British Journal of Anaesthesia **86 (5)**: 727–30 (2001)

Undiagnosed myasthenia gravis unmasked by neuromuscular blockade

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Myasthenia gravis is an uncommon autoimmune disease resulting in destruction of the post-synaptic nicotinic receptors at the neuromuscular junction. We describe a 43-yr-old, 95 kg patient who presented for elective laparoscopic cholecystectomy. She was given vecuronium 10 mg to facilitate tracheal intubation. At the end of the procedure the patient could not maintain adequate spontaneous ventilation despite administration of two doses of neostigmine 2.5 mg. Subsequent investigation led to a diagnosis of myasthenia gravis. We discuss the investigation, diagnosis, and subsequent management of such a patient and emphasize that tactile estimation of the train-of-four ratio is not a reliable indicator of adequate recovery of neuromuscular function.

Br J Anaesth 2001; **86**: 727–30

Keywords: complications, myasthenia gravis; measurement techniques, neuromuscular block; neuromuscular block, vecuronium; complications, thymoma

Accepted for publication: January 4, 2001

Myasthenia gravis is a well recognized cause of muscle weakness and can prolong the action of non-depolarizing neuromuscular blocking agents.[1 2] The dose of these drugs is, therefore, reduced in such patients or they are not used. We describe a case in which vecuronium 10 mg was given to a patient with undiagnosed myasthenia gravis and the ensuing problems that developed. We also discuss the appropriate investigation and subsequent management of such patients and the pitfalls in train-of-four (TOF) monitoring.

Case report

A 43-yr-old, 95 kg, female (ASA class I) presented for laparoscopic cholecystectomy and intra-operative cholangiogram. The patient had no significant past medical history, took no regular medications and had undergone two uneventful general anaesthetics for open reduction and internal fixation of her right ankle in 1993, with subsequent removal of pins in 1994. She did not smoke nor drink alcohol. Pre-operative investigations (full blood count, urea and electrolytes, coagulation studies, liver function tests, chest x-ray, and electrocardiograph) were normal.

In the anaesthetic room, i.v. access was obtained and in addition to routine monitoring a forced air warming device was used. Anaesthesia was induced with propofol 200 mg and fentanyl 100 μg. Vecuronium 10 mg was given to facilitate tracheal intubation. Droperidol 0.5 mg was given as an anti-emetic and cefotetan 1 g as antibiotic prophylaxis. Anaesthesia was maintained with isoflurane 1.5% and nitrous oxide 50% in oxygen and the lungs were artifically ventilated. Morphine in increments up to 8 mg was given i.v. for analgesia. After 90 min of uneventful anaesthesia and surgery, neostigmine 2.5 mg and glycopyrrolate 0.4 mg were given to antagonize any residual neuromuscular block. The TOF ratio was checked using a Fischer Paykel 'Innervator' peripheral nerve stimulator with a current of 60 mA at the ulnar nerve after the reversal agents had been given. There was no fade evident by tactile estimation; the first and fourth twitches were apparently equal in size. Anaesthesia was discontinued and the patient allowed wake up. It quickly became obvious that the patient was having difficulty breathing (rapid shallow breaths) and the end-tidal carbon dioxide concentration (E'_{CO_2}) rose rapidly to 80 mm Hg with the trachea still intubated. Oxygen saturation remained at 97% throughout. At this time, the patient was unable to raise her head from the bed or to sustain a handgrip. The TOF ratio was re-checked and again no fade was evident by tactile means; a further dose of neostigmine 2.5 mg was given. (Although it would have been appropriate

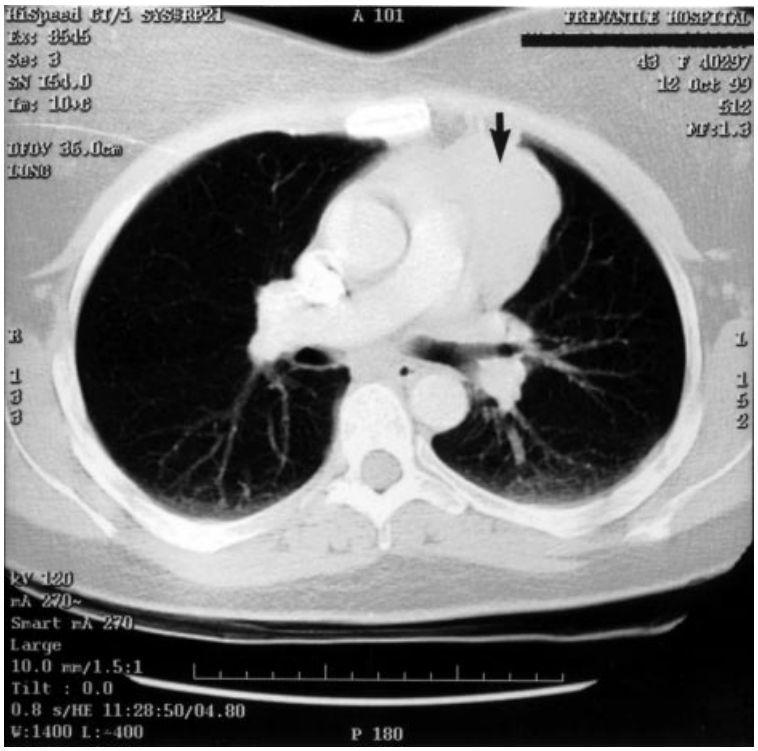

Fig 1 CT scan with i.v. contrast shows large thymoma (arrowed) anterior to the ascending arch of the aorta and right pulmonary artery.

to check for fade in the double burst stimulus at this time, the nerve stimulators with this capacity were being repaired and we were unable to do so.) There was no improvement in respiratory function over the next 10 min, so the patient was re-anaesthetized using propofol 100 mg.

A search for causes of inadequate respiratory effort commenced whilst anaesthesia was maintained. There was no clinical evidence of a pneumothorax. A suction catheter was easily passed down the tracheal tube; there was no airway obstruction, nor any evidence of aspiration. Electrolyte abnormalities were thought unlikely as the patient had normal renal and liver function pre-operatively. She had not been given any medication that would have interfered with neuromuscular transmission. Her pupils were mid size and she had only received morphine 8 mg. Her temperature was 35.8°C. The TOF was checked 25 min after the second dose of neostigmine with no tactile evidence of fade. At this stage, it was postulated that she might have an underlying neuromuscular disorder. Anaesthesia was maintained for a further 2 h until her ventilatory function had improved as assessed by an increase in tidal volume and a reduction in E'_{CO_2} to 45 mm Hg. The trachea was successfully extubated 2.5 h after the end of surgery. The patient was monitored for a further 3 h in the recovery room where it became obvious that she had generalized muscle weakness as evidenced by her limited ability to raise her head from the bed or to sustain a handgrip for 5 s. She was discharged to the ward that evening where she remained stable overnight.

The patient was re-interviewed the next morning when she admitted that she had been attending her general practitioner for the past 18 months complaining of symptoms of tiredness, occasional hoarse voice (for which she had seen a speech therapist), difficulty chewing, and occasional slurred speech. On further questioning she also admitted to having problems hanging out her washing because of easily fatigued arms and being unable to rise from a squatting position. This information was not volunteered at the original anaesthetic consultation as the patient's general practitioner had told her these symptoms were nothing to worry about and she had dismissed them as unimportant. On examination, she had weakness of her facial muscles, neck extensors, and fatigable proximal weakness of both upper and lower limbs. There were no sensory abnormalities.

The case was discussed with the neurologists who felt that the most likely diagnosis was myasthenia gravis. The 'Tensilon test' was positive after edrophonium 5 mg given i.v. Repetitive nerve conduction studies were negative. Plasma acetylcholine receptor antibody (AchR) levels were 4.3 local units (normal range <0.1). Computerized tomography (CT) of the mediastinum (Fig. 1) showed a large anterior mass compatible with a thymoma despite the chest x-ray being normal. Thyroid function tests were normal. A search was made for coincidental autoimmune disease but this proved negative.

These results confirmed the clinical diagnosis of myasthenia gravis. The patient was discharged home on

Table 1 Osserman and Genkins classification of disease severity[5]

Grade 1	Ocular disease only
Grade 2A	Generalized muscle weakness with ocular symptoms
Grade 2B	Generalized moderate weakness and/or bulbar dysfunction
Grade 3	Acute fulminating presentation and/or respiratory dysfunction
Grade 4	Late severe generalized disease

no treatment. The patient underwent an uneventful thymectomy 4 weeks later. Histological examination proved this to be a benign thymoma. This time she had an uneventful general anaesthetic using propofol, alfentanil, oxygen, nitrous oxide, isoflurane, and morphine. No neuromuscular blocking drugs were used. The trachea was extubated at the end of the procedure. She was managed uneventfully on the ward post-operatively.

Discussion

The incidence of myasthenia gravis is 1 in 10 000–20 000 adults.[3] The hallmark of the disease is weakness and rapid fatigability of voluntary skeletal muscles with repetitive use followed by partial recovery with rest.[3] The muscular disorder is generalized in 85% of patients and confined to the extra-ocular muscles in 15%. Extremity musculature is symmetrically affected with weakness of proximal muscle groups preferentially involved. Myasthenia gravis occurs in a bimodal age distribution. It occurs predominantly in women in their twenties and thirties and in men in their sixties and seventies. The mean age of onset is 26 yr.[4] Overall, women are more commonly affected than men in the ratio 3:2. The disease is graded using the Osserman and Genkins staging classification (Table 1);[5] our patient fell into category 2A with her mild generalized weakness.

Approximately 10% of patients with myasthenia gravis have an associated autoimmune disorder. These include hyper- or hypothyroidism, which may exacerbate symptoms or masquerade as myasthenia gravis itself. Rheumatoid arthritis and systemic lupus erythematosis present their own problems respectively.

Myasthenia gravis results from production of autoantibodies against the nicotinic AchR at the neuromuscular junction which reduces the number of functioning receptors either by competitive block, increased degradation of receptors or by complement mediated lysis of receptors.[6] In general, myasthenics have one-third as many normally functioning AchRs as those who are disease free. In normal individuals, repetitive nerve stimulation results in a decrease in the amount of Ach released with each successive stimulus. Drachman[7] refers to this as 'rundown'. The combination of less neurotransmitter release and fewer receptor sites leads to muscular weakness in myasthenics. It has long been appreciated that there is a relationship between the thymus and myasthenia gravis[8] with the three commonest abnormalities being hyperplasia, thymoma (benign or malignant) and atrophy. Thymomas are more common in patients over 30 yr whereas hyperplasia is commoner in younger age groups. There is a consensus that all adults with generalized myasthenia gravis should have a thymectomy as this improves symptoms, reduces or abolishes the need for drugs and can induce long-lasting remission. Currently quoted figures are clinical improvement in 78–96% and drug free remission in 42–69%.[9]

The 'Tensilon test' is a simple first line test for myasthenia gravis. Edrophonium (Tensilon), a short-acting anticholinesterase, is administered i.v. in doses of 2–10 mg and an improvement in muscle strength is expected. It is said to be positive in 95% of those with myasthenia gravis. It is least sensitive in patients with ocular symptoms alone. It also has a low specificity. False positive tests occur in patients with other neurological disorders such as amyotropic lateral sclerosis or Lambert–Eaton myasthenic syndrome. Performing it after the patient has exercised when the weakness is maximal may increase the sensitivity of the test. Repetitive nerve stimulation involves stimulating a peripheral nerve at 2–3 Hz and recording the resulting action potential via surface electrodes over the target muscle. A decrease of 15% in successive action potentials is considered positive. The test is safe and simple but is insensitive and may not be positive in up to 50% of patients especially those with mild disease. AchR antibody assay detects antibodies in 80–90% of patients with myasthenia gravis. However, detection rates may be as low as 50% in those with mild disease.[4] Single fibre electromyography requires experienced personnel, is expensive and is seldom used. As in this patient, CT scanning of the mediastinum is used to visualize the anterior mediastinum for evidence of thymoma.

The other issue of importance well illustrated by this case is the inaccuracy of tactile measurement of the TOF ratio. On the first occasion it was performed, a consultant anaesthetist observed it and on second and subsequent times a consultant and senior registrar observed it. Our interpretation of the TOF ratio was clearly inaccurate. It was obvious, clinically, that the patient had residual neuromuscular block despite the absence of visible fade in the TOF ratio. Recent studies would appear to support our finding that it is not possible to exclude significant residual paralysis by visual or tactile evaluation of the TOF ratio,[10 11] and that even experienced anaesthetists are unable to feel fade if the TOF ratio has recovered to 0.4 or greater.[11 12] Unfortunately, double-burst stimulation (DBS) was not performed in this patient, as the nerve stimulator did not have the facility for this function. Perhaps if we had been able to perform this test, fade would have been more evident as it is easier to demonstrate fade in DBS than the TOF.[13]

It has been stated that a TOF ratio of $\geqslant$0.7 measured at the thumb is compatible with adequate neuromuscular recovery.[14] Recent studies, however, have confirmed that a TOF ratio of 0.7 does not guarantee adequate recovery of neuromuscular function and at this TOF ratio chemoreceptor sensitivity to hypoxia is reduced,[15 16] further reducing the stimulus to breathe. It has also been shown that at this

TOF ratio the muscles of the upper oesophagus and pharynx show functional impairment, thus predisposing to regurgitation and aspiration.[17] Accordingly it as been stated that normal vital function and normal pharyngeal function requires a TOF ratio of $\geqslant 0.9$.[18 19]

On all occasions, there was no fade evident despite two doses of neostigmine (2.5 mg each) being given. There is some debate of the value of a second dose of neostigmine. Work published some years ago suggested that a second dose of neostigmine 2.5 mg, given 2–5 min after a first dose, could lead to a neostigmine-induced block in normal patients.[20] However the neuromuscular blocking drugs being antagonized in that study (tubocurarine, dimethyltubocurarine, gallamine) are no longer in clinical use. More recent work demonstrated that two doses of neostigmine 2.5 mg, given 2 min apart to normal patients recovering from atracurium-induced neuromuscular block, were no more effective than one dose. However, there were no reports of neostigmine-induced block.[22] Work by Hunter[22] in a series of myasthenics receiving vecuronium, also confirmed that a second dose of neostigmine 2.5 mg given 5 min after the first conferred no additional benefit.

It has been suggested that more objective methods such as accelerography, mechanomyography or electromyography,[23] be used if there is any doubt about possible residual block. However, these techniques are expensive, impractical and most departments do not possess them. Perhaps the simplest way to avoid post-operative residual curarization is to monitor all patients who receive neuromuscular blockers with DBS at regular intervals throughout anaesthesia. It is imperative to appreciate that reliance on TOF monitoring using visual or tactile methods to assess residual neuromuscular block is at best inaccurate and at worst dangerous.

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