

## CASE REPORT

# Respiratory insufficiency due to acute bulbar palsy

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## Abstract

Dyspnoea is a common symptom in patients visiting the emergency department and has a wide differential diagnosis. Bulbar paresis caused by myasthenia gravis is an uncommon disorder and can therefore easily be missed. Unmasking of myasthenia gravis by ciprofloxacin, an antibiotic which is frequently prescribed, is a rare side effect of the drug that has seldom been reported.

We describe a patient who developed severe respiratory distress due to a myasthenic crisis induced by ciprofloxacin in combination with steroids.

## Introduction

Respiratory insufficiency due to pulmonary or cardiac disease is the most important reason for admission to the intensive care unit (ICU). Acute bulbar paralysis as a cause of rapid progressive respiratory insufficiency is a rather uncommon disorder which can be difficult to differentiate from a cardiac or respiratory origin.

## Case report

A 76-year-old man presented to the emergency department with a five-day history of progressive dyspnoea, orthopnoea, dysphagia and hypophonia. He had an unproductive cough without complaints of chest pain. Ten days earlier he visited his general practitioner because of fever up to 40°C with chills and a diagnosis of prostatitis was made, for which the antibiotic ciprofloxacin was prescribed. Three days before presentation to the emergency department, the patient had stopped taking the ciprofloxacin because of progressive dysphagia, which he suspected to be caused by the antibiotic therapy.

His medical history included hypertension, chronic obstructive pulmonary disease (COPD), atrial fibrillation, percutaneous transluminal coronary angioplasty and congestive heart failure. Two years earlier he had also suffered from mild and transient dysphagia. A dynamic swallowing study at that time did not

show any abnormalities.

His medication list included desloratadine 5 mg once daily, acetylsalicylic acid 80 mg once daily, paracetamol/codeine 500/20 mg three times a day, diltiazem 200 mg once daily, tiotropium bromide inhaler 18 µg once daily, tamsulosin 0.4 mg once daily, montelukast 10 mg once daily, budesonide/formoterol inhaler 400/12 µg twice daily, omeprazole 20 mg once daily and telmisartan 80 mg once daily, none of which had been changed recently.

On physical examination his body temperature was 36.4°C. Initial neurological examination did not reveal any focal abnormalities. Inspection of the oropharynx showed a normal tongue and tonsils and examination of the neck did not show any abnormalities. There was no stridor, and his respiratory rate was 22/min. On auscultation of the chest, diminished breath sounds in the left lower quadrant were observed. The peripheral saturation was 90% while breathing ambient air. His blood pressure was 160/80 mmHg with a pulse rate of 82 beats/min. There was no peripheral oedema.

Additional laboratory tests showed a slightly elevated leukocyte count ( $14.2 \times 10^9/l$ ), a normal C-reactive protein (9 mg/l), mild hypoxaemia (arterial blood gas analysis: pH = 7.38; pCO<sub>2</sub> = 6.0 kPa; pO<sub>2</sub> = 8.8 kPa; bicarbonate = 28 mmol/l; SaO<sub>2</sub> = 92%) and a normal procalcitonin level (0.031 ng/ml). Chest X-ray showed a small consolidation in the left lower lobe.

The patient was admitted to the internal medicine ward with the diagnosis of lower respiratory tract infection. Cefuroxime was started and he received supplemental oxygen through a nasal cannula. Because an allergic reaction to ciprofloxacin could not be entirely excluded as a cause of the dysphagia, prednisolone was added to the therapy. His clinical condition deteriorated one day after admission. Because of the deterioration and the unexplained dysphagia and dysphonia, a CT scan of the head, neck and thorax was performed which was unremarkable and

an endoscopic evaluation of his nasopharynx and larynx by the ENT surgeon did not show any abnormalities.

In the ensuing hours he developed a severe bulbar paresis and was hardly able to speak or swallow. Additionally there was an overt paresis of the cervicobrachial musculature and the patient became respiratory insufficient for which he was transferred to the ICU, intubated and mechanically ventilated.

The consulted neurologist suspected an acute myasthenic crisis. Alternatively, a rapidly progressive, atypical, Guillain-Barré syndrome variant (pharyngeal-cervico-brachial form) was considered, however deemed less likely. Treatment with pyridostigmine and intravenous immunoglobulin was started and cefuroxime was continued. Prednisolone was discontinued due to the possible aggravation of symptoms of myasthenia gravis. Additional blood tests showed an elevated level of acetylcholine receptor antibodies of 47.3 nmol/l (normal range 0.0-0.3 nmol/l). After five days of mechanical ventilation his muscle weakness had improved and he could be successfully extubated. He was discharged to the neurological ward two days later.

### Discussion

The adult patient with acute dyspnoea presents difficult challenges in diagnosis and management. Dyspnoea is a common chief symptom among patients who come to the emergency department. The most common causes of acute respiratory distress are decompensated heart failure, pneumonia, exacerbation of COPD or asthma and pulmonary embolism. The combination of dyspnoea, hypophonia and dysphagia points in the direction of diseases of the laryngopharynx including angioedema, pharyngeal infections, deep neck infections, neuromuscular disease and intoxications. In our patient, the symptoms had developed after prescription of ciprofloxacin ten days earlier and had worsened over time in such a way that the patient had stopped taking the ciprofloxacin. His long-term medication had not been changed recently. On presentation to the emergency room, a bacterial pneumonia was suspected because of diminished breath sounds and a small infiltrate on the chest X-ray but was not supported by the laboratory findings. Our patient had a history of decompensated heart failure and COPD; however, acute congestive heart failure or an exacerbation of his COPD could be ruled out by physical examination and chest X-ray. Pulmonary embolism was considered to be very unlikely but could not completely be excluded. Initial inspection of the oral cavity and subsequent examination by the ENT surgeon as well as a CT scan of the area did not show any signs of epiglottitis, angioedema, abscesses or thymic abnormalities, which are known to be present in the majority of patients with myasthenia gravis.<sup>(1)</sup>

Myasthenia gravis is a heterogenic neuromuscular disorder. Different autoantibodies, such as acetylcholine receptor antibodies, anti-striated muscle and anti-muscle-specific

tyrosine kinase (MuSK) antibodies are known to play a role in the pathophysiology of this disease. Antibodies against the acetylcholine receptor, for example, result in a reduction of receptors over time. As a consequence, the neuromuscular transmission is affected, leading to weakness in ocular, bulbar, limb and respiratory muscles. Myasthenia gravis is a condition that fulfils all the major criteria for a disorder mediated by autoantibodies against the acetylcholine receptor (AChR-Ab), or against a receptor-associated protein, muscle specific tyrosine kinase (MuSK-Ab). Patients with positive AChR-Ab or MuSK-Ab assays have seropositive myasthenia gravis. Demonstration of these antibodies, which are present in approximately 90% of patients with generalised disease, provides the laboratory confirmation of myasthenia gravis.<sup>(2,3)</sup>

A myasthenic crisis is an acute or subacute severe muscle weakness resulting in respiratory failure. Intubation is almost always needed or extubation following surgery is delayed.<sup>(4,5)</sup> Muscle strength can improve with rest, so the initial physical examination may not reveal any neurological deficit.<sup>(6)</sup> Our patient had no evident muscle weakness at presentation to the emergency room and therefore a neuromuscular disorder was not considered very likely.

Most of the patients who develop myasthenia gravis have a precipitating factor; generally this is a respiratory infection.<sup>(7)</sup> Other precipitating factors are emotional stress, surgery, or specific drugs. A long list of drugs, including ciprofloxacin, need to be avoided or should be used with caution in myasthenic patients (*table 1*). The reported side

**Table 1.** Drugs that may unmask or worsen myasthenia gravis\*

<b>Anaesthetic agents</b>
Neuromuscular blocking agents
<b>Antibiotics</b>
Aminoglycosides – e.g. gentamicin, neomycin, tobramycin
Clindamycin
Fluoroquinolones – e.g. ciprofloxacin, levofloxacin, norfloxacin
Ketolides – e.g., telithromycin
Vancomycin
<b>Cardiovascular drugs</b>
Beta blockers – e.g., atenolol, labetalol, metoprolol, propranolol
Procainamide
Quinidine
<b>Other drugs</b>
Botulinum toxin
Chloroquine
Hydroxychloroquine
Magnesium
Penicillamine
Quinine

\*This is not a complete list of all drugs that may, in individual patients, adversely affect neuromuscular transmission

effects of ciprofloxacin include dyspnoea (rare) and aggravation of myasthenia gravis (very rare). Many drugs, particularly antibiotics, can aggravate or unmask myasthenia gravis by prejunctional and postjunctional blocking in a setting where the 'safety margin' for neuromuscular transmission has already been affected by disease.

We propose that ciprofloxacin exerted such an action in our patient, as evidenced by the close temporal relation between the onset of his severe symptoms and the introduction of the drug and by the resolution of symptoms on its withdrawal.

We reported our case to the Dutch databank of drug side effects (Lareb). Up to now, only one more case of unmasked myasthenia gravis by ciprofloxacin has been described.<sup>(8)</sup> In this case, the patient developed symptoms of dysphagia, dysarthria and left-sided ptosis that varied with fatigue, within 48 hours after ciprofloxacin was started. This patient had been mildly dysphagic for some months before the introduction of ciprofloxacin.

Prednisolone is part of the initial treatment of myasthenia gravis but can also lead to exacerbation of the disease and myasthenic crisis.<sup>(7)</sup> In our case prednisolone was given as treatment for a possible allergic reaction due to ciprofloxacin. Because myasthenia gravis was not considered at admission the patient was initially not monitored in the ICU.

On admission to the ICU, treatment was started with pyridostigmine, intravenous immunoglobulin and cefuroxime, and the prednisolone was discontinued. Anticholinergic agents stimulate glandular secretions and muscle fasciculation, which may worsen the respiratory failure. Godoy et al.<sup>(7)</sup> therefore recommend withholding anticholinesterase therapy in the management of myasthenic crisis when the patient is mechanically ventilated since, although exceptional, this may induce a cholinergic crisis. In their opinion, anticholinesterase therapy should be started when clinical improvement is imminent and the patient is able to start to wean off mechanical ventilation. In retrospect, pyridostigmine given as the treatment of muscle weakness and/or as a diagnostic test was not appropriate at this time in our patient.

Immunomodulatory therapy is the gold standard for treating myasthenia gravis.<sup>(7)</sup> Intravenous immunoglobulin and plasma

exchange are considered equally effective. There is not enough evidence to support one therapy over the other.<sup>(7,9)</sup> Prednisolone is advised in the treatment of myasthenia gravis but, as noticed before, may also exacerbate the symptoms. The timing of initiation of steroid treatment is debatable, but is generally advised when a patient cannot be extubated two weeks after the start of immunotherapy. Patients who are on steroids should not stop taking them at the time of a crisis.<sup>(7)</sup> Our patient had steroids prescribed on admission, which may have aggravated the myasthenic crisis. Fortunately, he responded very well to the immunotherapy and was extubated after five days.

### Conclusion

In our patient the bulbar paresis leading to respiratory insufficiency was caused by myasthenia gravis unmasked by ciprofloxacin and probably aggravated by steroids.

The adult patient with acute dyspnoea presents difficult challenges in diagnosis and management. Bulbar paresis caused by a myasthenic crisis in the setting of a previously undiagnosed myasthenia gravis is a rare cause of dyspnoea which can lead to rapid progressive respiratory insufficiency. Many drugs are reported to be able to induce a myasthenic crisis. This diagnosis needs to be considered in case of unexplained respiratory failure.

### Disclosures

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