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Review Article

Anesthetic Management of Charcot-Marie-Tooth Disease

Jae Won Kim MD[1], Jin Ho Choi MD[2], Goo Kim MD[1], Keon Hee Ryu MD, PhD[1], Sun Gyoo Park, MD, PhD[1], Chang Young Jeong MD, PhD[1], Dong Ho Park MD, PhD[1*]

[1]Department of Anesthesiology and Pain Medicine, Eulji University Medical Center, Daejeon, Korea
[2]Department of Thoracic and Cardiovascular Surgery, Eulji University Medical Center, Daejeon, Korea

[*]**Corresponding Author:** Dr. Dong Ho Park, Department of Anesthesiology and Pain Medicine, Eulji University Medical Center, Daejeon, Korea, Tel: 82-42-611-3883; Fax: 82-42-611-3882; E-mail: donghop6212@naver.com

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Abstract

Charcot-Marie-Tooth (CMT) disease, which is the most common inherited neuropathy, is also referred to as hereditary motor and sensory neuropathy (HMSN) and shows a genetically heterogeneous pattern. CMT is diagnosed mostly by a neurologic specialist. It can be divided into autosomal dominant, autosomal recessive, or X-linked type, based on the transmission pattern. It can also be divided demyelinating or axonal type, based on the electrophysiological findings. Therefore, it is practically not feasible for anesthesiologists to make the diagnosis, and diagnosis becomes even more difficult with the continued emergence of subtypes with the identification of new genes. Moreover, each type has a different phenotype, and each may be managed slightly differently based on the actual symptoms presented. For each case, there are conflicting opinions on the methods for anesthetic management, causing much confusion. Accordingly, in this review, we aimed to discuss the diagnostic methods, types, and treatment methods for CMT from an anesthetic perspective and to review anesthetic management.

Keywords: Charcot-Marie-Tooth disease; Anesthesia; Diagnosis and treatment; Malignant hyperthermia; Neuromuscular blocking agents; Respiratory dysfunction

1. Introduction

Charcot-Marie-Tooth (CMT) disease is the most common inherited neuropathy characterized by progressive distal to proximal weakness, usually affecting the feet and legs and progressing proximally. It is typically accompanied by atrophy and sensory deficits, while the clinical phenotype can range from mild symptoms to severe symptoms that can disrupt activities of daily living. At least 25 genes are known to be involved, and over 70 subtypes have been identified [1].

CMT is classified as autosomal dominant, autosomal recessive, or X-linked type based on the transmission pattern; demyelinating or axonal type based on the electrophysiological findings; or others based on the mutant genes involved. Symptoms and signs start with distal atrophy of the lower limbs and subsequent involvement of the hands and forearms, leading to pes cavus, hammer toes, foot drop, intrinsic muscle weakness, difficulty in walking, hand tremors, and clawed hands, involving even the respiratory muscles in severe cases [2, 3]. Various diagnostic methods can be used according to clinical symptoms, inherited mode, electrophysiological examination, and molecular tests on each gene. The classification criteria for each type vary, and clinical symptoms also appear in various manners, from no symptoms to severe symptoms that require the patient to rely on a wheelchair.

Although it is one of the most common genetic diseases, various anesthetic modalities for surgeries involving patients with CMT have been suggested for different cases due to various classifications. However, articles describing anesthetic management are relatively rare. Accordingly, this review will discuss considerations that should be given for preanesthetic diagnosis, symptoms, treatment, and perioperative anesthetic management for cases involving CMT through a review of existing literature.

2. Clinical Manifestations and Diagnosis

Demyelinating types of CMT predominantly affect the myelin sheath. Myelin is involved in increasing the nerve conduction velocity (NCV), while demyelination slows the NCV. On the other hand, axonal types affect the axons, and thus, the NCV is conserved, but the amplitude of motor and sensory potentials is reduced. The most common types of CMT are CMT1 and CMT2, while CMT1A is the most common type of CMT1 type. As an exception, CMT1B is the more common type in Japan [4, 5]. Among CMT2 type, CMT2A is the most common type [6].

2.1 CMT1

CMT1 involves autosomal dominant transmission (shows NCV<38m/s) and appears from a duplication of peripheral myelin protein 22 (PMP22) that regulates myelination and cell growth. Approximately 50% of CMT1A occurs due to duplication of PMP22 [3], and besides this, PMP22 point mutations and point mutations in myelin protein zero (MPZ) are involved as mutated genes in CMT1 [3, 7-9]. Symptoms include foot drop and steppage gait due to foot deformity. Also, claw hand from the involvement of the upper extremity and scoliosis as spinal deformity may also appear. Symptoms usually appear during childhood or adolescence. Concerning disease severity, variability may be found within the same family, and even monozygotic twins may show different disease severity. CMT1B appears from the involvement of MPZ mutation, and symptoms may present in the pupils or the ears.

2.2. CMT2

CMT2 is an axonal form (with normal NCV>38 m/s), while it shows reduced amplitudes of motor and sensory potentials, along with pathologically axonal degeneration and preservation of myelin. Most cases show autosomal dominant inheritance, but some cases also show a recessive inheritance pattern. CMT2 appears from mutation of the

mitofusin-2 protein (MFN2) involved in the fusion of mitochondria [10-14] and it shows a highly heterogeneous pattern. Furthermore, genes for MPZ and neurofilament light chain (NEFL) are involved.

2.3 Minor CMT

CMT3 (Déjèrine-Sottas neuropathy) is the most severe form of demyelinating CMT. CMT4 is caused by a mutation in the ganglioside-induced differentiation-associated protein-1 (GDAP1), and it shows severe motor and sensory neuropathy. Of these, CMT4A has been reported to be associated with vocal cord paresis [15]. CMTX is an X-linked type, which appears from a point mutation in the gap-junction B1 (GJB1) gene.

Type	**Phenotype**	**Inheritance**	**Genes**
CMT1 (Demyelinating)	NCV < 38 m/s Biopsy: onion bulbs	AD	PMP22 duplication or point mutation MPZ
CMT2 (Axonal)	NCV < 38 m/s Axonal degeneration	AD or AR	MFN2 MPZ NEFL GDAP1
Intermediate	NCV>25m/s and < 38 m/s	AD	
CMT3	Early onset More severe than CMT1	AD or AR	PMP22 MPZ
CMT4	Variable phenotypes	AR	GDAP1
CMTX		X-linked	GJB1
CMT5	Pyramidal involvement		MFN2
CMT6	Optic atrophy		MFN2

Abbreviations : CMT: Charcot-Marie-Tooth disease, NCV: nerve conduction velocity, AD: autosomal dominant, AR: autosomal recessive, PMP22: peripheral myelin protein 22, MPZ: myelin protein zero, MFN2: mitofusin 2 protein, NEFL: neurofilament light chain, GDAP1: ganglioside-induced differentiation-associated protein-1, GJB1: gap-junction B1.

Table 1: Schematic overview of CMT types and phenotypes and related genes.

2.4 Diagnosis of CMT

CMT can be diagnosed based on clinical phenotype, inheritance pattern, electrophysiological examination, molecular analysis, and nerve biopsy. Clinical phenotypes begin in the feet, exhibiting high arches, hammer toes, and intrinsic muscle weakness, and gradually progress proximally to the lower third of the thighs, hands, and forearms. Deep tendon reflex is reduced or lost, and scoliosis may also appear. Consequently, symptoms such as

foot drop, walking difficulty, steppage gait, hand motor impairment, and tremor may appear. Also, cranial nerve involvement, vocal cord palsy, optic atrophy, pyramidal involvement, and sensory abnormality may also appear [3]. Furthermore, restrictive pulmonary impairment and obstructive sleep apnea may also appear when involving the respiratory system [16].

Concerning inheritance patterns, CMT1 and most CMT2 cases show autosomal-dominant inheritance, while CMTX show X-linked dominant inheritance, and axonal types of CMT2 and CMT4 show autosomal-recessive transmission. Based on NCV in electrophysiological examinations, a diagnosis could be made as demyelinating CMT (CMT1 and CMT4) if NCV<38 m/s and CMT2 if normal or mildly reduced NCV (NCV>38 m/s) together with a reduction in the amplitudes of muscle and sensory action potentials [3]. It has been challenging to identify all these genes by molecular analysis since there are many mutated genes associated with CMT. However, since PMP22, MPZ, MFN2, GJB1, and GDAP1 account for most of the associated genes that have been identified [3, 16], identifying just these mutated genes should eliminate difficulties in diagnosing CMT in most cases. Additionally, family history could help diagnose CMT, but some mutated genes trigger new mutations, whereby family history ultimately disappears nonspecifically in some cases [17]. Nerve biopsy is not performed in most cases. Usually, a biopsy is performed if a differential diagnosis is needed—if genetic test findings are not helpful—or if a nerve biopsy could provide some critical information.

Clinical phenotype
CMT으| symptoms and signs
Inheritance pattern
AD: CMT1 and most CMT2
X-linked: CMTX
AR: CMT4 and CMT2 (axonal type)
Electrophysiological examination
NCV < 38 m/s: demyelinating CMT
(CMT1 and CMT4)
NCV > 38 m/s: CMT2
Molecular analysis
PMP22, MPZ, MFN2, GJB1 and GDAP1 (most important genes for CMT diagnosis)
Nerve Biopsy

Abbreviations: AD: autosomal dominant, AR: autosomal recessive, NCV: nerve conduction velocity, PMP22: peripheral myelin protein 22, MPZ: myelin protein zero, MFN2: mitofusin 2 protein, GJB1: gap-junction B1, GDAP1: ganglioside-induced differentiation-associated protein-1

Table 2: Diagnosis of CMT.

3. Treatment

Currently, there is no effective drug therapy for CMT. Despite multicenter clinical trials that have been conducted, there is still a lack of data for use of medication in clinical practice [18-22]. Therefore, treatment modalities currently available are limited to supportive and surgical treatments.

3.1 Drug therapy

Since skeletal deformities, posture abnormalities, and muscle fatigue, along with true neuropathic type pain, may appear in patients with CMT [23, 24], analgesics drug therapy for such symptoms may be needed. Progesterone is known to cause overexpression of MPZ and PMP22, and thus, anti-progesterone therapy could be used. Onapristone, which falls into this category, can improve motor strength and have a protective effect on axonal loss without causing any changes to myelin thickness or NCV [25]. However, it has the disadvantage of showing significant side effects. In this context, the exacerbation of CMT symptoms during pregnancy could be understood. In addition, due to an increased risk of complications during delivery, the risk of abnormal fetal presentation or postpartum bleeding is also increased, and there is a higher likelihood of being exposed to emergencies [26].

Others include coenzyme Q10, curcumin, and neurotrophin-3 (NT3). Curcumin acts to reduce the cytotoxicity of mutant proteins and may be particularly useful for CMT involving MPZ and PMP22 mutations [3, 16]. NT3 is a neurotrophic factor that promotes axonal growth. Besides these, linoleic acid and potassium channel blockers are also being researched.

In studies on ascorbic acid, which is a promoter of myelination, the results showed reduced PMP22 expression, and increased life span and myelination [27, 28]. However, in studies on children and young adults, the results showed no significant effect on NCV and neurophysiological secondary outcome measures [29-33]. Moreover, since the immune system is known to be involved with the pathophysiology of CMT, steroid or immunoglobulin treatment could also be considered. Agents that can cause neurotoxicity, such as vinca alkaloids, cisplatin, oxaliplatin, and taxol derivatives, should be avoided [34]. These agents are believed to cause interruption of axonal transport, exacerbation of existing neuropathy, and precipitation of de novo neuropathy.

3.2 Rehabilitation and physical supportive treatment

Gait training, exercise, postural stabilization, fall risk prevention, energy conservation techniques, and training with assistive devices for patients with CMT belong to this, and it improves walking ability and limb strength through exercise and prevents tendon retraction through stretching. Ankle-foot-orthoses improve lower extremity control and help increase gait speed. Depending on the patient, some may feel uncomfortable from not becoming well acclimated to the orthoses, and thus, training is necessary, and custom-fitted ankle-foot-orthoses are more comfortable and have better compliance.

3.3 Surgical treatment

Correction by a surgical procedure is an option in cases of chronic ankle sprains, feeling uncomfortable to ankle-foot-orthoses, and no pain reduction from wearing orthoses. Correction methods include soft-tissue surgery, osteotomies, and joint fusions. Surgical goals are to realign joints, correct bony deformities, and maintain muscle balance and different methods for different patients to achieve these goals. Soft-tissue surgery is an early minimally invasive procedure, which includes plantar fasciotomy, tendon transfers, and tendon lengthening.

In cases of severe forms of CMT, respiratory and sleep disorders with restrictive pulmonary impairment, obstructive sleep apnea, and vocal cord dysfunction may appear, and correction may be needed if spinal deformities or hip dysplasia are present. The incidence of spinal deformity in CMT is 26-37%, which includes scoliosis (58%), kyphoscoliosis (31%) and thoracic kyphosis (11%) [35]. In such cases, instrumentation-based surgical stabilization may be needed. Hip dysplasia may require reconstructive procedures on the proximal femur, and acetabulum and there is a very high risk of advancing to osteoarthritis during long-term follow-up.

For respiratory disorder, noninvasive positive pressure ventilation could be used if any one or more of the following conditions are met: FVC<50% predicted, 5 minutes or more of nocturnal desaturation <88%, MIP<60 cm H_2O, and $PaCO_2$ >45 mmHg. For restless legs syndrome, dopaminergic agents, carbamazepine, or gabapentin may be used. To treat vocal cord dysfunction, cordotomy, vocal cord lateralization, medicalization to preserve phonation, and tracheotomy could be considered.

Drug therapy
1. Pain control
2. Progesterone antagonists
3. Curcumin, NT3, Coenzyme Q10
4. Ascorbic acid
5. Steroid
6. Immunoglobulin
Rehabilitation, supportive treatment
1. Gait training, exercise, postural stabilization
2. Fall risk prevention
3. Ankle-foot-orthoses
4. Respiratory and sleep disorder
1) Positive pressure ventilation
5. Restless legs syndrome
1) Dopamine
2) Carbamazepine
3) Gabapentin
6. Vocal cord dysfunction

1) Cordotomy
2) Vocal cord lateralization
3) Medialization to preserve phonation
4) Tracheotomy
Surgical treatment
1. Soft-tissue surgery
1) Plantar fasciotomy
2) Tendon transfer
3) Tendon lengthening
2. Osteotomy
3. Joint fusion
1) Triple arthrodesis
4. Spine & hip
1) Surgical stabilization
2) Reconstructive procedures

Table 3: Treatment of CMT.

4. Anesthetic Management of Charcot-Marie-Tooth Disease

Various types of CMT findings appear depending on the clinical findings, genetic patterns, electrophysiologic findings, and mutated genes involved. Anesthetic method for CMT may vary according to each clinical symptom. In general, anesthetic management for CMT should consider the following: hyperkalemia associated with using succinylcholine, association with malignant hyperthermia, prolong the muscle relaxation action of neuromuscular blocking agent, as well as cardiac manifestations and respiratory and vocal cord dysfunction that may appear in patients with CMT.

4.1. Hyperkalemia and malignant hyperthermia

Patients with CMT are in a state of chronic denervation [36], which could act as a potent predisposing factor of hyperkalemia that may appear after using succinylcholine for up-regulation of the cholinergic receptor. Findings of hyperkalemia could be easily recognized based on changes in EKG and hemodynamic change. In most cases, however, findings of hyperkalemia do not appear, which is perhaps due to the denervation process being much slower than the atrophic process in the muscles, resulting in relatively less potassium release [37]. Moreover, potassium release could be reduced by administering defasciculating dose of non-depolarizing muscle relaxant. Even if there are no specific problems with using succinylcholine, it should be used with caution or its use should be avoided if significant muscle denervation and wasting are expected [37].

The association with malignant hyperthermia (MH) during inhalation anesthesia in patients with CMT is still unclear. It is believed that sevoflurane can trigger MH in susceptible patients [38], while anesthesia using succinylcholine and inhalation agents did not trigger MH in 90% of the patients. However, due to the small sample size, such a possibility cannot be completely dismissed [37]. Pasha et al. [39] reported that the reason why MH does not appear in CMT is that CMT is a form of peripheral neuropathy, not myopathy. Therefore, inhalation agents should be used with caution when dealing with patients with CMT, while using total intravenous anesthesia (TIVA) may be a wise choice as well.

4.2 Inhalation agents

Theoretically, prolonged use of N_2O could show neurotoxicity from inhibition of methionine synthases, and thus, it should be used with caution. Other inhalation agents act to enhance muscle relaxation effects in addition to the muscle relaxation effects of neuromuscular blocking agent, and thus, they should be used while remembering that they may produce an undesired prolonged effect of muscle relaxation [40-42]. It should be kept in mind that such effect is amplified even more in patients with muscle weakness. Sevoflurane has been reported to cause prolongation of the QT interval, and thus, it should be used with caution in patients with QT prolongation (long QT syndrome) [43].

4.3 Cardiac symptoms and signs in Charcot-Marie-Tooth disease

Cardiac dysrhythmia and conduction disturbances may also appear in cases involving CMT with several studies reporting an increased incidence of mitral valve prolapse [44, 45]. However, increased cardiac manifestations in patients with CMT, as compared to a normal population, has not yet been proven. Other reported manifestations include long QT syndrome, paroxysmal atrial flutter, cardiomyopathy, and A-V block [45-47]. Therefore, it is important to select drugs that do not affect arrhythmia and conduction disturbance. Among those, propofol does not affect the cardiac conduction system, and thus, it could be used on a patient with CMT who have arrhythmia [48].

4.4 Neuromuscular blocking agents in CMT

Studies on non-depolarizing neuromuscular blocking agents (NMBAs) in CMT have reported conflicting results, with NMBA effect being normal, increased, or decreased. Pogson et al. [40] reported on the prolonged neuromuscular blockade of vecuronium used in general anesthesia, while Baraka et al. [49] reported that the actions of vecuronium were normal in patients with generalized areflexia and muscle weakness. Naguib et al. [50] reported that the muscle relaxation effect of atracurium and mivacurium was normal, while a review of 86 patient cases by Antognini [37] reported that patients with CMT responded normally to muscle relaxants. Schmitt et al. [51] also reported that after using mivacurium on pediatric patients with CMT, they showed no difference as compared to a normal population, while Ortiz-Gómez et al. [52] reported that no prolonged duration was found after using rocuronium. Prolongation of NMBA in patients with CMT theoretically occurs from muscle weakness and atrophy due to loss of motor units, and up-regulation of acetylcholine receptors occurs at the neuromuscular junction. Such

up-regulation occurs due to denervation, burns and chronic administration of anticonvulsants or muscle relaxants, and due to such up-regulation, prolongation of NMBA occurs from increased sensitivity of non-depolarizing neuromuscular blocking agents.

However, up-regulation increases the number of cholinergic receptors to show normal or moderate resistance of NMBA ultimately, and as a result, a prolonged muscle relaxation of NMBA may not appear [49]. Moreover, there is a possibility of prolonged block if the nerves that monitor neuromuscular function monitor posterior tibial, ulnar, and facial nerves infiltrated by CMT [37].

During neuromuscular function monitoring, monitoring of facial nerves is more appropriate than that of ulnar and tibial nerves, which is due to clinical involvement of the extremities [40], and because effective nerve monitoring could be used for easier titration of neuromuscular blocking agent and identification of adequate reversal signs. Moreover, facial nerves are normally spared, and relaxation of the eye muscles corresponds well with relaxation of the diaphragm [53]. However, clinically monitoring being difficult still remains a problem [54].

4.5 Respiratory and vocal cord dysfunction

When using neuromuscular blocking agents in CMT, caution should be taken regarding respiratory and vocal cord dysfunction. Pulmonary impairment may occur and sometimes could be accompanied by weakness in the intercostal muscles and diaphragm [2]. If there are findings of diaphragmatic dysfunction, the risk of prolongation of a neuromuscular blocking agent may be significantly increased. If patients with CMT are comorbid with phrenic nerve and vocal cord dysfunction, aspiration risk would also increase significantly. Patients with even severe pulmonary dysfunction may appear normal on the outside, while proximal muscle weakness in the arms could be a predictor of respiratory muscle weakness.

Hyperkalemia
Release of potassium after exposure to succinylcholine Well tolerated (probably safe)
Defasciculating dose of a nondepolarizing muscle relaxant
Malignant hyperthermia
Susceptible patients: avoid triggering agent
Reasonably use of inhalation agents
TIVA with propofol, remifentanil
Inhalation agents
N2O: neurotoxicity (theoretically)
Sevoflurane: prolongation of QT interval
Enhance the effects of NMBA

Neuromuscular blocking agents
Safe use of NMBA, but continuous monitoring of NMBA
Respiratory and vocal cord dysfunction
(+) symptoms & signs: prolongation of NMBA
(-) symptoms & signs: safe use of NMBA
Regional anesthesia
Important that neurologic deficits are assessed before RA
Sugammadex
Advantage in CICV situations

Abbreviations: NMBA: neuromuscular blocking agents, RA: regional anesthesia, CICV: cannot intubate, cannot ventilate

Table 4: Anesthetic considerations in CMT.

4.6 Regional anesthesia

Performing regional anesthesia (RA) on patients who already have a neurological disorder is controversial. Moreover, because the possibility of an existing neurological disease becoming worse, some anesthesiologists are fearful, while lack of patient-controlled studies is another reason it is not performed often. Ultrasound-guided nerve blocks could be a method that can reduce the risk of neurologic complications. However, what is most important is identifying the presence of any deficits by neurologic examination before performing RA [55].

4.7 Sugammadex

Sugammadex, a modified gamma-cyclodextrin, is a selective NMBA binding agent that can inactivate steroidal NMBA, such as rocuronium or vecuronium. In a study that compared the time required to reach TOF-ratio ≥0.9 between neostigmine and sugammadex, sugammadex showed excellent efficacy in moderate and deep block, and immediate reversal of high dose rocuronium effect [56]. Moreover, the use of sugammadex for emergency reversal during 'cannot intubate, cannot ventilate' (CICV) situations has been reported [57-59]. However, it should be noted that there have been reported cases of rash, erythema, hypotension, wheezing, and periorbital edema [60, 61]. In addition, QT prolongation and AV block have been reported, and because it is excreted by urine in an unchanged form, it is not recommended when there is indication of renal failure [62].

4.8 Risk factors for residual neuromuscular blockade

It should be kept in mind that when the effect of NMBA is prolonged in cases with higher dose of NMBA, absence of neuromuscular blockade monitoring, inhalation agents, aminoglycoside antibiotics, hypercarbia, acidosis, hypothermia, hypocalcemia, and hypercalcemia.

5. Conclusion

In conclusion, succinylcholine should be used reasonably as long as the patient is not susceptible to malignant hyperthermia, and if there is no involvement of the respiratory muscles, NMBA could also be used through appropriate monitoring of the neuromuscular blocking agent. Moreover, if neurologic deficits have been adequately assessed, regional anesthesia should not be problematic, while using sugammadex for reversal of NMBA could be considered as well. Drugs should be used with caution, and if an appropriate dose is administered by dose titration, anesthesia for cases involving CMT should not present major problems. However, because new phenotypes may appear due to the expression of other mutated genes, caution and close monitoring are always needed. Furthermore, communication among physicians, neurologists, surgeons, and anesthesiologists is also essential in improving the outcome of CMT.

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