New weakness in a critically ill patient

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A 24-year-old woman was admitted to her local hospital with an infective exacerbation of asthma. Apart from asthma, which had resulted in several previous uncomplicated admissions to hospital, she was otherwise well. She had no history of any neuromuscular problems and neurological examination on admission was unremarkable. She was treated with intravenous hydrocortisone (200 mg 6 hourly), aminophylline and augmentin and nebulized salbutamol and ipratropium bromide, but became increasingly wheezy and distressed and required mechanical ventilation. Arterial blood gas analysis on 60% oxygen prior to ventilation revealed the pH to be 7.09, and the partial pressures of O₂ and CO₂ to be 19 and 10.5 kPa, respectively. Other investigations were unremarkable, apart from a peripheral leucocytosis of $14 \times 10^9/l$. In the intensive care unit, muscle relaxation was achieved with intravenous suxamethonium, atracurium and a continuous infusion of vecuronium, and sedation with intravenous midazolam, propofol and alfentanil. Initial treatments were continued, but the dose of hydrocortisone was increased to 200 mg every 2 hours and intravenous cefotaxime and metronidazole were introduced.

On day 3 the patient was transferred to the regional intensive care unit because of deteriorating renal function. This resolved spontaneously without the need for dialysis, the maximum serum urea and creatinine levels being 24 mmol/l and 137 μ mol/l, respectively. On one occasion when renal function was recovering serum potassium was 2.4 mmol/l; all other electrolytes including serum phosphate, calcium and magnesium were unremarkable.

On day 11 airway obstruction was not evident on examination. On day 12 muscle relaxants, which had been administered from admission to the intensive care unit, and sedation were stopped. Mechanical ventilation was required for a further 8 days, however, because of severe generalised weakness. Examination on day 14 revealed the patient to be alert and obeying commands. A partial left sixth nerve palsy, mild facial weakness and flaccid tone in the limbs were noted. Power in the limbs was graded as a flicker of movement proximally and grade 2–3 distally. All deep tendon reflexes were absent. Sensory examination was normal. The patient was transferred to the neurology department on day 22 being able to maintain adequate ventilation although she was still profoundly weak.

Questions

- 1 What are the most probable causes of this patient's new weakness resulting in difficulty weaning from the ventilator?
- 2 What investigations should be performed to confirm the diagnosis?
- 3 What is the prognosis for recovery?

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Answers

QUESTION 1

The decreased tone, areflexia and preserved mental state in this patient with severe weakness suggest a neuromuscular disorder. A central disorder, of either the brain or spinal cord, causing acute severe weakness can be difficult to exclude in patients in the intensive care setting because of difficulties with communication. A central disorder was felt to be unlikely in our patient, however, as upper motor neuron signs were never detected at any stage. Likewise a spinal cord lesion as the sole cause of the patient's weakness was excluded because she had cranial nerve signs. Where the possibility of a spinal lesion exists, however, the spinal cord should be imaged by magnetic resonance scanning. The principal neuromuscular diseases causing new generalised weakness in critically ill patients are shown in box 1.

Of the neuropathies, critical illness polyneuropathy may be the most common cause of weakness in critically ill patients. This condition is thought to result from inadequate perfusion of the peripheral nerves.¹ It is usually associated with encephalopathy and multi-organ failure and often results in more severe distal than proximal weakness,¹ all of which were in contrast to the findings in our patient.

Guillain-Barre syndrome (of which acute inflammatory demyelinating polyradiculoneuropathy and acute motor axonal neuropathy are two variants) results in flaccid weakness with or without prominent sensory symptoms and typically occurs two weeks or so after an infective illness, as was the case for our patient. Prompt recognition of this condition is important because early treatment with plasma exchange or immunoglobulin improves outcome.

Acute intermittent porphyria often results in abdominal pain, psychiatric disturbances or autonomic dysfunction, none of which occurred in this case.

Although myasthenia gravis often presents with weakness, the extreme nature of the weakness in our patient was not typical of this condition. In addition, the minimal involvement of the extra-ocular muscles and absent reflexes (which are typically normal in myasthenia gravis) made this diagnosis unlikely.

Prolonged blockade at the neuromuscular junction from the long-term administration of muscle relaxants, typically results in flaccid paralysis, which may be very severe, and areflexia.² It usually occurs in the context of impaired hepatic or renal function and has mostly been described in cases where vecuronium has been administered; two of these precipitants were present in our case. No cholinergic features (miosis, sweating, bradycardia) were present, making inadvertent organophosphate exposure unlikely.

Clinically, it is impossible to exclude either acute necrotizing myopathy or critical illness myopathy as the cause of this patient's weakness. Both may result in flaccid weakness with areflexia and little or no sensory disturbance in critically ill patients exposed to neuromuscular blocking agents or high-dose corticosteroids.

QUESTION 2

The minimum investigations necessary to differentiate between the various causes of weakness in the critically ill patient, once simple biochemical abnormalities have been excluded, are shown in box 2.

The creatinine kinase level was never elevated in our patient, essentially excluding acute necrotizing myopathy. Likewise cerebrospinal fluid (CSF) analysis performed 11 days after the onset of weakness was normal. Although this made Guillain-Barre syndrome, or its related conditions unlikely (the CSF protein usually being elevated in these conditions) it did not completely exclude them. Nerve conduction studies performed 16 days after the onset of the weakness, however, did not reveal

Causes of new weakness in critically ill patients

Neuropathies

- acute inflammatory demyelinating polyradiculoneuropathy
- acute motor axonal neuropathy
- critical illness polyneuropathy
- acute intermittent porphyria

Neuromuscular-transmission disorders

- prolonged neuromuscular blockade from muscle relaxants
- myasthenia gravis
- organophosphate poisoning

Myopathies

- acute necrotizing myopathy
- critical illness myopathy

Biochemical abnormalities

- hypokalaemia
- hypophosphataemia
- hypocalcaemia
- hypermagnesaemia

Box 1

Investigations required to determine cause of weakness in critically ill patient.

Serum

- potassium, phosphate, calcium, magnesium, urea
- immunoglobulins and plasma protein electrophoresis
- creatinine kinase

Urine

- porphyrins

Cerebrospinal fluid

- protein
- cell count

Electrophysiology

- nerve conduction studies
- repetitive nerve stimulation
- electromyography

Muscle biopsy

Box 2

the typical findings of Guillain-Barre syndrome or its variants, such as slowing of peripheral nerve conduction or conduction block. Critical illness polyneuropathy or a disease of the neuromuscular junction were not excluded by these investigations. Electromyographic sampling of muscle, however, did not reveal the features of denervation, which would be expected for all of the potential neuropathic causes of weakness, including critical illness polyneuropathy. Repetitive nerve stimulation likewise did not show the decremental response typical of prolonged neuromuscular blockade or myasthenia gravis. Instead, electromyography demonstrated small, brief polyphasic motor unit potentials, with good recruitment and a complete interference pattern, in keeping with a myopathic process. Muscle biopsy of the left quadriceps confirmed a myopathic process demonstrating features such as diffuse myofibre degeneration. Electron microscopy of the same specimen also showed loss of thick filaments as has been described in critical illness myopathy.³ By a process of exclusion, critical illness myopathy was therefore felt to be the cause of this woman's weakness.

QUESTION 3

Recovery in any critically ill patient who develops new muscle weakness is ultimately dependent on the prognosis of the primary illness which necessitated admission to the intensive care unit. If the patient survives this illness, however, it is the cause of the weakness that will

determine how much return of power that will occur. Critical illness myopathy is increasingly being recognised as a cause of new weakness in critically ill patients. This condition, first described in 1977 by MacFarlane and Rosenthal,⁴ typically results in difficulty weaning from the ventilator and is associated with diffuse weakness of a varying degree, without or without ophthalmoplegia or facial weakness, attenuation of reflexes, subtle or no sensory disturbance, and preservation of higher functions.⁵ Usually, in addition to being critically ill, patients who develop this condition have had a febrile illness, or have been septicaemic, and have received high doses of corticosteroids and/or neuromuscular blocking agents. In contrast to other causes of weakness in this setting, such as critical illness polyneuropathy which often occurs in the absence of neuromuscular blocking agents or steroid administration, the outlook for recovery has generally been reported as being good.⁵ As recovery is spontaneous the need for specific therapies, such as plasmapheresis or human immunoglobulin for Guillain-Barre syndrome which are more often associated with complications in these patients, is also unnecessary.

Final diagnosis

Critical illness myopathy.

Keywords: critical illness myopathy; muscle weakness

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A woman with amenorrhoea

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A 26-year-old woman was referred by her general practitioner with primary amenorrhoea. She denied galactorrhoea or headaches. She had undergone ligation of a patent ductus arteriosus at 2 years of age and was noted in childhood to have a partial hearing defect in her right ear. On examination she was a phenotypically normal female with a BMI of 23.2 kg/m². She had Tanner stage II breast and pubic hair development. Investigations revealed a normal full blood count, urea and electrolytes, with a glucose of 5 mmol/l, prolactin of 100 mU/l (normal < 400 mU/l). Hypogonadotrophic hypogonadism was confirmed with a low plasma oestradiol of 108 pmol/l (normal > 130), luteinising hormone (LH) < 0.5 U/l and follicle-stimulating hormone (FSH) < 0.5 U/l. She had impaired responses to LHRH stimulation of LH < 0.5 U/l and FSH 0.6 U/l. Dynamic testing of pituitary function revealed a normal growth hormone, cortisol and prolactin response to insulin-induced hypoglycaemia. Thyroid function tests, pituitary magnetic resonance imaging, and karyotype were normal.

Questions

- 1 What other clinical test would be useful?
- 2 What is the diagnosis?

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