Case Reports/Case Series

Ultrasound-guided peripheral regional blockade in patients with Charcot-Marie-Tooth disease: a review of three cases

[Bloc régional périphérique échoguidé chez les patients souffrant de la maladie de Charcot-Marie-Tooth : compte-rendu de trois cas]

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Purpose: To describe the clinical presentation of three patients with Charcot-Marie-Tooth disease, who underwent uneventful upper limb surgery following successful peripheral nerve blockade, and to review the anesthetic implications in patients with Charcot-Marie-Tooth disease.

Clinical features: In three patients with Charcot-Marie-Tooth disease presenting for surgery of the upper limb, the motor response, following nerve stimulation, was suboptimal. However, ultrasound guidance was effective in visualizing the needle-nerve interaction, and local anesthetic was injected around the nerves. Good block ensued and surgery proceeded in all patients without complications. No exacerbation of the neurological condition was observed in any patient.

Conclusions: Charcot-Marie-Tooth disease is a demyelinating, hereditary, motor and sensory neuropathy characterized by abnormalities of nerve conduction. Regional anesthesia of the upper limb is feasible in these patients, and these cases show that ultrasound guidance makes peripheral nerve block possible in patients for whom traditional methods of nerve localization fail.

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Objectif *: Décrire la présentation clinique de trois patients souffrant de la maladie de Charcot-Marie-Tooth subissant une chirurgie d'un membre supérieur sans complications à la suite la mise en place réussie d'un bloc des nerfs périphériques, et réitérer les implications anesthésiques chez les patients souffrant de la maladie de Charcot-Marie-Tooth.*

Éléments cliniques *: Dans le cas de trois patients souffrant de la maladie de Charcot-Marie-Tooth se présentant pour une chirurgie d'un membre supérieur, la réaction motrice était sous-optimale après stimulation nerveuse. Cependant, l'échoguidage a permis de visualiser l'interaction entre l'aiguille et le nerf, et un anesthésique local a été injecté autour des nerfs. Ainsi, un bloc efficace a été réalisé et la chirurgie s'est déroulée sans complications chez les trois patients. Aucune exacerbation de l'état neurologique n'a été observée chez ces patients.*

Conclusions *: La maladie de Charcot-Marie-Tooth est une neuropathie sensori-motrice héréditaire due à une démyélinisation et caractérisée par des anomalies au niveau de la conduction nerveuse. L'anesthésie régionale des membres supérieurs est réalisable chez les patients souffrant de cette maladie, et les cas présentés ici montrent que l'échoguidage permet une anesthésie des nerfs périphériques chez les patients chez lesquels les méthodes conventionnelles de localisation des nerfs échouent.*

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HEREDITARY motor and sensory neuropathies are rare conditions with a wide variety of phenotypes that are thought to be related to discrete genetic lesions,[1,2] the most common of these being Charcot-Marie-Tooth disease (CMTD). This disease can present with a spectrum of disabilities ranging from very mild to severe peripheral motor, sensory, and autonomic symptoms. Current evidence suggests the existence of several different genotype and phenotype subgroups,[3] some of which may have significant anesthetic implications.

There is some concern regarding the use of regional techniques in CMTD, as possible exacerbation of the basic disease is feared. Use of neuraxial, regional anesthesia has been reported in CMTD.[4] We report uneventful use of ultrasound-guided brachial plexus block in three patients suffering from CMTD, in whom nerve stimulation was difficult to obtain. All patients received their care at St. Joseph's Hospital, London, Ontario, during the period 2005–2007. Consent for publication was obtained from all three patients according to guidelines of the St. Joseph's Hospital and the University of Western Ontario.

Case 1

A 43-yr-old man was scheduled for reconstructive hand surgery to correct clawing of the left ring finger and the little fingers. He was diagnosed with CMTD at the age of 15 yr, and he experienced constant and high level of fatigue, sleep disturbance, loss of muscle mass, and problems with balancing. He demonstrated typical distal extremity wasting with delayed (< 20 $m \cdot sec^{-1}$) nerve conduction velocity (NCV). He had impaired mobility and generalized weakness, although he was able to manage activities of daily living without assistance. At age 15, he underwent repair of a pectus excavatum, and at age 35, he had reconstructive foot surgery; both procedures were performed under general anesthesia. Further details were unknown. The patient's co-morbidities included rheumatoid arthritis (stable on etanercept and celecoxib), heavy smoking, and some degree of long standing liver dysfunction (mildly elevated enzymes with no platelet dysfunction or clotting abnormality).

On examination, he was in a stable clinical condition. Airway examination revealed Mallampati class-3, and he had a past history of difficult tracheal intubation. There was a considerable chest wall deformity, and his left shoulder was stiff, secondary to glenohumeral arthritis. The patient stated that he did not wish to proceed with surgery if general anesthesia was required. The procedure and the possible risks of a regional anesthetic technique were discussed with him.

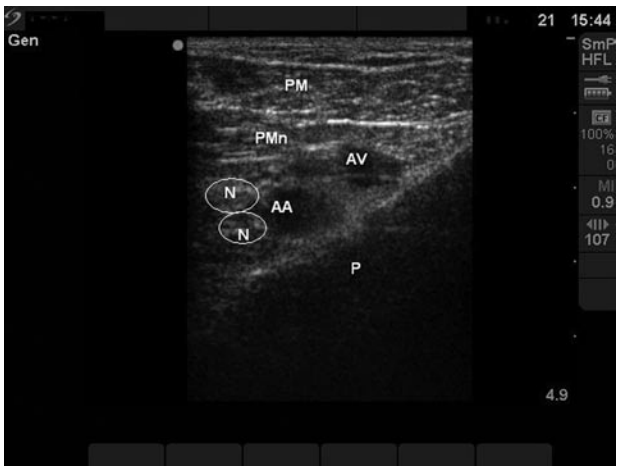

FIGURE Ultrasound image of the infraclavicular area (case 1). AA = axillary artery; AV = axillary vein; N = nerve; P = pleura; PM = pectoralis major; PMn = pectoralis minor.

In the block room, following application of routine monitors, an ultrasound-guided, nerve-stimulator-assisted, left axillary brachial plexus block was attempted. Shoulder abduction was limited to 30°, making access to the axilla somewhat difficult. The axillary artery could not be satisfactorily identified. On nerve stimulation, the patient felt sensory paresthesiae in the median nerve distribution, although no twitches could be elicited. This approach was then abandoned. We performed an ultrasound of the infraclavicular area in the paracoracoid area, and, although the axillary artery was very superficial, it could be identified at a depth of 2 cm despite the chest wall deformity (Figure). An infraclavicular block with a 22G, 2 inch, short-bevelled stimulator needle (Pajunk®, Geisingen, Germany) was attempted with ultrasound guidance (Micromax, Sonosite Medical Systems® Bothell, WA, USA). Nerve stimulator (Pajunk®, Geisingen, Germany) settings were adjusted to deliver a 1.2 mA current, with a 0.3 msec pulse duration, at a frequency of 2 Hz. When the needle approached the posterior cord area, the patient felt a twitch-like sensation in the posterior cord distribution, though no motor response was observed. Ropivacaine, 0.5% 20 mL, was freely injected under ultrasound visualization, and a good sensory and motor block ensued. The surgery proceeded without complications, and the postoperative course was unremarkable. There was a subsequent follow-up in the neurology and surgery clinics and, at the end of

six months, no worsening of the patient's neurological symptoms was observed.

Case 2

A 39-yr-old man was scheduled for a thumb opponensplasty, using the long finger flexor digitorum superficialis (FDS). He had a positive family history of CMTD and was diagnosed at the age of 12 yr, when he presented with difficulty in walking, fatigue, problems with balancing, and loss of muscle mass. Delayed NCV were reported. Electrophysiological studies had been done at the time of diagnosis, but the reports were not available for review. On examination, the patient was in stable condition. He demonstrated intrinsic muscle wasting of both hands, with a claw deformity of all fingers and an inability to abduct or oppose his thumbs. There were minimal sensory deficits, in the form of hypesthesia in the lower limbs, distally. He wore an ankle-foot brace for peroneal nerve palsy. In addition, he had gastroesophageal reflux disease and possible obstructive sleep apnea (observed by partner, but not investigated). The procedure and the possible risks of a regional technique were discussed with him.

In the block room, following application of routine monitors, a left axillary brachial plexus block was performed using peripheral nerve stimulation (22G, 2 inch, short-bevelled stimulator needle, Pajunk®, Geisingen, Germany) and ultrasound guidance (Micromax, Sonosite Medical Systems®, Bothell, WA, USA). The only observable twitch response was a weak index finger flexion, with the nerve stimulator setting delivering a 1.2 mA current, with 0.2 msec pulse duration, at a frequency of 2 Hz. No radial, ulnar, or musculocutaneous twitches could be elicited. Mepivacaine, 1.5% 35 mL, was freely injected under ultrasound visualization. A good sensory and motor block ensued, and surgery proceeded uneventfully. The postoperative course was unremarkable. There was subsequent follow-up in the surgery clinic and by the patient's general practitioner, and his condition remained stable at the end of six months.

Case 3

A 50-yr-old man was scheduled for a corrective FDS oppenensplasty. At age 28 yr, he presented with muscle atrophy, motor deficits with normal sensations, and gait disturbance. After full, neurological assessment and investigations, a diagnosis of CMTD had been made. The patient had degenerative cervical disc disease, with multilevel disc bulging and protrusion confirmed by magnetic resonance imaging. He expressed a desire to avoid tracheal intubation and preferred a regional technique. The procedure and the risks were discussed with him.

In the block room, following application of routine monitors, an axillary brachial plexus block was performed with peripheral nerve stimulation (22G, 2 inch, short-bevelled stimulator needle, Pajunk®, Geisingen, Germany) and ultrasound guidance (Micromax, Sonosite Medical Systems®, Bothell, WA, USA). On nerve stimulation with a 0.6 mA current, pulse duration of 0.2 msec, at a frequency of 2 Hz, some elbow flexion and wrist extension were noted. Ropivacaine, 0.5% 40 mL, was freely injected under ultrasound visualization. A good motor and sensory block ensued, and the surgery proceeded uneventfully. Three months later, he presented again for corrective surgery of the contralateral hand (FDS oppenensplasty) and requested that the procedure be done under regional anesthesia. An axillary block was performed under ultrasound guidance and peripheral nerve stimulator assistance with ropivacaine, 0.5% 30 mL. In this instance, no motor response could be elicited, despite adjustments in nerve stimulator settings (current 1.2 mA, pulse duration 0.3 msec, frequency 2 Hz, Pajunk®, Geisingen, Germany). Again, a good sensory and motor block ensued, and the surgery proceeded uneventfully. The postoperative course was unremarkable. He was seen in the neurology clinic at the end of six months and the neurological condition remained stable.

Discussion

Charcot-Marie-Tooth disease is a hereditary motor and sensory neuropathy, and is one of the most commonly encountered inherited neuropathic disorders, with an incidence estimated at about one in 2,500.[5] The first description of distal muscle weakness and wasting, beginning in the legs, was published in 1886 by Jean Martin Charcot and his student, Pierre Marie, under the name of peroneal, muscular atrophy.[6] The same disease was described by Howard Henry Tooth, in his Cambridge dissertation in 1886, under the name of peroneal progressive muscular atrophy.[7] Charcot-Marie-Tooth disease, or hereditary motor and sensory neuropathy,[8] is dominantly inherited, and a large number of subtypes have been described.[1] The majority (e.g., CMT1) are dominantly inherited, whereas others, such as CMTX, are inherited as autosomal recessive or X-linked recessive diseases.[9] The common X-linked dominant form is caused by mutations in the GJB1 gene, which encodes a gap junction protein called connexin 32 (cx 32).[10] An extensive description of the classification is beyond the scope of this article, but a simple clinical classification is shown in the Table.

TABLE Classification of hereditary sensory motor neuropathies or CMTD

Type	*Pathology*	*Clinical features*
CMT1	Demyelination	• Commonest • Autosomal dominant, mutation in PMP-22 gene • Weakness, atrophy, sensory loss in legs • NCV: delayed < 38 $m \cdot sec^{-1}$ (similar to unmyelinated nerves • ↓ number of myelinated fibres • Onset: adolescence • Histology: hypertrophic 'onion bulb' like appearance • Multiple genetic subtypes: types1A – 1F with defects on chromosomes 17, 1, 16, 10, 17 & 8 respectively
CMT2	Neuronal disorder of axons	• Autosomal dominant • NCV: normal limits, ↓ amplitude • Distal weakness • Onset: adolescence to later age • Histology: axonal degeneration • Subtypes: 2A – 2L
CMT3	Severe demyelination	• Rare • Dejerine-Sottas disease • Infantile onset, delayed milestones & motor skills • Severe distal weakness, faster progression • Histology: demyelination with thinning of myelin sheath
CMT4	Demyelination	• Autosomal recessive, rare • Several types • Motor & sensory • Leg weakness • Onset: early childhood • Gene abnormality: on chromosomes 5, 8, 10, 11, 12, 19
CMTX	Schwann cells & axons communication defect	• X-linked dominant, male > female • Moderate to severe • Onset: late childhood or adolescence • Gene abnormality: point mutation in connexin-32 gene on X chromosome • Types: X1-3
Others Cowchock syndrome, Tomaculous neuropathy, Congenital hypomyelination, CMT R		

CMTD = Charcot-Marie-Tooth disease; PMP = peripheral myelin protein; NCV = nerve conduction velocity.

Although demyelination is the initial effect of these mutations, the severity of all of these neuropathies is directly related to the degree of axonal loss, rather than demyelination.[11] Most forms of CMTD have slowly progressive, length-dependent weakness; atrophy; and reduction of deep tendon reflexes. Clinically, the condition is characterized by peripheral motor and sensory deficit with muscle atrophy, predominantly distal, and hypo or areflexia. The weakness is due to a combination of factors; including axonal death, deconditioning, and disuse atrophy.[12,13] Electrophysiological studies reveal slowing of nerve conduction.[14] Though CMTD does not usually shorten the life expectancy, the slowly progressive neuropathy causes eventual disability secondary to distal muscle weakness and deformities.

Muscle wasting causes a relative increase in the extracellular potassium levels, therefore, depolarizing muscle relaxants are avoided in these patients to prevent hyperkalemia. The response to non-depolarizing neuromuscular blocking drugs is variable in patients with CMTD.[15] A near-normal acceleromyographic neuromuscular response to mivacurium has been observed. Prolonged neuromuscular blockade has been reported with vecuronium in patients with CMTD.[16] There are many reports describing the successful use of general anesthesia for surgical procedures in patients with CMTD. The Charcot-Marie-Tooth Disease North American database is an extensive collection of recorded, clinical details of CMTD patients, mainly in the United States and Canada, and is housed in the Department of Medical and Molecular Genetics at Indiana University. Apart from other clinical information, the database attempts to document exposures to suspected medications, duration of exposure, and perceived neuropathic effects. Nitrous oxide is included in the moderate to significant risk group in this database. The unexpectedly high percentages of cases

listed in the database suggest that some patients with CMTD have reported worsening of CMTD-related neuropathy after anesthesia incorporating nitrous oxide. Possible causes include irreversible oxidization of the cobalt core of the cobalamin molecule, and precipitating myeloneuropathy in patients with borderline vitamin B-12 levels.[17] Charcot-Marie-Tooth disease patients may have an increased sensitivity to thiopental, and the dose required is strongly related to the severity of the motor and sensory disturbance.[18] Propofol and fentanyl, as part of a total intravenous technique, are thought to be safe and effective,[19] although sensitivity to central depressants, including opioids, can be encountered.[20] Concerns have been expressed about the use of inhalational agents in CMTD patients, but a potential link between malignant hyperthermia and CMTD remains unknown.[21] It has been recommended that temperature be monitored, even if a regional technique is used.[22]

Nerve stimulation requires intact nerve fibres and muscles. Neuropathy can diminish the excitability of a nerve. Conduction failure may occur if the reduction in nerve impulse transmission worsens because of demyelination, axonal loss, or both. In CMTD, there is slowing of NCV.[23] It is known that there is decreased electrical excitability of peripheral nerves in demyelinating polyneuropathies,[24] as demyelinization requires higher nerve stimulation currents to obtain muscular responses, as is also seen in patients with diabetes mellitus.[25] The final stimulus current intensity, so as to predict a successful block for the different neuropathies, remains unknown. Use of higher current (> 1 mA) and a longer stimulation duration (> 0.3 msec) is recommended in these situations, but does not guarantee a successful block.[26] It has been suggested that local anesthetics may have an exaggerated effect on the spinal cord in the presence of demylination,[27] although this has not been confirmed in relation to peripheral nerve blocks. The patient described in case 1 had a chest wall deformity, and a good spread of local anesthetic around the axillary artery, was seen with a smaller volume requirement of local anesthetic.

The argument against the use of regional analgesia in CMTD is similar to that applied to other progressive neurological diseases. Patients with an underlying peripheral neurological disorder may be more susceptible to nerve injury with the use of regional techniques,[28] and the presence of chronic, underlying neural compromise, secondary to mechanical, ischemic, toxic, or demyelinating conditions, may theoretically, place these patients at increased risk of further neurological injury.[29] This phenomenon of "double-crush"[30] was originally described by Upton and McComas in 1973. Later on, Osterman[31] emphasized that not only are two low grade compressions along a nerve trunk worse than a single site, but also, the damage resulting from dual compression far exceeds the expected damage caused by each, isolated compression.

Recently, severe brachial plexopathy has been reported following ultrasound-guided, single injection nerve block in a multiple sclerosis patient.[32] Data from prospective randomized trials assessing the role of nerve injury following regional blockade in demyelinating conditions, are lacking. Fear of litigation, should exacerbation occur, could lead some to avoid regional anesthesia in this situation. These issues must be thoroughly discussed with the patient before surgery, on a case-by-case basis, as broad recommendations are rarely supportable. It is important that patients understand that the natural course of CMTD may progress after surgery. Despite lack of evidence, regional anesthesia may be erroneously blamed for any subsequent deterioration in motor or sensory deficits.[33] Currently, there is no convincing evidence that regional analgesia will affect the course of CMTD. We feel that a patient with CMTD should be able to choose this form of anesthesia.

In summary, these cases show that ultrasound guidance may make peripheral nerve block possible in patients for whom traditional methods of nerve localization fail. There is uncertainty about neurostimulation behaviour in these patients. Patients with underlying neurological disease, who are at increased risk of nerve injury, may undergo peripheral nerve blocks more effectively with ultrasound. Ultrasonography facilitates performance of successful peripheral nerve blocks and renders these pain-relieving techniques available for a larger group of patients.

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