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Case report

A bolt from the blue; A case report of an unusual asthma exacerbation

C. Moloney [a,*], A. Long [a], G.M. Pastores [b], B.J. Plant [c], D.M. Murphy [c]

[a] Cork University Hospital, Wilton, Cork, Ireland
[b] Mater Misericordiae Hospital, Dublin, Ireland
[c] Department of Respiratory Medicine, Cork University Hospital, Wilton, Cork, Ireland

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ABSTRACT

Background: We describe this case of a young gentleman presenting with acute dyspnoea on a background history of known, long-standing asthma. His dramatic presentation, notable for profound hypoxia and cyanosis, led to an unexpected additional diagnosis of type one congenital methaemoglobinaemia.

Case presentation: A 26-year-old Irish gentleman was transferred urgently to the emergency department resuscitation room with marked cyanosis and tachypnoea. His oxygen saturation was 70% on 100% high flow oxygen. His arterial blood gas (On Fi02 90%) demonstrated a PaO2 = 76.8 kPa, SpO2 = 99%, pCO2 = 3 kPa and pH = 7.51. A saturation gap was evident and on further analysing the arterial blood gas, the methaemoglobin level was noted to be 28%. No contributing drugs were identified. Our patient was diagnosed with type one congenital methaemoglobinaemia. He recovered well from this admission, however, has had recurrent presentations to hospital since with high methaemoglobin levels noted on each occasion.

Discussion: Congenital methemoglobinemia is a rare, often overlooked differential diagnosis in patients presenting with cyanosis and dyspnoea. This is the only case, to our knowledge, of a patient with both asthma and congenital methaemoglobinaemia. Congenital methaemoglobinaemia was first described in 1943 by Dr Deeny who described two siblings as suffering from 'Familial Idiopathic Methaemoglobinaemia'. The case we present is the first reported Irish case of congenital methaemoglobinaemia, we are aware of, since 1943.

Current treatment strategies include high-flow oxygen, methylene blue infusion (contraindicated in glucose-6-phosphate-dehydrogenase deficiency) and red cell exchange transfusions in the emergency setting whilst oral ascorbic acid and riboflavin are preventative.

1. Main manuscript body

1.1. Background

Congenital Methaemoglobinaemia is a rare, life-threatening illness characterised by elevated methaemoglobin levels in the blood. The aetiology of methaemoglobinaemia can be congenital or acquired. The acquired form is namely secondary to the use of drugs such as local anaesthetic agents (lidocaine, benzocaine, prilocaine), antibiotics (dapsone, sulphonamides and trimethoprim) and phenacetin due to associated oxidising effects [1–3]. Congenital methaemoglobinaemia occurs secondary to a deficiency of NADH cytochrome b5 reductase. Normally, methaemoglobin is produced at a low rate through the process of oxygen transport when the iron molecule in haem is oxidised from ferrous (Fe^{2+}) to ferric (Fe^{3+}) form. When produced, methaemoglobin is then reduced back to the ferrous state by cytochrome-b5 reductase. In NADH cytochrome b5 reductase deficiency, this reduction reaction does not take place and the ferrous state that remains is incapable of transporting oxygen [4].

Congenital methaemoglobinaemia is believed to be inherited in a recessive manner and has two subtypes. Type two disease is associated with neurological impairment and early death. In type one disease, the deficiency is limited to the erythrocytes and usually, but not always, causes cyanosis from birth and well-tolerated symptoms of mild headaches, fatigue and exertional shortness of breath [5]. In a minority of patients, such as the patient we describe, patients can have acute severe episodes of hypoxia and dyspnoea.

Congenital Methaemoglobinaemia was first described by Dr James Deeny in 1943. Dr Deeny was a general practitioner with a special interest in the therapeutic use of ascorbic acid. He set about exploring

* Corresponding author.
E-mail addresses: carolyn.moloney@hse.ie (C. Moloney), 112330471@umail.ucc.ie (A. Long), Gpastores@mater.ie (G.M. Pastores), barry.plant@hse.ie (B.J. Plant), desmond.murphy@hse.ie (D.M. Murphy).

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whether two siblings in his community, who had a blueish appearance, would benefit from its use. After a month of treatment with daily ascorbic acid, Dr Deeny reported a dramatic improvement in the men's appearance. Dr Deeny then went on to diagnose the siblings with 'Familial Idiopathic Methaemoglobinaemia [6]. In 2002, analysed DNA from one of the surviving siblings showed mutations in the cytochrome b5 reductase gene [7].

The case we present is the first reported Irish case of congenital methaemoglobinaemia, that we are aware of, since 1943. This is the only case, to our knowledge, of a patient with both asthma and congenital methaemoglobinaemia.

1.2. Case Presentation

A 26-year-old Irish gentleman presented to the outpatient department for a routine appointment and complained of being unwell over two days with dyspnoea and dizziness. The patient had deferred medical attention for this acute illness prior to this presentation. Nursing staff noted the patient was cyanotic in appearance and took observations. The pulse rate was 145 beats per minute and regular. The blood pressure was 110/90 mm Hg. The respiratory rate was 35 beats per minute. Oxygen saturations were recording at 70% on 100% high flow oxygen. The patient was transferred urgently to the emergency resuscitation room.

As the patient's background was significant for asthma diagnosed in infancy, an acute severe episode of asthma was initially suspected. The differential diagnosis however included a pulmonary embolus, lower respiratory infection, cardiac defect or more unusually, methaemoglobinaemia.

On examination, the chest was clear to auscultation without wheeze which was noted to be atypical for asthma but also in keeping with an acute severe episode of asthma. Normal heart sounds were auscultated. Initial investigations carried out including an electrocardiogram and chest x-ray were unremarkable. An arterial blood gas (On Fi02 90%) showed a PaO2 = 76.8 kPa, SpO2 = 99%, pCO2 = 3 kPa and pH = 7.51 demonstrating a discrepancy (or saturation gap) between arterial blood gas and pulse oximetry oxygen saturation values. On further analysing the arterial blood gas, the methaemoglobin level was noted to be 28%. Normally levels are less than 1% on arterial blood gas [4]. Routine bloods including a full blood count were unremarkable. The patient remained oxygen dependant over the next 24 slowly and was managed in the high dependency unit. He was treated for both an acute severe episode of asthma and also methaemoglobinaemia with high flow oxygen, intravenous steroids, nebulisers and frequent arterial blood gas monitoring via an arterial line during this time. Due to the ongoing oxygen requirement and to out rule other causes in the initial differential diagnosis, a CT pulmonary angiogram and echocardiogram were carried out during the first day of admission. Methaemoglobinaemia levels reduced to normal over the next 24 hours as the patient clinically improved.

On further questioning of the patient's background history, during many of the patients previous hospital presentations, he had displayed similar signs and symptoms of marked cyanosis associated with dyspnoea. No contributing medications or foods were identified on taking a full drug and diet history. Family history was significant for a maternal grandmother who died with severe asthma in her sixties. There is no history of growth or developmental delay. An obstructive picture consistent with asthma has been confirmed in the past on spirometry testing. On a previous admission with an asthma exacerbation, where the patient had presented with dyspnoea and wheeze, reversibility had been shown on peak flow testing in the emergency department after bronchodilator use. Methaemoglobin levels was not checked on that occasion.

Our patient was diagnosed with type one congenital methaemoglobinaemia. He recovered well from this admission, however, has had multiple similar presentations to hospital since with high methaemoglobin levels >25 noted on each occasion in the setting of severe cyanosis and dyspnoea. There has been no recognised precipitant for subsequent presentations in line with a congenital cause. The condition has recurred despite the use of ascorbic acid and riboflavin. Testing for cytochrome b5 reductase deficiency has been negative. Further genetic testing for rare causal effects associated with methaemoglobinaemia has been offered to the patient.

2. Discussion and conclusions

Congenital methemoglobinemia is a rare, often overlooked differential diagnosis in patients presenting with cyanosis and dyspnoea. In the absence of routine habit to look for the methaemoglobin value on an arterial blood gas reading, especially in the setting of a known diagnosis of asthma, the diagnosis can be missed.

On review of the literature, onset in type one congenital methaemoglobinaemia is usually noted from birth and symptoms can include mild headaches, fatigue and exertional shortness of breath [8]. An Indian study reported on the clinical spectrum of a group of 18 patients with type one congenital methaemoglobinaemia; 10 of the 18 patients included were reported to have 'moderate' symptoms (cyanosis associated with dyspnoea) while one patient was reported to have 'severe' symptoms (cyanosis associated neurological impairment). The median age of the patients studied was 28 years [9]. In a literature review by Soliman et al. which included 16 cases, a male preponderance of 73% was reported. The majority of patients within the group improved clinically with the addition of daily ascorbic acid [10].

We have found only two cases reports describing patients with onset of symptoms not apparent at birth but at age 8 years and 16 years. In the case of the 16 year old boy, there was no improvement in symptoms with the addition of ascorbic acid [11,12].

Current treatment strategies for this condition include high-flow oxygen, methylene blue infusion (contraindicated in glucose-6-phosphate-dehydrogenase deficiency) and red cell exchange transfusions in the emergency setting. Methylene blue works by forming a substrate for NADPH-MetHb reductase which can reduce Fe^{3+} back to Fe^{2+} [13]. Oral ascorbic acid and riboflavin are recommended for prevention of symptoms [14,15]. There is a need for more preventative treatment options for patients who remain symptomatic despite ascorbic acid and riboflavin. It is possible our patient's already existing lung disease in addition to type one congenital methaemoglobinaemia makes him more symptomatic of high methaemoglobin levels.

Ethics approval and consent to participate

Verbal and written consent has been obtained from the patient.

Consent for publication

This case report details information regarding a human patient, and was reported with the express written consent of this patient.

Availability of data and material

Not applicable.

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Authors' contributions

CM and AL produced the first draft of the manuscript. All authors (CM, AL, BJP, GMP, DMM) reviewed, edited, and approved the final version of the submitted manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100983.

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