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Nonmotor symptoms in essential tremor: Comparison with Parkinson's disease and normal control

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ABSTRACT

Background: Recently, the definition of essential tremor (ET) has evolved to have two different meanings. One refers to classic ET, a benign mono-symptomatic disorder, and the other refers to a heterogeneous neurodegenerative disorder. The aim of this study was to categorize nonmotor symptoms according to ET phenotype, and compare them, along with autonomic function, in people with Parkinson's disease (PD) and normal controls.
Methods: We divided patients with ET into 3 subtypes according to their motor features: 23 Pure-ET, 25 Cerebellar-ET, and 12 Parkinsonism-ET. Comparisons were made between 30 PD subjects and 22 normal controls, and 60 subjects with ET. The following assessments were conducted: the Nonmotor Symptoms Scale, the Mini-Mental State Exam, Montreal Cognitive Assessment, the Montgomery–Asberg Depression Rating Scale, Neuropsychiatric Inventory Questionnaire, Beck Anxiety Inventory, the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale and the Scales for Outcomes in Parkinson's Disease—Autonomic.
Results: There were significant differences in the Nonmotor Symptoms Scale total scores of the ET, PD, and control groups (ET: 25.500 ± 2.346; PD: 27.960 ± 3.267; Control: 3.328 ± 3.796.). There were no significant differences in terms of each ET phenotype. ET patients had significant cognitive dysfunction, neuropsychiatric problems including depression and have complained about significant autonomic dysfunction and excessive daytime somnolence compared to normal controls.
Conclusions: Patients with ET have several nonmotor symptoms similar to those of patients with PD, which have a similar impact on their quality of life. Therefore, nonmotor symptoms should be considered in the clinical evaluation and management of ET.

1. Introduction

Evidence is accumulating that essential tremor (ET) has several motor and nonmotor features. The concept that ET is a mono-symptomatic and benign movement disorder has been replaced by the view that it may be a neurodegenerative disorder characterized by a wide spectrum of motor and nonmotor features [1,2]. Although postural and kinetic tremors are the main motor features of ET, other motor features (gait ataxia, postural instability, eye motion abnormalities, resting tremor and mild bradykinesia) are also observed and influence subjective difficulties in some cases of ET [3–5]. There are clinical and electrophysiologic evidences of cerebellar disturbance in ET patients [6–9]. In addition, several nonmotor features (cognitive decline, depression, anxiety, and sleep problems) are being increasingly recognized, and affect the quality of life of ET patients [1].

Together with the classical nonmotor symptoms described in essential tremor, patients can also show with relatively high frequency alterations in the voice features and dysfunction of the upper respiratory airways [10,11]. Reflecting these current concepts, recent ET studies have mainly focused on the heterogeneity of motor features, ET phenotypes, and their relationships with several nonmotor features. Evidences concerning ET pathology and epidemiology support these studies [2,12,13].

The purpose of this study was to evaluate differences in nonmotor features according to the motor phenotypes of ET, and to compare autonomic function and the entire spectrum of nonmotor symptoms in ET, PD, and the control groups.

2. Subjects and methods

2.1. Subjects

ET, PD, and normal control groups were included in this study. All subjects were enrolled at the outpatient clinic at the Department of Neurology in Korea University Guro Hospital, Parkinson's Disease Centre, during the period from May 2012 to October 2013.

All patients were clinically diagnosed with ET or PD, and clinical diagnosis was based on diagnostic criteria set by the NIH Essential Tremor Consortium for ET, and United Kingdom Parkinson's Disease Society Brain Bank Criteria for PD [14,15]. ET patients who fulfilled

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criteria for "probable" or "definite" were included. We divided ET patients into three subtypes according to their motor features: *Pure-ET*, *Cerebellar-ET*, and *ET with Parkinsonism* (*Parkinsonism-ET*). Having satisfied ET diagnostic criteria, we included patients for the *cerebellar-ET* phenotype, who had the following: (1) features on neurologic examination inclusive of cerebellar signs, such as oculomotor abnormalities, gait ataxia, postural instability, cerebellar speech, dysmetria, positive findings for the Romberg test, and abnormal tandem gait; or (2) intentional tremor above 2+ amplitude for bilateral hands. Inclusion criteria for *ET with Parkinsonism* were the following: presence of consistent ET tremor, with either (1) true bradykinesia (bradykinesia with fatiguing) that is inconsistent with PD diagnostic criteria, or (2) isolated resting finger or wrist tremor without bradykinesia.

We included PD patients who had no motor complications and a Hoehn and Yahr (H&Y) stage of less than 3, and excluded any with a possibility of secondary Parkinsonism, atypical Parkinsonism, Parkinson's disease dementia, or young onset Parkinson's disease.

Control group subjects were recruited either from volunteers or patients from medical outpatient clinics who had no history of movement disorders, dementia, psychiatric disorders, or structural brain lesions such as stroke.

2.2. Evaluation & assessment

All patients were assessed by a neurologist. A detailed physical examination, neurological examination, and an interview for demographic factors (including gender, age, family history of ET, medical and medication history, neurological and psychiatric history, and educational history) were performed.

Tremor and Parkinsonism were evaluated using the Fahn–Tolosa–Marin Tremor Rating Scale (FTMTR) and Unified Parkinson's Disease Rating Scale—Part III (UPDRS-III).

For evaluation of several nonmotor features, the following questionnaires and scales were used for each domain of nonmotor symptoms: for *overall nonmotor symptoms*, the Korean version of the Nonmotor Symptoms Scale (K-NMSS) [16]; for *cognition*, the Korean version of the Mini-Mental State Exam (K-MMSE), and the Montreal Cognitive Assessment—Korea (MoCA-K); for *psychiatric problems*, the Montgomery–Asberg Depression Rating Scale (MADRS) [17], the Neuropsychiatric Inventory Questionnaire (NPI-Q), and the Beck Anxiety Inventory (BAI) [18]; for *sleep problems*, the Pittsburgh Sleep Quality Index (PSQI) [19] and the Epworth Sleepiness Scale (ESS) [20]; and for *autonomic dysfunction*, the Scales for Outcomes in Parkinson's Disease—Autonomic (SCOPA-AUT) [21]. The normal control group was evaluated using the same tools. Simple laboratory tests were conducted to exclude other tremorgenic medical conditions like hyperthyroidism or Wilson's disease.

We performed analyses to compare the scores of several questionnaires and scales: for nonmotor symptoms by ET subtypes, and for differences between the three groups comprising ET, PD, and Control.

2.3. Statistics

This was a cross-sectional case control questionnaire and scale-based study. All patients and controls gave informed consent before participating. Institutional Review Board approval was obtained. Analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL). The data was tested for normality using the Kolmogorov–Smirnov test. The independent *t*-test, one-way analysis of variance (ANOVA), and Chi-square tests were used to compare basic characteristics such as age, disease duration, educational level attained, and the scores from several scales if these were normally distributed. Analysis of covariance (ANCOVA) was used if age adjustments were needed. For measures that were not normally distributed, non-parametric tests were used such as the Mann–Whitney U and Kruskal–Wallis tests. Data were reported as mean ± SD, or mean ± SE where indicated, and differences were considered significant if $p < 0.05$. Post-hoc analysis was performed using Bonferroni's correction and Tukey's method. For analyzing the correlations between NMSS score, disease duration, tremor severity, and subjective assessments of daily living, Spearman's correlation and partial correlation coefficients were used.

3. Results

3.1. Demographics and basic characteristics

Sixty ET patients (mean age, 52.48 ± 16.86 years; male:female, 28:32), 30 PD patients (mean age, 65.47 ± 7.49 years; male:female, 12:18), and 22 normal controls (mean age, 65.86 ± 17.52 years; male: female, 9:13) were enrolled in the study. As expected, PD patients were significantly older than ET patients ($p = 0.01$). Disease duration for the ET group was longer than that for the PD group (ET: 121.23 ± 98.56 months, PD: 29.04 ± 4.69 months, $p = 0.00$). There was no significant difference in education span among them. The mean Hoehn and Yahr (H&Y) stage of PD patients was 2.12 (2.117 ± 0.31).

For ET subtypes, the Pure-ET group comprised 38.3% of the ET patients, the Cerebellar-ET group comprised 41.7%, and the Parkinsonism-ET group comprised 20%. The Parkinsonism-ET group was significantly older than the Pure-ET and Cerebellar-ET groups. Disease duration was significantly longer, and tremor severity was significantly more severe in the Parkinsonism-ET subtype. More detailed demographic and basic clinical information for each group is presented in Table 1.

3.2. Comparison of Nonmotor Symptoms Scale

There were significant differences in the NMSS total scores between ET, PD, and Control groups (ET: 25.500 ± 2.346; PD: 27.960 ± 3.267; Control: 3.328 ± 3.796). ET and PD groups had significantly higher scores than the control group for dysfunction in cardiovascular, sleep/fatigue, emotion/cognition, attention/memory, genitourinary, and sexual function domains. Only the PD group had õsignificantly high scores than the other groups in gastro-intestinal, smell/taste, and weight change domains (Fig. 1a).

For the ET subtype analysis, the Parkinsonism-ET group only had significantly higher scores in the genitourinary domain and there was no significant difference for other domains (Fig. 1b).

The partial correlation coefficients for disease duration, symptom severity, and NMSS are summarized in Table 2. In the ET group, there were no significant correlations between tremor severity and NMSS total scores, and between disease duration and NMSS total scores. However, in the analysis of domains of NMSS, there were significant correlations between tremor severity and perception/hallucination, pain, and weight change domains. In the PD group, there were significant correlations between the H&Y stage, disease duration, and NMSS scores. These were found in total NMSS score, and in gastro-intestinal, smell/taste, and pain domains.

3.3. Comparison of autonomic function scale

For comparisons of SCOPA-AUT, there were significant differences between ET and normal controls in the total score (ET: 10.25 ± 7.49, Control: 6.24 ± 3.87; $p = 0.006$), genitourinary (ET: 4.40 ± 3.53, normal control: 3.00 ± 1.54; $p = 0.026$), and cardiovascular (ET: 0.92 ± 1.48; Control: 0.12 ± 0.33; $p = 0.001$) domains. However, there were no significant differences in SCOPA-AUTO for each ET phenotype. The PD group had the highest scores in total and for all domains except for sexual function.