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Scientific/Clinical Article

Kinematic evaluation for impairment of skilled hand function in chemotherapy-induced peripheral neuropathy

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ARTICLE INFO

ABSTRACT

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) usually affects both sensory and motor function of hands and feet, resulting in impaired skilled hand function (e.g., typing a keyboard). However, quantitative and objective evaluations for this condition have not been established.
Purpose of the Study: We evaluated skilled hand function using a kinematic analysis and investigated relationships among hand kinematic function and the clinical sensory and motor features of CIPN.
Study Designs: Clinical measurement.
Methods: Twelve CIPN patients and 12 age-matched control participants were enrolled. We recorded their reach and grasp movements using a three-dimensional measurement system, and calculated the normalized jerk of these movements as quantitative indexes of skilled hand function. Additionally, we used the number of sequential hand grip–release cycles in 10 seconds as an evaluation of clinical motor function.
Results: Our kinematic analyses revealed significant difference in normalized jerk of grasp movement (CIPN: 3.7 ± 0.2, control: 3.4 ± 0.1; $P = .005$), but this was not the case for reach movement (CIPN: 2.5 ± 0.1, control: 2.5 ± 0.2; $P = .43$), indicating that the distal part of the forearm is particularly affected in CIPN. Such disturbed grasp movement was directly correlated with poor scores on the hand grip–release test and the sensory tests.
Discussion: We revealed deficit impaired hand function objectively and quantitatively in CIPN patients using a kinematic analysis. Further, the hand grip test could represent such kinematic abnormality and could be useful for evaluating skilled hand function of CIPN patients.
Conclusions: Our kinematic and clinical measurements objectively and quantitatively evaluate skilled hand function in individuals with CIPN in clinical settings.
Level of Evidence: Cross-sectional observational study.

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Introduction

Cancer is a major burden of disease worldwide. Improvements in early diagnosis and treatment have led to an ever-increasing number of cancer survivors, and cancer survivorship is currently a worldwide concern. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common complications of cancer treatments, with an incidence of 30%-70% in cancer patients receiving chemotherapy.[1-3] Patients with CIPN feel moderate-to-severe numbness in the distal portion of the extremities, spreading to the stocking-glove pattern, and CIPN usually interferes with both the sensory and motor function of the hands and feet, resulting in impaired activities of daily living. Particularly, impairment of skilled hand function (eg, typing a keyboard) due to CIPN can affect the ability of cancer patients to function at work.[4] Given the serious impact of this condition, the National Cancer Institute Common Terminology Criteria for Adverse Events includes CIPN,[5] and physical and occupational rehabilitation were thought to be effective for such hand function disorders after chemotherapy.[6] However, the severity of the impaired skilled hand function is evaluated almost entirely based on CIPN patients' descriptive reports. Several assessment tools have been developed to measure movement disorders for CIPN, but most of these use

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Conflict of interest: All named authors hereby declare that they have no conflicts of interest to disclose.
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questionnaires and lack consistent reliability and validity.[7-9] These tools do not seem to be sensitive enough to determine the effects of rehabilitation accurately. Furthermore, as severe CIPN can lead cancer patients and physicians to interrupt or discontinue chemotherapy in clinical practice, the objective evaluation tool of CIPN is a necessity.

In the present study, we addressed 2 aims. The first was to objectively and quantitatively conduct kinematic analyses of skilled hand function (ie, eye-hand coordination) in patients with CIPN using a 3-dimensional measurement system. The second aim was to investigate relationships between skilled hand function and clinical features, such as motor dysfunction and numbness of the hands, and identify a surrogate marker for hand function in clinical settings.

Methods

Participants

Twelve patients with CIPN (age, mean, 64.9 ± 8.0 standard deviation years; 5 women) and 12 age-matched adults (mean, 66.7 ± 13.7 standard deviation years; 4 women) participated in this study. All the CIPN patients reported perceived numbness with or without neuropathic pain due to chemotherapy. Participants included 6 patients with breast cancer; 2 with lymphomas, 1 with multiple myeloma, 1 with lung cancer, 1 with pancreatic cancer, and 1 with prostate cancer. They had been treated with 1 or a combination of antineoplastic agents, such as taxanes, platinum compounds, and vincristine, which are all known to be strongly neurotoxic. The CIPN disease duration of those in the CIPN group was 25.1 ± 21.3 months. All CIPN patients were outpatients at The University of Tokyo Hospital. Control participants who did not have any diseases affecting their hands were selected randomly from middle-aged or senior patients who were referred to the hospital after complaints of lumbago or pain in their lower leg. The ethical review board of the institute approved this study. We explained the purpose and protocol of this study to all participants and obtained their written informed consent. The following clinical and kinematic data were collected for the dominant hand. This study is registered in the University Medical Information Network (UMIN; trial ID: UMIN000017129).

Clinical sensory evaluation

To evaluate tactile sensory function, we measured the detection threshold for light touch using von Frey filaments (log of force, 1.65-6.65) based on the standard testing measures.[10] Applying each filament until it bent onto the volar surface of the distal phalanx for 1.5 seconds at least 5 times, we conducted the tactile sensory evaluation in an ascending fashion to minimize patient fatigue. Starting with the 2.36 filament as the baseline, the evaluation was continued using filaments of increasing weight until immediately when the participants stated that they perceived a touch or 6.65 was reached. We interpreted the tactile detection threshold as the force value of the first filament weight that participants perceived. All CIPN patients in the present study felt numbness in the distal portion of the extremities, so the numbness was rated on an 11-point numerical rating scale (NRS: 0 = no numbness and 10 = highest possible degree of numbness).

Clinical motor function test

We clinically evaluated skilled hand function using the hand grip—release test, which has been validated in patients with cervical myelopathy.[11-13] The participants were asked to make a grip and release movement with their fingers as rapidly as possible, with their arm kept in the same position. We counted the number of complete cycles of sequential grip-and-release movements during a 10-second period. Normal adults can reportedly perform the sequential grip-and-release movement more than 20 times in 10 seconds.[11-13]

Three-dimensional kinematic analyses of skilled hand function

We recorded kinematic data with a portable electromagnetic motion tracking system (3 SPACE FASTRAK; Polhemus Inc). This system generated a hemispherical electromagnetic field with a radius of 76 cm, which is sufficiently large to measure upper limb movements. The system measured the 3-dimensional position and orientation of 3 sensors that were attached to the tips of the index finger and thumb and to the lateral epicondylus of the wrist. The locations of the sensors in the field were collected at a sampling rate of 40 Hz, and the data were stored on a personal computer.

Participants were seated comfortably in front of a table. Two vertical bars (both 3 cm in diameter and 10 and 30 cm high, respectively) were placed on a flat board located on the table. Both bars were aligned with respect to the sagittal body at midline of the participant. The top ends of the bars were set as the start and goal points. The shorter start bar was placed 10 cm away from the participant, and the goal bar was located 30 cm further from the start bar (ie, 40 cm away from the participant) (Fig. 1). The participants were asked to first pinch the tip of the start bar with their thumb and index finger, which were oriented in an anteroposterior direction (starting position), and then move their hand from the start position to reach and pinch the tip of the goal bar (goal position). The participants were asked to repeat this sequential movement process 10 times at a comfortable pace.

Recorded data from the 3 sensors were filtered with a second-order Butterworth band pass filter at 10-40 Hz. All data analyses were performed using custom-made algorithms in Matlab, version R2014b (MathWorks, Natick, MA, USA). The data
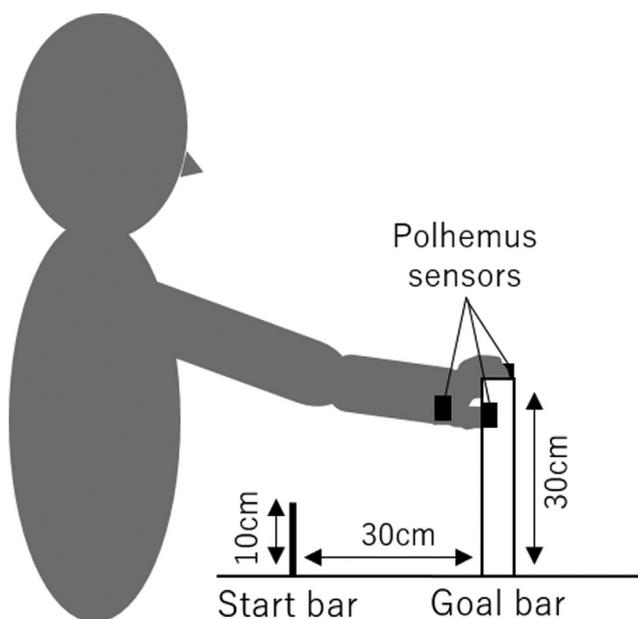

Fig. 1. Experimental setup of 3-dimensional kinematic recording for evaluating skilled hand function.

recorded from the wrist reflected reach movement, and distance between the index finger and thumb reflected grasp movement. Movement phases of reach or grasp movements were defined as the phases in which the absolute velocity of the movements exceeded 5 cm/s.

Reach and grasp movements were quantified by normalized jerk (NJ) measures. Jerk is mathematically defined as the third time derivative of a specific limb position variable, and minimization of jerk indicates smooth movement of a limb.[14-16] NJ_{reach} and NJ_{grasp} were calculated by the following equations. We calculated the jerk as the third time derivative of the distance data and calculated the integral value of the squared jerk. The calculated integral value was divided by 2. To normalize the dependency on movement duration (MD) and length (L), the calculated value was multiplied by MD^5/L^2. In these equations, MD represents the time between the start and end of a reach or grasp movement. L_{hand} represents the shortest distance between the start and end positions of the hand, and L_{grasp} represents the difference in grasp aperture between the start and end of a grasp movement. NJ_{reach} and NJ_{grasp} were log transformed to meet the assumptions for normality.

$$NJ_{reach} = \sqrt{\frac{1}{2}\int_{t(start)}^{t(end)} jerk_{reach}^2(t)\mathbf{d}t * \frac{MD^5}{L_{hand}^2}}.$$

$$NJ_{grasp} = \sqrt{\frac{1}{2}\int_{t(start)}^{t(end)} jerk_{grasp}^2(t)\mathbf{d}t * \frac{MD^5}{L_{grasp}^2}}.$$

Statistics

The Shapiro-Wilk test demonstrated that the results of $LogNJ_{reach}$, $LogNJ_{grasp}$, NRS of numbness, and the grip-release test had normal distributions but that the tactile threshold did not. We analyzed $LogNJ_{reach}$, $LogNJ_{grasp}$, NRS of numbness, and the grip-release test results using independent t tests to compare kinematic and clinical data between the CIPN patients and control participants. The Mann-Whitney U test was used to compare tactile threshold in the CIPN patients with that in the control participants. We used the Pearson correlation test to investigate the relationships among $LogNJ_{reach}$, $LogNJ_{grasp}$, NRS of numbness, and scores on the hand grip–release test. Regarding the correlations between tactile threshold and other variables, we used Spearman's rank correlation test because the tactile threshold showed a non-normal distribution. We used SPSS, version 17.0 (SPSS, Chicago, IL) for statistical analyses, and the level of significance was set to 5%.

Table 1
Comparison of the kinematic and clinical outcomes between CIPN patients and control patients

Outcomes/Groups	CIPN patients ($n = 12$)	Control subjects ($n = 12$)	P
$LogNJ_{grasp}$	3.7 ± 0.2	3.4 ± 0.1	.005[a]
$LogNJ_{reach}$	2.5 ± 0.1	2.5 ± 0.2	.43
Tactile detection threshold (log force)	3.58 ± 0.67	2.68 ± 0.27	<.001[a]
Numbness (NRS)	5.3 ± 3.1	0.0 ± 0.0	<.001[a]
Hand grip–release test (number)	16.6 ± 6.2	21.2 ± 6.2	.08

CIPN = chemotherapy-induced peripheral neuropathy; NJ = normalized jerk; NRS = numerical rating scale.
[a] Significant at $P = .05$ level.

Results

We revealed that not only clinical measurements (ie, tactile threshold and numbness), except for the hand grip–release function, but also kinematic data are impaired in CIPN patients compared with control participants. The hand grip test results were not significantly different but were relatively impaired in CIPN patients, and these results demonstrated correlations with other clinical and kinematic measurements.

Comparisons of clinical measurements between CIPN patients and control participants

The tactile detection threshold and degree of numbness in CIPN patients (tactile = 3.58 ± 0.67; numbness = 5.3 ± 3.1) were higher than those in control participants (tactile = 2.68 ± 0.27, P < .001; numbness = 0.0 ± 0.0, P < .001) (Table 1). Hand grip–release test scores in CIPN patients were not significantly different but tended to be higher than those in control participants (CIPN: 16.6 ± 6.2, control: 21.2 ± 6.2; P = .08).

Comparisons of kinematic data between CIPN patients and control participants

Figure 2 shows examples of the time-series kinematic data concerning aperture length, grasping velocity, acceleration, and jerk in patients with CIPN and control participants. We found a significant difference in $LogNJ_{grasp}$ values between groups (CIPN: 3.7 ± 0.2; control: 3.4 ± 0.1; P = .005), but this was not the case for $LogNJ_{reach}$ (CIPN: 2.5 ± 0.1; control: 2.5 ± 0.2; P = .43).

Correlations among clinical measurements and kinematic data

In CIPN patients, $LogNJ_{grasp}$ was significantly correlated with the tactile detection threshold ($r = 0.54$; $P = .03$), numbness ($r = 0.64$; $P = .01$), and hand grip–release test scores ($r = -0.59$; $P = .02$; Fig. 3; Table 2). In contrast, the control participants did not show significant correlations: tactile threshold: $r = -0.03$, $P = .46$; numbness: *statistics could not be conducted because all data were 0*; and hand grip–release test: $r = -0.31$, $P = .16$ (Fig. 3). $LogNJ_{grasp}$ values for both CIPN patients and the control participants were not significantly correlated with $LogNJ_{reach}$ values (CIPN: $r = 0.32$, $P = .14$; control: $r = 0.38$, $P = .11$; Fig. 3). The correlation between tactile detection threshold, numbness, and hand grip–release test scores did not reach significance in either CIPN patients or control participants ($P < .05$) (Table 2).

Discussion

CIPN is associated with motor and sensory abnormalities in the distal upper and lower limbs, with a glove-and-stocking distribution.[1,2] Regarding sensory abnormalities, CIPN patients complain of sensory loss or hypoesthesia, usually perceive numbness, and sometimes report neuropathic pain. Motor abnormalities in individuals with CIPN are characterized by impaired skilled hand function, coupled with sensory abnormality. The results of the present kinematic analyses demonstrate that reach movements are smooth, whereas grasp movements are clearly affected in individuals with CIPN. The difference in the $LogNJ_{grasp}$ values between the CIPN patients and the control participants reached significance, and such an impaired $LogNJ_{grasp}$ would be clinically relevant, based on the following. In a previous report using post-stroke patients with clinically relevant motor paralysis,[14] the $LogNJ_{grasp}$ data were almost comparable with our results. In fact, the aperture trajectories indicated the impaired movement
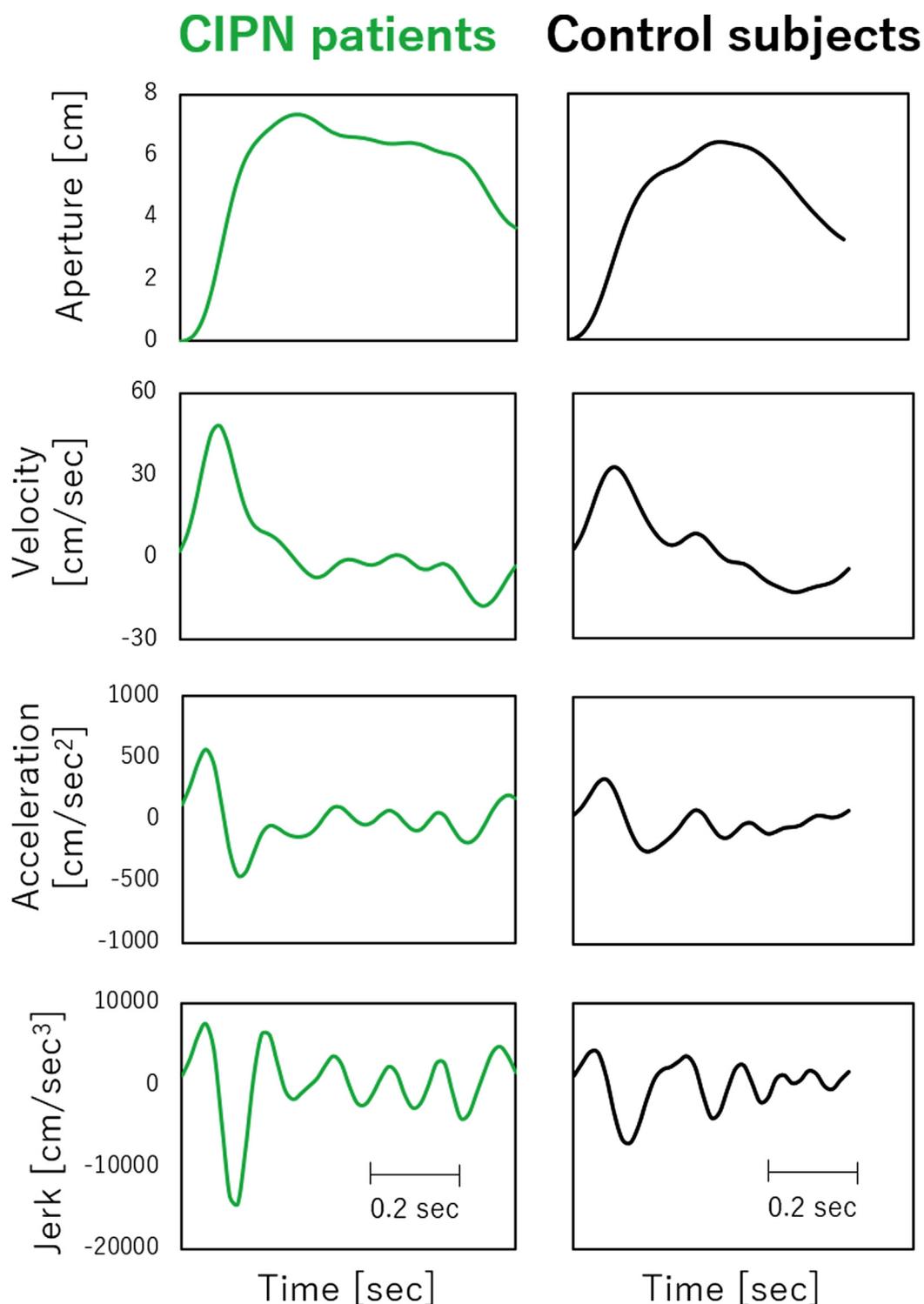
Fig. 2. Examples of kinematic analyses data concerning aperture length, aperture velocity, aperture acceleration, and aperture jerk in a CIPN patient (*green*) and control participant (*black*). The amplitude of the jerk in the CIPN patient was higher than that in the control participant. CIPN = chemotherapy-induced peripheral neuropathy.

smoothness (Fig. 2), and the present patients complained about their difficulty with skilled finger movements (eg, fastening the buttons on their coat). Reach movements mainly reflect the motor function of the proximal muscles of the upper limb, and grasp movements require fine movement control of hands and fingers as well as eye-hand coordination.[17,18] Thus, our methods appear to have successfully captured the features of CIPN, indicating that our

kinematic analysis could be a useful technique for evaluating CIPN objectively and quantitatively.

Previous evaluations using questionnaires about CIPN are certainly qualitative but not quantitative. Answers from patients can be biased by their psychological conditions and hand function before chemotherapy (eg, "Do you have trouble buttoning buttons?" "Do you have trouble feeling the shape of small objects
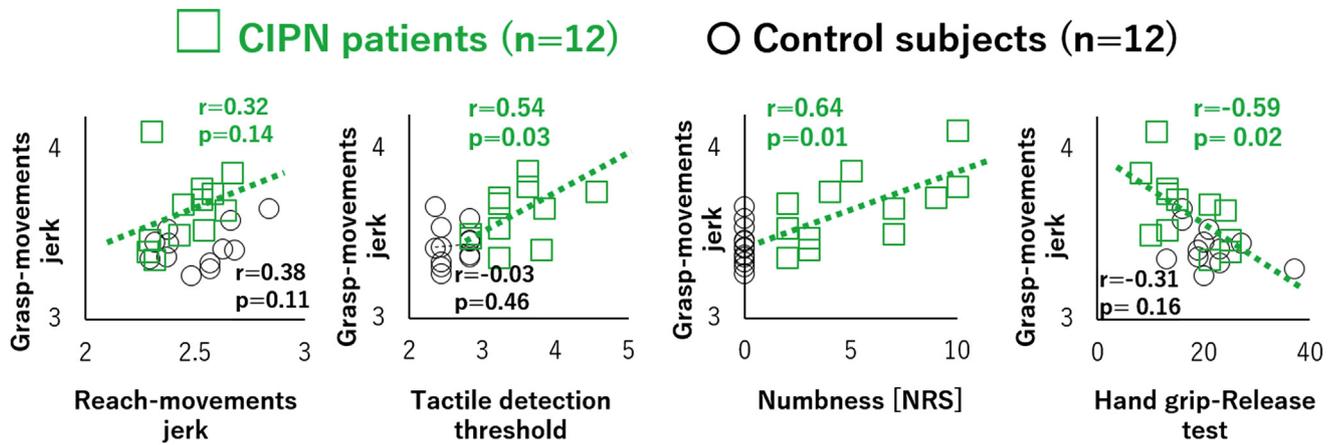
Fig. 3. Correlations between grasp movement jerk and the tactile detection threshold (von Frey test), numbness, hand grip−release test data in CIPN patients (*green square*) and control participants (*black circle*). In CIPN patients, grasp movement jerk, which was normalized by a log conversion, was positively correlated with tactile detection thresholds and numbness and negatively correlated with hand grip−release test scores but did not reach movement jerk. CIPN = chemotherapy-induced peripheral neuropathy; NRS = numerical rating scale.

when they are in your hand?").[4] Such evaluations are not enough to determine tailored physical and occupational therapy for individual CIPN patients. Alternatively, our kinematic evaluation can be purely quantitative and minimize such subjective bias. Based on the precise kinematic data, we could plan the rehabilitation program for individual CIPN patients. However, our kinematic analysis has a disadvantage in a clinical setting. Obtaining the precise data required a set of complicated pieces of apparatus and procedural training. Conversely, the hand grip−release test is simple and easy for almost all populations to complete and provides objective and quantitative evaluations of hand function in a clinical setting. The score on the hand grip−release test in the present study significantly correlated with the kinematic data. This test able to sensitively trace the progress of skilled hand function in accordance with nerve damage has been previously confirmed.[11-13] Along with the previous literature and our correlation analysis, the hand grip−release test has a potential as a surrogate assessment tool for the impairment of skilled hand function characteristic of CIPN. In addition, the hand grip−release test can be conducted in only 10 seconds, and patients can evaluate its severity by themselves. In

future, longitudinal changes associated with cycle numbers of chemotherapy should be recorded to verify its usefulness as a screening tool of both sensory and movement disorders of CIPN.

In addition, we thought the usefulness of movement evaluation as an indicator for nerve damage. Clinical sensory evaluations (hypoesthesia and numbness) were also correlated with skilled hand abnormalities. Meanwhile, none of these correlations were observed in control participants. Numbness and pain are modulated in an interactive way and are vulnerable to several factors such as analgesics and psychosocial conditions.[19] As a result, these subjective sensory complaints are usually mismatched with the extent of nerve damage.[20,21] Meanwhile, measurements of the degree of motor dysfunction are generally accurate reflections of nerve damage.[22] Effective evaluations of CIPN in cancer patients are important for preventing irreversible nerve damage subsequent to CIPN, as well as maintaining patient quality of life and cancer survivorship.[23] As mentioned, severe CIPN may lead physicians and patients to unwillingly interrupt or discontinue chemotherapy. Motor assessments of CIPN are advantageous because motor function is more directly linked to nerve conditions. Future studies, including those with

Table 2
Correlation coefficient among kinematic and clinical evaluations, *r* (*P*)

Outcomes/Groups	LogNJ$_{grasp}$	LogNJ$_{reach}$	Tactile threshold	Numbness	Grip-release test
LogNJ$_{grasp}$					
CIPN	−	0.33 (0.14)	0.54 (0.03)[a]	0.64 (0.01)[a]	−0.59 (0.02)[a]
Control		0.38 (0.11)	−0.03 (0.46)	NA	−0.40 (0.09)
LogNJ$_{reach}$					
CIPN		−	0.23 (0.23)	0.19 (0.28)	−0.43 (0.08)
Control			−0.41 (0.09)	NA	−0.01 (0.49)
Tactile threshold					
CIPN			−	0.38 (0.11)	−0.12 (0.35)
Control				NA	0.15 (0.31)
Numbness					
CIPN				−	−0.45 (0.07)
Control					
Grip-release test					
CIPN					−
Control					

NJ = normalized jerk; CIPN = chemotherapy-induced peripheral neuropathy NA = not available.
NA = statistics could not be conducted because all data were 0.
[a] Significance was set at *P* = .05 level.

larger samples, should examine the sensitivity and specificity of this test with respect to CIPN diagnosis, tracing temporal symptom changes, and clinical utility in decision making regarding chemotherapy, quality of life, and survivorship in cancer patients.

We should consider the present limitations of this study and future perspectives. We could not determine the cutoff values of respective measurements for the impairment of skilled hand function because of the present small sample size and the cross-sectional observation. Using more participants and age-matched controls, a longitudinal study design would help to determine the cutoff values to screen CIPN. Also, the relationships between our quantitative evaluation of skilled hand function and neurotoxicity should be observed in future studies, in which validated international standard outcome measures of CIPN are evaluated, like the Total Neuropathy Score and the National Cancer Institute-Common Toxicity Criteria.[24]

Conclusion

We used a kinematic analysis to reveal the impairment of skilled hand function in CIPN objectively and quantitatively. Furthermore, the hand grip test correlated well with the kinematic abnormality. These quantitative evaluations will contribute to tailored physical and occupational therapy for individual CIPN patients.

Acknowledgments

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Quiz: # 588

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\# 1. CIPN usually involves
  a. sensory elements
  b. motor elements
  c. sensory and motor components
  d. psychosocial components

\# 2. Prior to this study there was
  a. little to no compelling data on evaluation of CIPN
  b. a plethora of data on evaluation of CIPN
  c. controversy as to how to manage CIPN
  d. universal agreement on how to manage CIPN

\# 3. Kinematic analysis focused on
  a. grip strength
  b. AROM
  c. limitations due to the anticipation of pain
  d. grasp and reach tasks

\# 4. Kinematic data were recorded
  a. manually by the supervising CHT
  b. by clinical videography
  c. with a sophisticated tracking system that is typically not found in most hand therapy clinics
  d. with a standard tracking system found in most hand therapy clinics

\# 5. Hand grip test results correlated well with kinematic abnormality
  a. true
  b. false

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