile. Examination of heart, chest and abdomen were unremarkable. Venous blood gas findings were as follows: pH 7.06, pCO2 4.5kPa, base excess -19.7 mmol/L. She was given oxygen therapy and normal saline bolus with improvement of heart rate and blood pressure.

She was transferred to the paediatric intensive care unit for further management. Despite a high flow oxygen supplement of 5 L/min and a SpO2 reading of 94%, the child remained in deep central cyanosis. Complete blood picture, serum electrolytes and anion gap were unremarkable. Haemoglobin was 12.4 g/dL and serum bilirubin was 10 umol/L with no sign of acute haemolysis. Dark chocolate-brown coloured blood was drawn from the arterial line (Figure 2). The diagnosis of methaemoglobinaemia was thus suspected, and was confirmed by co-oximetry (methaemoglobin was 44.1%, oxyhaemoglobin 55.9%, and deoxyhaemoglobin <1%). Normal status of glucose-6-phosphate dehydrogenase enzyme (G6PD) was confirmed by visual fluorescent method.[1] Intravenous methylene blue 1 mg/

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Received March 30, 2019

kg bolus was given. The baby quickly turned pink with improvement of circulation. Heart rate gradually normalised. SpO2 became 99-100% on 2 L/min of oxygen through nasal cannula. Metabolic acidosis improved. Co-oximetry 1 hour later showed that methaemoglobin level had gone down to 1.5%, while oxyhaemoglobin increased to 98%. She then continued on oral methylene blue and ascorbic acid.

Feeding with cow's milk-based formula was resumed three days after admission. She developed watery diarrhoea again. Metabolic acidosis recurred, while methaemoglobin level rose. The condition improved after stopping feeds with provision of intravenous fluid and sodium bicarbonate. Milk formula was changed to hydrolysed protein formula with the suspicion of cow's milk protein intolerance. It was well tolerated with resolution of diarrhoea and normalisation of methaemoglobin level and acid-base balance. The child had good weight gain afterwards.

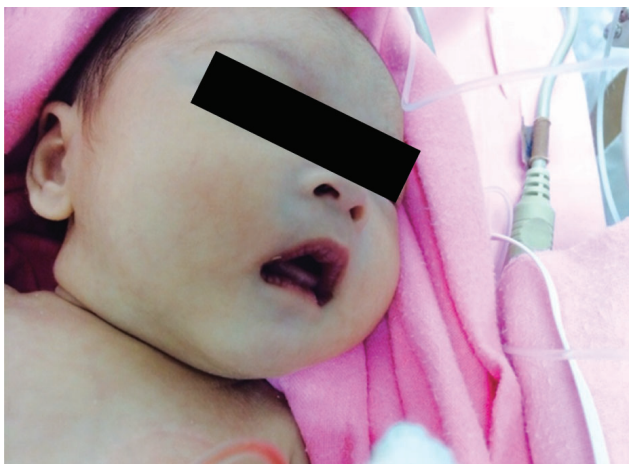

Figure 1 Cyanotic appearance of our patient at presentation.

Figure 2 Dark chocolate brown coloured blood withdrawn from arterial line.

Serum and urine screening for metabolic diseases and toxicology was negative. No viral or bacterial pathogen was identified in blood or stool hence infective gastroenteritis was unlikely. Stool was positive for fat globules but negative for reducing substance. The level of immunoglobulin E against cow's milk protein was normal. During the acute episode, urine nitrate was elevated to 1265 mg/L, with high nitrate to creatinine ratio 360 mg/mmol Cr (Normal value: <100 mg/mmol Cr). It returned to normal after patient was put on hydrolysed protein formula. Haemoglobin pattern by electrophoresis was normal. Genetic study for congenital methaemoglobinaemia type I and II with polymerase chain reaction of the CYB5R3 gene followed by direct DNA sequencing revealed no mutation. Methylene blue and vitamin C were then taken off. MRI scan of brain showed no evidence of hypoxic damage. On the last follow-up at 4 years old, she enjoyed normal growth and development without recurrence of methaemoglobinaemia.

Discussion

Methaemoglobin is a form of haemoglobin in which the usual ferrous (Fe2+) form of iron in the haem group is oxidised into its ferric state (Fe3+). The latter not only cannot carry oxygen, but also increases the oxygen affinity of the remaining haem in the haemoglobin.[2] This results in decreased oxygen delivery and tissue hypoxia. Physiologically, there is a gradual, constant formation of methaemoglobin by endogenous oxidation. This is counteracted by several enzymatic pathways which maintain the level of methaemoglobin under 1%. The major one is the cytochrome b5-methaemoglobin reductase pathway, where methaemoglobin is reduced back to haemoglobin using nicotinamide adenine dinucleotide (NAD) as a cofactor.[2] Another pathway involves the nicotinamide adenine dinucleotide phosphate (NADPH)-Methaemoglobin reductase, in the presence of NADPH as a cofactor. The production of NADPH requires G6PD. This pathway plays a minor role in usual physiological state, but can be activated by methylene blue.[2] Methaemoglobinaemia occurs when there is an increased production of methaemoglobin, or a failure in the protective reducing mechanisms. With accumulation of methaemoglobin to values higher than 1.5 g/dL (15% of

total haemoglobin), cyanosis becomes clinically noticeable. Anxiety, headache, dizziness and tachycardia may occur when level rises to above 20%. Levels between 30% and 50% can produce fatigue, confusion, and tachypnoea. Above 50%, there may be arrhythmias, acidosis, seizures, and coma. Levels exceeding 70% are usually fatal.[2,3]

Methaemoglobinaemia is classically in the list of differential diagnosis of cyanosis. However, its clinical encounter is rare. High index of suspicion is pivotal for timely diagnosis and treatment. Clinical features that should raise suspicion of this condition include: cyanosis which does not improve with oxygen therapy, mild or absent respiratory or cardiac symptoms; discrepancy in the SpO2 measured by a pulse oximeter and clinical cyanosis; chocolate-brown colour blood which does not turn bright red on exposure to atmospheric oxygen.[3] Pulse oximeter is not reliable in measuring oxygen saturation in patients with methaemoglobinaemia. The SpO2 measured can be normal or may plateau at 85% when methaemoglobin level rises above 35%.[4,5] Saturation gap(the difference between the calculated oxygen saturation from blood gas machine and the reading from pulse oximetry) of greater than 5% suggests the diagnosis of abnormal haemoglobin such as methaemoglobinaemia.[3] Definitive diagnosis is made by co-oximetry, which measures the level of methaemoglobin in the blood.

Treatment should be started promptly after diagnosis. Mild cases may resolve with withdrawal of offending drug or enhanced hydration. Treatment by methylene blue is indicated in cases with severe symptoms and high methaemoglobin level.[3] The recommended dose is 1-2 mg/kg administered intravenously over 5 to 10 minutes.[2,6] Improvement is usually seen within minutes and maximum effect occurs at 30 minutes. Additional doses may be given after 1 hour if response is inadequate. This treatment should be avoided in patient with G6PD deficiency as it would increase the risk of haemolysis and paradoxical methaemoglobinaemia. Ascorbic acid directly reduces methaemoglobin, but the rate is too slow when used alone.[7] Alternative treatments include hyperbaric oxygen and exchange transfusion.[3,7]

In patients with methaemoglobinaemia, an underlying cause needs to be identified. Congenital methaemoglobinaemia is very rare, and is caused by deficiency of cytochrome b5 reductase or Haemoglobin M disease. The former is an autosomal recessive disease with two subtypes, where the enzymatic deficiency is limited to erythrocytes, or involves all body cells.[7] Diagnosis can be made by measuring cytochrome b5 reductase activity or genetic studies. Haemoglobin M disease is an autosomal dominant disease caused by structural alteration of the haem pocket, where the iron remains in ferric state. It is diagnosed by electrophoresis or DNA sequencing.[8]

Most cases of methaemoglobinaemia are acquired. The most common culprits are oxidising drugs such as dapsone and benzocaine.[2] Consumption of well water contaminated by nitrate is another well-known cause. Diarrhoea has been reported as an aetiology of methaemoglobinaemia in young infants.[5,9,10] A study performed blood test in 43 infants with diarrhoea found that 64% had elevated methaemoglobin levels with a mean level of 10.5%, which may be subclinical.[9] In a case series of 45 infants with methaemoglobin associated with diarrhoeal disease, 18% were diagnosed to have intolerance to cow's milk or soy protein-based formula.[10] One of the proposed mechanisms for the pathogenesis is that diarrhoea causes bacterial overgrowth in the intestine, which synthesizes nitrites and/or nitrates.[10,11] Nitrate is converted to nitrite by gut flora, which promotes formation of methaemoglobin. In patients with milk-protein sensitivity, altered colonic homeostasis in nitrate metabolism also plays a role, with increased nitrate formation by inflammatory cells of the colonic mucosa, and decreased epithelial catalase activity to metabolise nitrite.[11] Hence, nitrate level in blood and excreted in urine is significantly increased. Infants younger than six months are more prone to methaemoglobinaemia due to the following reasons: fetal haemoglobin is more easily oxidised than adult-type haemoglobin; cytochrome b5-methaemoglobin reductase methaemoglobin reductase activity is lower compared to adults; and the higher intestinal pH which promote the over-growth of nitrate-producing bacteria.[5,10]

Our patient presented with methaemoglobinaemia associated with diarrhoea and increased urine nitrite level. The drugs taken by the patient were not known to induce methaemoglobinaemia. With no history suggestive of nitrate contamination of water or diet, and the fact that symptoms resolved on stopping cow's milk but recurred on re-challenge, the diagnosis was cow's milk protein intolerance causing diarrhoea-induced methaemoglobinaemia.

This case illustrates the importance of recognising methaemoglobinaemia as a rare medical emergency, where prompt treatment is life-saving and results in good outcome. A correct diagnosis of the underlying cause will prevent the relapse of this life-threatening condition.

Acknowledgement

We are thankful to the family for their consent for the publication of their clinical photo.

Declaration of Interest

None.

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