The hand in Charcot-Marie-Tooth disease 1A
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Chapter Eight

General discussion

Videler AJ
With an estimated prevalence of 1:5,000, Charcot-Marie-Tooth disease type 1A represents the most common inherited neuromuscular disease affecting the upper limbs. Nevertheless, literature on hand function and manual dexterity in CMT1A has been sparse. Insight into hand function, manual dexterity, daily life functioning and into the factors that determine limited manual dexterity is important for clinicians and therapists to be able to provide more specific intervention strategies for patients with CMT1A. This thesis focuses on hand function and manual dexterity and addresses upper limb involvement in CMT1A on all three ICF\textsuperscript{1} levels: body functions and structures, activities and participation. In this chapter, the main findings and their clinical implications are discussed. Furthermore, the limitations of the studies and future research perspectives are considered.

Impairments in body functions and structures

Hand strength

Hand involvement was reported by 78\% of the CMT1A patients. Grip and pinch strength were significantly reduced compared to healthy controls and a large variation in strength was observed. Grip strength of CMT1A patients ranged between 10\% and 112\% of the normal reference value, with a mean (SD) grip strength of 65\% (± 25.4) (chapter 7). Two-point, tripod and lateral pinch strength were markedly reduced to approximately 50\% (± 22.4 – 28.5) (chapters 2 & 7). Froment’s sign, a flexed position of the interphalangeal joint of the thumb during pinch grip, was seen in 41\% of the CMT1A patients indicating a weak m. adductor pollicis. Our findings on grip and pinch strength are generally in line with other CMT studies reporting hand strength reductions of more than 50\%\textsuperscript{1-4} and confirm that motor function of the hands is also severely impaired in patients with CMT1A.

Dominant and non-dominant hand strength

Recently, differences in strength between the dominant and the non-dominant hand of patients with CMT have been discussed\textsuperscript{5,6}. In a cohort of 106 CMT patients Vinci et al. found that the dominant hand was weaker than the non-dominant hand and postulated that this could be the result of overwork weakness\textsuperscript{5}. If this were true, it would have implications for training guidelines and patients should be advised not to overuse their hands. In contrast, two other studies did not report differences in strength between both hands\textsuperscript{6,7}. The results presented in this thesis also contrasted with those of Vinci et al. A significant difference between the dominant and non-

dominant hand for grip strength was demonstrated, but in favour of the dominant hand (chapter 7). Although the difference in hand strength between the dominant hand and non-dominant hand of CMT1A patients (3% more strength in dominant hand) was small compared to healthy subjects (5-10%), our results made the overwork hypothesis unlikely. CMT1A patients did indicate to perceive most limitations in hand function for their dominant hand. However, this was determined by a difference in satisfaction between both hands presumably caused by higher expectations and requirements for the dominant hand (chapter 6).

Hand fatigue
In this cohort of CMT1A patients, 43% perceived hand fatigue (chapter 7). Despite this subjective complaint, our study on fatigue of grip strength failed to show a difference in the rate of decline of maximal grip strength during effort between CMT patients and healthy controls (chapter 2). Normally there is an inverse relationship between the percentage of maximum force attempted and the time to perceive fatigue. Therefore, we hypothesized that the manifestation of fatigued hands can be explained by weakness. If CMT patients, despite weakness of the hands, perform equally to healthy and stronger subjects fatigue will probably occur sooner.

Sensory impairment
The sensory abnormalities in the hands of CMT1A patients were generally mild in comparison with the prominent motor impairments. An impaired threshold for touch was found in 51% of the CMT1A patients, an impaired discrimination sense in 27%, and a disturbed vibration sense in 20%. In the literature, the severity and distribution of sensory loss in the hands vary strongly; with sensory impairments reported in 14-64 % of the patients4,8-14. However, it is difficult to compare our results with those of others as various assessment methods and cutoff values are used.

Joint mobility
Only in 6% of the CMT1A patients a restricted passive range of motion was found, indicating very little presence of joints contractures in the fingers. Apparently, most CMT1A patients with affected hand function are able to maintain their joint mobility. Limited active mobility, caused by intrinsic muscle loss, was a more frequent feature; with impaired thumb opposition found in more than half of the CMT1A patients (chapter 7).

The relation of motor axon loss and hand function
The study in chapter 5 investigated the relation between motor axon loss, as indicator of disease severity, and hand function and manual in CMT1A. Motor axon loss was estimated with motor unit number estimation (MUNE), a relatively new and
non-invasive technique\textsuperscript{15} and with compound muscle action potentials (CMAP). MUNE and CMAP values of CMT1A patients were low compared to healthy controls. In 20\% of the patients MUNE was reduced while CMAP was normal, suggesting that reinnervation, subsequently giving rise to larger motor units, had compensated for motor unit loss. Since this was found in a small proportion of the cohort, one has to conclude that reinnervation does not keep up with denervation in the majority of the CMT1A patients.

A relationship between MUNE and clinical disease severity in CMT1A has been shown previously\textsuperscript{4,11}, however, the association between MUNE, grip and pinch strength, and the ability to use the hands during functional activities was not addressed before. Fine motor functions of the hand and manual dexterity were correlated to MUNE and CMAP of the thenar muscles. From all strength measurements, loss of tripod pinch strength correlated most strongly with axonal dysfunction. This observation is of clinical relevance as grip strength is often measured in CMT1A. We advocate that the evaluation of fine motor functions of the hand, and in particular tripod pinch strength should be an essential part of the clinical assessment in CMT1A.

**Limitations in activities and restrictions in participation**

**Manual dexterity**

Manual dexterity of CMT1A patients was reduced in nearly all patients (chapters 3 and 4). Ninety-four percent of the patients scored below the normal Sollerman hand function test (SHT) sum-score of 80 points and dexterity scores obtained with the Functional Dexterity Test (FDT) were categorised as ‘moderately functional’. The results of the Jebsen test of hand function (chapter 3) showed that, compared to the age and gender related norm, CMT patients needed much more time to manipulate mainly flat and large objects. This may be caused by a dyskinetic finger flexion (chapter 1) or by the inability to open the hand, abduct and oppose the thumb sufficiently to grasp a large object adequately (chapter 1). Surprisingly, with the Jebsen test less time than the prescribed norm was needed for writing and picking-up small objects, which require finger grips such as the two-point, tripod or lateral pinch. With the SHT and FDT, those activities that were the most difficult to perform all required two-point, tripod or lateral pinch grips (chapter 4). An explanation for these contrasting findings may be that Jebsen test scores are solely based on the time needed to perform the task. During the assessment of the Jebsen test it was noted that patients performed several sub-tests within the time limits (normative data), but with various compensatory movement patterns. With the Jebsen test, these CMT patients may be classified as having normal dexterity,
whereas both the SHT and FDT incorporate the need to use compensatory movement patterns into their scoring systems and hence, classify these patients as having an impaired manual dexterity.

It is interesting to discuss the purpose of manual dexterity tests. Is it important to assess how patients use their hands during the execution of a task or is the only interest whether a task can be done within an acceptable amount of time? The evaluation of manual dexterity with a dexterity test that also incorporates qualitative aspects of movement, like the SHT, does not only render information about the patient’s ability to execute a task or an action, but also provides information on the compensatory movement patterns that accompany the performance. This is an essential requirement to understand the relations between activity limitations and the underlying impairments in body functions for hand use. These relationships need to be known to design and evaluate meaningful rehabilitation interventions to improve hand use in daily activities in CMT1A.

Data to support the use of the SHT and FDT in CMT1A was lacking. Therefore, feasibility and reproducibility of both tests were assessed (chapter 4). Feasibility appeared to be good in both tests, and homogeneity of the SHT subtests scores was high indicating good internal consistency. Test-retest reliability was excellent for the SHT, and good for the FDT. The results of the Bland and Altman test showed that for the SHT differences greater than 3 points can be interpreted as a change in dexterity, which seems to be reasonable for use in clinical practice in CMT1A. However, the FDT test limits were wide. Based on these findings, we recommend the use of the SHT for monitoring disease progression and for the evaluation of hand therapy programmes in CMT1A. The FDT can serve as a quick test to assess the severity of impaired manual dexterity.

*Tripod pinch strength and thumb opposition are the major determinants of manual dexterity in CMT1A.*

Motor and sensory impairments in the hands may hamper manual dexterity in CMT1A. The impact of hand strength, joint mobility, and sensory function on manual dexterity in CMT1A was determined in chapter 7. It was expected that both motor and sensory impairments would be determinants of manual dexterity in CMT1A, but it was found that motor impairments, due to axon loss, are most likely the major cause of hand dysfunction and impaired manual dexterity (chapter 5 & 7). Sensory impairments were found to be less severe than motor impairments and appeared to have only limited consequences for manual dexterity. Only vibration sense was independently associated with manual dexterity in CMT1A (chapter 7).

Tripod pinch strength appeared to be the strongest determinant of impaired manual dexterity in CMT1A. This finding can be clarified by the fact that in CMT1A, as a
result of the paralytic intrinsic thenar muscles, this grip pattern in particular may become affected. Furthermore, a tripod pinch grip is one of the most frequently used grip patterns in daily activities. The limited additional effect of impaired opposition is more difficult to explain as the thumb is positioned and stabilized by the same thenar muscles used with a pinch grip. An explanation may be that some patients were not able to hold the dynamometer and perform a tripod pinch grip. In these patients tripod pinch strength was recorded as 0 Newton, despite some thenar strength, and a further differentiation could be made based upon the degree of thumb opposition.

**Perceived functional limitations**

In the literature no attention has yet been paid to the perceived functional limitations of patients with CMT1A. This is surprising, since loss of functional abilities is probably of major concern to the patients involved. The studies presented in chapters 3 & 6 are the first to evaluate perceived upper limb functioning and restrictions in participation in CMT1A.

The majority of the CMT1A patients perceived limited upper limb functioning and experienced mild restrictions in participation. Compared to scores reported for other pathological conditions of the hand, like full-thickness hand burns, Dupuytren's contracture other peripheral nerve, and wrist disorders, our results indicate that CMT1A patients perceived on average moderate limitations in upper limb function, though ranging from severe to mild. In 50% of the CMT1A patients, the problems in one or both arms hampered but still allowed activities like dressing, washing or brushing hair, turning a key, eating and doing zippers. About 25% perceived major limitations in upper limb related activities such as making the bed, cleaning, doing the laundry, dressing, and especially with fastenings of buttons, zippers, shoelaces and jewellery. Most limitations were indicated in the domains of overall hand function, work, and satisfaction with hand function.

**Restrictions in participation**

In CMT1A, perceived upper limb functioning appeared to have a clear impact on restricted participation. Restrictions were particularly perceived in the domains of work, family role, and autonomy outdoors. Although, most CMT1A patients found their participation to be sufficient in the domains addressed, a limited group (2-12%) indicated severe problems with participation. Overall, the severity of participation restrictions in this cohort of CMT1A patients was comparable to other chronic diseases, such as multiple sclerosis, rheumatoid arthritis, and spinal cord injury. Although, evidently the nature of the restrictions may differ. The slow progression of CMT1A impairments may contribute to the relative mildness of perceived disability,
allowing for adaptation to the declining hand function. CMT1A patients may learn to cope with their slow decline in dexterity, or adjust their expectations, and as a result value their disability differently as time goes by. This phenomenon is known in the literature as ‘response shift’.

For the evaluation of perceived functional limitations and restrictions in participation we used various questionnaires: the Dutch versions of the Disabilities of Arm, Shoulder and Hand (DASH-DLV) and the Michigan Hand Outcomes Questionnaire (MHQ-DLV) questionnaires, the Rehabilitation Activities Profile (RAP), the Impact on participation and autonomy (IPA) questionnaire and the upper and lower limb domains of the Guy’s Neurological Disability Scale (chapters 3 & 6). Although the DASH questionnaire is specifically designed for the upper limb, and very frequently used in research and clinical practice, it turned out to be not very suitable for our CMT1A study. The DASH values for pain, function and activities produce a single score and therefore cannot identify disease-specific problems, which may be relevant for CMT1A. The also well-known MHQ does provide separate domains scores, such as hand function, ADL, work and pain which makes it possible to understand the consequences of the disease on different dimensions.

**Clinical implications**

Based on the results presented in this thesis, we propose that the clinical evaluation of hand function of CMT1A patients should at least consist of a thorough history, of inspection of the upper limb and in particular of the hand and forearm, and of the following assessments: the ability to oppose the thumb (Kapandji opposition score), tripod pinch strength (hand-held dynamometry) and the evaluation of vibration sense (Rydel-Seiffer tuning fork). The extent of clawing of the fingers provides additional information on the imbalance between the intrinsic and extrinsic muscles of the hand. Furthermore, our study findings underline that the evaluation of manual dexterity and perceived upper limb function must be included in the functional assessment of CMT1A patients.

Based on our study findings, the SHT is recommended to evaluate manual dexterity during disease progression and treatment programmes in CMT1A. The FDT can serve as a quick test to assess the severity of impaired manual dexterity (chapter 4). The MHQ and the IPA questionnaires were found to be most appropriate for the evaluation of perceived upper limb limitations in CMT1A (chapter 6). Performance tests and self-assessment instruments (questionnaires) consider different concepts of functional health status and provide important and complementary information on functional abilities relevant to set treatment goals and to decide on the choice of
METHODOLOGICAL CONSIDERATIONS

This thesis is the first to evaluate upper limb involvement extensively in a large sample of DNA-confirmed CMT type 1A patients. A few methodological considerations should be taken into consideration.

1. Our study population was not a random sample of CMT1A patients. Some selection bias may have occurred because patients with advanced upper limb involvement could have been more willing to participate than those with less impairment. However, it is reasonable to believe that the results provide a fair representation of the spectrum of upper limb involvement in CMT1A because a high percentage (78%) of the known patients in our departments participated.

2. Reproducibility of our fatigue protocol used in chapter 2 was poor. Several reasons may explain the poor reproducibility. The variability in voluntary force may be due to a day-to-day biological fluctuation in motor function. Variability may also be caused by the design of the dynamometer. The absence of an anatomically shaped handle might have been uncomfortable for the patients, limiting their maximal effort. Finally, reproducibility of the fatigue measurements may have been poor as maximal voluntary contraction force depends strongly on motivation. The protocol required for each contraction a maximal effort and it is conceivable that not all of the contractions were maximal. In further research a reliable fatigue protocol is needed to be able to investigate if increased hand fatigability in CMT1A is caused by a steeper decline in strength or by a diminished initial strength.

3. In chapter 5 in which we investigated whether motor axon loss is related to hand function and manual dexterity, MUNE could not be determined in 7 out of 48 CMT1A patients because no CMAP or no reliable CMAP could be elicited. These patients were more severely disabled compared to the rest of the study sample, limiting the generalization of our electrophysiological findings.

4. There are no manual dexterity tests or questionnaires available that were specifically designed for CMT1A. The measurements and questionnaires used in this study have been chosen based on clinical experience but have not been validated for patients with CMT1A.

First the Jebsen test of hand function was used, because this well-known test was recommended in the Dutch rehabilitation guideline for CMT patients\textsuperscript{23}. Other well-known dexterity tests, such as the Box and Block test, the Nine-hole-peg
test, the Purdue pegboard test have been used in CMT by others, but as the Jebsen test, these only provide data on the speed of hand and finger use. Both the Sollerman hand function test (SHT) and the Functional dexterity test (FDT) incorporate the need to use compensatory movement patterns into their scoring systems. Compared to the FDT, the tasks of the SHT are more representative for activities of daily living and also include bilateral tasks. The FDT on the other hand is less time consuming.

5. There are also no CMT1A-specific questionnaires to evaluate perceived limitations in upper limb functioning. The Guy’s Neurological Disability Scale has been applied previously in a CMT1A study and allows for a similar evaluation of upper and lower limb disability. Nevertheless, its ordinal 6-step scale appeared to be insensitive to small differences in disability in patients with CMT1A.

6. Part of the study focused on patients’ perception and used self-assessment questionnaires. As in any study based upon self-assessment, the patients’ own perception might be influenced by factors such as the attention given by the study, the presence of an investigator, or the questionnaire itself and, therefore, only approaches reality.

FUTURE PERSPECTIVES

In search of better outcome measures

While muscle strength is commonly measured subjectively, using the MRC scale, hand-held dynamometry is regarded as more precise, sensitive and objective. Furthermore, it has been recommended as a measure of outcome in the evaluation of peripheral nerve function. Therefore, in our study grip and pinch strengths were assessed using digital handgrip dynamometers (Lode Medical Technology). However, it is obvious that grip and pinch strength measurements provide information on the combined function of intrinsic and extrinsic muscles of the hand and are not direct measures of isolated intrinsic muscle strength. Recently, the Rotterdam Intrinsic Hand Myometer (RHIM) has been introduced, a new hand-held dynamometer designed to measure isolated intrinsic muscle strength. The RHIM was found to be reliable in patients with CMT. For future research this instrument may therefore be a valuable supplementary tool in the evaluation of hand function in CMT1A.

A disadvantage of the SHT is that it is quite time-consuming for the clinical practice. Recently, a selection of 3 items of the SHT (picking up coins from purses, picking up nuts and screw them on bolts and doing up buttons) has been proposed and found to correlate with the full outcome of the SHT in patients with intrinsic muscle loss.
due to peripheral nerve injury\textsuperscript{25,27}. Although its clinimetric properties in CMT are unknown, the 3-item version has been used previously in a CMT study, where a high correlation between the 3-item SHT and intrinsic muscle strength was found\textsuperscript{1}. In our cohort of CMT1A patients, a strong correlation ($r = .95$, $p = < 0.001$) between the 3-item and the full version of the SHT was found (data not published). The 3-item version seems therefore promising as a quick manual dexterity assessment but future research on the validity and responsiveness of the 3-item version in CMT1A is needed to determine if this short version of the SHT can be recommended in this patient population.

In search of effective interventions

Rehabilitation ought to play an essential role in preserving upper limb functioning of CMT1A patients, but evidence on the effectiveness of rehabilitation interventions is lacking. Currently, when patients with CMT1A with limited upper limb function seek the help of a multidisciplinary rehabilitation team, the physical or occupational therapist will try to improve hand function and manual dexterity with exercise therapy and all sorts of splints, such as a ‘knuckle bender’, a ‘Swanneck-correction splint’, and a thumb opposition splint. Nevertheless, these therapy modalities are neither standardized nor evidence-based in CMT1A. In the literature, orthotic management, assistive devices, surgical procedures and exercise programs have only been described for the lower limbs\textsuperscript{28-32}.

Tripod pinch strength and thumb opposition, being the major determinants of manual dexterity in CMT1A, should be the focus of intervention strategies that aim to preserve or enhance manual dexterity in CMT1A. It is known that thumb opposition of patients with CMT can be improved with tendon transfer surgery, although studies reporting the efficacy are scarce\textsuperscript{33,34}. An opposition splint is a conservative measure to position the thumb in a more functional position, but unfortunately, there is no literature available on splint therapy in CMT. Therefore, we recently conducted a pre- and post-intervention pilot study to evaluate the feasibility of a short thumb opponens splint, and its initial efficacy on manual dexterity and perceived physical functioning.

A neoprene thumb opposition splint (Figure 1) was custom-made in 10 CMT patients. Manual dexterity with the use of the splint was evaluated with the SHT and the FDT. Perceived limitations in upper limb function were evaluated with the MHQ and occupational performance with the Canadian Occupational Performance Measure (COPM). Feasibility of the splint was evaluated with a questionnaire specifically designed for this pilot study.
All patients (6 male, 4 female, mean (SD) age 53 (12) years) wore the splint daily for at least one week. Patients were satisfied with the appearance of the splint, did not have difficulties putting the splint on. The mean (SD) for comfort was rated on a scale from 0-10 as 5.8 (2.5). Seventy percent of the patients indicated to experience advantages of the splint during daily activities and rated these advantages on a 0-10 scale as 5.2 (2.9). Activities requiring pinch grips, such as grasping small objects, using eating utensils, doing up buttons, zipping and picking up money were frequently mentioned as easier to perform (Figure 2). With the splint a better grip position and stability was perceived. Disadvantages that were mentioned were: less useful during hygienic/wet activities such as self-care and cooking and uncomfortable to wear for prolonged periods during hot weather.

With the splint, dexterity scores improved, although not significantly. COPM scores improved significantly, both for the self-perception of performance and satisfaction with performance. The MHQ showed a significant improvement in the domain ‘Activities of daily living’. 
Manual dexterity improved less than expected with the splint. An explanation for this may be that the splint only improves the position of the thumb but not the strength in this position (pinch grip). Although the splint makes it easier to grasp an object, patients may still lack the strength to manipulate that object. With a surgical procedure like an opponensplasty, this might be taken into account and improved pinch strength may be obtained as well\textsuperscript{33-35}. Nevertheless, if surgery is considered, a thumb opponens splint may very well be useful to mimic some potential effects of a tendon transfer pre-operatively.

The results presented in this thesis provide the evidence-based foundation for outcome assessment in future intervention studies such as splint therapy or surgical tendon transfer procedures, aimed at improving thumb opposition, tripod pinch strength and manual dexterity in CMT1A. In such studies the timing of orthotic or surgical interventions in relation to disease progression has to be considered as well as persistent compensatory movement patterns, which may have developed in long standing cases. For example, one of our CMT patients had used only her fingers to grasp objects for many years, and was confused when her thumb was placed in a different position with a splint. Another consideration is that older patients may have more difficulties adapting to a different movement pattern. Future study is needed in this field.

In conclusion, this thesis showed that in CMT1A fine motor functions of the hand, in particular tripod pinch strength, are severely impaired, strongly associated with axonal dysfunction, and that they are the major determinants of impaired manual dexterity. Furthermore, the majority of patients perceived their upper limb functioning as limited. Based on these findings, it is clear that patients with CMT1A deserve a thorough clinical and functional upper limb evaluation. Future, well-designed research is needed to develop and evaluate intervention strategies aimed at improving hand function, manual dexterity and ultimately daily life functioning of patients with CMT1A.
REFERENCES


