

Anaesthesia and Charcot-Marie-Tooth Disease

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SYNOPSIS OF PATIENTS

Case 1

A 14-year old male weighing 54.9kg, height 178cm, presented for foot reconstruction. He had bilateral cavovarus deformities that were painful. He was otherwise healthy. He first presented as a 7-year old with some difficulty running, and a tendency to fall. He had walked on his toes since he started walking at 14 months. He complained of occasional cramps and pain in both legs that improved with stretching exercises. He did physical exercise at school but could not climb ropes. His handwriting was untidy and awkward. On examination he had wasting of both calves, wasting of the thenar eminence and the interossei of both hands and feet. Deep tendon reflexes were absent. He had slight sensory changes in his hands and feet (diminished temperature). He had facial symmetry, normal eyelid closure and no evidence of other cranial nerve involvement or autonomic disturbance (normal sweating, normal tears and thermal regulation). A recent hip radiograph revealed mild hip dysplasia on the right but this was asymptomatic. He was adopted but was still in contact with his biological mother who had a strong family history of peripheral motor and sensory neuropathy that had been diagnosed as Charcot-Marie-Tooth (CMT) disease type 1. He had undergone genetic testing which showed a duplication of the peripheral myelin protein (PMP 22) gene consistent with CMT Type 1A. The previous anaesthetic for right foot surgery was reported to be uneventful. On this occasion he was given a propofol induction, maintained on sevoflurane in 35% oxygen, and a left popliteal nerve block was placed using a nerve stimulator and 8ml 0.375% bupivacaine. A saphenous nerve block was also performed using 5ml 0.375% bupivacaine. Anaesthesia was uneventful and the patient was comfortable postoperatively.

Case 2

A 19-year old boy weighing 64kg, height 179cm, presented for removal of an osteophyte of his left hallux-interphalangeal joint, and tendon transfer on his painful left foot. He had had numerous reconstructive operations to both feet. He had a strong family history of CMT on his mother's side although she herself did not have evidence of CMT. His symptoms had started some three years earlier when he complained of peroneal spasms. He had sensory

loss in his lower limbs that was associated with muscle wasting in both calves. He had no evidence of hip dysplasia or respiratory difficulty. A previous DNA test had confirmed CMT Type 1A. He was experiencing pain on the anterior aspect of the ankle that was worse after 20 minutes of weight bearing. His foot sometimes got stuck in eversion, and he was able to correct it himself. He had recently suffered an infected ingrown toenail and had a callous under his 5th metatarsal. Anaesthesia consisted of a sevoflurane induction and maintenance was with sevoflurane in oxygen-enriched air (FiO₂ 0.35). A continuous peripheral nerve catheter (Arrow®) was placed with the aid of a nerve stimulator. An initial dose of 8ml 0.5% bupivacaine was used followed by a continuous infusion of 3ml.hr 0.25% bupivacaine. Anaesthesia was uneventful and the patient was comfortable postoperatively. The catheter was removed after 48 hours.

Introduction

Charcot-Marie-Tooth disease is named after three neurologists. Charcot and Marie first described this unusual slowly progressive hereditary motor and sensory neuropathy in France in 1886¹. The muscle atrophy was characterized by weakness and wasting of the feet and leg muscles, followed by involvement of the hands. Tooth, in England, also described this peroneal type of progressive muscular atrophy with essentially the same clinical features in the same year. Tooth correctly postulated correctly that the disease was due to a neuropathy and not a myelopathy as was proposed by Charcot and Marie.

CMT is the most common form of peripheral neuropathy in children, with symptoms usually evident in the mid teens. Earlier onset is uncommon but may be at any time between the first and third decade. CMT is slowly progressive, with periods of remission and exacerbations. The incidence in the USA is in the order of 1:2500² –3300,³ but CMT is found worldwide in people of all race and ethnic groups. The worldwide incidence is estimated as 1:10000⁴.

CMT disease is also referred to as peroneal muscular atrophy or hereditary hypertrophic neuropathy. CMT has a heterogeneous spectrum of inheritance and clinical presentation. Some family members may have such a mild form of the disease that they are unaware of the problem until they are evaluated because another member of the family may have the disease. The challenge for the clinician is to differentiate CMT from other neurological causes of weakness and sensory loss in the "glove and stocking" distribution. The exact nature of the disorder can be distinguished from other

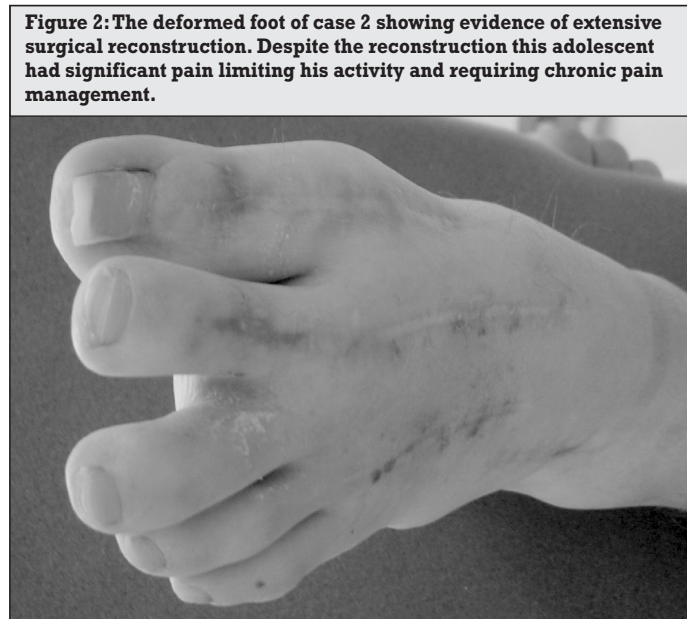
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non-genetic causes of neuropathy by the age of onset, family history and inheritance pattern, clinical examination, nerve conduction and genetic studies.

Clinical Features

CMT is a group of conditions that affects the lower limbs resulting in weakness and muscle wasting below the knees and in the feet, causing significant foot deformities (Fig 1). Typically CMT is a slowly progressive hereditary motor and sensory neuropathy with muscle wasting and early loss of deep tendon reflexes. The hands may be affected but this usually occurs later in the disease process.



The hallmark is peroneal muscle atrophy. The lower leg is classically described as having an "inverted champagne bottle" or "stork leg" deformity. As a result of the weak dorsiflexors of the feet, patients frequently trip over objects and have a tendency to sprain their ankles. The foot drops with each step and forces the patient to lift their knee ("equine gait"). Patients may complain of leg cramps after long walks. The foot deformities usually precede the muscle atrophy by some years.

Many have a mild 'sensory' component resulting in a loss of sensation (heat, cold and pain) in the glove and stocking distribution on the hands and feet. Typically these patients have difficulty using zippers and buttons and other tasks that require fine finger movement. Handwriting is often clumsy and untidy. The abnormally thick nerve may be palpable in the arms of some patients.

Autonomic dysfunction is impaired in some forms of the disease. This manifests as impaired temperature regulation and absence of

sweating. The symptoms may be exacerbated in pregnancy, probably by hormonally induced neuronal oedema. The symptoms may return to baseline after delivery while in others new symptoms may appear.

Hip dysplasia is an under recognised manifestation of CMT.⁶ (Early asymptomatic hip dysplasia was noted on X-ray in our first patient.) Proximal weakness is rare but respiratory insufficiency has been described in the latter stages of severe disease. This is postulated as a disturbance in the diaphragmatic function⁷.

Diagnostic tests

The types of CMT may be differentiated by medical and family history and examination, nerve biopsy, nerve conduction velocity studies (NCV), electromyogram (EMG) and genetic studies.³⁻⁵ In Type 1 CMT the NCV is slow <38m/sec i.e. similar to unmyelinated nerves. In Type 2 NCV is within normal limits but with low amplitude. The EMG has a characteristic pattern as a consequence of abnormal nerves that innervate the muscle. Electrophysiologic abnormalities may precede clinical symptoms by 2 years but the severity of the disease does not correlate with the degree of conduction slowing. Biopsy of the sural nerve may be helpful. Typically the nerve in type 1 has a decreased number of myelinated fibres and the hypertrophic changes resemble an "onion bulb" histologically.

Genetic studies

Classification is based on inheritance patterns and genetic studies.^{2,4} CMT is caused by mutations in the encoding genes for peripheral myelin protein, predominantly PMP22 or the MPZ genes, which are necessary for the normal function of peripheral nerves.²⁻⁴ Absence of these genes leads to demyelination. Broadly speaking about 60-80% have Type 1 CMT which affects the myelin sheath (PMP22 gene) and 5-15% have Type 2 which affects the axons (MPZ gene). Inheritance is autosomal dominant. Type 1 can be further subdivided by genetic studies; Type 1A for example has the defect on chromosome 17, while in Type 1B the defect is on chromosome 1.^{3,4} An extensive description of the genetic classification is beyond the scope of this article but a simplified clinical classification is shown in Table 1.

Table 1: Classification of hereditary sensory motor neuropathies or CMT disease		
<i>Type</i>	<i>Pathology</i>	<i>Clinical features</i>
CMT 1	Demyelination	Autosomal dominant, commonest Weakness, atrophy, sensory loss in legs Delayed nerve conduction Multiple genetic subtypes
CMT 2	Neuronal disorder	Autonomic dominant Decreased amplitude of CMAP Distal weakness
CMT 3	Severe demyelination	Dejerine-Sottas Rare Infantile onset Delayed milestones -motor skills Severe
CMT 4	Demyelination	Autosomal recessive. Rare Several types, Leg weakness Onset childhood or adolescence
CMT X	Defect in communication Schwann cells and axons	X-linked dominant Male>female Moderate to severe Onset late childhood or adolescence

An autosomal recessive form, type 4, is rare and genetically heterogenous. A rarer more severe form, Dejerine-Sottas disease is sometimes referred to as Type 3 disease. There is a rarer X-linked dominant and recessive form of the disease due to mutations in the gene encoding the gap junction protein, connexin 32. Some 30 different genetic subtypes have been identified by DNA studies.²⁻⁴

Outcome

There is no cure for CMT but physiotherapy, occupational therapy, orthopaedic devices or surgery can help affected individuals cope with the disabling symptoms of the disease. The degree of disability is unpredictable between and within families; even identical twins may be differently affected. Some may have very mild forms and never seek medical attention while others are severely handicapped. Life expectancy is normal. Paradoxically, despite the peripheral neuropathy, some patients may require chronic pain management for severe pain.

Anaesthetic considerations

Some concern has been expressed about the use of muscle relaxants and regional anaesthesia in these patients.

Both depolarising and non-depolarising muscle relaxants have been used with few problems. Suxamethonium has not caused problems in stable patients. Similarly there is little evidence that these patients are sensitive to non-depolarising muscle relaxants,⁸⁻¹⁰ although Brian et al expressed concern in one case report in a patient with advanced disease¹¹. In a recent study on five children with CMT, aged 7-12 years, the clinical duration of mivacurium-induced neuromuscular block was similar to that in normal children.⁸

The use of regional anaesthesia in patients with pre-existing neurological disorders is controversial. Anaesthesiologists fear possible exacerbation of the basic neurological disease. Controlled studies in affected individuals evaluating the potential risks in different neurological disorders are lacking. Epidural anaesthesia and spinal block have been used for orthopaedic procedures¹² and caesarean section^{11,13,14} without exacerbation of the disease or other problems. Neither of our patients reported any problems following a single shot popliteal block or a continuous popliteal nerve block using a 23G catheter for 48 hours.

Sensitivity to thiopentone was reported in 20 patients with CMT compared to a control group.¹⁵ This has not been reported with other induction agents. Total intravenous anaesthesia (TIVA) has been used (propofol / fentanyl and alfentanil)^{9,16}. No problems or undue sensitivity were reported.

As this is a peripheral nerve disorder an association with malignant hyperthermia seems unlikely. In a retrospective review of 86 CMT cases, Antognini reported the use of suxamethonium in 41 patients and triggering agents (halothane) in 77 patients without problem.¹⁷

Other considerations include positioning during surgery since nerve compression could worsen the underlying neuropathy. Nitrous oxide, by inhibiting the cobalamin dependent enzyme, methionine synthase, may be considered neurotoxic in prolonged cases. No case of neurotoxicity has been reported. Very rarely patients may have laryngeal dysfunction and are prone to aspiration. Laryngeal dysfunction may be recognised by voice changes.

Musculoskeletal pain can be treated with paracetamol or non-steroidal anti-inflammatory agents (NSAIDS). Neuropathic pain may respond to tricyclic antidepressants, carbamazepine or gabapentin.

Conclusion

Charcot-Marie-Tooth disease is a disease that is often under diagnosed because the disability may be slight. The onset and severity of the disease is variable. Concerns with regard to regional anaesthesia, muscle relaxants and malignant hyperthermia seem unfounded. Despite the sensory loss, pain may significantly limit normal activity.

References

1. Charcot J-M, Marie P. Sur une forme particulière d'atrophie musculaire progressive souvent familiale debutant par les pieds et les jambes et atteignant plus tard les mains. *Rev Med* 1886, 6: 97-138.
2. Skre H. Genetic and clinical aspects Charcot-Marie-Tooth disease. *Clin Genetics* 1974, 6:98-118.
3. Bird T. Charcot-Marie-Tooth hereditary neuropathy overview. www.genetests.org 2006.
4. Gondim F de AA, de Oliveira GR, Thomas FP. Hereditary Neuropathies of the Charcot-Marie-Tooth Disease type. www.emedicine.com
5. Murakami T, Garcia C, Reiter LT, Lupski JR. Charcot-Marie-Tooth Disease and related inherited neuropathies. *Medicine* 1996, 75:233-250.
6. Walker JL, Nelson KR, Heavilon JA et al Hip abnormalities in children with Charcot-Marie-Tooth disease. *J Pediatr Orthop* 1994, 14: 54-9.
7. Hardie R, Hardng AE, Hirsch NP et al. Diaphragmatic weakness in hereditary motor and sensory neuropathy. *J Neurology Neurosurgery and Psychiatry* 1990, 53: 348-50
8. Schmitt HJ, Wick S, Munster T. Onset and duration of mivacurium-induced neuromuscular blockade in children with Charcot-Marie-Tooth disease. A case series with five children. *Paediatr Anaesth.* 2006; 16: 182-7.
9. Naguib M, Samarkandi AH. Response to atracurium and mivacurium in a patient with Charcot-Marie-Tooth disease. *Can J Anaesth.* 1998, 45(1):56-9.
10. Greenberg RS, Parker SD. Anesthetic management for the child with Charcot-Marie-Tooth disease *Anesth Analg.* 1992; 74:305-7.
11. Brian JE Jr, Boyles GD, Quirk JG Jr, Clark RB. Anesthetic management for cesarean section of a patient with Charcot-Marie-Tooth disease. *Anesthesiology*, 1987; 66:410-2.
12. Schmitt HJ, Muenster T, Schmidt J. Central neural blockade in Charcot-Marie-Tooth disease. *Can J Anaesth.* 2004; 51:1049-50.
13. Reah G, Lyons GR, Wilson RC. Anaesthesia for caesarean section in a patient with Charcot-Marie-Tooth disease. *Anaesthesia.* 1998, 53(6):586-8.
14. Scull T, Weeks S. Epidural analgesia for labour in a patient with Charcot-Marie-Tooth disease. *Can J Anaesth* 1996; 43: 1150-2
15. 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.
16. Gratarola A, Mameli MC, Pelosi G. Total intravenous anaesthesia in Charcot-Marie-Tooth disease. Case report. *Minerva Anestesiol.* 1998; 64:357-60.
17. Antognini JF. Anaesthesia for Charcot-Marie-Tooth disease: a review of 86 cases. *Can J Anaesth* 1992; 39: 398-400.