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ORIGINAL PAPER

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Substantia nigra hyperechogenicity in depressive subjects relates to motor asymmetry and impaired word fluency

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Abstract *Background* Substantia nigra hyperechogenicity (SNH) is a characteristic transcranial sonography (TCS) finding in Parkinson's disease (PD). SNH, found also in about 10% of healthy adults, was related to a subclinical malfunction of the nigrostriatal dopaminergic system on positron emission tomography studies. Both, liability for developing PD and frequency of SNH were found to be increased in depressed subjects. Here, we investigated whether SNH in depression is related to motor or cognitive abnormalities resembling early PD. *Methods* Fourty-one patients with major depressive disorder and 15 with adjustment disorder with depressed mood were studied clinically and with TCS. *Results* Frequency of SNH was similar in both groups (39, 33%; Chi-square test, $P = 0.70$). Larger SN echogenic size correlated with larger right-to-left asymmetry of finger tapping (Spearman test, $r = 0.37$, $P = 0.009$) and lower verbal fluency ($r = -0.35$, $P = 0.038$). These correlations were stronger in patients at ages ≥ 50 years ($r = 0.52$, $P = 0.007$; $r = -0.50$, $P = 0.020$), and, independently from age, in patients with reduced echogenicity of brainstem raphe suggested to reflect alteration of the serotonergic system ($r = 0.40$, $P = 0.045$; $r = -0.51$, $P = 0.044$). Whereas bilateral sum score of finger tapping was negatively correlated with severity of depression on the beck depression inventory ($r = -0.50$, $P = 0.001$) and the Hamilton depression rating scale ($r = -0.34$, $P = 0.019$), no correlation was found between depression severity and tapping asymmetry, or between depression severity and verbal fluency. *Conclusion* Data suggest that TCS detects a subgroup of patients with depression characterized by symptoms of early parkinsonism who are possibly at an elevated risk of later developing definite PD.

Key words transcranial sonography · major depression · adjustment disorder with depressed mood · substantia nigra · dopaminergic system

Introduction

Depression is a frequent comorbid condition in Parkinson's disease (PD), prevalent in 31% of PD patients [13], and may precede the diagnosis of PD by 10–20 years [31]. In large register studies, each spanning 15–16 years, the risk for depressed patients for developing PD was 2.2 to 3.1-fold compared to non-depressed controls [21, 26, 30]. In a more recent register study, persons taking antidepressants were found to be at increased risk of subsequent treatment with antiparkinsonian drugs, also showing an association between anxiety/affective disorder and PD [12]. Results of these studies imply that either depression is an early symptom of PD or that depression is associated with a risk factor for PD.

Transcranial sonography (TCS) has proved reliable and sensitive in detecting abnormalities of substantia nigra (SN) and basal ganglia in PD [4, 36]. In about 90% of PD patients, TCS reveals characteristic SN hyperechogenicity, which remains stable during the course of the disease and is discussed to reflect increased amounts of iron, bound to proteins other than ferritin, but not the progressive neurodegeneration in the SN [10, 11, 36, 38]. Marked SN hyperechogenicity, found also in 10% of healthy adults aged between 20 and 80 years, has been related to a func-

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tional impairment of the nigrostriatal dopaminergic system in pharmacological, PET and SPECT studies and was proposed to indicate an increased risk for developing PD [7, 8, 33, 37].

In patients with depressive disorders, SN hyperechogenicity is found with threefold increased frequency compared to non-depressed controls [39]. Here, we studied whether SN hyperechogenicity in depressed subjects is already related to mild motor or cognitive abnormalities suggestive of early stages of PD.

Methods

Patients

Fifty-six patients treated at the Department of Psychiatry and Psychotherapy of the University of Rostock were eligible for inclusion. Inclusion criteria were (1) a depressive state classified according to DSM-IV diagnostic categories [2], severe enough to demand inpatient treatment, and (2) transcranial insonability. Exclusion criteria were (1) psychotic symptoms, (2) symptomatic psychic disorders, (3) other psychic comorbid disorders, or (4) recent concomitant neurological disorders. None of the patients received lithium, valproic acid, neuroleptics, or other medications that could potentially cause parkinsonian symptoms, except from 23 patients who were on selective serotonin reuptake inhibitors (SSRI) that were reported to casually induce parkinsonism [35]. Informed consent was obtained from each patient. Following the Structured Clinical Interview for DSM-IV Axis-I Disorders [17], 41 patients met the diagnostic criteria for MDD and 15 for ADDM. Table 1 shows demographic and clinical data of patients.

Motor and cognitive examinations

Severity of depression, motor retardation and cognitive impairment were assessed using the clinical scores given in Table 1 [3, 16, 18, 19, 32]. Moreover, patients underwent the trail-making test (TMT) [27], verbal-fluency and finger-tapping tests, that were reported to be abnormal in early stages of PD [14, 15, 34]. The TMT is primarily a test of motor speed and visual attention. TMT-A requires the subject to connect up a sequence of 25 numbers dispersed across a page as quickly as possible and TMT-B to alternately combine 12 numbers and 12 characters in ascending order. The outcome parameter is the time (in seconds) required to complete each section of the test. The difference score of these two subtests, TMT (B-A), was used as an index cognitive flexibility to switch attention between two competing tasks independent of motor speed [20]. Verbal fluency was assessed with the H/T-word test (HTWT) which requires the subject to produce as many different words as possible within 2 min beginning alternately with the letters "H" and "T" [25]. The result is given as percentile related to performance of an age-matched normal population. To quantify hand motor function, subjects were asked to tap the space bar of a computer keyboard as fast as possible with the third finger of each hand separately twice for 10 s. The individual mean value for each hand, bilateral tapping sum score and tapping asymmetry index were calculated, the latter by division of the larger by the smaller mean value of referring hands. Handedness of each subject was assessed using a validated questionnaire [28].

Transcranial sonography

Transcranial sonography was performed through the preauricular acoustic bone windows using an ultrasound system with a 2.5-MHz phased-array transducer (Sonoline; Siemens, Erlangen, Germany).

Table 1 Demographic data, clinical scores, and antidepressant medication of patients at the time of transcranial sonography (TCS)

	MDD	ADDM	*P* value*
Number of patients	41	15	
Gender (M/F)	11/30	1/14	
Age			
Mean ± SD (years)	56.4 ± 12.8	49.2 ± 11.3	0.053
Range (years)	20–76	30–75	
BDI score			
Mean ± SD (*n*)	21.5 ± 12.1	20.6 ± 7.5	0.75
HDRS score			
Mean ± SD (*n*)	21.3 ± 5.6	19.5 ± 6.9	0.39
MMSE score			
Mean ± SD (*n*)	28.3 ± 1.9	28.9 ± 1.1	0.33
MARS score			
Mean ± SD (*n*)	34.0 ± 6.8	30.2 ± 8.6	0.14
Agitation subscore			
Mean ± SD (*n*)	12.9 ± 2.3	12.2 ± 2.5	0.35
Retardation subscore			
Mean ± SD (*n*)	21.1 ± 5.0	18.0 ± 6.6	0.11
UPDRS-III			
Mean ± SD (*n*)	5.5 ± 4.6	3.1 ± 2.8	0.025
Doxepin			
Number; mean dosage (*n*; mg)		2; 112 ± 18	
Mirtazapine			
Number; mean dosage (*n*; mg)	18; 32 ± 12	8; 28 ± 10	
Trimipramine			
Number; mean dosage (*n*; mg)	6; 138 ± 74		
Paroxetine			
Number; mean dosage (*n*; mg)		1; 20	
Sertraline			
Number; mean dosage (*n*; mg)	2; 125 ± 35		
Venlafaxine			
Number; mean dosage (*n*; mg)	15; 220 ± 82	3; 175 ± 87	
Reboxetine			
Number; mean dosage (*n*; mg)	2; 5.0 ± 1.4		

MDD major depressive disorder, *ADDM* adjustment disorder with depressed mood, *BDI* Beck depression inventory,[3] *HDRS* Hamilton 21-item depression rating scale,[19] *MMSE* mini-mental state examination,[18] *MARS* motor agitation and retardation scale,[32] *UPDRS-III* unified Parkinson's disease rating scale, motor part,[16] *SD* standard deviation

* *t* test

System settings were: dynamic range 50 dB, high persistence, reject 7. SN echogenic size was measured on axial scans encircling the outer circumference of SN's echogenic area. SN was classified as hyperechogenic at sizes of more than 0.25 cm^2, representing upper 10% percentile in normal population [7]. Echogenicity of brainstem raphe (BR) was rated as reduced when its structure was interrupted or not visible [5]. TCS was performed independently by two sonographers (U.W., L.M.) who were blind to clinical data. A structure was only regarded as abnormal, if ratings of both sonographers agreed.

Statistical analysis

Descriptive statistics are given as median with lower (25th percentile) and upper (75th percentile) quartile. For group comparison of SN echogenic sizes the Mann–Whitney *U* test was used. Groups with normal and hyperechogenic SN were tested for difference in demographic data and clinical scores: categorial data by χ^2 test, means by *t* test. Correlation between echogenic sizes and clinical scores was analyzed by Spearman test, and also by partial correlation test controlled for age. As TCS findings of two brain structures (SN, BR) were tested for their relation to clinical scores, a Bonferroni correction for multiple correlations was employed by dividing a P value < 0.05 by 2. Thus, a P value of <0.025 was taken

here as being statistically significant. TCS interrater reliability was assessed by Spearman test (echogenic sizes) and Cohen's kappa (echogenicity scores).

Results

Transcranial sonography findings

Considering the small size of the sonographically assessed brain structures, interrater reliability was high with respect to measurement of SN echogenic sizes (Spearman correlation, $r = 0.79$, $P < 0.001$), classification of SN (Cohen's kappa = 0.88, $P < 0.001$) and BR echogenicity (kappa = 0.86, $P < 0.001$). Typical TCS images are shown in Fig. 1. The median SN echogenic size (including bilateral measurements) of group MDD was 0.21 (0.16; 0.26) cm^2, and of group ADDM 0.18 (0.13; 0.24) cm^2 (U test, $P = 0.31$). The frequency of SN hyperechogenicity did not differ in groups MDD (39%) and ADDM (33%; χ^2 test, $P = 0.70$), nor did the frequency of reduced BR echogenicity (54, 53%; $P = 0.98$). Therefore, TCS data of groups MDD and ADDM were pooled for further analysis. In the combined group of MDD and ADDM patients, the frequency of SN hyperechogenicity was 37%, and that of reduced BR echogenicity 54%. The frequency of SN hyperechogenicity did not differ in the patient groups taking or not taking SSRI (39, 36%; $P = 0.83$), nor did the frequency of BR echogenicity (48, 57%; $P = 0.47$). There was no correlation between SN echogenic size and depression severity on the Beck depression inventory (BDI) ($P = 0.14$) or the Hamilton depression rating scale (HDRS) ($P = 0.19$).

Relationship of sonography findings and motor assessment

Larger SN echogenic size correlated significantly with larger tapping asymmetry index (Spearman correlation, $r = 0.37$, $P = 0.009$). This correlation remained significant if controlled for age ($r = 0.35$, $P = 0.017$), and if the subjects assessed to be left-handed ($n = 4$) were excluded from analysis ($r = 0.36$, $P = 0.017$). The correlation was significant also if only MDD patients were analyzed ($r = 0.38$, $P = 0.022$). The correlation was stronger in patients at ages ≥ 50 years (controlled for age: $r = 0.52$, $P = 0.007$), but not found in patients at ages < 50 years ($P = 0.70$) (Fig. 2). Age itself, however, did not correlate with SN echogenicity ($P = 0.15$) or with tapping asymmetry index ($P = 0.70$). Irrespective of age, the correlation of larger SN echogenic size with larger tapping asymmetry index was stronger in patients with reduced BR echogenicity ($r = 0.40$, $P = 0.045$) than in those with normal BR ($P = 0.08$). There was no correlation of SN echogenicity with tapping sum score or scores measuring motor retardation (Table 2). Whereas tapping sum score was negatively correlated with severity of depression on the BDI ($r = -0.50$, $P = 0.001$) and the HDRS ($r = -0.34$, $P = 0.019$), no correlation was found between tapping asymmetry index and severity of depression. The group of patients taking SSRI did not differ from the group not taking SSRI with respect to score on the motor part of the Unified Parkinson's disease rating scale (5.0 ± 3.3, 4.8 ± 5.0, t test, $P = 0.81$) [16], the retardation subscale of the motor agitation and retardation scale (20.7 ± 4.5, 20.0 ± 6.3; $P = 0.62$) [32], the tapping sum score (112 ± 19,

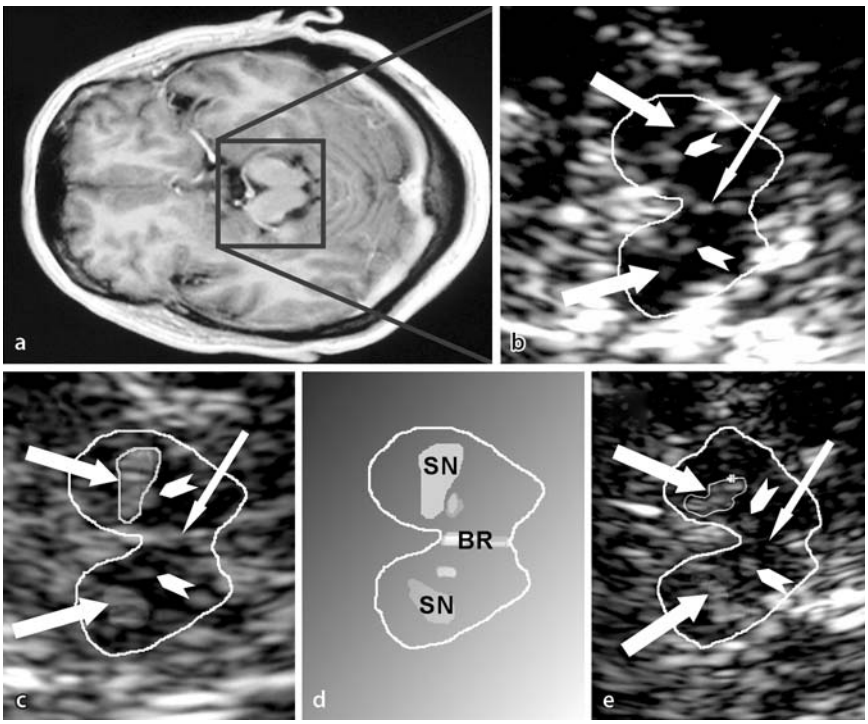

Fig. 1 MRI (**a**) and transcranial sonography (*TCS*) images (**b**, **c**, **e**) of corresponding midbrain axial sections in three subjects. The butterfly-shaped midbrain was encircled for better visualization. *Thick arrows* indicate bilateral substantia nigra (*SN*); *thin arrow* brainstem raphe (*BR*), *arrow heads* bilateral red nuclei. **a** MRI image corresponding to the TCS image shown in **b**. **b** TCS image of a subject with normal, nearly invisible SN and normal, highly echogenic BR. **c** Subject with abnormal, hyperechogenic SN but normal, highly echogenic BR. Echogenic area of the right SN was encircled for computerized measurement. **d** Schematic illustration of **c**: within the encircled midbrain axial section, bilateral SN, red nuclei and BR are highlighted. **e** Subject with bilateral SN hyperechogenicity and abnormal, reduced BR echogenicity. Echogenic area of the right SN was encircled for computerized measurement

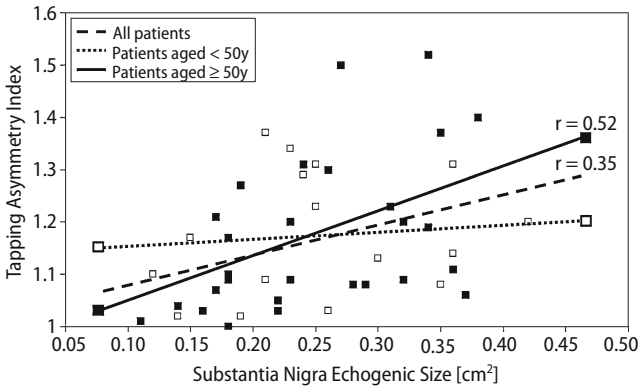

Fig. 2 Correlation between SN echogenic size in patients with depressive disorder and right-to-left tapping asymmetry index, estimated by division of larger by smaller tapping score of both hands. After bilateral measurement, the larger individual SN echogenic size was used; shown are data of patients at ages < 50 years (*open square*), and patients at ages ≥ 50 years (*filled square*). SN echogenic size was correlated with tapping asymmetry index in the group of all patients ($r = 0.35$, $P = 0.017$; *dashed line*), and even stronger if only patients at ages ≥ 50 years were considered ($r = 0.52$, $P = 0.007$; *continuous line*) but not if only patients at ages < 50 years ($P = 0.70$; *dotted line*)

Table 2 Demographic data and clinical scores at the time of TCS, of depressive patients with normoechogenic and hyperechogenic substantia nigra (SN)

	SN normal	SN hyperechogenic	*P* value
Number of patients	35	21	
Gender			
M/F	7/28	5/16	0.74*
Age			
Mean ± SD (years)	55.8 ± 13.2	54.3 ± 12.8	0.69†
Disease duration			
Mean ± SD (m)	46.9 ± 70.9	45.7 ± 55.2	0.95†
Inhospital stay duration			
Mean ± SD (w)	5.5 ± 2.3	5.9 ± 3.2	0.63†
BDI score			
Mean ± SD (*n*)	20.0 ± 11.9	23.3 ± 8.9	0.28†
HDRS score			
Mean ± SD (*n*)	19.5 ± 5.6	23.0 ± 6.0	0.035†
MMSE score			
Mean ± SD (*n*)	28.4 ± 1.9	28.5 ± 1.6	0.76†
MARS score			
Mean ± SD (*n*)	32.4 ± 7.3	34.0 ± 7.8	0.44†
Agitation subscore			
Mean ± SD (*n*)	12.7 ± 2.2	12.7 ± 2.7	1.0†
Retardation subscore			
Mean ± SD (*n*)	19.7 ± 5.7	21.3 ± 5.5	0.29†
UPDRS-III			
Mean ± SD (*n*)	4.3 ± 4.4	5.7 ± 4.3	0.25†
Tapping sum score			
Mean ± SD (*n*)	107.6 ± 22.7	107.1 ± 25.0	0.94†
TMT-A			
Mean ± SD (s)	54.4 ± 28.8	57.0 ± 31.1	0.80†
TMT-B			
Mean ± SD (s)	139.8 ± 122.4	140.1 ± 98.8	0.99†
TMT (B-A)			
Mean ± SD (s)	88.3 ± 100.1	83.1 ± 73.7	0.86†
HTWT			
Mean ± SD (%)	57.9 ± 21.6	37.6 ± 30.8	0.043†

SN substantia nigra, *BDI* Beck depression Inventory,[3] *HDRS* Hamilton 21-item depression rating scale,[19] *MMSE* mini-mental state examination,[18] *MARS* motor agitation and retardation scale,[32] *UPDRS-III* unified Parkinson's disease rating scale, motor part,[16] *TMT-A* trail-making test, subtest A,[27] *TMT-B* trail-making test, subtest B, *TMT (B-A)* difference of TMT-B and TMT-A, *HTWT* H/T-word test,[25] *SD* standard deviation
* χ^2 test, † *t* test

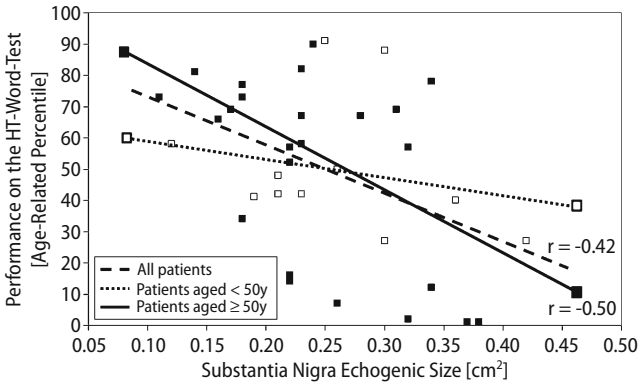

Fig. 3 Correlation between SN echogenic size in patients with depressive disorder and performance on the verbal fluency test (H/T-word test; for details, see text). Shown are data of patients at ages < 50 years (*open square*), and patients at ages ≥ 50 years (*filled square*). SN echogenic size was negatively correlated with verbal fluency in the group of all patients ($r = -0.42$, $P = 0.013$; *dashed line*), and even stronger if only patients at ages ≥ 50 years were considered ($r = -0.50$, $P = 0.020$; *continuous line*) but not if only patients at ages < 50 years ($P = 0.48$; *dotted line*)

104 ± 26; $P = 0.26$), and the tapping asymmetry index (1.14 ± 0.10, 1.19 ± 0.15; $P = 0.15$).

Relationship of sonography findings and cognitive assessment

Larger SN echogenic size correlated with worse performance on the HTWT ($r = -0.35$, $P = 0.038$). This correlation was significant if controlled for age ($r = -0.42$, $P = 0.013$), and remained significant if only MDD patients were analyzed ($r = -0.45$, $P = 0.015$). This correlation was stronger in patients at ages ≥ 50 years (controlled for age: $r = -0.50$, $P = 0.020$), but not found in patients at ages < 50 years ($P = 0.48$) (Fig. 3). Age itself, however, did not correlate with performance on the HTWT ($P = 0.35$). Irrespective of age, the correlation of larger SN echogenic size with worse performance on the HTWT was stronger in patients with reduced BR echogenicity ($r = -0.51$, $P = 0.044$) than in those with normal BR ($P = 0.28$). Other cognitive scores were not related to SN echogenicity (Table 2). HTWT scores did not correlate with depression severity on the BDI ($P = 0.39$) and the HDRS ($P = 0.72$). The group of patients taking SSRI did not differ from the group not taking SSRI with respect to HTWT score (56.2 ± 26.1, 45.0 ± 27.4; *t* test, $P = 0.22$).

Discussion

Transcranial sonography data of this study show that the finding of SN hyperechogenicity, which is characteristic for idiopathic PD, is related to motor asymmetry and reduced verbal fluency in patients with depressive disorders. This relationship is stronger in patients at ages > 50 years and, independent from age, in patients with reduced BR echogenicity.

It has been demonstrated earlier that the frequency of abnormal SN and BR TCS findings is increased in depressed subjects compared to non-depressed controls [5, 39]. Whereas SN hyperechogenicity in non-parkinsonian subjects was associated with a malfunction of the nigrostriatal dopaminergic system [7, 8, 33, 37], reduced BR echogenicity in depressed subjects was related to alteration on MRI of the dorsal raphe nucleus and to better responsivity to serotonin reuptake inhibitors [6, 40], and was therefore proposed to reflect dysfunction of the serotonergic system. Results of the present study are in line with previously found mild parkinsonian symptoms in elderly healthy subjects with SN hyperechogenicity [9]. Here, we did not investigate the correlation of SN echogenicity with degree of motor asymmetry in non-depressed healthy subjects. Results of a recent study, however, suggest that also in younger healthy subjects there is an association of SN hyperechogenicity and subtle motor asymmetry [29], even though distinctive motor features as well as the TCS finding of SN hyperechogenicity are considerably less frequent in non-depressed than in depressed young subjects [39].

In the present study the correlation of SN hyperechogenicity with motor asymmetry and impaired word fluency was even stronger in subjects with reduced BR echogenicity. In a previous study, co-occurrence of SN hyperechogenicity and reduced BR echogenicity in non-parkinsonian depressed patients was associated also with right-to-left asymmetry on the unified PD rating scale and, in PD patients, with a history of depressive disorder prior to PD onset [39]. In preclinical PD stages, motor asymmetry and impaired verbal fluency are characteristic findings [15, 22, 23, 29]. Mild, subclinical motor asymmetry may occur 10–20 years before the diagnosis of PD can be established according to diagnostic criteria [23]. Since psychomotor retardation is frequent in depressive disorders [24], as demonstrated here also by the clear correlation of more severe depression with lower tapping sum score, a prevalent liability to motor asymmetry might unmask with the depressive state. The underlying mechanisms might be (a) alteration of nigral dopaminergic neurons, indicated by SN hyperechogenicity, and (b) impaired serotonin-mediated regulation of striatal dopamine transmission [1], indicated by reduced BR echogenicity. In this context, the possibility of drug-induced parkinsonian symptoms in patients taking SSRI needs to be considered, however, this appears unlikely since no differences in motor performance were found between the groups taking or not taking SSRI in our study.

Data of the present study suggest that TCS detects a subgroup of patients with depression characterized by mild clinical signs of parkinsonism who are possibly at an elevated risk of developing definite PD. Since both, liability for developing PD and frequency of PD-like TCS findings were found to be increased in depression, patients with depressive disorders might be an important population to screen for sonographic and clinical signs of early PD. Such a screening will be of enhanced value if protective therapeutic regimens in subclinical stages of PD are available. To further assess the predictive value of clinical and TCS findings for later development of PD in depressive subjects, long-term follow-up investigations in the patient cohort presented here are under way.

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