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Prolonged vecuronium neuromuscular blockade associated with Charcot Marie Tooth neuropathy

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Charcot Marie Tooth (CMT) disease comprises a group of disorders characterized by progressive distal muscle weakness and wasting. Review of the anaesthetic literature produced conflicting reports concerning the responses to neuromuscular blocking drugs in these patients. We describe a case in which vecuronium 0.11 mg kg^{-1} produced prolonged neuromuscular blockade lasting 115 min in a patient with the condition. Conduction velocity in the facial nerve is usually less affected than the ulnar or peroneal nerve in CMT patients. This nerve may be more useful in monitoring neuromuscular blockade, both in titrating the dose of neuromuscular blocking drug and ensuring adequate reversal at the end of a procedure. Recent advances in molecular biology have enabled identification of the underlying genetic abnormalities and pathophysiology of CMT. These advances are reviewed and implications of CMT for the anaesthetist discussed.

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Charcot Marie Tooth (CMT) neuropathy affects 1 in 2500 people and accounts for a large proportion of the neuropathic diseases encountered in clinical practice.[1] The condition causes atrophy and weakness of the distal muscles due to diminished nerve conduction. The spectrum of severity varies from asymptomatic individuals to those with severe limb abnormalities requiring corrective surgery.

There are few descriptions of the anaesthetic management of patients with CMT. Both prolonged and attenuated responses to neuromuscular blocking drugs have been described.[2-5] Such variation between patients may be accounted for by variations in disease severity. Autosomal dominant and X-linked genetic defects may occur in these patients, resulting in point mutations or multiple expression of genes encoding myelin proteins.[6] Axonal loss or demyelination occurs, enabling classification of CMT according to nerve biopsy and conduction studies.[7] CMT is now considered to be a heterogeneous group of polyneuropathies. The severity of symptoms may differ between the subtypes.

It is appropriate to review recent advances in our understanding of the condition and the anaesthetic experience that has been described.

Case report

A 59-yr-old, 74 kg male with CMT neuropathy presented with a fractured right proximal fibula and distal tibia, requiring open reduction and internal fixation with a tibial nail. The patient had been diagnosed as having CMT in May 1987 in a medical report for retirement on the grounds of ill health. The diagnosis was made on clinical grounds, with examination revealing high foot arches and distal muscle wasting involving the forearms, interossei in the hands, and all muscles below the knee. His arm tendon reflexes were brisk and symmetrical but knee and ankle jerks were absent with flexor plantar responses. Sensation was normal and there was no ataxia. He described himself as always having been weak. He had no siblings but described his father as having been of the same build. Electromyography had not been performed.

The patient underwent L5-S1 discectomy in 1983, receiving thiopental 225 mg, tubocurarine 40 mg and halothane. The operation lasted 75 min. There was no comment in the anaesthetic record regarding reversal of residual neuromuscular blockade, nor were any problems recorded. In 1996, he underwent insertion of a dynamic hip screw of his left femur and received midazolam 2 mg, propofol 100 mg, and atracurium 30 mg at

induction followed by atracurium 10 mg after 30 min. This operation lasted 50 min. Acetylcholinesterase inhibitors were not given. On neither occasion was any neuromuscular monitoring used. No adverse events or clinical evidence of prolonged neuromuscular block were noted.

After his hip fracture, a diagnosis of osteoporosis was made using bone density studies. He received alendronate 10 mg day^{-1} and calcium supplementation. His corrected serum calcium was 2.59 mmol $litre^{-1}$ with an inorganic phosphate of 1.00 mmol $litre^{-1}$ prior to this operation. Serum potassium was 4.6 mmol $litre^{-1}$.

On this occasion the patient was unpremedicated. He received morphine 10 mg and thiopental 350 mg at induction. Vecuronium 0.11 mg kg^{-1} was administered and after 2 min the trachea was intubated easily with a size 9 mm cuffed oral tracheal tube. Anaesthesia was maintained with isoflurane 1% in nitrous oxide/oxygen 2:1. No further opiates were given. A peripheral nerve stimulator was not used at the outset because no problems had been identified from the previous anaesthetic records.

The operation lasted approximately 115 min, during which time no further drugs were given. At the end of the procedure the lungs were ventilated with $F_{I_{O_2}}$ 1.0 and the patient received neostigmine 2.5 mg with glycopyrrolate 500 μg. A peripheral nerve stimulator was not used at this stage. It was felt that sufficient time had passed since induction for recovery from neuromuscular blockade to occur. Spontaneous diaphragmatic breathing with an adequate tidal volume followed and the tracheal tube was removed uneventfully although the patient was not fully conscious. He was then transferred to the recovery room with oxygen administered by facemask. In recovery, the patient became anxious and distressed, with signs of incomplete reversal of neuromuscular block including twitching of the limbs and uncoordinated movements. Oxygenation and ventilation remained normal.

A peripheral nerve stimulator was applied first to the right ulnar nerve. Trains of four stimuli were applied. There was a palpable twitch response to the first stimulus only. As clinically obvious muscle wasting was present in the forearm muscles the nerve stimulator was applied to the right facial nerve. Again, a twitch response was only visible to the first stimulus of the train of four. Double burst stimulation was not used as partial reversal was clinically obvious and it was felt this would subject the patient to further distress.

A second dose of neostigmine 2.5 mg was given, resulting in all four twitches of the train of four response in the facial muscles being visible within 2 min. The patient's condition improved and he was transferred to the high dependency unit for overnight observation and returned to the ward on the next day.

Discussion

Charcot Marie Tooth neuropathy comprises a heterogeneous group of peripheral nerve diseases affecting adults and children.[7] There is a typical clinical picture with distal muscle weakness and atrophy affecting the intrinsic muscles of the foot, the peronei and tibialis anterior. Both motor and sensory function may be affected. Deep tendon reflexes are diminished or absent. There is a spectrum of clinical presentation from severe atrophy with limb abnormality to pes cavus. A significant proportion of CMT patients are not identified because their symptoms do not cause them to consult a doctor. Most patients with the condition have manifestations by their second decade, seldom presenting after 30 yr. Upper limb involvement tends to occur later.

Clinical studies in CMT families using nerve biopsies and nerve conduction studies enabled a separation of these patients into two main groups.[8] In CMT1 there is a marked reduction in nerve conduction velocity with demyelination; nerve conduction velocity in the ulnar, median and peroneal nerves is commonly half that in normal subjects.[7] The muscle action potential amplitude is half normal, and the nerve latency three times as long on average; 25% of patients have clinically thickened peripheral nerves. Those adolescents with the slowest conduction velocities tended to have a worse neurological deficit in later life.

In CMT2 the nerve conduction velocity is normal or low normal.[9] There is axonal loss but no prominent demyelination. In this type the clinical symptoms may present later, even in middle age. Although the features are similar to CMT1, there is said to be less upper limb involvement and the peripheral nerves are less enlarged.

The two types cannot be distinguished solely on clinical grounds because there is such a range of severity of symptoms. Nerve conduction studies are often performed in the median or ulnar nerves because distal nerve degeneration is often complete in the lower limbs. In fact, motor nerve conduction velocity is commonly less than 60% normal in all nerves studied, including the facial nerve.

Advances in molecular biology and gene mapping have enabled the underlying genetic abnormalities in CMT to be identified. In the majority of cases of CMT1 and CMT2 the inheritance is autosomal dominant.[10] There are also much rarer X-linked and autosomal recessive variants. CMT1 can be subdivided on the basis of the gene defect. In CMT1a there is a duplication at the 17p11, 2–12 locus. This area codes for the PMP22 gene resulting in multiple expression. PMP22 is a major component of peripheral nerve myelin. The result may be a new Schwann cell phenotype that has defective myelin stability and increased turnover.[10] In CMT1b there are point mutations in the myelin protein P0 gene.[6] This codes for the major myelin protein in peripheral nerves, accounting for 50% of the mass. It has been suggested that the neurological disability in CMT1b is worse than in CMT1a. In X-linked CMT (CMTX), which is clinically similar to CMT1, there are mutations in the

connexin 32 gene. This encodes a gap junction channel protein that may play a role in transmission at nodes of Ranvier. Dejerine Sottas disease, or CMT3, is a severe variant with onset in infancy. There may be point mutations in the P0 or PMP22 genes. The clinical features overlap with severe CMT1. CMT2 accounts for 25% of cases.[9] There does not appear to be a unifying genetic defect.

As 1 in 2500 people has some form of CMT, it is surprising that case reports concerning anaesthesia in CMT sufferers are rare. In one report, the notes of seven patients under 16 yr who were anaesthetised over a 10 yr period were reviewed.[11] These patients received both depolarizing and nondepolarizing neuromuscular blocking drugs. There were no recorded adverse effects of succinylcholine and no cases of prolonged response to a range of non-depolarising neuromuscular blocking drugs. However, the authors conceded that the methods used to assess neuromuscular function varied widely.

Antognini reviewed the operative charts of 86 patients with CMT identified by postal questionnaire to members of a CMT help group.[12] In 161 surgical procedures on these patients anaesthetic complications were few, although the study is necessarily biased because non-responders are excluded. In addition, anaesthetic management and inclusion criteria for CMT could not be standardized. 48% of patients received succinylcholine with no recorded adverse effect. A paralysing dose of non-depolarizing neuromuscular blocking drug was used in 45% of patients. How neuromuscular block was monitored and reversed is not known. There were no descriptions of objective weakness or prolonged intubation. Despite the absence of adverse effects after succinylcholine, it would seem prudent to avoid this drug in CMT if possible as hyperkalaemia is well reported in other similar polyneuropathies and denervation injuries. There is no evidence to suggest that patients with CMT are susceptible to malignant hyperthermia.

Another report studied 20 patients with CMT presenting for orthopaedic procedures.[2] The authors found that CMT sufferers required less thiopental for induction than controls. The report is of interest because one female patient received vecuronium 0.07 mg kg^{-1} at induction and subsequently did not exhibit a normal twitch response or spontaneous ventilation for 280 min. In addition, the ulnar nerve twitch response was absent in six of the 20 patients. In these six patients, the facial nerve was used for evaluation of neuromuscular block.

A review of the literature concerning anaesthesia for CMT revealed few detailed case reports. One describes prolonged artificial ventilation due to respiratory muscle involvement in pregnancy.[13] Another describes a 17-yr-old who underwent anaesthesia on two occasions and showed no prolonged response to either mivacurium or atracurium.[3] Baraka described a 16-yr-old girl who underwent a tendon transfer under general anaesthesia using vecuronium. In this case, the T4/T1 ratio recovered to 25% after 20 min and further supplementation was required. Residual neuromuscular blockade was readily reversed after 90 min. The author suggested that upregulation of acetylcholine receptors at the neuromuscular junction due to the generalized polyneuropathy might account for the resistance to vecuronium even in the presence of muscle weakness and atrophy.[4]

One case report demonstrated a potential difficulty in monitoring neuromuscular block in CMT patients. In a 17-yr-old neurosurgical patient, it was not possible to elicit responses from either tibial nerve following vecuronium 0.1 mg kg^{-1} after 100 min. The muscle response was either too delayed or too small in amplitude to be recorded.[5] This is perhaps unsurprising as the tibial nerves are among the worst affected by demyelination in CMT. The use of peripheral nerve stimulators in CMT has been shown to be misleading if a nerve with delayed conduction or increased latency is chosen. One solution would be to monitor relaxation after induction using a less affected peripheral nerve such as the facial nerve. A suitable site for neuromuscular monitoring should be identified before a neuromuscular blocking drug is administered. The drug can then be titrated to effect and adequate reversal identified.

Case reports have been described in the literature of patients with CMT undergoing central neural blockade without neurological sequelae.[14 15] Posterior column demyelination has been noted in autopsies of some CMT patients, however. A balanced risk assessment in considering central blockade would seem prudent lest any deterioration be blamed on the anaesthetic technique. Autonomic neuropathy is not a major finding in CMT. It is usually limited to decreased sweating in the extremities. Autonomic neuropathy does not feature as a clinical problem in any anaesthetic case reports.

Clinically palpable nerve enlargement occurs in 25% of patients with CMT 1. These patients may be at greater risk of positional nerve injuries due to pressure during prolonged procedures. In addition, the use of regional blockade in areas such as the elbow may carry additional risk.

Given the incidence of CMT and the fact that many cases go unrecognized, it would seem that anaesthesia for these patients must be generally uneventful. The cases presenting for corrective limb surgery must be the worst affected and yet adverse events are seldom described.

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Severe unilateral bronchospasm mimicking inadvertent endobronchial intubation: a complication of the use of a topical lidocaine Laryngojet injector

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A healthy young woman is described in whom the left chest was unable to be inflated after intubation. The differential diagnosis and management are discussed. Severe unilateral bronchospasm was probably caused by topical lidocaine injected at the vocal cords and, inadvertently, into the left main bronchus with a Laryngojet device.

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A healthy 19-yr-old woman, weighing 64 kg, was scheduled for angiography and alcohol sclerosis of a facial arteriovenous malformation. She had no history of chest disease but smoked 10 cigarettes per day.

She received no premedication. Anaesthesia was induced slowly with midazolam 1.5 mg and propofol 110 mg, during which time she breathed oxygen. Anaesthesia was maintained with an infusion of propofol at 660 mg h^{-1} initially, reducing to 500 and 400 mg h^{-1} at 15 and 25 min respectively. Neuromuscular block was obtained with vecuronium. Before laryngoscopy, 40 mg of lignocaine was given i.v. A clear view of the larynx was obtained. The tip of a Laryngojet lidocaine (4%) injector was passed about 2 cm through the glottis, so that about half of the side-holes were above and half were below the cords. Five millilitres of solution were injected and the trachea was intubated with a 7.5 mm reinforced tracheal tube which was secured at 21 cm at the lips. On immediate inspection, both sides of the chest appeared to inflate equally and capnography revealed a normal waveform. The patient was transferred to the adjacent x-ray table and was ventilated with oxygen and air ($F\mathrm{I}_{\mathrm{O}_2}$ = 0.35) via a Bain system and a Nuffield 200 ventilator with a tidal volume of approximately 600 ml. Within 2 min of intubation the $S\mathrm{p}_{\mathrm{O}_2}$ had fallen from 100 to 90%. The inspired oxygen fraction was increased to 1 and the chest was re-examined. The right chest was expanding and breath sounds were vesicular with no wheeze. On the left, there was no expansion and there were no breath sounds or added sounds at all. Inadvertent right-sided endobronchial intubation was suspected. The tube position was rechecked. It remained at 21cm at the lips. The tube tip was checked immediately by dynamic x-ray screening and was