

Anaesthesia recommendations for patients suffering from

Charcot-Marie-Tooth disease

Disease name: Charcot-Marie-Tooth disease

ICD 10: G60.0

Synonyms: Hereditary motor and sensory neuropathy. Includes: Charcot-Marie-Tooth, Déjerine-Sottas, hereditary motor and sensory neuropathy (however this term includes several entities different from Charcot-Marie-Tooth with heterogeneous inheritance), hypertrophic neuropathy of infancy, Peroneal muscular atrophy (axonal type) (hypertrophic type), Roussy-Lévy syndrome

Charcot-Marie-Tooth (CMT) disease is the most prevalent peripheral inherited neuropathy (1/2500 to 10 000; 2.8/10 000 in Spain), and the mean age at onset is 16 years (range 2 to 50 years, but presentation in the early infancy and as late as the 80's has been reported). Patients present with motor and sensory polyneuropathic semiology (distal lower limb weakness and atrophy, gait abnormalities and frequent falls) and pes cavus. Apart from the motor nerve related deficits, most patients suffer slight sensory loss in hands and feet. The treatment of the disease is supportive. Life expectancy is not shortened - except in some forms of Déjerine-Sottas and severe forms of CMT-, but disabilities are the rule.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

The slow increase in physical disability in adulthood may well be explained by decreased reserves and compensatory mechanisms together with progression of skeletal deformations due to muscle weakness. However this classic concept is controversial, as can be related to CMT1A only: progression of axonal loss definitely occurs in most if not all CMT types and is a cause of progressive wasting and weakness in many patients.

Sometimes CMT disease is associated with moderate to severe chronic extremity pain, that is usually related to bone, joint and muscle involvement, and rarely neuropathic.

CMT is more frequently an autosomal dominant disease (but there is genetic heterogeneity and more than 30 pathogenic genes have been implicated, X-linked and autosomal recessive forms, even mitochondrial DNA mutations showing a CMT-like phenotype have been reported). The most common syndrome is CMT1A, which accounts for 55% of all CMT cases and 66.8% of CMT1 cases, and which is usually caused by an allelic trisomy of a region spanning 1.5Mb in 17p11.2, containing the PM P22 gene (causing excessive gene dosage, and overproduction of PMP22 and its accumulation in Schwann cells that is a proposed mechanism resulting in programmed cell death, the ultimate mechanism of CMT development remaining unknown), but the percentages can vary according to different series reported and geographic origin. The 1970's classification from Dyck is valid, but molecular genetics has changed the nosology (see Berciano J, et al for complete information): a) type I (CMT1, demyelinating or hypertrophic) with AD or AR inheritance; b) type II (CMT2, neuronal or axonal) with AD or AR inheritance; c) type III (CMT3, usually with de novo heterozygous gene mutations, AR uncommon) reserved for Déjérine-Sottas disease or patients with severe forms of hypomyelinating CMT; d) X-linked forms, and e) complex forms (e.g. associated with pyramidal involvement, optic atrophy, deafness -occurring in several CMT types-; pigmentary degeneration of the retina suggest mitochondrial disease). The disease shows the more prevalent phenotypes caused by mutations in the gene encoding peripheral myelinprotein-22 (duplication), dynamin-2 being very rare.

Diagnostic: lineage of affected ancestors, and/or (in the case of negative family survey), onset during childhood; prolonged and slowly progressive clinical course; presence of pes cavus, and -unlike in acquired neuropathies- absence of positive sensory symptoms (paraesthesias or dysaesthesias) despite a clear semiology of sensory deficit. An electrophysiologic examination should follow (CMT1 and CMT2 classification depends on the cutoff value 38m/s -by convention-, for the upper limb motor nerves conduction velocity, both median and ulnar nerves), and, in selected cases, neuropathologic criteria (nerve biopsy). Finally genetic testing specifically targeted (molecular diagnosis).

Typical surgery

Orthopaedic procedures are common: soft tissue, osteotomies and arthrodesis (both isolated or combined), i.e. multiple tendinous transposition in foot deformities, and scoliosis. Nerve biopsy. A case of diaphragmatic plication has been reported.

Type of anaesthesia

Case reports or case series are the source of information.

General anaesthesia is usually selected: balanced (halogenated agents) and total intravenous (propofol based) anaesthesia have been safely used, with or without muscle relaxation.

Neuraxial blocks have been successfully performed (epidural, spinal and combined spinal-epidural anaesthesia).

In a few cases, ultrasound guided nerve blocks for postoperative analgesia have been used, without long lasting neurologic complications. Muscle response to neurostimulation can be abnormal (low).

Necessary additional diagnostic procedures (preoperative)

Patients need to be closely evaluated in a few cases, restrictive pulmonary impairment has been described in association with phrenic nerve dysfunction, diaphragm dysfunction, or thoracic cage abnormalities. Central sleep apnea may be associated with diaphragm dysfunction and hypercapnia, whereas obstructive sleep apnoea has been reported as possibly due to a pharyngeal neuropathy. Restless legs and periodic limb movement during sleep are found in some patients with CMT2. Vocal cord dysfunction, possibly due to laryngeal nerve involvement, is found in association with some CMT types and there are some risks of progression to bilateral paralysis and aspiration.

Patients should be assessed for the presence of autonomic denervation as this is common.

Assessment for other co-morbidities should be undertaken as the presence of diabetes mellitus can lead to further deterioration in neuropathy.

Particular preparation for airway management

Not reported.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transport or mobilisation

Cautious positioning and protection of pressure points is recommended because nerve compression may aggravate the neuropathy.

Probable interaction between anaesthetic agents and patient's long term medication

Drugs for neuropathy (restless legs syndrome) or chronic pain.

Some patients can be under psychoactive drug therapy due to psychiatric symptoms (i.e. depression, anxiety).

In a few cases spinal cord stimulation has been used to treat chronic limb pain.

Anaesthesiologic procedure

In a case series, thiopental dose required for induction in CMT was less than in control patients, and was related with the severity of the neuropathy.

Theoretically nitrous oxide use could cause neurotoxicity through its inhibition of methionine synthase in patients with CMT and it is quoted as 'moderate to significant' risk of potential toxicity and worsening neuropathy in people with CMT by the CMT Association (USA), CMT Association of Australia, CMT International (Canada) and CMT United Kingdom. Nevertheless a systematic review (11 studies, 41 exposures) observed no neurologic worsening, with the authors quoting the drug as safe in adults and children.

Avoiding succinylcholine is recommended.

Response to nondepolarizing neuromuscular blocking agents can be unpredictable.

Safe sugammadex neuromuscular block reversal has been reported.

Patients severely affected (as the kyphoscoliotic ones) can develop respiratory insufficiency after neuraxial anaesthesia (higher than expected sensory and motor block level).

Particular or additional monitoring

Neuromuscular block monitoring is recommended. Monitoring at the ulnar nerve-adductor pollicis brevis is recommended as lower limbs are often severely denervated. However sometimes monitoring can be difficult especially if upper limbs are affected too.

Possible complications

Probably this disease is not especially associated with hyperkalemic response after succinylcholine, but it has been recommended to avoid it.

Response to nondepolarizing neuromuscular blocking agents can be quite variable, prolonged and attenuated responses have both been described.

Lung aspiration due to vocal cord paresis has been described.

If associated pulmonary diseases present: postoperative ventilatory assistance (i.e. BiPAP or CPAP) should be considered. This includes patients under spinal anaesthesia.

Postoperative care

Care should be taken regarding possible disautonomy and lower urinary tract dysfunction (male and female).

See before for ventilatory support.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

Respiratory insufficiency can develop after surgery. The cause may be multifactorial. Patients whose respiratory system is affected (thoracic muscles and diaphragm) can be at risk of this complication, and this should be taken into account to minimize other factors (drugs, type of surgery, surgical approaches).

Ambulatory anaesthesia

In this setting, avoiding neuromuscular blocking agents might be recommended.

Obstetrical anaesthesia

In a study (Medical Birth Registry of Norway, n=108), women with CMT had a higher occurrence of presentation anomalies and bleeding post partum; the rate of operative delivery was twice that of the reference group), and forceps was used three times as often in the CMT group. The majority of CMT caesarean sections were emergency sections.

Epidural or combined spinal-epidural anaesthesia for labour and caesarean delivery can be chosen. Most published cases showed no symptoms or functional status worsening.

Spinal anaesthesia has been used for caesarean section (both scheduled and emergency), as has been epidural anaesthesia.

Literature and internet links

Anaesthesia related:

1. Barbary JB, Remérand F, Brillhault J, Laffon M, Fusciardi J. Ultrasound-guided nerve blocks in the Charcot–Marie–Tooth disease and Friedreich’s ataxia. *Br J Anaesth*.2012;108(6):1042-3. DOI:10.1093/bja/aes160
2. Skaribas IM, Washburn SN. Successful treatment of charcot-marie-tooth chronic pain with spinal cord stimulation: a case study. *Neuromodulation*. 2010; 13: 224-8. DOI 10.1111/j.1525-1403.2009.00272.x
3. Errando CL. Anestesia en el paciente con enfermedades neuromusculares para cirugía torácica [Anesthesia in patients with neuromuscular diseases for thoracic surgery]. In: Granell Gil M, editor. *Actualización sobre Anestesiología y Reanimación en Cirugía Torácica [Update on Anesthesia and Critical Care in Thoracic Surgery]*, 4th ed. Madrid: Ergón; 2012. pp. 3-7
4. Pasternak JJ, Lanier WL. Diseases of the autonomic and peripheral nervous systems. In: Stoelting R, Dierdorf S, editors. *Stoelting’s anesthesia, coexisting disease*. Philadelphia, PA: Elsevier Saunders; 2012. pp. 264-273
5. Gálvez-Cañellas JL, Errando CL, Martínez-Torrente F, Mayor F, Zasadowski M, Villanueva Y, Soria-Bretones C. Anaesthesia and orphan disease: difficult monitoring of neuromuscular blockade in a patient with severe Charcot-Marie-Tooth disease type I. *Eur J Anaesthesiol* 2013; 30:770-80. DOI:10.1097/EJA.0b013e3283623dea
6. Aceto P. Cisatracurium-induced neuromuscular block during total intravenous anaesthesia in a patient with Charcot-Marie-Tooth disease. *Eur J Anaesthesiol* 2010; 27: 670-72. DOI 10.1097/EJA.0b013e3283357060
7. Brock M, Guinn C, Jones M. Anesthetic management of an obstetric patient with Charcot-Marie-Tooth disease: a case study. *AANA J*. 2009; 77: 335-7
8. Bui AH, Marco AP. Peripheral nerve blockade in a patient with Charcot-Marie-Tooth disease. *Can J Anesth* 2008; 55: 718-9. DOI 10.1007/BF03017751
9. Dhir S, Balasubramanian S, Ross D. Ultrasound-guided peripheral regional blockade in patients with Charcot-Marie-Tooth disease: a review of three cases. *Can J Anesth* 2008; 55: 515-20. DOI 10.1007/BF03016671
10. Fernandez Perez AB, Quesada Garcia C, Rodriguez Gonzalez O, Besada Estevez JC. [Obstetric epidural analgesia, a safe choice in a patient with Charcot-Marie-Tooth disease]. *Rev Esp Anesthesiol Reanim* 2011; 58: 255-6
11. Freire Vila E, Criado Alonso MJ, Barjacoba Perez L, Chamadoira B, Taboada Ben MR. [General anesthesia with laryngeal mask and remifentanil for remodelling and corrective osteosynthesis of neuropathic foot in a case of type I Charcot-Marie-Tooth disease]. *Rev Esp Anesthesiol Reanim* 2000; 47: 178-9
12. Garcia-Ferreira J, Hernandez-Palazon J. Response to cisatracurium in patient with Charcot-Marie-Tooth disease. *Eur J Anaesthesiol* 2005; 22: 160-1
13. Greenwood JJ, Scott WE. Charcot-Marie-Tooth disease: peripartum management of two contrasting clinical cases. *Int J Obstet Anesth* 2007; 16: 149-54. DOI 10.1016/j.ijoa.2006.10.005
14. Hashimoto T, Morita M, Hamaguchi S, Kitajima T. [Anesthetic management for pancreaticoduodenectomy in a patient with Charcot-Marie-Tooth disease and liver cirrhosis]. *Masui* 2009; 58: 1313-5
15. Isbister GK, Burns J, Prior F, Ouvrier RA. Safety of nitrous oxide administration in patients with Charcot-Marie-Tooth disease. *J Neurol Sci* 2008; 268: 160-2. DOI 10.1016/j.jns.2007.12.004
16. Kapur S, Kumar S, Eagland K. Anesthetic management of a parturient with neurofibromatosis 1 and Charcot-Marie-Tooth disease. *J Clin Anesth* 2007; 19: 405-6. DOI 10.1016/j.jclinane.2007.03.001
17. Kotani N, Hirota K, Anzawa N, Takamura K, Sakai T, Matsuki A. Motor and sensory disability has a strong relationship to induction dose of thiopental in patients with the hypertropic variety of Charcot-Marie-Tooth syndrome. *Anesth Analg* 1996; 82: 182-6
18. Kuczkowski KM, Fernandez CL, Drobniak L, Chandra S. Anesthesia for cesarean section in a parturient with Charcot-Marie-Tooth disease: unresolved controversies. *Arch Gynecol Obstet* 2010; 282: 347-8. DOI 10.1007/s00404-010-1417-1

19. Niiyama Y, Kanaya N, Namiki A. [Anesthetic management for laparoscopic surgery in a patient with Charcot-Marie-Tooth disease]. *Masui* 2003; 52: 524-6
20. Pasha TM, Knowles A. Anaesthetic management of a patient with Charcot-Marie-Tooth disease for staged diaphragmatic plication. *Br J Anaesth* 2013; 110: 1061-3. DOI 10.1093/bja/aet142
21. Pelaez Romero R, Alonso Chico A, Villamandos BQ, Garcia de Lucas E. [Subarachnoid anesthesia for an emergency cesarean section in Charcot-Marie-Tooth disease]. *Rev Esp Anesthesiol Reanim* 2003; 50: 106-7
22. Schmitt HJ, Munster T. Mivacurium-induced neuromuscular block in adult patients suffering from Charcot-Marie-Tooth disease. *Can J Anesth* 2006; 53: 984-8. DOI 10.1007/BF03022526
23. Shankar V, Markan S, Gandhi SD, Iqbal Z, Novalija J, Nicolosi AC, Pagel PS. Perioperative implications of charcot-marie-tooth disease during coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2007; 21: 567-9. DOI 10.1053/j.jvca.2006.08.014
24. Soto Mesa D, Bermejo Alvarez MA, Rubio Marauri P, Garcia Menendez MJ. [Anesthetic considerations in Charcot-Marie-Tooth disease]. *Rev Esp Anesthesiol Reanim* 2011; 58: 256-8
25. Sugai K, Sugai Y. [Epidural anesthesia for a patient with Charcot-Marie-Tooth disease, bronchial asthma and hypothyroidism]. *Masui* 1989; 38: 688-91
26. Sugino S, Yamazaki Y, Nawa Y, Sato K, Sonoda H, Namiki A. [Anesthetic management for a patient with Charcot-Marie-Tooth disease using propofol and nitrous oxide]. *Masui* 2002; 51: 1016-9
27. Tanaka S, Tsuchida H, Namiki A. [Epidural anesthesia for a patient with Charcot-Marie-Tooth disease, mitral valve prolapse syndrome and IInd degree AV block]. *Masui* 1994; 43: 931-3
28. Valles Torres J, Martinez-Ubieto J, Colas Rodriguez A, Abengoechea Beisty JM. [General anesthesia with a laryngeal mask in a patient with long-standing Charcot-Marie-Tooth disease]. *Rev Esp Anesthesiol Reanim* 2009; 56: 194-5.

General:

29. (<http://omim.org/entry/606482>, <http://omim.org/entry/118220>)
30. (<http://emedicine.medscape.com/article/1173484-overview#aw2aab6b3>)
31. <http://neuromuscular.wustl.edu/time/hmsn.html>
32. Berciano J, Sevilla T, Casasnovas C, Sivera R, Vílchez JJ, Infante J, Ramón C, Pelayo-Negro AL, Illa I, Programme 3 (Neuromuscular Diseases), and Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III. Guidelines for molecular diagnosis of Charcot-Marie-Tooth disease. *Neurologia*. 2012; 27:169-78
33. Verhamme C, van Schaik IN, Koelman JHTM, de Haan RJ, de Visser M. The natural history of Charcot-Marie-Tooth type 1A in adults: a 5-year follow-up study. *Brain* 2009; 132; 3252-62. doi:10.1093/brain/awp251
34. Kang JH, Kim HJ, Lee ER. Electrophysiological evaluation of chronic inflammatory demyelinating polyneuropathy and Charcot-Marie-Tooth Type 1: Dispersion and correlation analysis. *J. Phys. Ther. Sci.* 2013;25: 1265-8. DOI 10.1589/jpts.25.1265
35. Aboussouan LS, Lewis RA, Shy ME. Disorders of pulmonary function, sleep, and the upper airway in Charcot-Marie-Tooth disease. *Lung* 2007; 185: 1-7. DOI 10.1007/s00408-006-0053-9
36. Colomban C, Micallef J, Lefebvre MN, Dubourg O, Gonnaud PM, Stojkovic T, Jouve E, Blin O, Pouget J, Attarian S. Clinical spectrum and gender differences in a large cohort of Charcot-Marie-Tooth type 1A patients. *J Neurol Sci* 2013; DOI 10.1016/j.jns.2013.10.029
37. Dziewas R, Waldmann N, Bontert M, Hor H, Muller T, Okegwo A, Ringelstein EB, Young P. Increased prevalence of obstructive sleep apnoea in patients with Charcot-Marie-Tooth disease: a case control study. *J Neurol Neurosurg Psychiatr* 2008; 79: 829-31. DOI 10.1136/jnnp.2007.137679
38. Eklund E, Svensson E, Hager-Ross C. Hand function and disability of the arm, shoulder and hand in Charcot-Marie-Tooth disease. *Disabil Rehab* 2009; 31: 1955-62. DOI 10.1080/09638280902874170

39. Hoff JM, Gilhus NE, Daltveit AK. Pregnancies and deliveries in patients with Charcot-Marie-Tooth disease. *Neurology* 2005; 64: 459-62. DOI 10.1212/01.WNL.0000150933.65709.96
40. Krhut J, Mazanec R, Seeman P, Mann-Gow T, Zvara P. Lower urinary tract functions in a series of Charcot-Marie-Tooth neuropathy patients. *Acta Neurol Scand* 2013. DOI 10.1111/ane.12176
41. Sivera R, Sevilla T, Vilchez JJ, Martinez-Rubio D, Chumillas MJ, Vazquez JF, Muelas N, Bataller L, Millan JM, Palau F, Espinos C. Charcot-Marie-Tooth disease: Genetic and clinical spectrum in a Spanish clinical series. *Neurology* 2013; 81: 1617-25. DOI 10.1212/WNL.0b013e3182a9f56a
42. Steiner I, Gotkine M, Steiner-Birmanns B, Biran I, Silverstein S, Abeliovich D, Argov Z, Wirguin I. Increased severity over generations of Charcot-Marie-Tooth disease type 1A. *J Neurol* 2008; 255: 813-9. DOI 10.1007/s00415-008-0693-1
43. Ursino G, Alberti MA, Grandis M, Reni L, Pareyson D, Bellone E, Gemelli C, Sabatelli M, Pisciotta C, Luigetti M, Santoro L, Massollo L, Schenone A. Influence of comorbidities on the phenotype of patients affected by Charcot-Marie-Tooth neuropathy type 1A. *Neuromusc Disord* 2013; 23: 902-6. DOI 10.1016/j.nmd.2013.07.002
44. Kang JH, Kim HJ, Lee ER. Electrophysiological Evaluation of Chronic Inflammatory Demyelinating Polyneuropathy and Charcot-Marie-Tooth Type 1: Dispersion and Correlation Analysis. *J Phys Ther Sci* 2013; 25: 1265-68. DOI 10.1589/jpts.25.1265
45. Pons Odena M, Piqueras Marimbaldo I, Colomer Oferil J, Segura Matute S, Palomeque Rico A. [Respiratory disease and diaphragm paralysis in Charcot-Marie-Tooth disease]. *An Pediatr (Barc)* 2010; 72: 267-71. DOI 10.1016/j.anpedi.2009.11.017
46. Taniguchi JB, Elui VM, Osorio FL, Hallak JE, Crippa JA, Machado-de-Sousa JP, Kebbe LM, Lourenco CM, Scarel-Caminaga RM, Marques W, Jr. Quality of life in patients with Charcot-Marie-Tooth disease type 1A. *Arq Neuro-psiquiatr* 2013; 71: 392-6. DOI 10.1590/0004-282X20130045
47. Vallat JM, Mathis S, Funalot B. The various Charcot-Marie-Tooth diseases. *Curr Opinion Neurol* 2013; 26: 473-80. DOI 10.1097/WCO.0b013e328364c04b
48. Fiacchino F, Grandi L, Ciano C, Sghirlanzoni A. Unrecognized Charcot-Marie-Tooth disease: diagnostic difficulties in the assessment of recovery from paralysis. *Anesth Analg*. 1995 Jul;81(1):199-201.

Last date of modification: March 2014

These guidelines have been prepared by:

Author

Carlos Errando, Anaesthesiologist, Consorcio Hospital General Universitario de Valencia, Spain
errando013@gmail.com

Peer revision 1

Tina Pasha, Anaesthesiologist, Mayo Clinic and Foundation, Rochester MN, USA
tmpasha1@gmail.com

Peer revision 2

Davide Pareyson, Functional Department on Rare Neurological Diseases, Clinic of Central and Peripheral Degenerative Neuropathies Unit, C. Besta Neurological Institute, Milan, Italy
davide.pareyson@istituto-besta.it
