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Comparison of Clinical vs. Electrophysiological Methods of Diagnosing of Essential Tremor

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Abstract: Essential tremor (ET) may be differentiated from normal or enhanced physiological tremor based on a clinical examination or electrophysiological tests such as quantitative computerized tremor analysis. There have been few head to head comparisons of the two methods. Our objective was to estimate diagnostic agreement between these two methods. Cases and controls underwent a clinical evaluation (interview and videotaped examination) and an electrophysiological evaluation (quantitative computerized tremor analysis using accelerometry and electromyography) on the same day, and diagnoses were independently assigned using clinical vs. electrophysiological criteria. Agreement between diagnoses was assessed with a concordance rate and kappa statistic (κ).Thirty-two (59.3%) of 54 subjects were diagnosed clinically as ET (possible, probable, or definite), compared with 35 (64.8%) of 54 based on tremor analysis. The concordance rate between the two methods of diagnosis was 94.4% (51 of 54). κ was 0.88, indicating a level of agreement between diagnoses that was in the "near perfect" range. All of the subjects who received electrophysiological diagnoses of definite ET also received clinical diagnoses of ET. Conversely, all of the subjects who received clinical diagnoses of definite ET also received electrophysiological diagnoses of ET. The agreement between the clinical and electrophysiological diagnosis of ET was substantial, suggesting that study protocols that were to utilize either technique would arrive at similar diagnostic conclusions. In addition, physiological testing can quantify potentially valuable subclinical measurements as well as detect possible additional cases of ET not diagnosed as such during clinical assessments. © 2001 Movement Disorder Society.

Key words: essential tremor; diagnosis; physiology; reliability; validity

The diagnosis of essential tremor (ET) and its differentiation from other types of tremor is frequently difficult.[1,2] One study suggested that as much as 50% of clinical diagnoses of ET are incorrect.[2] It can be particularly difficult to differentiate mild ET from normal or enhanced physiological tremor. This is problematic both in research studies (especially genetic studies),[3–5] where investigators frequently are confronted with the task of trying to diagnose ET among mildly tremulous family members, and in clinical practice settings, where clinicians may be confronted with young patients who have rapid tremor of relatively low amplitude. In many instances, ET and normal or enhanced physiological tremor may be differentiated using clinical criteria[6–9] or electrophysiological tests such as quantitative computerized tremor analysis.[10–12] Because of the objectivity and precision of tremor analysis, and its ability to collect information on tremor frequency, it could be perceived as a gold standard against which the clinical diagnosis of ET could be validated. Despite this, there are few case by case comparisons of the two methods.[10]

We studied a group of ET cases and normal control subjects, independently assigning diagnoses based on a set of clinical vs. electrophysiological criteria. Our goal was to examine the diagnostic agreement between these two methods. Ultimately, the accurate diagnosis of tremor is of fundamental importance to clinicians and patients because discussions about prognosis and the selection of appropriate medical treatment depend on tremor type.[13]

METHODS

ET Cases and Control Subjects

All subjects were participating in a case control study of the functional correlates of tremor.[14,15] In order to

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study individuals with a broad range of tremor severities, ET cases were ascertained both from a community and from a treatment center.[14] Therefore, ET cases came from either one of two sources: the Washington-Heights Inwood community in northern Manhattan, NY,[16,17] or the Center for Parkinson's Disease and Other Movement Disorders at Columbia-Presbyterian Medical Center, New York, NY. Control subjects also came from the same two sources; either they were control subjects from the Washington-Heights Inwood community,[16,17] or they were normal spouses of patients at the Center Parkinson's Disease and Other Movement Disorders. Details regarding the ascertainment of subjects from these different sources and the assignment of diagnoses have been documented previously.[14–17]

All subjects who were enrolled underwent a clinical evaluation (interview and tremor examination). Because some subjects lived as far as 2 hours from Columbia-Presbyterian Medical Center, they were given the choice of an in-home evaluation or an evaluation at the medical center. Subjects who chose to be evaluated at the medical center underwent physiological testing using the protocol described below; those who were evaluated in their homes did not. Because the purpose of the current analyses was to compare clinical vs. electrophysiological methods of diagnosis, we analyzed data only on the subjects who underwent both a clinical evaluation and electrophysiological testing. There were no differences in age or disease duration between the 36 ET cases who underwent electrophysiological testing and the 53 who did not.

Clinical Protocol and Assignment of Clinical Diagnoses

All subjects underwent an in-person semi-structured tremor interview and a videotaped tremor examination.[14–17] The interviewer collected information on the distribution and severity of tremor, and use of different tremor medications. The 26-item videotaped tremor examination was designed to elicit tremor during one posture (sustained arm extension) and five actions (pouring water, drinking water, using a spoon, finger-to-nose movements, and drawing spirals). Each was performed with the dominant arm and nondominant arm.[16,17] The examination was videotaped using a manually operated video camera recorder (Sony CCD-TR700, Park Ridge, NJ). Hi-8 videotapes were used to increase the resolution of the recording, and physiological or enhanced physiological tremor was visible in 96% of the control subjects' recordings.[18]

One neurologist (E.D.L.) reviewed each subject's videotaped tremor examination, and rated the severity of tremor observed during the posture and different tasks.[14,15] Ratings were: 0 (no visible tremor); 1 (low amplitude tremor or intermittent tremor); 2 (tremor of moderate amplitude which was clearly oscillatory and usually present); 3 (large amplitude tremor resulting in difficulty completing the task). A total tremor score (range = 0–36 [severe tremor]) was assigned to each subject based on the 0–3 ratings for 12 items (six tasks with each arm). The neurologist then assigned a diagnosis of ET or normal.[16,17] Diagnoses of clinically definite ET required: postural tremor rated as ≥ 2, kinetic tremor rated as ≥ 2 during four of five actions, and tremor that by history interfered with ≥ 1 activity of daily living (ascertained through six interview questions). Clinically probable ET required a kinetic tremor rated as ≥ 2 during four of five actions. Clinically possible ET required a tremor rated as ≥ 2 during a minimum of three actions.[16,17] Patients with isolated head tremor were not included in the current analyses; therefore, all ET cases met clinical criteria for ET based on the presence of arm tremor.

Electrophysiological Protocol and Assignment of Electrophysiological Diagnosis

Subjects who were evaluated at the medical center underwent a standardized electrophysiological protocol to characterize objectively and quantitatively kinematic and physiologic features of distal arm tremors. For this study, the protocol consisted of quantitative computerized tremor analysis using accelerometry and electromyography. Analyses were performed in the Motor Neurophysiology Laboratory at Columbia-Presbyterian Medical Center by a trained engineer.

Testing was performed within 1 hour of the videotaped tremor examination. Frequency, amplitude, electromyographic (EMG) burst discharge firing patterns, and intersignal coherence were evaluated with subjects at rest, with their arms extended, and while performing finger-to-nose movements. Tremors were measured as close to the clinical state as possible by minimizing psychological stress factors and using only essential hardware. Ultra-light piezoresistive uni-axial miniature accelerometers (EGA-25, Entran Devices, Inc., Fairfield, NJ) measured tremor frequency and displacement from the dorsum of each hand at the distal middle metacarpal bone. Silver/silver chloride EMG surface electrodes recorded wrist flexor and extensor activity, preamplified at a gain of 100, and a high-pass filter at 0.1 Hz (BioAmp 100, Axon Instruments, Inc., Foster City, CA) and amplified at a gain of 50 with a low-pass filter at 20 kHz. Analog to digital acquisition occurred at 500 Hz using a 15-μs 16-bit hardware (CyberAmp 380, Axon Instru-

ments, Inc.) over six multiplexed channels (two accelerometry, four EMG). Proprietary software in the Clinical Motor Physiology Laboratory controlled the acquisition and assisted in the analyses of digitized data in the time and frequency domains. Rest measurements were performed with the patients' elbows 90° flexed and supported by the sides of the chair to prevent transmitted upper arm movement. During postural measurements, both arms were flexed at the shoulders, with the forearms, hands, and fingers held straight in a horizontal plane level with the shoulders. Tremor amplitudes were derived off-line by double integration of wrist accelerometric data after filtering out low frequency drift (less than 2 Hz) and averaging. Tremor frequencies were calculated using a fast Fourier transform algorithm to generate autocorrelation spectra. EMGs were full-wave rectified, integrated, and processed with the accelerometric data.

The contribution of peripheral or "mechanical-reflex" factors was determined using 500 gram inertial weights placed over the dorsum of the hands while maintaining the arms extended. For each subject, inertial loading was performed in one hand at a time. Evaluation consisted of time series amplitude analysis, EMG burst pattern measurements, and quantification of their corresponding changes in peak frequencies and power, with and without inertial loading.

The primary neurophysiologist (S.L.P.) was intentionally not present during the acquisition of electrophysiological data and did not meet the subjects. He was provided with the subjects' ages, but not their histories or clinical diagnoses. He was not even aware of the approximate proportion of study subjects who were cases and who were controls. Electrophysiological data were used to assign one of three electrophysiological diagnoses: definite ET, possible ET, or normal. Definite ET required that each of the following three criterion be present: (1) finger-to-nose tremor that had a frequency which was < 8Hz in at least one arm; (2) finger-to-nose tremor that had an amplitude that was > 2.5 mm (measured from the dorsum of each hand at the distal middle carpus bone) in at least one arm; and (3) frequency-invariant EMG peaks with inertial loading. Subjects were diagnosed as possible ET when any one or two of these criteria were met. Subjects who fulfilled none of the criteria were diagnosed as normal. These criteria were based on review of reference data from more than 200 patients with ET evaluated over the past 10 years in the Clinical Motor Physiology Laboratory, and published information on tremor frequency,[19] amplitude,[20] and response to inertial loading.[12,21]

Statistics

Data were analyzed by chi-square (χ^2) tests (categorical variables) and Student's t tests (continuous variables). Because the total tremor score (Fig. 1), and tremor amplitudes and frequencies were not normally distributed, when assessing differences, a nonparametric test (Mann-Whitney U) was used.

We examined the agreement (i.e., reliability) between diagnostic methods. This agreement was assessed using two methods, concordance rates and kappa statistics (κ).[22–24] The concordance rate was the proportion of diagnoses that were the same using clinical vs. electrophysiological criteria. This proportion was converted to a percentage (range = 0% [no agreement]–100% [complete agreement]). Agreement beyond chance was assessed with the kappa statistic (κ).[22–24] κ values were assigned as follows: $\kappa < 0.0$ (poor agreement); 0.0 (no agreement); 0.01 to ≤ 0.2 (slight agreement); 0.21 to ≤ 0.4 (fair agreement); 0.41 to ≤ 0.6 (moderate agreement); 0.61 to ≤ 0.8 (substantial agreement); 0.81 to < 1.0 (near perfect agreement); 1.0 (perfect agreement).[22–24]

RESULTS

Fifty-eight subjects (36 ET cases and 22 control subjects) underwent both a clinical evaluation and a tremor analysis, but four ET cases were excluded from further analyses because they had isolated head tremor. Therefore, 54 subjects remained. Based on their clinical evaluation, each of these 54 received a clinical diagnosis. Thirty-two (59.3%) of 54 were assigned diagnoses of ET (nine possible ET, 10 probable ET, and 13 definite ET) and 22 were diagnosed as normal. Twenty-one (65.6%) of these 32 ET cases were ascertained from the Washington-Heights Inwood community, and 11 (34.4%) from the Center for Parkinson's Disease and Other Movement Disorders at Columbia-Presbyterian Medical Center. ET cases and normal subjects had similar mean ages (74.2 vs. 75.8 years, $F = 0.17$, $P = 0.69$), age ranges (23–98 years vs. 39–94 years), and gender (50.0% vs. 59.1% female, $\chi^2 = 0.43$, $p = 0.51$).

The mean total tremor score of the 32 ET cases was 18.9 (S.D. = 7.6, range = 8–36) compared with 3.4 (S.D. = 2.2, range = 0–10) among the 22 normal subjects ($z = 6.16$, $P < 0.001$; see Fig. 1 for distribution of total tremor scores). One normal subject had a total tremor score that fell within the range of total tremor scores observed in the ET cases (Fig. 1), but this subject, who had eight tremor ratings of 1 and one tremor rating of 2, did not meet our diagnostic criteria for possible ET, which required a kinetic tremor rated as 2 during three actions.

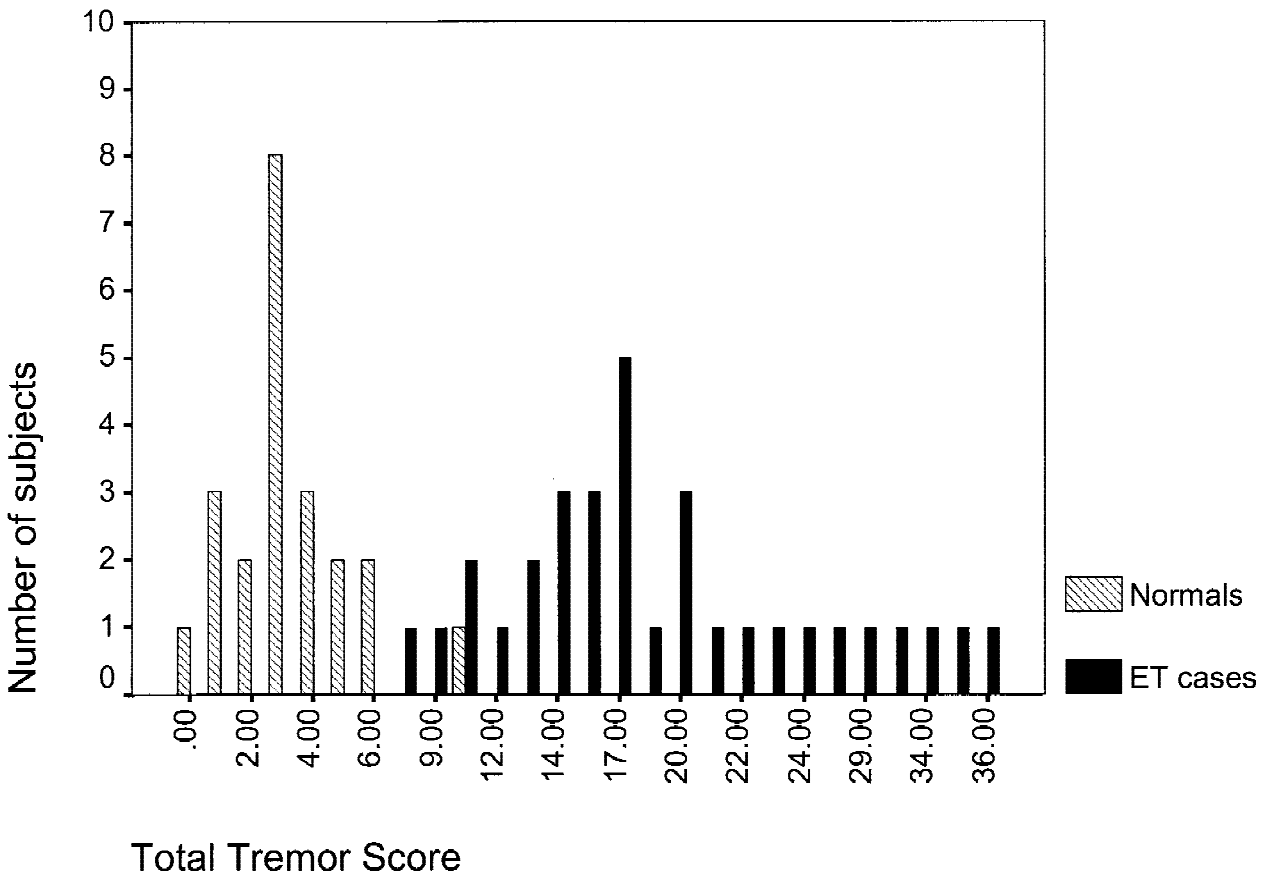

FIG. 1. Total tremor scores of cases and normal subjects. One normal subject had a total tremor score that fell within the range of total tremor scores observed in our essential tremor (ET) cases.

Thirty-five (64.8%) of the 54 subjects received electrophysiological diagnoses of ET (18 definite ET and 17 possible ET). Among these 35, the mean frequency of the finger-to-nose tremor (including data from both the right and left arms) was 5.58 Hz (S.D. = 1.52 Hz), compared with 9.98 Hz (S.D. = 1.82 Hz) among the 19 subjects who were assigned electrophysiological diagnoses of normal ($z = 5.44$, $P < 0.001$). The mean amplitude of the action tremor (including data from both the right and left arms) was 2.66 mm (S.D. = 1.71 mm) among the 35 subjects who received electrophysiological diagnoses of ET, and 1.53 mm (S.D. = 0.76 mm) among the 19 subjects who were assigned electrophysiological diagnoses of normal ($z = 3.04$, $P = 0.002$).

Agreement between clinical and electrophysiological diagnoses is shown for all diagnostic categories (Table 1) and after combining diagnoses of possible, probable, and definite ET into one category (Table 2). The diagnostic concordance rate was 94.4% (Table 2). κ was 0.88 (Table 2), indicating a level of diagnostic agreement that was in the "near perfect" range. Each of the 18 subjects who received an electrophysiological diagnosis of definite ET also received a clinical diagnosis of ET (12 definite ET, five probable ET, and one possible ET). Conversely, each of the 13 subjects who received a clinical diagnosis of definite ET also received an electrophysiological diagnosis of ET (12 definite ET and one possible ET).

Of the 35 subjects who received an electrophysiologi-

TABLE 1. *Comparison of clinical vs. electrophysiological diagnoses of essential tremor (ET)*

	QCTA Diagnosis definite ET	QCTA Diagnosis possible ET	QCTA Diagnosis normal	Total C
Clinical diagnosis Definite ET	12	1	0	13
Clinical diagnosis Probable ET	5	5	0	10
Clinical diagnosis Possible ET	1	8	0	9
Clinical diagnosis Normal	0	3	19	22
Total	18	17	19	54

QCTA, Quantitative computerized tremor analysis.

TABLE 2. *Comparison of clinical vs. electrophysiological diagnoses of essential tremor (ET)*

	QCTA diagnosis ET*	QCTA diagnosis normal	Total
Clinical Diagnosis ET**	32	0	32
Clinical Diagnosis Normal	3	19	22
Total	35	19	54

Diagnoses of ET reflect all levels of diagnostic certainty (possible, probable, and definite).
QCTA, Quantitative computerized tremor analysis.
*Possible and definite ET.
**Possible, probable, and definite ET.

cal diagnosis of ET, 32 (91.4%) received a clinical diagnosis of ET. Three subjects who were clinically normal (with total tremor scores ranging from 3 to 5) received electrophysiological diagnoses of possible ET. All of these had low-frequency finger-to-nose tremor (range = 2.80–7.30 Hz), and two had finger-to-nose tremor with an amplitude in excess of 2.5 mm in the nondominant arm. No subject received a clinical diagnosis of ET in the setting of an electrophyisological diagnosis of normal.

DISCUSSION

The ideal gold standard for the diagnosis of a disease is an easily identifiable pathological finding, and in the absence of this, a disease-specific biological marker. Because of the lack of either of these in ET,[8,25] there is a problem validating clinical diagnoses. An alternative strategy is to determine whether several different diagnostic approaches yield similar conclusions (i.e., agreement).

Quantitative computerized tremor analysis using accelerometry and EMG has the ability to precisely measure several important physiological parameters (e.g., tremor frequency) which are difficult to quantify with precision based on a clinical examination alone.[10–12] Also, it is a technique that is gaining acceptance.[10–12] Despite this, there is a paucity of literature comparing the performance of tremor analysis against clinical diagnoses of ET and vice versa.[10] Our goal was to compare the performance of these two techniques when one was confronted with the problem of differentiating ET from normal or enhanced physiological tremor. This diagnostic issue arises commonly in clinical practice,[6,26,27] epidemiological studies,[18,28,29] and family or genetic studies of ET,[3,4,30] and therefore it seems reasonable to publish data comparing clinical diagnoses with electrophysiological diagnoses.

We found that the diagnostic concordance rate was 94.4% (95% confidence interval [CI] = 88.3–100%), and the κ was 0.88, indicating a level of agreement that was in the "near perfect" range. In one other study, Elble[10] examined accelerometry and EMG results in a group of 100 elderly people, among whom 77 had clinically normal tremor and 23 had clinically abnormal tremor which resembled ET. In that study,[10] the concordance between the clinical and electrophysiological diagnosis was 85% (95% CI = 78.0–92.0%), which was similar to our concordance. Such high concordance rates suggest that research studies that were to utilize either of the two methods we presented would arrive at similar, although not identical, diagnostic conclusions.

We recognize that other electrophysiological methods (e.g., digitizing tablets) are available for the diagnosis of ET, and that our electrophysiological protocol did not include these other methods.[31] However, even when using an electrophysiological approach that was limited to accelerometry and EMG, we found that there was a high level of agreement between clinical and electrophysiological diagnoses of ET.

Although the diagnostic agreement was substantial, it was not perfect. The proportion of individuals who received diagnoses of ET using electrophysiological criteria was 64.8% (35 of 54) compared with 59.3% (32 of 54) diagnosed as ET using clinical criteria. Three subjects who were clinically normal received electrophysiological diagnoses of possible ET. Some of their physiological parameters fell within the range of abnormal, yet the subjects appeared to be normal based on their clinical examinations. Similarly, Elble[10] reported that physiological testing identified at least one laboratory abnormality in 31% of study subjects, compared with only 23% who had clinically abnormal tremor. Whether or not these cases represent forme frustes of ET is unclear, and the absence of a diagnostic gold standard makes this issue a difficult one to resolve. Electrophysiological studies certainly are able to detect clinically subtle as well as subclinical tremors; however, the interpretation of these data must take clinical findings into consideration. If these cases did represent early subclinical forms of ET, then electrophysiological studies could play an important role in certain research settings (e.g., genetic linkage studies) in which minimally or partially expressed forms of ET are common.

There are several issues. First, we realize that the characteristics of the ET cases in large measure determine how well one is able to differentiate them from normal subjects. Differentiation of severe cases should be achieved more easily than differentiation of mild cases. Nearly two-thirds of our ET cases were ascertained from a community, and only two of these had ever sought treatment. Community cases often have milder ET than

those typically seen in a clinic.[9] If our ET cases had been ascertained entirely from a clinic, the differentiation between an ET case and a normal subject may have been achieved more easily, resulting in even greater agreement between clinical and electrophysiological diagnoses. Second, our ET cases were relatively old; only four (12.5%) of 32 were ±60 years of age. Tremor frequency in younger cases is likely to be higher[32] (i.e., closer to the range of frequencies observed in normal physiological tremor), making the differentiation based on frequency more challenging in younger subjects and less challenging in older subjects . On the other hand, the majority (90.9%) of our control subjects were ≥60 years of age, resulting in a greater degree of age-associated tremor in our control group,[33] making the differentiation based on amplitude more challenging. Finally, this study focused on the diagnostic agreement between electrophysiological testing and the clinical examination when confronted with a group of normal subjects and a group with ET. Our goal was not to assess the merit of electrophysiological testing as a method for following clinical severity in the setting of clinical trials or to assess its use in distinguishing ET from Parkinson's disease or dystonia.

In summary, the agreement between the clinical and electrophysiological diagnosis of ET was substantial, suggesting that study protocols that were to utilize either technique would arrive at similar, although not identical, diagnostic conclusions. In addition, physiological testing may be able to detect possible additional cases of ET not diagnosed as such during clinical assessments.

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