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

Hand strength and fatigue in patients with Hereditary Motor and Sensory Neuropathy (Type I and II)

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ABSTRACT

Objectives: To compare maximal isometric hand strength and fatigue between subjects with Hereditary Motor and Sensory Neuropathy (HMSN) and healthy controls and to test the reproducibility of handgrip strength (peak force of handgrip [PFgrip]) and fatigue.

Design: PFgrip and the decline in PFgrip during 3 sets of 15 contractions were compared.

Setting: University hospital in The Netherlands.

Participants: Twenty subjects with HMSN and 20 age- and sex-matched healthy controls; 15 healthy subjects for the reproducibility part of the study.

Interventions: Not applicable.

Main outcome measures: PFgrip and the decline in PF grip were compared by using a digital handgrip dynamometer. Two-point and lateral pinch measurements of subjects with HMSN were standardized against reference values. Reproducibility measurements were performed on 15 healthy subjects on 2 separate occasions within 1-week interval.

Results: PFgrip was significantly lower in the HMSN subjects compared with controls (p < 0.05). Pinch measurements also showed a large variance from average normal performance. No significant difference was found in the decline in percentage of PFgrip. Reproducibility was excellent for PFgrip (Intraclass correlation coefficient [ICC], 0.98; 95% confidence interval [CI], 0.95-0.99) but poor for fatigue (ICC, 0.62; 95% CI, 0.20-0.85).

Conclusion: PFgrip and two-point and lateral pinch in HMSN subjects were significantly reduced compared with healthy controls. Our findings indicated that the rate of decline of PFgrip during effort does not vary between groups.
INTRODUCTION

With an estimated prevalence of 100 per million, hereditary motor and sensory neuropathy (HMSN) represents the most common inherited neuromuscular disease affecting the upper extremity\(^1,2\). HMSN, also known as Charcot-Marie-Tooth disease (CMT), forms a heterogeneous group of slowly progressive diseases of the peripheral nerve system. Clinical features include a symmetrical distal muscle weakness and atrophy, loss of sensibility and absent or diminished deep tendon reflexes. There is a remarkable diversity in clinical representation, ranging from patients with severe distal atrophy and deformities of hand and foot to individuals whose only clinical finding is minimal distal muscle weakness\(^3\). Based on electrophysiologic and histopathologic findings, HMSN is classified into 3 major groups. Type I is considered a primary demyelinating neuropathy with reduced motor nerve conduction velocities, whereas type II refers to individuals with an axonal neuropathy and normal or near-normal nerve conduction velocities (>40 m/s). The age of onset of HMSN type I is in the first decade and of type II in the second decade or later. Type III, also known as Dejerine-Sottas disease, represents a severe hypertrophic demyelinating polyneuropathy and has an onset early in life\(^3,4\).

Muscle weakness and atrophy usually start in the foot and leg muscles. In a later stage, the hand may be affected. In the literature, the period between the onset of the disease and the involvement of the hand varies from 9 to 19 years\(^1,5,6\). Although in the literature and clinical practice the attention lies predominantly on the problems of the lower extremity, many patients with HMSN present with loss of hand strength and manual dexterity\(^1,7\). The intrinsic muscles of the hand are primarily affected. This may result in a clawing position of the hand and loss of opposition. Some patients experience difficulties with the manipulation of small objects and with activities that require a strong grip, such as carrying a shopping bag or opening a jar.

Measuring the strength of the hand muscles with a dynamometer is frequently used as a parameter to assess hand function\(^8-11\). In studies and in clinical practice, it is common to measure only the peak force, but many patients indicate that during daily activities, they experience most difficulty when an effort has to be maintained for a longer period of time\(^12,13\).

Therefore, the aim of this study is to test the hypothesis that, during effort, the decline in strength is more prominent in subjects with HMSN compared with healthy subjects. To our knowledge, no data are available on fatigue of hand muscles in HMSN patients. We have chosen to measure fatigue by using an intermittent protocol with short bouts of maximal voluntary contractions (MVCs). We did this to avoid overestimating exercise level when testing fatigue at a percentage of MVC and
to avoid limitations in force caused by a reduced circulation. The research questions of our study were (1) What is the difference in maximal isometric strength of handgrip, two-point pinch and lateral pinch between subjects with HMSN and healthy subjects of the same age and sex and (2) Is there a difference in the rate of decline of maximal isometric handgrip strength during series of contractions between subjects with HMSN and healthy subjects? In addition, we investigated the reproducibility of maximal voluntary isometric grip strength and fatigue in healthy subjects.

METHODS

The study consisted of 2 parts. In the first part, strength and fatigue were compared between subjects with HMSN and healthy control subjects. The second part focussed on the reproducibility of the measurement of maximal voluntary isometric handgrip strength and fatigue in healthy subjects.

Participants

In the comparative part, 20 subjects with HMSN and an equal number of age- and gender-matched healthy controls were included. HMSN subjects were recruited from the outpatient rehabilitation clinic of the Academic Medical Center in Amsterdam and from the Dutch Association for Neuromuscular Diseases (Vereniging Spierziekten Nederland). Inclusion criteria for subjects with HMSN were (1) diagnosis of HMSN or CMT types I and II confirmed by an electrophysiologic, histopathologic, or DNA study; (2) age between 18 and 70 years; and (3) ability to hold the measurement equipment during the strength tests. Subjects were excluded if there were any disabling disorders in their medical history that might influence muscle strength or fatigue of the hand. Another group of 15 healthy subjects participated in the testing of reproducibility. Healthy subjects were excluded if they perform heavy labor with the upper extremities during work, hobbies or sports.

The Medical Ethics Committee of our hospital approved the study, and written informed consent was obtained from all participants.

Measurement Instruments

Handgrip strength and fatigue

A digital handgrip dynamometer was used to measure maximal isometric grip strength and fatigue. The dynamometer was suspended from the ceiling with an adjustable cord to eliminate the weight of the dynamometer and to position it in front
of the subject. The cord was partly elastic to enable minor movements of the upper extremity during the grip effort. A static construction could have limited maximal grip strength. This isometric force measurement system was connected to an amplifier and a computer for data acquisition and analysis. The subject was seated on an adjustable chair with both feet placed flat on the floor with the ankles, knees, and hips 90° flexed. Grip strength was measured in the standardized grip posture of humeral adduction, elbow flexion to 90°, neutral forearm rotation, self-selected wrist position, and without support of the arm\textsuperscript{14,15} (Figure 1). The handle of the dynamometer was set in the second position, representing a grip of 45 mm distance. This position of the dynamometer is recommended to test maximal grip strength irrespective of age, weight, or hand dimensions\textsuperscript{8}. Only the dominant hand was tested. Because none of the subjects were familiar with the equipment beforehand, the procedure was explained and shown. Also, each person was given the opportunity to experience a single maximal grip effort with the non-dominant hand. During the test, the subject received strong verbal encouragement. Subjects performed 3 bouts of 15 isometric MVCs separated by 1-minute rest intervals. Each contraction lasted 3 seconds with an interval of 1 second. The beginning and end of each contraction was indicated by an auditory signal. Grip strength was digitized\textsuperscript{a} at a sampling rate of 15 Hz and stored on computer for subsequent off-line analysis.

**Pinch strength**

With a pinch gauge\textsuperscript{b} the maximal voluntary isometric force of the two-point (tip) and lateral (key) pinch were measured, as described by Mathiowetz et al.\textsuperscript{15}.
**Protocol**

In the first part of the study, testing adhered to a standard sequence. First, all subjects with HMSN were questioned about the duration, spectrum, severity, and progression of the symptoms. The age of onset of the disease was determined by questioning the subjects about their first disabling symptoms; therefore, it characterized the first functional manifestations rather than the onset of the disorder itself.

Second, the two-point and lateral pinch measurements were performed followed by the measurements of grip strength and fatigue. Before the measurement of grip strength and fatigue, subjects were given the opportunity to rest for half an hour or longer if they did not feel fully recovered. To assess reproducibility, the handgrip measurements were performed twice at 2 separate sessions with an interval of 7 days. To reduce the variability of all strength and fatigue measurements, tests were performed by the same investigator, subjects avoided strenuous activity before testing sessions, and repeated tests were performed at the same time of the day. Preceding the strength tests, all devices were calibrated according to the manufacturers’ instructions.

**Data analysis**

Maximal voluntary isometric grip force, indicated as peak force of grip (PFgrip), was calculated as the mean force of contraction 2, 3, and 4 of set 1. The first contraction was excluded because it is used as a trigger to start data collection. To quantify endurance, a fatigue index (FI) was calculated as the relative decline in mean PFgrip from the beginning of set 1 (contraction 2/3/4) to the end of set 3 (contraction 43/44/45):

\[
FI \% = \frac{x \cdot PF_{grip\ 43/44/45}}{x \cdot PF_{grip\ 2/3/4}} \times 100
\]

Peak force of the two-point pinch and the lateral pinch of HMSN subjects were calculated as the mean force of 3 trials. The results were standardized against reference values \(^6\) and expressed as z-scores, indicating the number of standard deviations (SDs) from average normal performance given the patient’s age and gender.

Groups (HMSN, controls) were compared by using the paired-samples t-test or Mann-Whitney-U test if the data were not normally distributed. The Kolmogorov-Smirnov test was used to ascertain normality. The reproducibility of the measurement of PFgrip and FI was determined by using the intraclass correlation coefficient (ICC) as estimated from a 1-way random effects analysis of variance model and the Bland and Altman method for assessing agreement\(^7\). For all
analyses, an α-level of p less then 0.05 was used. All data analyses were performed by using SPSS, version 9.0, statistical programc.

RESULTS

Participants
Of the 20 HMSN subjects, 12 were determined as having type I, 7 with type II, and 1 subject was diagnosed with CMT (presumably type I). The mean age at examination was 40 ±13 years (range,18-65 y). Eleven of the 20 participants were women. The number of years between the onset of the disease and the onset of hand symptoms varied from 0 to 47 (median, 10.5 y; interquartile range, 2.7 – 28.8). Three subjects could not recall the onset of the hand symptoms, and 1 subject stated not to have any involvement of the hand. The majority of the HMSN subjects experienced the following subjective findings: loss of sensibility (70%), loss of hand strength (65%), tremors (60%), and cramp and pain (55%). The 20 healthy matched subjects had the same characteristics for age and gender as the HMSN subjects. A separate group of healthy subjects with a mean age of 36 ± 9 years participated in the second part of the study (reproducibility of PFgrip and FI). Eleven of these 15 healthy volunteers were women.

Comparison of the HMSN and Control groups

PFgrip
Compared with age- and gender-matched healthy control subjects, PFgrip was significantly lower in HMSN subjects (paired-samples t-test, p< 0.001; table 1). Mean PFgrip in HMSN subjects (227 ±130N) was 67% of the mean PFgrip in the control group (339 ±109N).

Peak force of the two-point and lateral pinch
Three HMSN subjects were unable to perform a two-point pinch. The mean values and z-scores of the two-point and lateral pinch are presented in table 2. The mean z-score of two-point pinch was –1.14 ±1.76 and of lateral pinch –1.39 ±2.57. A z-score of 0.80 or more can be seen as a large difference from average normal performance, according to the criteria of Cohen18.

Fatigue
Fatigue testing was well tolerated, as indicated by the fact that all subjects completed the 3 sets. All HMSN subjects and healthy controls showed a decline in PFgrip during the 3 sets, but no significant difference was found in the rate of
Table 1: Maximal grip strength (PFgrip) and Fatigue index (FI) in HMSN and control subjects

<table>
<thead>
<tr>
<th></th>
<th>HMSN subjects</th>
<th>Control subjects</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFgrip (N)</strong></td>
<td>mean ±SD</td>
<td>227 ±130</td>
<td>339 ±109</td>
<td>-113*</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>39 - 501</td>
<td>128 - 545</td>
<td></td>
</tr>
<tr>
<td><strong>FI (%)</strong></td>
<td>mean ±SD</td>
<td>34 ±18</td>
<td>40 ±16</td>
<td>-6</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>0 - 81</td>
<td>3 - 64</td>
<td>-19</td>
</tr>
</tbody>
</table>

NOTE. Mean ±SD values and ranges are given for PFgrip and the fatigue index. Mean differences between HMSN subjects and control subjects and the 95% confidence interval (CI) for the mean difference are presented.

* p< 0.001

Table 2: Mean values and z-scores of two-point and lateral pinch

<table>
<thead>
<tr>
<th></th>
<th>two-point pinch</th>
<th>Lateral pinch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mean in N ±SD</strong></td>
<td>47.9 ±24.5</td>
<td>68.9 ±32.1</td>
</tr>
<tr>
<td><strong>Mean z-score ±SD</strong></td>
<td>-1.14 ±1.76</td>
<td>-1.39 ±2.57</td>
</tr>
<tr>
<td><strong>95% CI of the mean</strong></td>
<td>-0.23 → -2.04</td>
<td>-0.19 → -2.60</td>
</tr>
</tbody>
</table>

decline (expressed as percentage of PFgrip) between HMSN subjects and healthy controls (p= 0.36). After 3 sets of 15 contractions, the mean decline in PFgrip was 34% ±18% in HMSN subjects compared to 40% ±16% in control subjects (Table 1).

Reproducibility

Reproducibility was excellent for the grip strength testing method (Table 3). PFgrip had an ICC of 0.98. The Bland and Altman test results for PFgrip showed a good agreement. The distribution of values in figure 2 shows that in all cases the difference between the two measures was 28N or less (mean PFgrip, 339 ±109N; table 1), and the points were distributed around zero. Reproducibility for testing fatigue in healthy subjects was poor, with an ICC of 0.62 (95% confidence interval, 0.20-0.85; table 3). The Bland and Altman plot also shows that the agreement
Table 3: Reproducibility - ICC’s and Bland and Altman tests

<table>
<thead>
<tr>
<th></th>
<th>ICC coeff</th>
<th>95% CI</th>
<th>Bland and Altman</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>−5.60</td>
<td>8.74</td>
<td>−14.34</td>
<td>3.14</td>
<td>15.79</td>
<td>−39.47</td>
<td>28.27</td>
<td></td>
</tr>
<tr>
<td>PFgrip (N)</td>
<td>0.98</td>
<td>0.95</td>
<td>→ 0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FI (%)</td>
<td>0.62</td>
<td>0.20</td>
<td>→ 0.85</td>
<td>1.55</td>
<td>4.81</td>
<td>−3.26</td>
<td>6.35</td>
<td>8.68</td>
<td>−17.07</td>
<td>20.16</td>
</tr>
</tbody>
</table>

$\bar{d}$ is the mean difference; SE of $\bar{d}$ is the standard error of the mean difference; 95% CI for $\bar{d}$ is the 95% confidence interval for the mean difference; SDiff is the standard deviation of the differences; ICCcoeff = intraclass correlation coefficient. Maximal voluntary isometric grip force is indicated as PFgrip and fatigue index as FI.

Figure 2

Distribution plot from Bland and Altman test showing mean measurements against differences between measurements for reproducibility of PFgrip. The straight line represents the mean difference between both measurements; the dotted lines represent the 95% limits of agreement.

Figure 3

Distribution plot from Bland and Altman test showing mean measurements against differences between measurements for reproducibility of FI. The straight line represents the mean difference between both measurements; the dotted lines represent the 95% limits of agreement.
between the test-retest results was poor (Figure 3), as shown by the wide 95% limits of agreement. This implies that a decline in PFgrip of, for example, 45% may actually lie between 28% and 65%.

**DISCUSSION**

Our study showed a reduced maximal isometric strength of handgrip and two-point and lateral pinch in subjects with HMSN compared with healthy controls. The mean PFgrip in HMSN subjects was approximately two thirds of the mean PFgrip in control subjects. Also, the z-scores of the two-point and lateral pinches indicated a large difference from average normal performance. Although no results of comparative studies between hand strength in HMSN and healthy subjects are available, upper extremity evaluations in HMSN have been published. In the study by Miller et al., the upper extremity was evaluated in 68 patients diagnosed with CMT disease. The results showed that the major complaint in 75% of these patients relate to motor deficits with loss of strength and dexterity as the main components. Motor abnormalities were found in 98% of patients tested with the Jamar and pinch dynamometers. Harding and Thomas reported in 228 patients with HMSN that two thirds of the patients with HMSN type I and half of the patients with HMSN type II had distal upper extremity weakness. In our study, the fatigue test of handgrip strength showed in all subjects a decline in PFgrip, but no differences were found in the rate of decline in PFgrip between HMSN subjects and healthy controls. This may be because of poor reproducibility of the fatigue measurements.

Various ways of assessing muscle fatigue are described in the literature. This underlines the difficulty of testing this complex clinical symptom. In this study, we chose to measure muscle fatigue by using an intermittent protocol with short bouts of MVCs for 2 reasons: 1) to avoid overestimating exercise level when testing fatigue at a percentage of MVC, and 2) to avoid limitations in force caused by a reduced circulation. McComas et al. have emphasized the difficulty in interpretation of voluntary endurance studies when voluntary activation is initially low. The level of exercise may be overestimated (as a percentage of MVC) when the level of true MVC is underestimated.

Assessing fatigue with the use of a sustained contraction may be disturbed by diminished muscle circulation. In maximal static contractions, the pressure within the muscle will exceed the systolic blood pressure, and blood flow through the active muscle is totally occluded. Schwid et al. studied the test-retest reproducibility of fatigue of hand grip strength with a sustained protocol. Reproducibility of the fatigue index (decline in strength as a percentage of initial peak force) was poor in control.
subjects, as well as in subjects with Multiple Sclerosis (ICC, 0.09; ICC, 0.46 respectively). With an intermittent protocol, we had hoped to find a reproducible way of measuring fatigue. Reasons for the poor reproducibility of our fatigue measures are not clear. Inhibitory effects at various levels in the central nervous system and at muscle level can limit voluntarily generated force. The variability in force may reflect the day-to-day biologic fluctuation in motor function. Variability may also be caused by the absence of an anatomically shaped handle of the dynamometer. A possible uncomfortable grip could have limited the maximal effort of the subjects. Finally, reproducibility of the fatigue measurements may have been poor because MVC force depends strongly on motivation. The protocol required a maximal effort for each contraction, and it is conceivable that not all of the contractions were maximal. Measurements of actual performance incorporating some type of electric stimulation to assess the adequacy of voluntary drive may contribute to an accurate evaluation and may improve the reproducibility of this test.

Because of the poor reproducibility of the fatigability index, we cannot answer the question whether the decline in strength is more prominent in HMSN subjects compared with healthy control subjects. In the study of Lindeman et al., fatigability was measured in HMSN subjects by means of an endurance test during which the subject extended the leg at 80% of MVC for as long as possible. Endurance was found to be less ($p=0.03$) for HMSN subjects than for controls, but reproducibility of this testing method has not been investigated. To our knowledge, there are no data available in the literature on fatigue characteristics of muscles in subjects with HMSN. One of the factors that determines fatigue is the proportion of fiber types in the muscles. Ericson et al. found a statistically significant higher percentage of type I muscle fibers in CMT1 ($p<0.01$) and CMT2 ($p<0.05$) when compared with normal controls. A larger proportion of type I muscle fibers may lead to a slower decline in strength rather than a more prominent decline. Fatigability of muscles is determined by a variety of other factors such as mitochondrial and glycolytic enzyme activity and capilarization (numbers of capillaries surrounding the muscle fibers). It is not known whether these factors differ between HMSN subjects and healthy controls. The frequent complaint of early fatigue by subjects with HMSN may be explained by weakness. If a person has become weak and attempts the same task as a healthy and stronger subject, fatigue must occur sooner. This conclusion depends on the fact that there is normally an inverse relationship between the percentage of maximum force attempted and the time to a set failure level (fatigue). Suppose that a person with a neuromuscular disorder can only develop half the initial force compared with the force of a healthy subject. The percentage of force needed to perform the same task will be 2 times as high. Clearly, the time to fatigue
will be less for a MVC in these circumstances than it would have been in a healthy subject\textsuperscript{19}. With this study, we can not confirm our hypothesis that during effort the decline in strength is more prominent in subjects with HMSN compared with healthy subjects. Further research is recommended to explore whether increased fatigability in subjects with HMSN is caused by a difference in the decline of strength or by a diminished initial strength. An important consideration when measuring muscle fatigue is the fact that there is no reproducible protocol available yet. In future study, it will be necessary to develop a protocol that is reliable and valid for patients with neuromuscular disorders. Care should be taken not to draw unjustified conclusions about fatigue from results that are obtained from a method with unknown reproducibility.

**Conclusion**

PFgrip, two-point pinch, and lateral pinch in HMSN subjects were significantly reduced compared with healthy controls. Reproducibility was excellent for PFgrip but poor for fatigue. Our findings do not indicate that the rate of decline of PFgrip during effort differed between the groups.
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** Suppliers **

a. Lode Medical Technology BV, Zernikepark 16, 9747 AN Groningen, The Netherlands

b. B & L Engineering, 3002 Dow Ave, Ste 416, Tustin CA 92780.

c. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago IL 60606.