Review

Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease

Eppie M Yiu ,[1,2,3] Paula Bray,[4,5] Jonathan Baets,[6,7,8] Steven K Baker,[9] Nina Barisic,[10] Katy de Valle,[1,2] Timothy Estilow,[11,12] Michelle A Farrar,[13,14] Richard S Finkel,[15] Jana Haberlová,[16] Rachel A Kennedy,[1,2,3] Isabella Moroni,[17] Garth A Nicholson,[18,19] Sindhu Ramchandren,[20] Mary M Reilly,[21] Kristy Rose,[22] Michael E Shy,[23] Carly E Siskind,[24] Sabrina W Yum,[25,26] Manoj P Menezes,[27,28] Monique M Ryan,[1,2,3] Joshua Burns[4,5]

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For numbered affiliations see end of article.

Correspondence to
Dr Eppie M Yiu, Neurology department, The Royal Children's Hospital Melbourne, Parkville, Victoria, Australia; eppie.yiu@rch.org.au

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ABSTRACT

Background and objectives Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy and often presents during childhood. Guidelines for the optimal management of common problems experienced by individuals with CMT do not exist, for either children or adults. We formed the Paediatric CMT Best Practice Guidelines Consortium to develop evidence and consensus-based recommendations for the clinical management of children and adolescents with CMT, with the primary objective of promoting optimal, standardised care globally.

Methods Development of this clinical practice guideline involved a series of systematic reviews covering 10 clinical questions, modified Delphi methodology involving an international panel of clinicians to generate consensus where evidence did not exist, and application of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to evaluate the body of literature and formulate recommendations.

Results The final guideline includes three evidence-based and 31 consensus-based recommendations. They encompass the management of muscle weakness, balance and mobility impairment, sensory symptoms, muscle cramps, impaired upper limb function, respiratory impairment, maintenance of joint range of motion and non-surgical management of joint deformity. Consensus was not achieved in some management areas, reflecting differences in practice between clinicians and healthcare settings, and highlighting the need for further research.

Conclusions This clinical practice guideline provides practical and implementable guidance on the management of common clinical problems experienced by children with CMT and advocates for improved access to multidisciplinary care. Successful dissemination and implementation of these recommendations will be critical in ensuring their application across multiple healthcare settings.

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) refers to a group of genetically heterogeneous neuropathies. It is the most common chronic peripheral neuropathy of childhood, affecting between 1 in 1214 and 3344 individuals.[1 2] Symptoms often begin in childhood and include limb weakness, mobility and balance impairment, muscle cramps and foot deformity. These impact daily function and quality of life.[3] Management of children with CMT involves accurate diagnosis, symptomatic care, rehabilitative approaches and surveillance for anticipated complications. There are no proven disease modifying therapies in children, and no clinical practice guidelines for the management of children or adults with CMT.

The lack of a clinical practice guideline for the treatment of common problems experienced by children with CMT results in variable practices between centres and poor clinician confidence in providing care to this population. We recognised a critical need for practical and implementable guidance on the management of paediatric CMT—not only for clinical care but also for clinical trial readiness. Acknowledging that recommendations in this rare disease would be largely consensus rather than evidence-based, we formed the Paediatric CMT Best Practice Guidelines Consortium to develop recommendations for the clinical management of paediatric CMT, with the primary objective of promoting optimal, standardised care.

METHODS

This clinical practice guideline was developed in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to evidence grading and guideline development.[4] Details of the process are provided in the online supplemental data (Section 1).

Formation of the consortium

The paediatric CMT Best Practice Guidelines consortium was formed in 2015 with a lead (EMY), deputy lead (JB), scientific advisory committee (SAC) and oversight committee. The SAC comprised 14 international members (physicians and allied health clinicians) and the oversight committee eight international members, including 2 consumer representatives. A methods expert (PB) was consulted through all stages of development. Details of the governance process, including statements of potential conflicts of interest, are provided in online supplemental data.

Box 1 Final clinical management questions

- In children with Charcot-Marie-Tooth disease (CMT), what treatments should be recommended for weakness?
- In children with CMT, what treatments should be recommended for maintaining and improving joint range of motion?
- In children with CMT, what treatments should be recommended for impaired mobility?
- In children with CMT, what treatments should be recommended for balance impairment?
- In children with CMT, what treatments should be recommended for muscle cramps?
- In children with CMT, what non-surgical treatments should be recommended for joint (foot, hand, hip, knee) or spine deformity?
- In children with CMT, what treatments should be recommended for sensory symptoms/impairment?
- In children with CMT, what treatments should be recommended for impaired upper limb function?
- In children with CMT, what treatments should be recommended for fatigue?
- In children with CMT, what treatments should be recommended for respiratory deficits?

Objective and scope

The primary objective was to provide evidence-based guidance for the management of children (up to 18 years of age) with CMT, and where appropriate evidence does not exist, obtain consensus for management.

A number of clinical questions were developed, with the focus being the treatment of common symptoms experienced by children with CMT. It was decided *a priori* that the diagnosis of CMT and measurement tools used to assess disease severity and progression would not be considered in this guideline. Further refinement of the scope was undertaken prior to the literature review. As part of this process, treatment of joint and spine deformity was limited to non-surgical approaches due to the committee becoming aware of a separate consensus effort for the surgical management of CMT.[5] The final 10 clinical questions are shown in box 1. Details of the original scope and refinement to its final form are provided in the online supplemental data.

Systematic reviews

A series of 10 systematic literature reviews were performed. The following databases were searched from the date of inception to 27 November 2017: Medline (Ovid), Embase (Ovid), Cochrane Library, Informit and PubMed. The search was updated on 31 May 2021. New citations identified were classified as emerging evidence and not formally graded. The search included all peer-reviewed publications in the English language and was limited to the paediatric population (up to 18 years of age). For publications that combined adult and paediatric participants, only studies in which the outcomes for children could be separately identified were included. The quality of the evidence was assessed as high, moderate, low or very low according to GRADE criteria[4] using the GRADEPro tool (GRADEpro GDT: GRADEpro Guideline Development Tool (software). McMaster University, 2015 (developed by Evidence Prime). Available from https://www.gradepro.org). Details of the systematic review including search strategies, study selection, data extraction and evidence appraisal are provided in the online supplemental data.

Modified Delphi survey

A modified Delphi survey was used to develop clinical consensus statements in areas where evidence-based recommendations could not be made. Ethics approval for the modified Delphi survey was obtained from the Royal Children's Hospital Research Ethics and Governance department (HREC approval: 36308B). Participant information was provided at the start of the Delphi survey and completion of the survey implied consent. A detailed description of the Delphi process is provided in the online supplemental data.

The 33 member Delphi panel was designed to have international, medical and allied health representation and included paediatric and adult neurologists, physical medicine and rehabilitation physicians and paediatric physiotherapists and occupational therapists. The guidelines consortium lead (EMY) and deputy lead (JB) abstained from participating in the Delphi survey. Clinical consensus statements and qualitative questions were developed by small working groups within the SAC based on areas of expertise. A summary of available evidence (where applicable) was presented as part of the Delphi survey.

Web-based software (REDCap) was used to administer the Delphi survey to panel members. All survey responses were deidentified. Up to three Delphi rounds were allowed *a priori*, with the survey completed within two rounds. The first round included 98 clinical consensus statements requiring agreement or disagreement on a 9-point Likert scale (where 1=strongly disagree, 3=disagree, 5=neutral, 7=agree and 9=strongly agree) as well as 16 qualitative and/or multiple choice survey questions. Criteria for consensus, near consensus and no consensus were established *a priori* as follows[6]: (i) consensus: mean score ≥7.00 and no more than one outlier (where an outlier is defined as >2 Likert points away from the mean), (2) near consensus: mean score ≥6.50 and no more than two outliers and (3) no consensus: statements that did not meet the criteria of consensus or near consensus.

The second round of the Delphi survey included 38 statements (redrafted near consensus statements and additional statements developed from qualitative round 1 questions). A statement about research priorities was also presented. After analysis of the second round of the Delphi survey, seven near consensus statements/statements judged to contain important content that required minor rewording were reviewed by the SAC and passed as consensus, either in their original format or with minor revisions. Thus, a third Delphi round was not necessary.

Due to the broad scope of the recommendations and variable range of expertise of the Delphi panel, panel members were asked to only provide responses to questions that fell within their scope of practice. Therefore, not all questions were answered by all members of the panel. The minimum and maximum number of responses were 15 and 32 and 10 and 32 for round 1 and round 2 of the survey, respectively.

Formulation of recommendations

Evidence-based recommendations were developed for clinical questions for which evidence could be assessed. Recommendations were assessed as 'strong' or 'conditional' based on the GRADE evidence to decision-making framework.[7] The factors considered in this framework are detailed in the online supplemental data. Strong recommendations are worded as 'we recommend' and conditional recommendations as 'we suggest'. The formulation of consensus-based recommendations was as described in the Modified Delphi survey methodology.

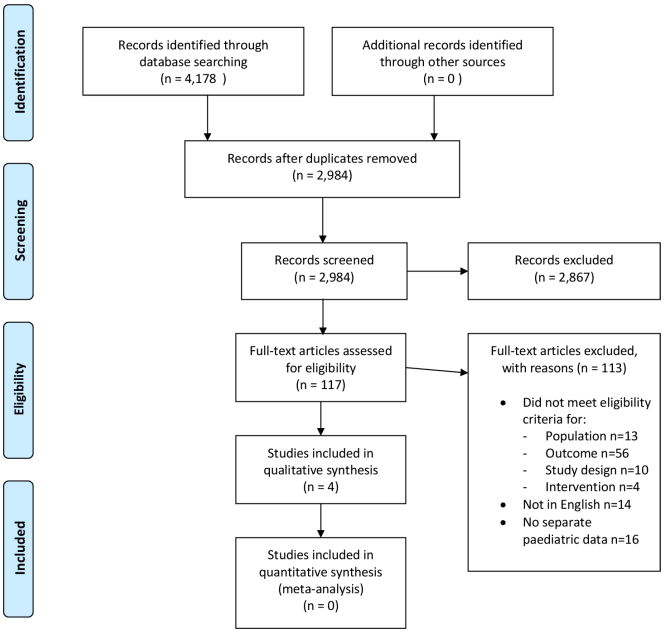

Figure 1 PRISMA flowchart showing study selection process.[27] PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Consultation of the draft recommendations

A consultation process was undertaken between May and September 2019. The draft recommendations were reviewed by the SAC and then the oversight committee. Feedback was then sought from four national and international consumer CMT organisations. The recommendations were revised after each consultation round. Details of the invited consumer organisations are provided in the online supplemental data.

Data availability

Data supporting the results of the systematic review and modified Delphi survey are available in the online supplemental data.

RESULTS

Systematic reviews

The study selection process is outlined in figure 1. A total of 4178 publications were retrieved from the literature search to answer the 10 clinical questions. Four publications met criteria and were appraised using the GRADE process.[8–11] A summary of the evidence grading is provided in table 1. Full GRADE evidence tables and a glossary of terms are provided in the online supplemental data (Section 2).

Evidence and consensus-based recommendations

Three evidence-based and 31 consensus-based recommendations were formulated and are presented in box 2. Evidence to recommendation tables as per GRADE methodology is shown in the online supplemental data (Section 2). Comments regarding the relevant recommendations for each clinical question are provided below.

1. In children with CMT, what treatments should be recommended for weakness?

Two randomised controlled trials informed evidence-based recommendations for the treatment of weakness.[8 10] A trial of high dose ascorbic acid in children with CMT1A showed no effect on muscle strength measures compared with placebo.[8] A trial of targeted progressive resistance exercise over 6 months in a single muscle group in children demonstrated attenuation of long-term progression of weakness of foot dorsiflexion. This study included both concentric and eccentric resistance training.[10] There was no evidence of overwork weakness or harmful effects of resistance training on muscle morphology assessed by MRI. The beneficial effect of resistance training was seen at 24 months but not at 6 or 12 months. There was no change in function, however, only one muscle group (the ankle dorsiflexors) was exercised. While progressive resistance exercise of muscle groups other than the ankle dorsiflexors is in principle likely to be effective, an evidence-based recommendation cannot be made, and the ultimate impact of improved strength on function, mobility and balance are yet to be demonstrated. The Delphi panel, however, achieved consensus that strength training of proximal, and core muscles should be encouraged. Conversely, consensus was not obtained regarding the use of progressive resistance exercise of the distal muscles of the upper limb (ie, hands and wrist).

2. In children with CMT, what treatments should be recommended for maintaining and improving joint range of motion?

Given no studies for maintaining and improving joint range of motion met inclusion criteria, all recommendations are consensus based. Three studies of adults and children with CMT assessed the effectiveness of serial night casting or night splints but were excluded from the systematic reviews as the data for adults and children were combined.[12–14] A randomised trial of 30 children and young adults with CMT compared 4 weeks of serial night casting followed by 4 weeks of weight-bearing stretches to no intervention. Four weeks of serial casting increased ankle dorsiflexion range compared with no intervention; however, this difference was no longer evident at 8 weeks.[14] In contrast, two smaller randomised controlled trials of prefabricated night splints in adults and children with CMT showed no effect on ankle range.[12 13] The Delphi panel nevertheless agreed that serial casting is beneficial for improving ankle dorsiflexion range of motion in children with restricted range of motion, and that serial night casting is a useful alternative in children for whom serial casting cannot be performed. There was no consensus regarding the use of night splinting to maintain gains in joint range of motion after these interventions.

Despite the use of passive, self and moderate length sustained stretches by many clinicians, there was a lack of consensus on whether these stretches should be recommended in children with either acceptable or restricted range of motion at any joint.

3. In children with CMT, what treatments should be recommended for impaired mobility?

A single evidence-based recommendation against the use of ascorbic acid in children with CMT1A for mobility impairment arose from the systematic review. While the trial of targeted progressive resistance exercise in children with CMT showed no effect on kinematic gait measures, functional measures of mobility were not assessed and an evidence-based recommendation could not be made from this study. A number of factors contribute to impaired mobility in children with CMT. Therefore, some of the recommended interventions for mobility may result in other gains, such as improved balance or joint protection. The Delphi survey assessed all clinical indications for the use of orthotics. Apart from consensus on the use of ankle–foot orthoses for foot drop, trips and falls and ankle instability, and the use of foot orthoses for foot pain, there was no consensus on other uses for orthotics. This included the use of above or below knee orthoses for foot deformity in the absence of foot

Table 1 Summary of evidence table

Outcome	Specific outcome measure	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Narrative summary
Ascorbic acid compared with no intervention in children with CMT1A[8]					
Muscle strength	Ankle dorsiflexion strength Follow-up: 12 months	Mean 4.9 N lower (12.5 lower to 2.7 higher)	81 (1)	Moderate* ⊕⊕⊕◯	No benefit of ascorbic acid on strength, mobility, balance or upper limb function in children with CMT1A at 12 months compared with placebo. These findings are referable only to children with CMT1A.
	Ankle plantarflexion strength Follow-up: 12 months	Mean 16 N lower (35.5 lower to 3.6 higher)	81 (1)	Moderate* ⊕⊕⊕◯	
	Hand grip Follow-up: 12 months	Mean 8.6 N lower (20.4 lower to 3.2 higher)	81 (1)	Moderate* ⊕⊕⊕◯	
Mobility	6 min walk test Follow-up: 12 months	Mean 0.7 m lower (23.4 lower to 21.9 higher)	65 (1)	Low*† ⊕⊕◯◯	
Balance	Bruininks-Oseretsky Test of Motor Proficiency second edition Follow-up: 12 months	Mean 0.3 points lower (2.1 lower to 1.5 higher)	72 (1)	Low*† ⊕⊕◯◯	
Upper limb function	9-hole peg test Follow-up: 12 months	Mean 0.4 s lower (1.9 lower to 1.1 higher)	78 (1)	Moderate* ⊕⊕⊕◯	
Resistance training compared with sham resistance training of ankle dorsiflexors in children with CMT[10]					
Muscle strength	Ankle dorsiflexion strength Follow-up: 6 months	Mean 0 (0.37 lower to 0.42 higher)‡	60 (1)	Moderate§ ⊕⊕⊕◯	Improved ankle dorsiflexion strength at 24 months compared with sham training, after 6 months of targeted resistance training.
	Ankle dorsiflexion strength Follow-up: 12 months	Mean 0.3 higher (0.23 lower to 0.81 higher)‡	60 (1)	Moderate§ ⊕⊕⊕◯	
	Ankle dorsiflexion strength Follow-up: 24 months	Mean 0.6 higher (0.03 higher to 1.12 higher)‡	60 (1)	Moderate§ ⊕⊕⊕◯	
Botulinum toxin in lower limbs (tibialis posterior and peroneus longus muscles) compared with no intervention in children with CMT1A with flexible cavus foot deformity[9]					
Foot deformity	Tibial-calcaneal angle Follow-up: 24 months	Mean 1.1 degrees higher (1.4 lower to 3.5 higher)	10 (1)	Low¶ ⊕⊕◯◯	No benefit of botulinum toxin injections compared with placebo on pes cavus at 24 months. These findings are only referable to children with CMT1A with flexible cavus foot deformity.
	Calcaneal-first metatarsal angle Follow-up: 24 months	Mean 1 degrees higher (2 lower to 4.1 higher)	10 (1)	Low¶ ⊕⊕◯◯	
Ankle range of motion	Ankle dorsiflexion range Follow-up: 24 months	Mean 2.3 degrees lower (5.2 lower to 0.5 higher)	10 (1)	Low¶ ⊕⊕◯◯	No benefit of botulinum toxin injections compared with placebo on ankle dorsiflexion range at 24 months.**
Spinal bracing in children with CMT[11]					
Scoliosis	Scoliosis angle (Cobb angle on spinal radiograph)	Not available (observational study, no comparator)	18 (1)	Very low†† ⊕⊕◯◯	No demonstrable benefit or lack of benefit of spinal bracing in children with CMT.‡‡

*The panel judged that as this was a secondary outcome measure and that the study was therefore not powered on this outcome (the primary outcome measure being a neurophysiologic marker), the evidence required rating down by one level for imprecision.
†The panel judged that as this outcome was not completed by all participants, the evidence required rating down by one level for risk of bias.
‡Values are ANCOVA-adjusted Z score differences.
§As there was a relatively large 95% CI and small sample size, the panel judged that the evidence required rating down by one level for imprecision.
¶The panel judged that as the sample size is very small and the 95% CI is large, the evidence required rating down by two levels for imprecision.
**Due to the quality of evidence being graded as low, the panel elected to only assess the primary outcome (pes cavus) in the Evidence to Decision framework. Ankle range of motion (1 of 3 secondary outcome measures) was not taken further to the Evidence to recommendations stage.
††The panel rated this study down by two levels for risk of bias (observational case series with differences in allocated interventions), two levels for imprecision (very small sample size, no 95% CI provided for treated group), and one level for indirectness (differences in timing and allocation of interventions).
‡‡This study also provided data on surgical management of scoliosis in children with CMT, however, this fell outside the scope of this systematic review and was not graded.
ANCOVA, analysis of covariance; CMT, Charcot-Marie-Tooth disease; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation.

pain, for ankle contracture or for fatigue with ambulation. There was also no consensus on the use of knee–ankle–foot orthoses or external orthotic/assistive devices for any clinical indication.

4. In children with CMT, what treatments should be recommended for balance impairment?

A single evidence-based recommendation against the use of ascorbic acid in children with CMT1A for balance impairment arose from the systematic review. As a number of factors contribute to impaired balance, some of the consensus-based recommendations such as balance retraining and core and postural strengthening may also have other gains such as improved mobility and strength. While consensus was obtained on the use of child-appropriate or adolescent-appropriate recreational/community-based activities, there was no consensus on the specific use of hydrotherapy or gaming devices to improve balance in children with CMT.

5. In children with CMT, what treatments should be recommended for muscle cramps?

There was no literature available to assess treatment of muscle cramps in children with CMT, and consensus was only obtained on stretching of affected muscle groups. Consensus was not achieved for other interventions including exercise, massage, magnesium or other over-the-counter or prescription medications.

6. In children with CMT, what non-surgical treatments should be recommended for joint (foot, hand, hip, knee) or spine deformity?

This management question focused on non-surgical treatment options for joint or spine deformity and indicators for referral for surgical assessment and management. Specific guidance on orthopaedic management of joint and spinal deformity was outside the scope of these recommendations. The authors refer the reader to the European Neuromuscular Centre workshop report and subsequent consensus statement on the surgical management of foot and ankle deformity in CMT.[5 15]

Box 2 Clinical practice guideline for the management of childhood Charcot-Marie-Tooth disease (CMT)

Evidence-based recommendations

Strong evidence-based recommendations:

- We recommend the use of progressive resistance exercise of the ankle dorsiflexors to improve muscle strength and slow progression of muscle weakness (⊕⊕⊕◯).

Conditional evidence-based recommendations:

- In children with CMT1A, we suggest not treating with high-dose ascorbic acid for weakness, impaired mobility, balance impairment or impaired upper limb function (⊕⊕◯◯).
- In children with CMT1A, we suggest not using botulinum toxin in the lower limbs for the management of flexible cavus foot deformity (⊕⊕◯◯).

Consensus-based recommendations

1. In children with CMT, what treatments should be recommended for weakness?

- A tailored strength training program should be encouraged, under the supervision of the child's treating physician and/or allied health clinician. The clinician should provide guidance in order to ensure that the exercise program is carried out safely, monitor progress and modify the program as appropriate.
- Strength training should start at low resistance and gradually build up (as per generic paediatric recommendations from the American Academy of Sports Medicine).[28]
- Strength training of proximal/core muscles (trunk, hip and shoulder girdle) should be encouraged.
- Exercise programs should include rest days to encourage recovery. That is, strength training should occur on non-consecutive days for the same muscle group (as per generic recommendations from the National Strength and Conditioning Association).[29]
- Exercise should cease temporarily and the exercise regimen should be modified, if there are any signs of exercise-induced muscle damage (eg, excessive muscle cramping, dark brown urine).

2. In children with CMT, what treatments should be recommended for maintaining and improving joint range of motion?

- Stretching of joints prone to contracture should form part of rehabilitation management.
- Serial casting should be used to improve ankle dorsiflexion range of motion in children who have restricted joint range of motion.
- Serial night casting may be used as an alternative to serial casting for improving ankle dorsiflexion range of motion in children for whom serial casting is contraindicated, or for those children unable to tolerate serial casting.

3. In children with CMT, what treatments should be recommended for impaired mobility?

- Ankle–foot orthoses should be used in carefully selected children with impaired functional ambulation due to:
  - foot drop (ankle dorsiflexion weakness)
  - trips and falls
  - ankle instability.
- Foot orthoses may be used in children with foot pain.
- Children with impaired mobility should wear well-fitting/supportive footwear.

Continued

Box 2 Continued

- Gait and mobility aids should be used for children with impaired community ambulation and prescribed by a qualified health professional with experience in their provision.

4. In children with CMT, what treatments should be recommended for balance impairment?

- Activities such as balance retraining or core and postural strengthening tailored to the individual child should be used to improve balance.
- Child-appropriate or adolescent-appropriate recreational/community-based activities (eg, dance, Pilates, non-contact martial arts and play-based therapy) may be used to improve balance.

5. In children with CMT, what treatments should be recommended for muscle cramps?

- Stretching of involved muscle groups may be used for the treatment of cramps.

6. In children with CMT, what non-surgical treatments should be recommended for joint (foot, hand, hip, knee) or spine deformity?

- Children should be referred to an orthopaedic surgeon for assessment and management of:
  - Painful, disabling or progressive pes cavus not responsive to conservative measures (eg, foot orthoses).
  - Ankle contracture not responsive to stretching interventions.
  - Features of hip dysplasia.
  - Features of moderate scoliosis (eg, Cobb angle >20–30°).
- A hip X-ray should be considered in all children to screen for hip dysplasia.

7. In children with CMT, what treatments should be recommended for sensory symptoms/impairment?

- Anticonvulsants such as gabapentin and pregabalin may be used for the treatment of positive sensory symptoms.
- Musculoskeletal pain may be secondary to structural, orthopaedic or mechanical causes. The underlying cause should be assessed and managed as appropriate.
- Physical therapy such as stretching and strengthening should be used for musculoskeletal pain.
- Non-pharmaceutical approaches should be used in conjunction with prescribed medications in chronic pain (pain lasting >6 months) and, if available, within a specialised multidisciplinary health care team.
- Potentially addictive medications such as muscle relaxants, narcotics and opioids should be avoided when possible for the treatment of pain.

8. In children with CMT, what treatments should be recommended for impaired upper limb function?

- Adapted equipment should be used to improve performance of activities of daily living in children who have impairment in the hands.
- Adapting keyboard settings to reduce frequency of errant key strokes, word prediction software and/or voice to text software should be used to improve typewritten communication in children who have impairment in the hands.
- In carefully selected children with upper limb impairment impacting performance of activities of daily living, functional splints (eg, neoprene thumb spica) may be used to improve function in targeted activities.

Continued

Box 2 Continued

- In carefully selected children with upper limb impairment impacting performance of activities of daily living, resting splints (eg, wrist cock up splint for children with wrist drop) may be used to improve function in targeted activities.

9. In children with CMT, what treatments should be recommended for fatigue?

- *No consensus-based recommendations.*

10. In children with CMT, what treatments should be recommended for respiratory deficits?

- Baseline pulmonary function testing should be undertaken in the following children when they are able to complete this reliably (usually from the age of 5–6 years):
  - Children with symptoms of sleep-disordered breathing (eg, unexplained headaches, daytime somnolence or symptoms of obstructive sleep apnoea).
  - Children with recurrent lower respiratory tract infections (defined as: >2 courses of antibiotics over 4 months or >2 hospital admissions for a respiratory tract infection in 12 months).
  - Children with scoliosis, with a Cobb angle of >40°.
  - All non-ambulant children.
- The following children are considered high risk for having respiratory deficits and should be referred to a respiratory physician/sleep physician for ongoing management (including for consideration of a sleep study):
  - Children with symptoms of sleep-disordered breathing.
  - Forced vital capacity <60% predicted for age.
  - Scoliosis, with a Cobb angle of >40°
  - Recurrent lower respiratory tract infections (defined as: >2 courses of antibiotics over 4 months or >2 hospital admissions for a respiratory tract infection in 12 months).
  - Non-ambulant children.
- In children who have an acute lower respiratory tract infection and are considered high risk for respiratory deficits (as outlined above):
  - Acute respiratory illness management should include a low threshold to start antibiotics.
  - Chest physiotherapy should be used when acutely unwell with a lower respiratory tract infection.
  - A respiratory physician should be involved for consideration of additional measures (eg, mechanical cough assistance or increased respiratory support) when acutely unwell with a lower respiratory tract infection.
- Formal evaluation of swallowing should be undertaken in children with recurrent respiratory tract illnesses or history of aspiration.
- All children at high risk of respiratory deficits (as outlined above) should have the influenza vaccination annually.

Grade ratings:
⊕⊕⊕⊕ High.
⊕⊕⊕◯ Moderate.
⊕⊕◯◯ Low.
⊕◯◯◯ Very low.

A systematic review for this clinical question yielded one study for the treatment of foot deformity. This randomised trial of 10 children with CMT1A showed no effect of botulinum toxin on pes cavus progression over 24 months.[9] There was also a single very low quality study of spinal bracing for scoliosis in children with CMT[11] from which an evidence-based recommendation could not be made. There was no consensus regarding appropriate referral guidelines to a hand surgeon.

Hip dysplasia occurs in 8%–12% of children with CMT, is reported in children with both demyelinating and axonal CMT subtypes and is often asymptomatic.[16 17] While consensus for radiologic screening for hip dysplasia was reached, there was no agreement as to how frequently radiologic surveillance should be performed in addition to clinical assessment.

7. In children with CMT, what treatments should be recommended for sensory symptoms/impairment?

This clinical question encompassed treatment of positive and negative sensory symptoms as well as musculoskeletal pain. There was no consensus-based recommendation for the treatment of negative sensory symptoms. Anticonvulsant medications such as gabapentin and pregabalin may be used for the treatment of positive sensory symptoms, but there was no consensus obtained on the use of topical agents, over-the-counter analgesics, tricyclic antidepressants or serotonin and norepinephrine reuptake inhibitors.

8. In children with CMT, what treatments should be recommended for impaired upper limb function?

One evidence-based recommendation recommends against the use of ascorbic acid in children with CMT1A for upper limb impairment. The Delphi survey covered a number of aspects of impaired upper limb function including limited joint range of motion and performance of activities of daily living. There was no consensus on the use of passive or self-stretches, night splints, serial casting or dynamic splinting for improving upper limb joint range.

9. In children with CMT, what treatments should be recommended for fatigue?

There are no evidence or consensus-based recommendations for the treatment of fatigue in children with CMT, assuming that other medical causes or contributors to fatigue have been excluded. The Delphi survey included but did not achieve consensus for interventions such as neurostimulants, ambulation aids, and resistance and aerobic exercise programmes.

10. In children with CMT, what treatments should be recommended for respiratory deficits?

While many children with CMT do not have respiratory difficulties, some children with more significant weakness, scoliosis or bulbar weakness are at higher risk of respiratory deficits. This section relates primarily to indications for assessment and/or monitoring of respiratory issues in children with CMT, and referral for respiratory management. Specific guidance on respiratory management issues is outside the scope of these recommendations.

Research priorities

Delphi participants were asked to identify their top three research priorities from a list of eight areas of research. The main areas of interest included evaluating the effect of physical activity and exercise, clinical drug trials, interventions for balance impairment and reduced joint range of motion, and natural history studies (table 2).

Emerging evidence

The systematic review was updated on 31 May 2021, identifying 641 new publications. Two papers were identified as emerging

Table 2 Research priorities in paediatric CMT

Area of research	Percentage
Effect of physical activity and exercise	88
Clinical drug trials	75
Interventions for balance impairment	69
Natural history studies	56
Interventions for improving joint range of motion	53
Interventions for impaired upper limb function	47
Non-surgical management of foot and ankle deformity	41
Surgical management of foot and ankle deformity	19

CMT, Charcot-Marie-Tooth disease.

literature. The first was a pilot study that assessed the effect of an adapted dance programme in children with CMT. The findings support the consensus statement that child-appropriate recreational/community activities including dance, may be used to improve balance and other motor impairments.[18] The second paper assessed the effect of prescribed ankle-foot orthoses on gait using comprehensive gait analysis techniques. The findings support the consensus statement that ankle-foot orthoses should be used in carefully selected children with impaired functional ambulation, and reinforce that child-specific factors need to be taken account in their prescription.[19]

DISCUSSION

This clinical practice guideline was developed by an international working group of clinicians with the aim of promoting evidence and consensus-based care for children with CMT, with wide applicability across multiple regions and clinical settings. Our approach employed rigorous and transparent methodology, guided by GRADE and in accordance with the AGREE II (Appraisal of Guidelines for Research and Evaluation II) framework.[20] We developed three evidence-based and 31 consensus-based recommendations covering 10 clinical questions, based on common symptoms experienced by children with CMT. The recommendations should be incorporated into an integrated management plan by the child's treating clinician, and ideally within a multidisciplinary team. With future clinical trials of disease-modifying therapies in paediatric CMT on the horizon, best practice guidelines are critical for standardised care and clinical trial readiness. A similar need for management guidelines in adult CMT exists and the methodology used for this paediatric clinical practice guideline could be employed for their development.

The series of systematic reviews identified four studies from which three evidence-based recommendations were made, highlighting the lack of high-quality evidence in paediatric CMT. The limitations of applying the GRADE process to rare diseases in which evidence is scarce became apparent, first, in assessing the quality of evidence,[21] and, second, in the formulation of recommendations in the evidence to decision framework. Additional methodological approaches to using GRADE in rare diseases, including assessment of the adult CMT literature (acknowledging the limitation of attributing adult-based findings to children), and the inclusion of 'expert-based evidence' should be considered for future iterations of this guideline.[22 23]

The modified Delphi process using a web-based approach allowed respondents to remain anonymous, and minimised influence of more outspoken panel members. This was also the most feasible approach, given the international representation of the panel. Consensus was not obtained on a number of statements, reflecting the challenge of consensus processes in rare diseases where evidence is scarce and clinical practice, therefore, highly variable. Although this made a comprehensive guideline difficult to produce, the recommendations provided have high levels of agreement and are, therefore, relevant and implementable. In retrospect, the prespecified criteria for consensus in terms of the allowed number of outliers were overly stringent for the size of the Delphi panel. Allowing the number of outliers to be a proportion of the total number of respondents rather than a prespecified number may have been more appropriate. Additional reasons for difficulties in achieving consensus included disagreements regarding definitions or wording of statements, the influence of local implementation issues and an inability to account for more specific consumer/clinician factors in a condition with considerable phenotypic variability.[24] Face-to-face meetings provide an opportunity to clarify these barriers and may improve the ability to achieve more comprehensive recommendations. This approach may be considered for future revisions of this clinical practice guideline.

Anticipatory monitoring of associated complications forms an important part of care. Apart from hip dysplasia and respiratory deficits, a comprehensive approach to anticipatory monitoring was outside the scope of this version of the guideline. Important areas for anticipatory monitoring include surveillance of vision and hearing impairment, gastrointestinal disorders and mental health. Similar challenges related to paucity of evidence and difficulties in achieving consensus are anticipated. Mutation/subtype-specific complications also need to be considered. Recommendations for the use of measurement tools used to assess disease severity and progression may also be considered for future iterations of this clinical practice guideline.

The Delphi panel identified a number of research priorities including clinical drug trials, trials of physical activity and exercise, and trials of interventions for improving joint range of motion and balance. Two identified research areas deserve further comment in light of the results of the Delphi survey. The first is the use of passive, self and moderate-length sustained stretches in the management of reduced joint range of motion. The lack of consensus was striking despite these interventions commonly being used by many clinicians. This highlights an important need to determine the efficacy of these commonly used interventions that despite being of low harm, consume significant time, energy and resources from a patient, family and clinician perspective. The second is the effect of physical activity, exercise and balance interventions on motor function. The Delphi panel reached some consensus in these areas but identified a clear need for further high-quality clinical trials to complement and broaden the applicability of the findings from the successful trial of progressive resistance exercise of ankle dorsiflexors.[10]

The challenges of conducting and obtaining funding for adequately powered, high-quality clinical research in rare diseases are well described.[25 26] This clinical practice guideline highlights a pressing need for further research and clinical trials in paediatric CMT. Knowledge gaps and research priorities have been identified and can be used to leverage future research funding.

This clinical practice guideline informs current best practice care for children with CMT. It provides implementable guidance on the management of common clinical problems experienced by children with this rare disease and can be used by clinicians to promote interventions of benefit, avoid those that may cause harm, and advocate for, and improve access to multidisciplinary care. A number of the recommendations are likely already in practice in some clinical settings and, therefore, will not have significant additional resource implications. In other settings,

this guideline can be used to improve access to appropriate care. Dissemination and implementation, using health professional networks and consumer groups internationally, represent the next step in ensuring that these recommendations are applied internationally and across multiple healthcare settings.

Author affiliations
[1]Neurology Department, The Royal Children's Hospital Melbourne, Parkville, Victoria, Australia
[2]Neuroscience Research Group, Murdoch Children's Research Institute, Parkville, Victoria, Australia
[3]Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia
[4]Paediatric Gait Analysis Service of New South Wales, Orthopaedics Department, The Children's Hospital at Westmead, Westmead, New South Wales, Australia
[5]School of Health Sciences, The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia
[6]Laboratory of Neuromuscular Pathology, Institute Born-Bunge, University of Antwerp, Antwerpen, Belgium
[7]Neuromuscular Reference Centre, Department of Neurology, Antwerp University Hospital, Edegem, Antwerp, Belgium
[8]Translational Neurosciences, Faculty of Medicine and Health Sciences, UAntwerpen, Antwerp, Belgium
[9]Peripheral Neuropathy Clinic, McMaster University, Hamilton, Ontario, Canada
[10]National Referral Centre for Pediatric Neuromuscular Disorders, Department of Paediatrics, University Hospital Centre Zagreb, Zagreb, Croatia
[11]Department of Occupational Therapy, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[12]Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[13]Department of Neurology, Sydney Children's Hospital Randwick, Sydney, New South Wales, Australia
[14]School of Women's and Children's Health, UNSW Medicine, UNSW Sydney, Sydney, New South Wales, Australia
[15]Center for Experimental Neurotherapeutics, St Jude Children's Research Hospital, Memphis, Tennessee, USA
[16]2nd Medical School, Motol University Hospital, Prague, Praha, Czech Republic
[17]Department of Pediatric Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Lombardia, Italy
[18]Centre for Motor Neurone Disease Research, Macquarie University, Sydney, New South Wales, Australia
[19]Molecular Medicine Laboratory, Concord Hospital, Sydney, New South Wales, Australia
[20]Janssen Pharmaceutical Companies of Johnson and Johnson, Titusville, New Jersey, USA
[21]Queen Square for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK
[22]Discipline of Physiotherapy, The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia
[23]Department of Neurology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA
[24]Department of Neurology, Stanford Health Care, Stanford, California, USA
[25]Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[26]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[27]Neurology, Children's Hospital at Westmead, Westmead, New South Wales, Australia
[28]Paediatrics and Child Health, The University of Sydney, Sydney, New South Wales, Australia

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Collaborators Membership of the Paediatric Charcot-Marie-Tooth disease Best Practice Guidelines Consortium: Eppie M Yiu (lead), Joshua Burns (deputy lead), Paula Bray (methods expert), Jonathan Baets, Steven K Baker, Nina Barisic, Katy de Valle, Timothy Estilow, Michelle A Farrar, Richard S Finkel, Jana Haberlova, Rachel A Kennedy, Manoj P Menezes, Isabella Moroni, Garth A Nicholson, Sindhu Ramchandren, Mary M Reilly, Kristy Rose, Monique M Ryan, Michael E Shy, Carly E Siskind and Sabrina W Yum.

Contributors EMY conceptualised the project, undertook the literature review, designed and analysed the survey, wrote the first draft, handled submission and was responsible for the final approval of the manuscript. J Burns conceptualised the project, undertook the literature review, designed and analysed the survey and was responsible for the final approval of the manuscript. PB conceptualised the project, designed and analysed the survey, acted as a methods expert during guideline development and was responsible for the final approval of the manuscript. J Baets, SKB, NB, KdV, TE, MAF, JH, RAK, IM, SR, KR and MPM contributed to the conception of the project, designed the survey, participated in the survey, revised the manuscript for intellectual content, and approved the final version of the manuscript. CES and SWY contributed to the conception of the project, designed the survey, revised the manuscript for intellectual content, and approved the final version of the manuscript. MoMR and GAN contributed to the conception of the project, participated in the survey, revised the manuscript for intellectual content, and approved the final version of the manuscript. RSF, MaMR and MES contributed to the conception of the project, revised the manuscript for intellectual content, and approved the final version of the manuscript.

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ORCID iD
Eppie M Yiu http://orcid.org/0000-0001-6704-8402

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