

## RESEARCH REPORT

# Testing overwork weakness in Charcot-Marie-tooth disease: Is it true or false?

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The occurrence of the overwork weakness (OW) in Charcot-Marie-tooth (CMT) disease has been debated for a long time. Especially at the hands level, it is still unclear as to whether OW occurs. Contrasting results may relate to the different muscle groups evaluated and the instruments used. We concentrated to the upper limbs (UL). We recruited 120 subjects, 60 CMT patients and 60 normal controls and evaluated the strength of the tripod pinch and of the hand-grip with a dynamometer, the opposition ability with the thumb opposition test (TOT) and applied an innovative instrumental testing of hand function using the sensor engineered glove test (SEGT), which previously demonstrated its sensitiveness to measure severity of hands dysfunction in CMT patients. In CMT patients, TOT scores were significantly higher in the non-dominant hand (NDH) compared to dominant hand (DH), strength in the NDH was slightly but not significantly better than the DH. Finally, SEGT results were similar between the NDH and DH, whereas in normal controls the DH performed better. In conclusion, this study supports the existence of the overwork weakness in CMT. We can speculate that the dexterity and overall ability of the hands appear more impaired in the DH as a result of a weakness and incapacity of opposition. Our results support the importance of avoiding supramaximal exercises and educating patients to prevent incorrect movements.

**KEYWORDS**

Charcot-Marie-tooth, CMT, hand dominance, overwork weakness

## 1 | INTRODUCTION

Overwork weakness (OW) refers to a syndrome which causes a permanent weakness of muscles due to excessive exercises, repetitive work or specific daily activities.<sup>1</sup> The first description dates back to a half century ago in post-polio patients.<sup>2,3</sup> After that, OW has been demonstrated in other neuromuscular diseases such as amyotrophic lateral sclerosis,<sup>4</sup> Duchenne and facio-scapulo-humeral dystrophies.<sup>5,6</sup> In these cases, supramaximal exercises speed up the progression of the disease. The role of OW in Charcot-Marie-tooth (CMT) neuropathy is still controversial. Clarifying whether it is present or not, may help in addressing the patients daily physical activities and the exercises type or load during the rehabilitation sessions. Furthermore, this could change the perspective of the physical or occupational therapy done to slow the progression of the disease before signs become evident.

The contrasting results regarding the OW topic in CMT may be a consequence of the different outcome measures used and the various muscles evaluated in the previous studies. In fact, small muscles like the intrinsic muscles of the hand may be more exposed to the effect of OW.

OW can be defined by 2 functional fields: the strength and the dexterity. In literature, strength is evaluated by Medical Research Council (MRC,<sup>7,8</sup> or by a dynamometer.<sup>8</sup> Indeed, both strength measurements showed controversial results, some authors reporting that the non-dominant hand (NDH) is stronger than dominant hand (DH)<sup>9-12</sup> and other authors stating that DH and NDH have similar strength.<sup>1,11,13</sup> Those who affirm that OW is not present because of both hands are similar, ignore in their discussions the 10% rule. This old rule establishes that grip strength in normal subjects is approximately 10% greater in the DH than in the NDH<sup>14</sup> and this is used by physical therapists as a general guide to set patients goals.<sup>15</sup>

Dexterity has been scarcely investigated. To the best of our knowledge, only 2 studies evaluate dexterity in CMT and they reach opposite conclusions.<sup>1,10</sup>

So, in conclusion there is no stronger evidence for the presence of OW in literature yet and the topic is open to debate.

We investigated strength and dexterity in both hands using different outcome measures in a large population of CMT patients, thus we evaluated the ability of opposition through the TOT,<sup>16</sup> the strength of hand grip and tripod pinch with a dynamometer and the dexterity with an sensor engineered glove test (SEGT) developed by the University of Genoa with the collaboration of ETT S.p.A (Sestri Ponente, Genoa, Italy) and previously tested on CMT patients by our group.<sup>17</sup> We excluded the use of Medical Research Council manual strength evaluation because it depends of the operator.

TOT and tripod pinch strength are reported to be major determinants of manual dexterity in CMT1A,<sup>18</sup> so we expect that these are good measures for the correct evaluation of hands patients.

Finally, we compared both strength and dexterity in CMT patients with normal controls to have a clearer view of the pathological patterns in a prototypical neuromuscular disease as CMT is.

In literature, there is only a paper that compares patients with normal controls strength. In our work, we have compared both strength and dexterity of the CMT patients with normal controls. These are important data because allow us to deepen knowledge in the healthy hand behavior and then understand the pathological pattern.

## 2 | METHODS AND MATERIALS

### 2.1 | Subjects

We selected 120 subject, 60 normal controls and 60 CMT patients attending the Multidisciplinary Outpatients Clinic for Diagnosis and Treatment of Inherited Peripheral Neuropathies at the Policlinico San Martino-IST and Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health (DiNOGMI), University of Genoa, Italy. All patients were diagnosed with CMT1 or CMT2 disease based on clinical, genetic, and electrophysiological findings and were between 19 and 80 years of age. We excluded patients with comorbidities that could interfere with muscle strength or hand function or if they had some surgery at the upper limb. Mean age of the CMT patients was  $51.97 \pm 15.72$  years and only 1 subject was left-handed.

Normal controls were recruited from University of Genoa and Hospital workers, physiotherapy students and their relatives. We excluded controls with carpal or other entrapment syndromes and with a surgery or with other pathologies in the upper limbs. Subjects were matched by age, sex, and hand dominance (Table 1).

Informed consent was obtained according to our institution policy and the declaration of Helsinki.

### 2.2 | Measures

We performed a TOT as described by Kapandji to test the ability of opposition. The opposition test consists of touching the 4 long fingers with the tip of the thumb. The score range is 1 to 10 and is 1 for the

**TABLE 1** General data of the populations examined. Each parameter is matched for the 2 populations

	CMT patients	Normal controls
N	60	60
Age (mean)	50.51 $\pm$ 16.63	51.08 $\pm$ 14.23
Age (range)	19-80	19-80
Male/female ratio	0.87 (28/32)	0.81 (27/33)
Hand dominance (right/left)	59/1	59/1

lateral side of the second phalanx of the index finger, 2 for the lateral side of the third phalanx of the index finger, 3 for the tip of the index finger, 4 for the tip of the middle finger, 5 for the tip of the ring finger and 6 for the tip of the little finger. Then, moving the thumb proximally along the volar aspect of the little finger, the score is 7 when it touches the distal interphalangeal crease, 8 on the proximal interphalangeal crease, 9 on the proximal crease of the little finger and 10 when it reaches the distal volar crease of the hand. This test is valid only if the first stages are possible: a crawling thumb in the palm is not an opposition motion.<sup>16</sup>

Maximal isometric voluntary contraction of both hands was assessed with a hand-held dynamometer (Citec CT 3001; CIT Technics BV, Groningen, The Netherlands) measuring in order triple pinch and hand grip. Both were performed according to a standardized testing procedure.<sup>18,19</sup> We made 3 attempts, alternating the DH and NDH, with a rest of 30 seconds between the tests.

The SEGT was used according to a previously published protocol.<sup>17</sup> Briefly, finger opposition movements were evaluated using motor sequences in a quantitative spatial-temporal way. An “eyes-closed paradigm” was chosen to avoid possible confounding effects because of the integration of acoustic and visual information. The patients were instructed to execute finger opposition movements of different complexities: finger tapping (FT) sequence (opposition of thumb to index) and index-medium-ring-little (IMRL) sequence (opposition of thumb to index, medium ring, and little fingers) at maximum velocity (MV). The tasks consisted in the execution of a repetition of each sequence lasting 30 seconds alternating the hands. Data were processed with customized software from Glove Analyzer System which permits selection to acquisition and experimental protocol. The following parameters were measured: touch duration (TD) or contact time between thumb and another finger (in ms); inter-tapping interval (ITI) or time between the end of the contact of the thumb and another finger and the beginning of successive contact (in ms); movement rate (MR,  $1/[TD + ITI]$ ) or frequency of complete motor task (in Hz).<sup>17</sup>

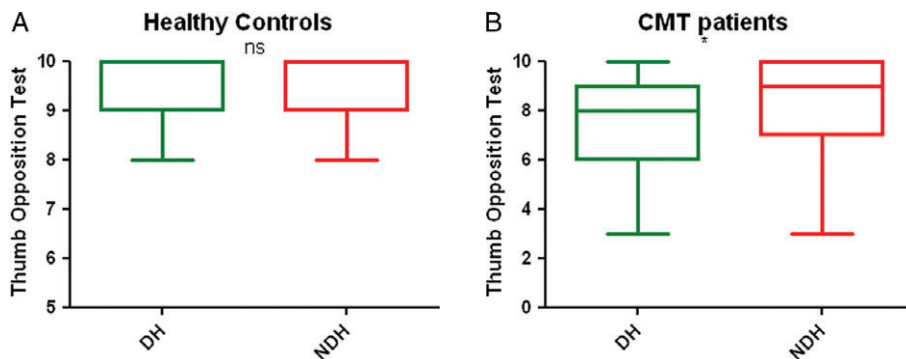
### 2.3 | Statistical analyses

We used a paired samples *t*-test to compare TOT, hand grip, tripod pinch and the different performances of the SEGT between DH and NDH in CMT patients and in normal controls. A *P* value  $\leq .05$  determined significance.

## 3 | RESULTS

### 3.1 | Thumb opposition test

In the TOT performance healthy controls show the same ability of opposition in both hands (Figure 1A; DH:  $9.62 \pm 0.56$ ; NDH:



**FIGURE 1** Thumb opposition test (TOT) in healthy controls compared to Charcot-Marie-tooth (CMT) patients. In the TOT performance healthy controls have shown the same ability of opposition in both hands and with parameters in the normality range (A, dominant hand [DH]:  $9.62 \pm 0.56$ ; non-dominant hand [NDH]:  $9.63 \pm 0.51$ ;  $P = .71$ ). CMT patients, instead, showed a statistically significant impairment of the DH and both hands have a slightly low rate if compared with normal controls (B, DH:  $7.78 \pm 1.95$ ; NDH:  $8.23 \pm 1.72$ ;  $P = .01$ )

$9.63 \pm 0.51$ ;  $P = .71$ ). CMT patients, instead, have a statistically significant impairment of the DH (Figure 1B; DH:  $7.78 \pm 1.95$ ; NDH:  $8.23 \pm 1.72$ ;  $P = .01$ ).

### 3.2 | Dynamometry

Tripod pinch and hand grip measurements are comparable. Normal subjects are stronger in the DH (Figure 2A, tripod pinch: DH:  $92.22 \pm 34.29$  N; NDH:  $84.26 \pm 32.55$  N;  $P < .0001$ ; Figure 2C, hand grip: DH:  $203.70 \pm 79.79$  N; NDH:  $185.40 \pm 72.16$  N;  $P = .0003$ ). CMT patients are not different in strength, between DH and NDH (Figure 2B, tripod pinch: DH:  $54.50 \pm 29.23$  N; NDH:  $53.10 \pm 28.97$  N;  $P = .43$ ; Figure 2D, hand grip: DH:  $117.80 \pm 65.61$  N; NDH:  $122.80 \pm 65.18$  N;  $P = .19$ ).

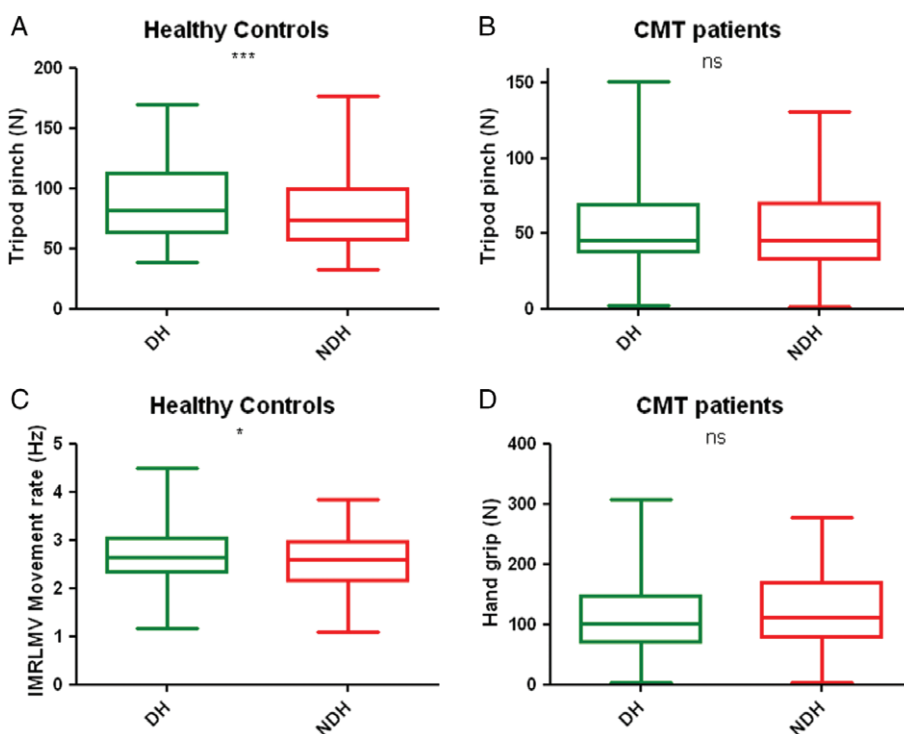
### 3.3 | Sensor engineered glove test

In healthy controls, FT performance, evaluated with MR value, is significantly better in the DH (Figure 3A, DH:  $4.50 \pm 0.85$  Hz; NDH:

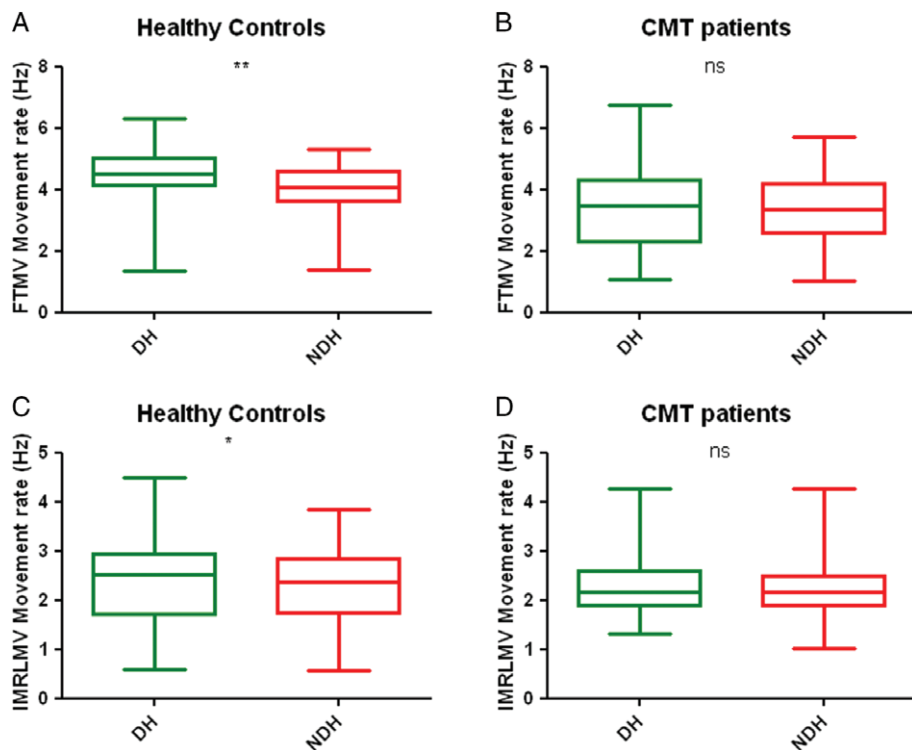
$4.01 \pm 0.88$  Hz;  $P < .0001$ ) and IMRL exercise behaves similarly (Figure 3C, DH:  $2.57 \pm 0.59$  Hz; NDH:  $2.44 \pm 0.57$  Hz;  $P = .02$ ). In CMT patients, FT and IMRL performance are virtually identical in the DH and NDH (Figure 3B, FT: DH:  $3.45 \pm 1.30$ ; NDH:  $3.38 \pm 1.04$ ;  $P = .37$ , Figure 3D, IMRL: DH:  $2.30 \pm 0.67$  Hz; NDH:  $2.30 \pm 0.64$  Hz;  $P = .93$ ).

## 4 | DISCUSSION

OW is a clinically relevant problem which consists in a more accentuated loss of strength in the over exercised or overused muscles. At the hands level this may overlap with the dominant side. The demonstration of OW in CMT patients is fundamental for the education to the right use of the upper limbs in the activities of daily living (ADL) and for a correct rehabilitation. OW is present, at the upper and lower limbs level, in other neurological disorders, as post-polio syndrome,<sup>3</sup> facio-scapulo-humeral dystrophy,<sup>6</sup> Duchenne muscular dystrophy<sup>5</sup>



**FIGURE 2** Dynamometry test in healthy controls compared to Charcot-Marie-tooth (CMT) patients. Triple-pinch and hand grip measurements are comparable in both healthy controls and CMT patients. Normal subjects are stronger in the DH (A, triple pinch: dominant hand [DH]:  $92.22 \pm 34.29$  N; non-dominant hand [NDH]:  $84.26 \pm 32.55$  N;  $P < .0001$ ; C, hand grip: DH:  $203.70 \pm 79.79$  N; NDH:  $185.40 \pm 72.16$  N;  $P = .0003$ ). CMT patients are not different in strength, between DH and NDH (B, triple pinch: DH:  $54.50 \pm 29.23$  N; NDH:  $53.10 \pm 28.97$  N;  $P = .43$ ; D, hand grip: DH:  $117.80 \pm 65.61$  N; NDH:  $122.80 \pm 65.18$  N;  $P = 0.19$ )



**FIGURE 3** Sensor engineered glove test (SEGT) performances in normal controls compared to Charcot-Marie-tooth (CMT) patients. In healthy controls, the exercises performances (in finger tapping, FT and in index-medium-ring-little, IMRL), evaluated with movement rate (MR) value, was significantly better in the dominant hand (DH) (A, FT DH:  $4.50 \pm 0.85$  Hz; non-dominant hand [NDH]:  $4.01 \pm 0.88$  Hz;  $P < .0001$ ; C, IMRL DH:  $2.57 \pm 0.59$  Hz; NDH:  $2.44 \pm 0.57$  Hz;  $P = .02$ ). In CMT patients, FT and IMRL performances are virtually identical in the DH and NDH (B, FT: DH:  $3.45 \pm 1.30$ ; NDH:  $3.38 \pm 1.04$ ;  $P = .37$ , D, IMRL: DH:  $2.30 \pm 0.67$  Hz; NDH:  $2.30 \pm 0.64$  Hz;  $P = .93$ )

and amyotrophic lateral sclerosis (ALS).<sup>4</sup> In these diseases, overuse of muscles increases the progression of deficit.

Despite opposite stances reported in the literature, we detected the OW in the hands function of CMT patients studying the strength and the functional aspects and, importantly, using healthy controls to investigate the normal behavior of both hands.

Furthermore, while other studies used as strength evaluation the Medical Resource Council (MRC) scale which is a subjective type of evaluation,<sup>20</sup> we used only quantitative methods.<sup>1</sup>

Finally, we tested the dexterity of the subjects with an innovative quantitative operator-independent method, the SEGT.<sup>17</sup> Although the effect of the hand dominance in the dexterity in normal subjects is unknown, we expect that DH performs better than NDH. In CMT patients, there are few works that affirms to evaluate the dexterity with the 9 hole peg test, and even if the results reported seem to be accurate and responsive, they refer to a small population.<sup>1,21</sup>

Healthy controls of our study are homogeneous to CMT patients in terms of number of subjects enrolled, age, sex, and hand dominance. Females, in both groups, are slightly more numerous than males. Finally, population sample is homogeneously distributed between axonal and demyelinating CMT.

We compared the TOT which is one of the major determinants of the manual dexterity in CMT,<sup>18</sup> so we hypothesized that this parameter could be affected by OW. Indeed, TOT evaluates the ability of opposition of the thumb and could be considered an indirect measure of the range of movement of the hand and, considering that in CMT hand deformities develop along the time, they may depend to overuse.

Healthy controls have no differences between DH and NDH and the average value is in the normal limits. As expected, in CMT patients the TOT is significantly impaired compared to normal controls.

However, according to our hypothesis of OW, the DH shows significant better scores than NDH. We can speculate that hand deformities occur first in the DH, because of muscular weakness.

Then, we evaluated the behavior of the strength of the intrinsic and extrinsic muscles, using the tripod pinch and the hand grip at dynamometry.<sup>22</sup> In healthy controls, the DH is stronger than NDH and we can confirm the 10% rule<sup>14,23-25</sup> in a population of prevalent right handed subjects. Likely, in a population of left-handed subjects there is not a stronger hands, as already demonstrated.<sup>15</sup> On the contrary, in CMT patients the strength of the tripod pinch and of the hand grip is similar in DH and NDH, not respecting the 10% rule. We then speculate that DH in CMT patients loses strength more than the NDH during the time following a normal overuse.

As expected, in both hand grip and tripod pinch, CMT patients show less strength than healthy controls, as expected.

Dexterity, a compromised ability in CMT patients, has been evaluated with an innovative quantitative tool, which is reliable and sensitive as previously demonstrated,<sup>17</sup> the SEGT. This glove is a very interesting instrument because is very easy to use and the evaluation takes little time. Based on previous observations, we considered the FT and IMRL exercises at the maximum velocity with eyes closed paradigm.<sup>17</sup>

In both exercises, normal subjects have a statistically significant better performance in the DH, proving the superiority of the DH<sup>25</sup> even in the dexterity.

As previously reported, CMT patients show worst performance than normal controls at the SEGT (Figure 3).

Interestingly, in CMT patients, the performances of the DH and the NDH are virtually identical. These data confirm our speculation that CMT patients DH lose the dexterity more in the DH than in the NDH, due to the overuse of the former to the latter.

Even in the SEGT measurements, control subjects' performances are significantly better than CMT patients (similarly to the shown results in the previous paper.<sup>17</sup>

In conclusion, this is the first study that considers different evaluations of the hand of CMT patients and compares data with healthy controls, matched for age, sex, and hand dominance. CMT patients show a reduced ability of opposition, strength and dexterity in both hands compared with normal subjects but their DH is worst than NDH at least in some measurements. Other ones are equal in DH and NDH of CMT patients. Taken together, those results an indirect demonstration of the existence of the OW phenomenon. This observation has practical implications to schedule preventive occupational therapy sessions and to plan a correct rehabilitative program. It is important to avoid the overload of the DH and to teach the patients to stop the activities when the fatigue sensation begins. These fundamental precautions are intended to slow the disease progression at least at the UL level.

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