

A challenging case of hypercapnic respiratory failure during pregnancy

Short title: Hypercapnic respiratory failure in pregnancy

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Summary

We describe a 40-year-old female who presented with progressive breathlessness and hypercapnic respiratory failure during pregnancy secondary to undiagnosed Muscle Specific Kinase (MuSK)-myasthenia gravis. Her presentation was progressive and protracted, having over five contacts with healthcare professionals over 9 months, many of these predating her pregnancy. Her atypical presentation for myasthenia with minimal limb weakness led to consideration of other causes of hypercapnic respiratory failure. Once diagnosed, she was treated with intravenous immunoglobulin and non-invasive ventilation for myasthenic crisis. She gave birth to a pre-term infant by planned caesarean section. Her insidious presentation and the progressive nature of her breathlessness were unusual and our report highlights the predominant involvement of respiratory muscles in MuSK-myasthenia. Her pregnancy may have further delayed her diagnosis due the attribution of some symptoms to normal pregnancy. Early recognition and treatment of myasthenia gravis is important to prevent life-threatening complications.

Introduction

Whilst breathlessness is common in pregnancy, hypercapnia is unusual with PaCO_2 levels normally less than 4.4kPa in the third trimester.¹ Hypercapnia may be caused by an imbalance between respiratory capacity — due to reduced respiratory muscle strength or endurance — and respiratory load — for example due to obesity, particularly combined with pregnancy. is either caused by respiratory insufficiency or respiratory muscle dysfunction, including respiratory muscle weakness. Symptoms of breathlessness and hypercapnia may also be attributed to obesity as part of obesity hypoventilation syndrome. However, careful consideration and exclusion of other causes is required before this diagnosis is made.²

Case

In August 2018 a 40-year-old-female who was 30 weeks pregnant was admitted to the Maternity unit. She presented with a one year history of progressive exertional breathlessness, with an exercise tolerance now of 5m. She did not report associated cough or wheeze, but had noticed persistent headaches. Over the preceding four months she described fatigue and new symptoms of weight loss, dysphonia, reflux and orthopnoea, resulting in her sleeping upright.

She was a never-smoker and was born in Zimbabwe, moving to the UK in 2003.

In October 2017 she had presented to the Emergency Department of her local hospital with breathlessness when climbing stairs or when walking up inclines. Chest radiography had shown basal atelectasis and she was discharged with oral antibiotics and respiratory clinic follow-up. Subsequently she had several respiratory outpatient appointments and further emergency department attendances. She had undergone an extensive work up of her symptoms, including CT imaging, echocardiography, pulmonary function tests, bronchoscopy and oesophagogastroduodenoscopy.

High-resolution CT imaging in October 2017 confirmed atelectasis and incidentally showed a focal area of lingular bronchiectasis that would not account for her symptoms. Echocardiography in October 2017 was normal. CT pulmonary angiography in February 2018 was negative. Pulmonary function tests in March 2018 showed a restrictive pattern with a forced vital capacity of 0.88 L (41%) and a transfer factor of the lung for carbon monoxide (TLCO) of 0.79 (10%). However, poor effort and poor reproducibility was noted. Bronchoscopy showed normal appearances with negative bacterial, fungal and mycobacterial cultures. Oesophagogastroduodenoscopy was

unremarkable. She was commenced on lansoprazole for gastro-oesophageal reflux disease.

On examination she had no clubbing, conjunctival pallor, or cervical lymphadenopathy. Her body mass index was 30 kg/m². She could talk in short sentences and had no accessory muscle use. Her resting respiratory rate was normal. Oxygen saturations were 96% on room air with no exertional desaturation. On auscultation, chest was clear and heart sounds were normal. She had no peripheral oedema and her JVP was not raised.

Neurological examination revealed mild restriction of lateral gaze bilaterally, mild weakness of jaw opening, and moderate weakness of shoulder abduction and neck flexion. The extent of respiratory muscle weakness, with a forced vital capacity consistently less than 1 L, was out of keeping with her other neurological signs.

Laboratory blood tests including full blood count, urea and electrolytes, CRP, troponin, D-dimer, ANA and HIV tests were all unremarkable.

Arterial blood gases showed persistent hypercapnia of 6.9-7.0 kPa with a normal partial pressure of oxygen.

Obesity and bronchiectasis were considered as potential causes of her hypercapnic respiratory failure. However, neither her BMI of 30 kg/m² nor her minor bronchiectasis was sufficient to explain her hypercapnia. Given her constellation of symptoms and signs, respiratory muscle weakness was considered the likely cause.

Neurophysiology testing showed features of either a primary myopathy with involvement of the neuromuscular junction or a primary neuromuscular junction disorder.

Antibody testing showed that she was negative for acetyl choline receptor (AChR) antibodies but was positive for muscle specific Kinase (MuSK) antibodies confirming a diagnosis of anti-MuSK myasthenia gravis. After identification of daytime hypercapnia but prior to confirmatory antibody results, she was commenced on non-invasive ventilation (NIV) at pressures of 14/4 cmH₂O and intravenous immunoglobulin (IVIg). IVIg was given for five consecutive days (total dose 2 g/kg). After two days of IVIg and

NIV, early morning carbon dioxide (CO₂) levels improved to 5.6 kPa. Concomitant progressive improvement in her symptoms was observed.

Following optimisation and multi-disciplinary discussion, at 35 weeks and 5 days of gestation she underwent an elective caesarean section with transfer to HDU post-operatively, due to concerns that vaginal delivery would cause respiratory muscle fatigue and failure. The use of opioid analgesia led to a transient hypercapnia of 6.5 kPa, but on the day of discharge, her morning CO₂ levels had improved to 6.0 kPa and her FVC was 1.3 L. She was discharged home with nocturnal NIV.

The female infant weighed 2500 g at birth and had APGAR scores of 6, 9 and 10 at 1, 5 and 10 minutes respectively. The baby did not show clinical features of myasthenia but was admitted to neonatal HDU for 24 hours for observation.

The patient was started on oral steroids while breastfeeding, the dose of which was slowly tapered down. A subsequent relapse was precipitated by non-compliance with NIV, and was treated with a further course of IVIg.

Discussion

Causes of hypercapnic respiratory failure

The most common causes of hypercapnic respiratory failure are chronic obstructive pulmonary disease (COPD) and obesity hypoventilation.³ Whilst our patient did not have COPD, she did have a BMI of 30 kg/m². However, respiratory failure is rare with this degree of obesity alone,² and it would also seem unlikely to be the dominant cause of her breathlessness given the symptoms worsened despite weight loss. Patients with severe bronchiectasis can develop hypercapnic respiratory failure but the extent of her bronchiectasis was minor and would not explain this degree of respiratory insufficiency.⁴ An overlap between obstructive sleep apnoea, obesity hypoventilation syndrome, and airways disease such as bronchiectasis can cause daytime hypercapnia at lower levels of obesity and whilst it may have contributed to respiratory failure in her case,² this could not explain all of her symptoms.

Neurological conditions that can mainly cause bilateral diaphragm weakness and therefore respiratory muscle weakness include motor neurone disease, cervical cord disease, poliomyelitis, Guillain-Barre syndrome, myopathies, bilateral neuralgic

amyotrophy, neuromuscular diseases, and connective tissue disease such as SLE or dermatomyositis.⁵

Neurological disorders causing respiratory muscle weakness are important causes of hypercapnic respiratory failure. This case highlights the difficulty in diagnosing respiratory muscle weakness in the absence of significant generalised weakness. Hypercapnia with a normal arterial oxygen concentration is indicative of hypoventilation and should prompt consideration of respiratory muscle weakness, of which myasthenia gravis is an important cause.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune condition affecting the post-synaptic transmission of nerve signals, typically due to antibodies against the nicotinic acetylcholine receptors (AChR).⁶ MG is characterised by fatigable weakness of skeletal muscles and can occasionally cause hypercapnic respiratory failure.⁷ Around 20% of patients are seronegative for AChR antibodies and up to 70% of these patients have antibodies against the Muscle Specific Kinase (MuSK).^{8,9}

Predominant involvement of bulbar and respiratory muscles without limb weakness is common in MuSK-MG.⁹⁻¹² Up to 35% of patients with MuSK-MG develop respiratory crisis which is much more common than in AChR-MG.¹¹⁻¹³ Our patient had a significant delay in diagnosis, perhaps due to lack of awareness of the respiratory predominance in MuSK-MG or her symptoms being attributed to normal breathlessness of pregnancy.

Myasthenia gravis in pregnancy

The impact of MG during pregnancy varies.^{14, 15} There is consensus on how to manage myasthenia gravis during pregnancy and peri-partum,¹⁶ although there are no specific guidelines for MuSK-MG other than to be vigilant of the risk of respiratory crisis.^{11, 17} Whilst patients with controlled MG should only have caesarean section for obstetric reasons, those with respiratory compromise need careful consideration due to the risk of labour increasing respiratory demand sufficiently to cause worsening ventilator failure.¹⁸ Further obstetric management plans should include a pre-labour review by obstetric anaesthetics and the avoidance of precipitants of such as magnesium sulphate (used as eclampsia prophylaxis and for neuroprotection in pre-term infants) and opioid analgesia.

Diagnosis of hypercapnic respiratory failure

There should be a low threshold for performing an arterial blood gas where oxygen saturations are lower than expected or where there is unexplained breathlessness; in this case saturations were 96%, whereas during healthy pregnancy at sea-level oxygen saturations are normally 97% or above.¹⁹

Vital capacity monitoring is helpful as a non-invasive measure of respiratory muscle strength with low levels indicating increased risk of hypercapnic respiratory failure. We have summarised key features that should alert clinicians to the presence of hypercapnic respiratory failure in *Figure 1*. A raised venous bicarbonate (>27 mmol/L) in the absence of other causes of a raised bicarbonate (e.g. diuretics, vomiting) is a useful integrated surrogate marker of hypercapnia.

Neonatal myasthenia gravis

Transient neonatal MG, due to transplacental passage of antibodies, can occur in 10-20% of cases with AChR-MG.²⁰ Transmission is less frequent in MuSK-MG,¹⁷ but

spontaneous abortion has been reported.²¹ All babies born to mothers with MG should be examined for weakness and should have rapid access to neonatal critical care.²² Maternal bulbar weakness can result in maternal and fetal malnutrition. Close monitoring of the mother and child antenatally, intrapartum and in the postnatal period is therefore important with a multi-disciplinary team approach.

Conclusion

Hypercapnic respiratory failure is rare in pregnancy where there is no history of pre-existing respiratory disease, but is important to consider in any breathless pregnant woman. The identification of hypercapnic respiratory failure should prompt consideration of neuromuscular weakness, even in the absence of other neurological signs. Unlike AChR-MG, MuSK-MG more frequently presents with significant and predominant respiratory muscle weakness, which may be subacute.

Figure 1

<i>Features of respiratory muscle weakness</i>
<ul style="list-style-type: none">• Orthopnoea• Difficulty in clearing respiratory secretions• Low forced vital capacity• Normal or increased gas transfer• Fall in forced vital capacity (>15%) from seated to supine position
<i>Indicators of hypercapnia</i>
<ul style="list-style-type: none">• Early morning headaches• Disturbed sleep• Daytime sleepiness• Bounding pulse• Asterixis (CO₂ retention flap)• Oxygen saturations <92% on air• Raised serum base excess/bicarbonate

Figure 1: Clinicians should think of respiratory muscle weakness and hypercapnia when any number of these features is present. Oxygen saturations of less than 92% on air should prompt blood gas analysis to identify whether there is hypercapnia. Isolated raised bicarbonate without hypercapnia frequently represents compensation for hypercapnia during sleep that has normalised upon waking.

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