

## Case Report

# A case of hereditary methaemoglobinaemia

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### Introduction

Methaemoglobinaemia is a condition in which the iron within hemoglobin is oxidized from the ferrous state to the ferric state. Clinically, this condition causes cyanosis, often posing a diagnostic dilemma. Methaemoglobinaemia in children usually results from exposure to oxidizing substances such as nitrates or nitrites, aniline dyes, or medications, including dapsone, primaquine, nitrofurans<sup>1,2,3,4</sup> or is the result of inborn errors of metabolism, especially glucose-6-phosphate dehydrogenase deficiency<sup>1</sup> and cytochrome b5 oxidase deficiency.

### Case report

A 2 year old girl presented to Lady Ridgeway hospital with a history of recurrent bouts of vomiting over the last 2 years. She was the first of a twin born at 38 weeks gestation to consanguineous parents with a birth weight of 2.2 kg, the other being a healthy boy. At 2 months of age she presented with vomiting and rigidity but had good weight gain. She had many similar episodes warranting a milk scan which revealed gastro-oesophageal reflux and she was started on omeprazole and domperidone. She continued to have symptoms despite this. At 5 months she had opisthotonos, excessive crying and poor feeding with no head control, and her weight, height and OFC were all below the third centile. Other twin remained clinically normal. At 1 year and 2 months of age she had a computed tomography (CT) scan of the head which revealed mild ventriculomegaly thought to be a development anomaly/ neuronal migration disorder. Mother noticed she had mild persistent cyanosis. There was no history of exposure to drugs or toxins.

On examination, the patient had central cyanosis and

was irritable. Occipitofrontal circumference was 40cm (10cm below 3rd centile), length 76 cm (3SD below 3rd centile), weight 9.6kg (below 3rd centile). Pulse was 116/min and blood pressure 85/60 mmHg. All 4 limbs were spastic with exaggerated tendon jerks. Pulse oxymetry showed an oxygen saturation of 86%.

She was treated with oxygen and intravenous fluids. Despite normal hydration the child was centrally cyanosed. There were no cardiac murmurs and an echocardiogram was normal. When venepuncture was performed the girl's blood was unusually brown in colour. Blood sent for methaemoglobin assay revealed 38% methaemoglobin (spectrometry method); a repeat assay done at a different laboratory showed 46% methaemoglobin. Haemoglobin electrophoresis was normal.

She was started on ascorbic acid 100mg thrice daily. Two weeks later her methaemoglobin was 18%. She was observed for a further one week after omitting drugs and repeat methaemoglobin assay showed 34% methaemoglobin.

### Discussion

Normally, ongoing red blood cell (RBC) exposure to various oxidizing agents produces small amounts of methaemoglobin maintained below 1%. The most important pathway of methaemoglobin uses a reduction enzyme system NADH-cytochrome b5 reductase. Methaemoglobinaemia occurs if the rate of oxidation is significantly increased and overwhelms the protective and reductive capacities of the cells. Methaemoglobinaemia may be acquired or congenital (hereditary).

Inherited methaemoglobinaemia may be divided into 2 categories: methaemoglobinaemia due to an altered form of hemoglobin (hemoglobin M) and enzyme deficiency. Clinically two distinct syndromes of enzyme deficiency are recognized. Type I NADH-cytochrome b5 reductase deficiency is the most common, and is limited to the erythrocytes causing

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isolated cyanosis. Type II NADH-cytochrome b5 reductase deficiency is seen in erythrocytes, liver, fibroblasts, and brain. It is associated with severe CNS symptoms, including encephalopathy, microcephaly, hypertonia, mental retardation, and cyanosis<sup>4</sup>.

Serum methaemoglobin levels greater than 1% are considered abnormal. Methaemoglobin levels of 10-25% are tolerated well whereas levels of 30-40% may cause headache and dyspnoea. At 60%, presentation may be dramatic, with cyanosis, dyspnoea, deterioration of mental functioning or stupor.

Central nervous system (CNS) involvement with confirmed methaemoglobinaemia supports the diagnosis of hereditary methaemoglobinaemia due to cytochrome b5 oxidase deficiency type II. However confirmation of this diagnosis will require enzyme assay which is not available in Sri Lanka. In this child neurological manifestations cannot be definitely attributed to this condition in view of the CT scan findings.

Pulse oxymetry in a child with respiratory or cardiac disease reflects the degree of hypoxia and is proportionate to the amount of reduced hemoglobin whereas in methaemoglobinaemia, the severity of the cyanosis does not correspond to the reading.

Methaemoglobin is assayed by spectroscopy and haemoglobin electrophoresis to confirm haemoglobin M disease which does not respond to methylene blue or ascorbic acid.

Cyanosis rarely requires treatment except for cosmetic purposes<sup>1</sup>. Methylene blue in oral daily doses of 100-300 mg and ascorbic acid 200-500 mg

daily are sufficient to maintain methaemoglobin level below 10%. Riboflavin may be as effective as ascorbic acid<sup>1</sup>.

This patient was treated with ascorbic acid and 24 hour urine oxalate was checked later after treatment, as hyperoxaluria and urolithiasis are adverse effects. The 24 hour urine oxalate was 30 $\mu$ mol/day (normal range 100-500 $\mu$ mol/day). Treatment in type II cases does not prevent or reverse CNS progression<sup>4</sup>.

Hereditary methaemoglobinaemia should be considered in cases of cyanosis in the absence of cardiac and pulmonary diseases.

## References

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