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Transcranial sonography (TCS) in Parkinson's disease (PD) and essential tremor (ET) in relation with putative premotor symptoms of PD

Joong-Seok Kim *, Yoon-Sang Oh, Yeong-In Kim, Ja-Seong Koo, Dong-Won Yang, Kwang-Soo Lee

Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 505, Banpo-dong, Seocho-gu, Seoul 137-701, Republic of Korea

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ABSTRACT

Background: Hyperechogenicity of substantia nigra (SN+) is a common finding in transcranial ultrasound studies of parkinsonian patients. However, this feature is also found in 13–16% of ET patients. The possible links between ET and PD are of special interest, particularly with the familial aggregated data supporting this association. However, few studies have been conducted regarding the factors associated with the emergence of PD in the ET population. In this study, we investigated the possible association between SN+ and putative premotor symptoms of PD in patients with ET. *Methods*: A total of 47 patients with PD and 64 patients with ET were enrolled in the study. All patients underwent TCS and completed a structured interview for putative premotor symptoms of PD. *Results*: As expected, there were significant differences observed in the frequency and size of SN+, and the prevalence of the putative premotor symptoms of PD. More interestingly, in the ET group a significant association between SN+ and each premotor symptom was observed and a trend was also found that ET cases with more putative premotor symptoms of PD had a greater size of SN+. In contrast, in the PD group, SN+ was not influenced by the cumulative effect of premotor symptoms. *Conclusion*: The results of this study suggest that SN+ in patients with ET is influenced by the putative premotor symptoms of PD.

1. Introduction

In addition to genetic predisposition, a number of clinical premotor markers are being developed and used more frequently to indicate vulnerability to PD, some of which may occur many years before disease manifestation. These include olfactory and autonomic dysfunction, mood and sleep disorders (Tolosa et al., 2009). Recently, many studies provided evidence that TCS is helpful in the diagnosis of PD (Berg, 2009; Behnke et al., 2010). In addition, another recent investigations proposed SN+ as promising evidence to detect subjects vulnerable to nigrostriatal impairment, and possibly at risk for the development of PD (Berg, 2009; Behnke et al., 2010).

ET is a neurological disorder that can occur throughout life with increasing incidence with aging, and is characterized by an action tremor. By definition, patients with ET do not have other clinical signs associated with Parkinsonism. However, recent studies suggested that ET was not "pure" motor disorder and there is growing evidence that this disease is a multiple-system disorder, because of additional motor features (e.g. ataxia) and non-motor features (hearing impairment, mild cognitive deficits and personality changes) (Deuschl and Elble, 2009; Louis, 2009; Chandran et al., 2011). In addition, clinicians have long observed that there seems to be a tendency for ET patients to develop incident PD, raising questions about a link between these two neurological diseases (Laroia and Louis, 2011).

Comparative studies using TCS have shown successful discrimination between these two diseases; SN+ was found in 75–91% of patients with PD, but in only 13–16% of ET and in 3–10% of controls (Stockner et al., 2007; Budisic et al., 2009). In healthy controls, the SN+ has been shown to be related to reduced motor performance, as well as other premotor symptoms for PD, such as loss of olfaction, depression and REM sleep behavioral disorder (RBD) (Walter et al., 2007; Stockner et al., 2009; Berg et al., 2010). The possible functional relevance is strengthened by the observation that several healthy individuals with SN+ developed PD after some years (Berg et al., 2011).

However, it remains unclear why the prevalence of SN+ in ET is higher than that of the controls. In this study, we focused on the possible associations between SN+ and putative premotor symptoms of PD in patients with ET. In addition, we also investigated the possible association of SN+ with other premotor symptoms in PD.

2. Patients and methods

2.1. Patients and clinical assessments

Only eligible patients who fulfilled the UKPDS brain bank criteria for idiopathic PD, and had either definite or probable ET,

* Corresponding author. Tel.: +82 2 2258 6078; fax: +82 2 599 9686.
E-mail address: neuronet@catholic.ac.kr (J.-S. Kim).

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based on the National Institute of Health diagnostic criteria were recruited for the study (Gibb and Lees, 1988; Jankovic, 2000). Consecutive, newly diagnosed patients attending the movement disorders clinic at Seoul St. Mary's Hospital, from January 2010 to December 2010 who fulfilled the outlined criteria were asked to participate. Clinical information included age, gender, disease duration, history of arterial hypertension, diabetes mellitus and cigarette smoking. All PD and ET patients completed a clinical assessment and neurological examination.

The structured interview for various putative premotor symptoms of PD was performed in all patients. The following diagnostic criteria or scales were applied to define the status.

(1) Positive family history for Parkinsonism was defined by pedigree analysis which included second-degree relatives.
(2) Definitions of autonomic dysfunctions, such as constipation, orthostatic hypotension and bladder dysfunction, were based on the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) (Visser et al., 2004).
(3) RBD-like symptoms were defined according to the minimal diagnostic criteria included in the International Classification of Sleep Disorders, revised (ICSD-R) (American Academy of Sleep Medicine, 2001; Bologna et al., 2003). In particular, an RBD episode was deemed to have occurred when a patient presented with violent injurious behavior during sleep, accompanied by limb and body movements. Single, isolated episodes were disregarded and only recurrent episodes were taken into consideration. Subjects reporting only somniloquy and/or vivid dreams were not included in this group.
(4) Depression was diagnosed as (i) presence of history for treatment of current depressive symptoms, (ii) the unequivocal classification of a depressive state according to DSM-IV diagnostic categories, as specified later (American Psychiatric Association, 1994).

This study was approved by the local ethics committee, and each patient gave written informed consent for participation.

2.2. TCS

TCS was performed using a 2.5-MHz transducer (LOGIQ S6, GE Healthcare, USA) with a depth of 16 cm and a dynamic range of 45 dB, as previously described (Berg et al., 2001). An experienced sonographer (Dr. Oh) who was blinded to the clinical history of the patients measured SN echogenicity through the preauricular temporal acoustic bone window in the mesencephalic axial plane. To compare the SN echogenicity between the groups, we measured the SN echogenic area and classified the findings according to previously determined cut-off values (i.e. more prominent SN+ $\geq 0.2\ cm^2$) (Berg et al., 2001).

2.3. Data analysis

Statistical analysis was performed with SPSS software version 15.0 (SPSS Inc., Chicago, IL). Group comparison for demographics and analysis of TCS results were performed using the independent sample *t*-test or Pearson's chi-square test. The premotor symptoms, including family history of PD, were initially analyzed as a categorical variable according to the presence or absence of each symptom, and then treated as groups with and without one or two premotor symptoms. In addition, the correlation between the mean size of SN echogenicity and the number of putative premotor symptoms of PD was tested with the Spearman's rank correlation coefficients, to determine if SN echogenicity increased with an increasing number of premotor symptoms. The statistical significance level was set at $p < 0.05$.

3. Results

The initial study cohort included 86 patients with PD and 100 with ET. There were no patients who declined enrollment. Among them, 39 PD and 36 ET patients were excluded, due to transcranial insonability, but no statistical differences between excluded vs. included patients in each group with regards to demographic or clinical variables were found. Thus, a final total of 47 PD and 64 ET patients were enrolled in this study. Clinical characteristics and TCS findings in PD and ET groups are summarized in Table 1. Data from patients with PD and ET were not statistically different, but there were tendencies observed for increasing age, male-predominance and more prevalent vascular factors in the PD group than in the ET group. In addition, the duration of illness was longer in the ET group than in the PD group.

The distribution of premotor symptoms was more extensive in the PD group and the number of patients with premotor symptoms was higher in the PD than in the ET group. The mean SN echogenecity was also higher in the PD group compared to the ET group, and the distribution of SN hyperechogenecity was different between the two groups (Table 1).

Patients with PD showed no association between the size of SN echogenecity and each premotor symptom, although patients with premotor symptom(s) had a tendency to develop a higher size of hyperechogenic SN and more patients had hyperechogenic SN than the group without premotor symptom(s) (Table 2). This abnormality was not gender specific ($0.29 \pm 0.12\ cm^2$ in males, and $0.27 \pm 0.11\ cm^2$ in females, $p = 0.608$). In addition, correlation analysis showed no association between the increasing number of premotor symptoms and mean SN echogenicity increases (Fig. 1A. $r = 0.116$, $p = 0.438$).

ET patients, however, showed significant correlation between several premotor symptoms (especially constipation and complex sleep behavior) and the size of hyperechogenic SN or number of patients with hyperechogenic SN (Table 3). In addition, the sum of

Table 1
Patient demographics and TCS findings.

	PD ($n = 47$)	ET ($n = 64$)	p
Age, year	66.6 ± 11.7	62.8 ± 12.2	0.064
No. of man	18 (38.3%)	14 (21.9%)	0.059
Duration of illness, year	1.8 ± 1.6	6.8 ± 8.1	<0.001
Hypertension	16 (34.0%)	13 (20.3%)	0.104
Diabetes mellitus	9 (19.1%)	5 (7.8%)	0.075
Smoking habit			0.831
Non-smoker	40 (85.1%)	52 (81.3%)	
Ex-smoker	4 (8.5%)	6 (9.4%)	
Current smoker	3 (6.4%)	6 (9.4%)	
Premotor symptoms			
Constipation	29 (61.7%)	19 (29.7%)	0.001
Complex sleep behavior	16 (34.0%)	19 (29.7%)	0.626
Orthostatic hypotension	13 (27.7%)	6 (9.4%)	0.012
Bladder dysfunction	8 (17.0%)	3 (4.7%)	0.032
Depression	28 (59.6%)	17 (26.6%)	<0.001
Family history of parkinsonism	1 (2.1%)	3 (4.7%)	0.475
No. of at least one premotor symptom	43 (91.5%)	39 (60.9%)	<0.001
No. of more than two premotor symptom	36 (76.6%)	19 (29.7%)	<0.001
Sum of premotor symptom risk	2.0 ± 1.0	1.0 ± 1.1	<0.001
TCS			
Mean size of SN+ (cm^2)	0.28 ± 0.12	0.12 ± 0.12	<0.001
Hyperechogenicity (%)	35 (74.5%)	8 (12.5%)	<0.001

Values represent mean with standard deviation or number of patients with percentages in parenthesis. Analyses were performed with independent *t*-test for continuous variables and chi-square test for nominal variables.