ULTRASOUND IMAGING OF VAGUS NERVES IN PATIENTS WITH PARKINSON'S DISEASE

Chechetkin AO ✉, Moskalenko AN, Fedotova EYu, Illarioshkin SN

Research Center of Neurology, Moscow, Russia

Parkinson's disease (PD) is a neurodegenerative multisystem disorder characterized by pathologic α-synuclein aggregation affecting, among other things, vagal fibers. The aim of this study was to investigate the cross-sectional area (CSA) of the vagus nerve (VN) in patients with PD using ultrasound imaging. The study was conducted in 32 patients with PD (15 men and 17 women; mean age 58 ± 10 years) and 32 healthy controls comparable with the main group in terms of sex and age. All study participants underwent ultrasound examination of the VN using a high-resolution transducer. Left VN CSA was significantly smaller in patients with PD than in the control group (1.78 ± 0.52 mm^2 vs 2.11 ± 0.41 mm^2; $p = 0.007$). A similar result was obtained for right VN CSA at the trend level. ROC analysis demonstrated that the threshold CSA value of < 2.10 mm^2 for the left VN has low diagnostic sensivity (59%) for VN atrophy in patients with PD. Right VN CSA was significantly larger than left VN CSA in both groups ($p < 0.001$). The analysis of the PD group did not reveal any associations between VN CSA and age, duration and stage of the disease, motor (UPDRS III) and non-motor (NMSQ) scores. Patients with akinetic-rigid form of PD had smaller left VN CSA than patients with the mixed form of the disease ($p < 0.05$). A moderate inverse correlation was established between left VN CSA and the area of substantia nigra hyperechogenicity on both sides ($p < 0.04$); for the right VN a similar correlation was established at the trend level. High-resolution ultrasound of patients with PD demonstrated atrophy of the VN and the association of VN CSA with the clinical form of the disease and the ultrasound features of the substantia nigra.

Keywords: Parkinson's disease, vagus nerve, ultrasound, cross-sectional area.

Author contribution: Chechetkin AO — study design, acquisition of ultrasound imaging data, data interpretation, manuscript preparation; Moskalenko AN — clinical data acquisition, analysis and interpretation; Fedotova EYu, Illarioshkin SN — study design, manuscript editing.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Center of Neurology (Protocol No. 2-6/20 dated March 18, 2020)

✉ **Correspondence should be addressed:** Andrey O. Chechetkin
Volokolamskoe shosse, 80, Moscow, 125367, Russia; andreychechetkin@gmail.com

Received: 25.10.2021 **Accepted:** 11.11.2021 **Published online:** 24.11.2021

DOI: 10.24075/brsmu.2021.054

УЛЬТРАЗВУКОВОЕ ИССЛЕДОВАНИЕ БЛУЖДАЮЩИХ НЕРВОВ У ПАЦИЕНТОВ С БОЛЕЗНЬЮ ПАРКИНСОНА

А. О. Чечеткин ✉, А. Н. Москаленко, Е. Ю. Федотова, С. Н. Иллариошкин

Научный центр неврологии, Москва, Россия

Болезнь Паркинсона (БП) является мультисистемным заболеванием, при котором нейродегенеративные изменения с накоплением α-синуклеина затрагивают волокна блуждающих нервов (БлН). Целью данной работы было провести ультразвуковое исследование (УЗИ) площади поперечного сечения (ППС) БлН у пациентов с БП. В исследование вошли 32 больных БП (15 мужчин и 17 женщин; средний возраст 58 ± 10 лет) и 32 человека контрольной группы, сопоставимые по полу и возрасту. Всем исследуемым проводили ультразвуковую оценку ППС БлН датчиком высокого разрешения. ППС левого БлН у пациентов с БП была меньше по сравнению с лицами контрольной группы (1,78 ± 0,52 мм^2 против 2,11 ± 0,41 мм^2; $p = 007$), для правого БлН аналогичное различие получено на уровне тенденции. ROC-анализ показал, что пороговая величина ППС для левого БлН менее 2,10 мм^2 имеет низкий показатель чувствительности (59%) для диагностики атрофии нерва при БП. ППС правого БлН была достоверно выше, чем левого БлН для пациентов обеих групп ($p < 0,001$). При анализе группы больных БП не выявлено зависимости ППС БлН от возраста, продолжительности и стадии заболевания, количества баллов при оценке по моторной (UPDRS III) и немоторной (NMSQ) шкалам. При этом у пациентов с акинетико-ригидной формой ППС левого БлН была значимо меньше по сравнению с пациентами со смешанной формой БП ($p < 0,05$). Выявлена умеренная обратная корреляция ППС левого БлН с площадью гиперэхогенности черной субстанции с обеих сторон ($p < 0,04$) и на уровне тенденции — для правого БлН. УЗИ пациентов с БП показало атрофические изменения БлН при данном заболевании, а также взаимосвязь ППС БлН с клинической формой БП и ультразвуковыми изменениями черной субстанции головного мозга.

Ключевые слова: болезнь Паркинсона, блуждающий нерв, ультразвук, площадь поперечного сечения

Вклад авторов: А. О. Чечеткин — разработка дизайна исследования, сбор ультразвуковых данных, анализ и интерпретация данных, написание рукописи; А. Н. Москаленко — сбор клинических данных, анализ и интерпретация данных; Е. Ю. Федотова, С. Н. Иллариошкин — разработка дизайна исследования, редактирование рукописи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом Научного центра неврологии (протокол № 2-6/20 от 18 марта 2020 г.)

✉ **Для корреспонденции:** Андрей Олегович Чечеткин
Волоколамское шоссе, д. 80, г. Москва, 125367, Россия; andreychechetkin@gmail.com

Статья получена: 25.10.2021 **Статья принята к печати:** 11.11.2021 **Опубликована онлайн:** 24.11.2021

DOI: 10.24075/vrgmu.2021.054

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Its annual incidence varies from 5 to over 35 cases per 100, 000 population [1]. In PD, autonomic dysfunction can develop years before the main motor symptoms set in. The prodromal period of PD is often characterized by gastrointestinal dysfunction manifesting as constipation, gastroparesis or nausea [2].

There is a hypothesis that pathologic deposition of α-synuclein in CNS observed in PD may start in the enteric nervous system and then spread rostrocranially via the vagus nerve (VN) [3]. According to pathomorphological reports, neuronal loss in the dorsal motor vagal nucleus can be as high as 50% [4]. Aggregates of α-synuclein are detected in some VN nuclei in the very early stages of the disease [5]. Importantly, subdiaphragmatic vagotomy is associated with a reduction in the subsequent risk of PD [6, 7]. A study conducted on an animal model has shown that α-synuclein derived from the brain lysate of patients with PD and recombinant α-synuclein injected into the intestinal wall are transported to CNS via the VN [8]. Abnormal α-synuclein aggregates have been detected in the glossopharyngeal and vagal

roots and in the cervical and pharyngeal segments of the VN of patients with PD [9, 10]. 11C-donepezil PET has found decreased acetylcholinesterase density in the gastrointestinal tract of patients with PD [11, 12]. This is believed to reflect parasympathetic denervation largely due to VN damage. Thus, adequate assessment of VN degeneration may serve as an additional tool to aid PD diagnosis. However, it is still unknown whether neurodegeneration observed in patients with PD is associated with VN atrophy that can be measured *in vivo*.

High-resolution ultrasound (HR-US) is a method of choice for visualizing peripheral and cranial nerves: ultrasound is often employed to detect peripheral nerve damage and polyneuropathy. For example, HR-US is capable of detecting mild and moderate VN atrophy in patients with lateral amyotrophic sclerosis and diabetic neuropathy [13–15]. A study reported that the cross-sectional area (CSA) of both VNs measured during HR-US was smaller in patients with PD than in the control group; this finding corroborates the hypothesis about the presence of nerve atrophy in PD patients [16]. There is ongoing debate about using high-resolution ultrasonography for estimating VN atrophy, a potential PD biomarker. The literature data on this problem are scarce and controversial [4, 16–23].

This study aimed to examine VNs in patients with PD using HR-US and to investigate possible associations between the obtained measurements, the clinical picture of the disease and the intensity of the hyperechoic signal from the substantia nigra of the middle cerebral peduncles.

METHODS

Patients

The study was conducted at the Research Center of Neurology from March 2020 to March 2021. Thirty-two patients with PD (15 men and 17 women) were included in the study. The mean age of the participants was 58 ± 10 years. Their clinical characteristics are provided in Table 1. The clinical history of PD varied from 1 to 26 years. The group was dominated by the mixed and akinetic-rigid forms of the disease (78%). The stage of the disease was determined using the Hoehn & Yahr scale. The severity of the patients' overall condition and motor function were assessed based on the total score on Part III of the Unified Parkinson's Disease Rating Scale (UPDRS). Non-motor symptoms were assessed using the Non-motor Symptoms Questionnaire (NMSQ). Four patients without clinically manifested polyneuropathy had type 2 diabetes mellitus controlled by adequate therapy. The following inclusion criteria were applied: any form of Hoehn & Yahr stage 1–3 PD. Exclusion criteria: severe diabetes mellitus with clinically manifested polyneuropathy; the absence of temporal bone acoustic window for transcranial ultrasound.

The control group consisted of 32 individuals comparable with the study group in terms of sex (16 men and 16 women) and age (mean age: 59 ± 6 years), without a medical history of diabetes mellitus, impaired glucose tolerance and neurological (including neurodegenerative) diseases.

Ultrasound examination

Transverse scans of the VN were performed using the iU 22 scanner (Philips; Netherlands) equipped with a L17-5 high-frequency linear array transducer. To measure CSA of the VN, the nerve was manually traced inside the hyperechoic epineural rim at the level of the distal portion of the common carotid artery, proximal to the bifurcation point (Fig. 1). During the scan, the pressure applied to the transducer was minimal to prevent nerve compression. The color Doppler mode was activated when necessary, so as not to confuse a small blood vessel in this hypervascularized region for VN. CSA was measured with 0.1 mm^2 precision. The average value derived from the sum of 3 measurements on each side was used in the subsequent statistical analysis.

Transcranial ultrasound of the substantia nigra was performed using the same scanner, an S5-1 sector array transducer and the standard technique described in [24]. Longitudinal scans were performed bilaterally using the transtemporal approach (temporal bone acoustic window). The images of the middle cerebral peduncles, which are visualized as a hypoechoic structure resembling a butterfly and surrounded by the hyperechoic basal cisterns, were captured and zoomed in 200% or 300%. If a hyperechoic signal was registered from the anatomic location of the substantia nigra (substantia nigra hyperechogenicity, SNH), that region was delineated with a cursor and CSA (cm^2) was calculated automatically.

Statistical analysis

Statistical analysis was carried out in StatTech v. 2.3.0 (StatTech; Russia). For quantitative variables, normality of distribution was tested using the Shapiro–Wilk test. Normally distributed quantitative variables were described as arithmetic means (M) and standard deviations (SD). Non-normally distributed quantitative variables were described as medians (Me) and the upper and lower quartiles (Q_1; Q_3). Intergroup differences in normally distributed quantitative variables with equal variances were estimated using Student's t-test. Intergroup differences in non-normally distributed quantitative variables were estimated in the Mann–Whitney U test. The direction and strength of correlations between two quantitative variables were assessed using Spearmen's correlation coefficient. ROC-curve analysis was applied to assess the diagnostic significance of quantitative parameters in predicting a given clinical outcome. The optimal cutoff point was calculated based on the maximum value of the Youden index. The significance threshold was assumed to be $p < 0.05$.

Table 1. Clinical characteristics of patients with PD included in the study

Disease characteristics	Patients with PD
Duration (Me [Q_1; Q_3])	3 [2; 8] years
Form	Akinetic-rigid — 7 (22%) Mixed — 25 (78%)
Hoehn & Yahr stage	1 — 8 (25%) 2 — 10 (31%) 3 — 14 (44%)
Severity of overall condition, UPDRS-III	37.0 ± 16.1 points
Severity of non-motor symptoms, NMSQ	8.2 ± 3.8 points

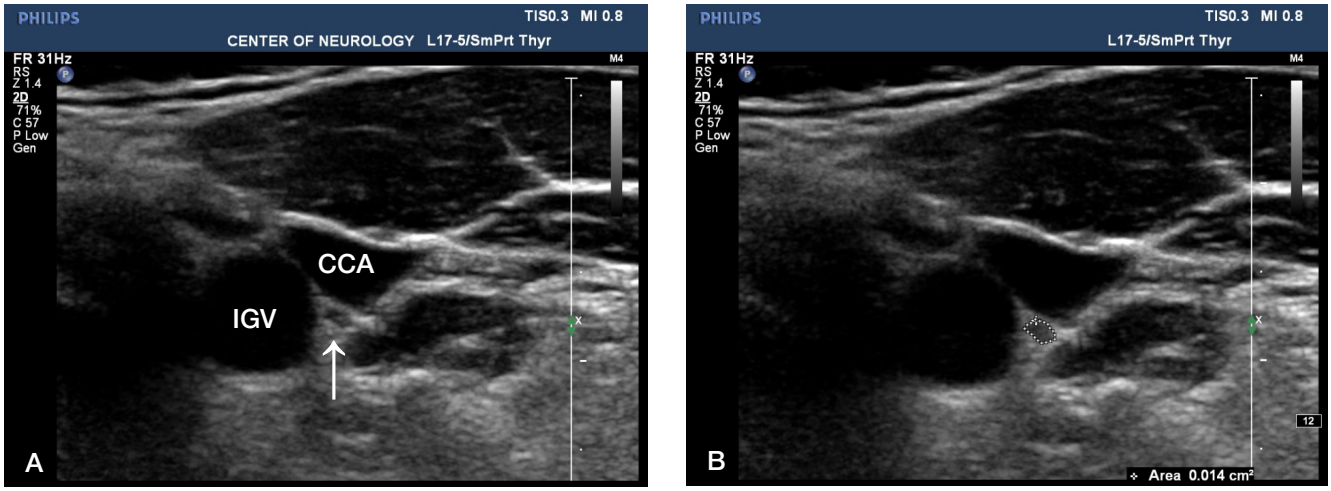

Fig. 1. A transverse ultrasound image of the vagus nerve. **A**. The left vagus nerve (indicated by the *white arrow*) is located between the common carotid artery (CCA) and the internal jugular vein (IGV). **B**. The same image showing delineation of the vagus nerve along the internal contour of the hyperechoic epineural rim. CSA (cross-sectional area) of the nerve = 0.014 cm^2, or 1.4 mm^2

RESULTS

The analysis revealed that CSA of the right VN was reliably larger than that of the left VN in both groups ($p < 0.001$; Table 2).

No significant sex-related differences between right and left VN CSAs were detected within the group of patients with PD ($p = 0.16$ and $p = 0.19$, respectively), although CSA tended to be bilaterally smaller in women (Table 2). In the control group, left VN CSA was smaller in women than in men ($p = 0.03$) but right VN CSA did not differ between the sexes ($p = 0.08$; Table 2).

The analysis also showed that left VN CSA was smaller in patients with PD than in the control group ($p = 0.007$). Right VN CSA did not differ significantly between the groups ($p = 0.13$) although it tended to be smaller in PD patients. Men with PD had smaller left VN CSA than men in the control group; by contrast, no significant difference in the right VN CSA was observed between the groups ($p = 0.09$). The right and left VN CSA did not differ between female participants ($p = 0.61$ and $p = 0.39$, respectively).

Considering the differences in the left VN CSA between the PD and the control groups, we conducted ROC analysis to determine a threshold value for the left VN CSA and assessed the model's sensitivity and specificity (Fig. 2). The threshold value of left VN CSA (the cutoff point) corresponded to the maximum value of the Youden index and was 2.10 mm^2; sensitivity and specificity of the model were 59.4% and 75.0%, respectively.

The analysis of the PD group data did not detect any associations between CSA and age, clinical duration or stage of the disease, UPDRS-III and NMSQ scores ($p > 0.05$). However, there was an association between the form of the disease and left VN CSA: the latter was smaller in patients with akinetic rigid PD ($p = 0.043$). Right VN CSA only tended to be smaller for this form of the disease ($p = 0.064$; Table 3).

During transcranial ultrasound, SNH was detected in 27 (84%) patients. The hyperechoic area was 0.23 (0.15; 0.26) cm2 on the right side and 0.22 (0.15; 0.27) cm2 on the left side. The analysis of possible associations between CSA and SNH areas on both sides demonstrated a moderate inverse correlation between left VN CSA and SNH areas on the left ($R = –0.38$; $p = 0.03$) and right ($R = –0.36$; $p = 0.04$) sides (Fig. 3). At the trend level, a similar association was observed for the right VN CSA: $R = –0.352$, $p = 0.05$ on the right and $R = –0.28$, $p = 0.12$ on the left side.

DISCUSSION

In our study, right VN CSA was reliably larger than CSA of the left VN in both groups. This pattern was observed for both male and female participants. Similar findings are reported by another study proposing reference VN CSA values for healthy populations [25] and by almost all publications on the HR-US-based assessment of the VN in patients with PD [4, 17–20, 22]. This is consistent with the difference between the right and left VNs observed during a morphological examination [26]. The amount of nerve fibers in the right VN is ~20% higher than in the left nerve [27]. This asymmetry may result from unequal innervation of unpaired organs in the abdominal cavity [28]. The right VN innervates a part of the small bowel, the colon and the anterior gastric plexus; the left VN ends in the anterior gastric plexus and branches off to the stomach, liver and the superior duodenum.

Table 2. CSA of the right and left vagus nerves in patients with PD and healthy controls

Group	Right VN CSA (mm^2)	Left VN CSA (mm^2)
PD ($n = 32$)	2.03 ± 0.50	1.78 ± 0.52 *
men ($n = 15$)	2.20 ± 0.44	2.03 ± 0.46 *
women ($n = 17$)	2.04 ± 0.46	1.87 ± 0.52
Control ($n = 32$)	2.21 ± 0.39	2.11 ± 0.41
men ($n = 16$)	2.33 ± 0.37	2.26 ± 0.37
women ($n = 16$)	2.09 ± 0.38	1.96 ± 0.39

Note: CSA — cross-sectional area; VN — vagus nerve; PD — Parkinson's disease; * — $p < 0.05$, comparison with the control group.

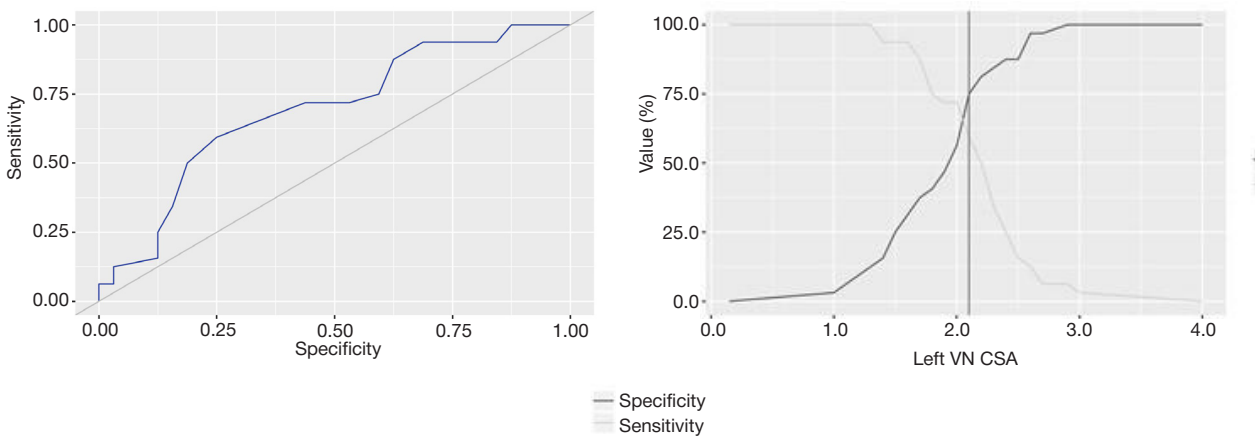

Fig. 2. Analysis of the model's sensitivity and specificity depending on the threshold values of the left VN CSA. CSA — cross-sectional area; VN — vagus nerve

According to our observations, VN CSA was smaller in women than in men in both groups ($p < 0.001$). These findings are consistent with the results of the largest study on the subject [4] in which HR-US of the VN was performed on 63 patients with PD and 56 healthy individuals. However, in another study VN CSA was larger in men than in women [19].

According to our measurements, left VN CSA was smaller in patients with PD than in the control group ($p < 0.05$); right VN CSA did not differ significantly between the groups although it did tend to be smaller in patients with PD. Eight identified publications on HR-US-based VN assessment in patients with PD yielded conflicting data despite the use of high-frequency high-resolution transducers (linear array transducer frequencies ranged from 12 to 19 MHz; Table 4). Significant atrophy of the right and left VNs of patients with PD was reported by 4 studies [16, 19, 20, 23]. Another 4 studies included in the analysis reported no differences between the VNs of patients with PD and healthy individuals [4, 18, 21, 22]. But although no differences in VN CSA between patients with PD and the control group were initially observed in the study [4], once the obtained data were corrected for sex, right (as opposed to left), VN CSA turned to be considerably smaller for female patients with PD ($p = 0.041$). In our study, left VN CSA was reliably smaller in men with PD than in healthy male controls, but no significant differences were found for right VBN CSA.

In our study, the average VN CSA was 8% smaller on the right side and 15% smaller on the left side in patients with PD than in the control group. Other studies report a reduction of 10% to 30% [16, 17, 19, 20, 23]. In order to determine the threshold value for left VN CSA, which, according to our data, was reliably smaller in the PD group, ROC analysis was carried out. Based on its results, a value below 2.10 mm^2 may serve as a VN atrophy indicator for patients with PD with 59% sensitivity and 75% specificity. In an earlier study conducted on 60 healthy volunteers, VN CSA was 3.0 ± 0.7 (1.7–4.3) mm^2 on the right and 2.3 ± 0.6 (1.1–3.5) mm^2 on the left side [25]. Knowing that typical VN CSA varies from 1 to 4 mm^2 and considering the low sensitivity of this indicator, we think that the obtained threshold value cannot be used in clinical practice for such small anatomical structures as VN. It should be noted that in all of the publications we included in the analysis, the area of the nerve was measured at different levels, which may have affected the results because there is some anatomical variability in nerve thickness in its cervical segment. Similar to our strategy, some researchers measured VN CSA at the level of the distal end of the common carotid artery [16, 21]; others took measurements at the level of the thyroid cartilage [4, 19]; some studies did not specify the level at which the measurements were taken [18]. However, the difference in the applied methodologies alone cannot explain why significant atrophy of the VN was observed in some studies and was undetected in others. The conflicting results may be explained by the fact that differences in the obtained measurements were minor and generally depend on the technical specifications of the scanner, transducer frequency and the experience of the sonographer.

We did not find any correlations between VN CSA and most of the clinical characteristics of PD. There were no reports of correlations between VN CSA and the patient's age, Hoehn & Yahr stage, duration of the disease, UPDRS-III scores, cognitive scores, gastrointestinal and other non-motor symptoms in almost all of the analyzed publications [4, 17, 18, 20–23]. The absence of correlations may be linked to the progressive degeneration of the dorsal motor vagal nucleus at the early stages of the disease [29]. However, there are publications suggesting an association between the VN caliber and the clinical manifestations of PD. For instance, left VN CSA is reported to correlate with the severity of PD symptoms on the UPDRS-III scale ($r = 0.58$; $p = 0.007$), in contrast with right VN CSA ($p = 0.53$) [19]. Besides, right VN CSA is correlated with bradykinesia assessed on the UPDRS-III scale ($r = 0.53$; $p = 0.003$) [18]. The authors of the cited studies hypothesize that bradykinesia-dominant PD subtypes seem to be associated with more advanced Lewy body pathology. Our findings corroborate this conclusion. In our study, the nerve caliber was associated with the form of the disease: left VN CSA was smaller in patients with akinetic rigid PD ($p = 0.05$) whereas a similar pattern for right VN CSA was observed at the trend level ($p = 0.06$).

Table 3. 3VN CSA in patients with different forms of PD

Parameter	Form of PD	
	Akinetic rigid	Mixed
Right CSA (mm^2)	1.70 ± 0.47	2.13 ± 0.48
Left CSA (mm^2)	1.46 ± 0.35 *	1.87 ± 0.53

Note: * — indicates statistically significant differences ($p < 0.05$).

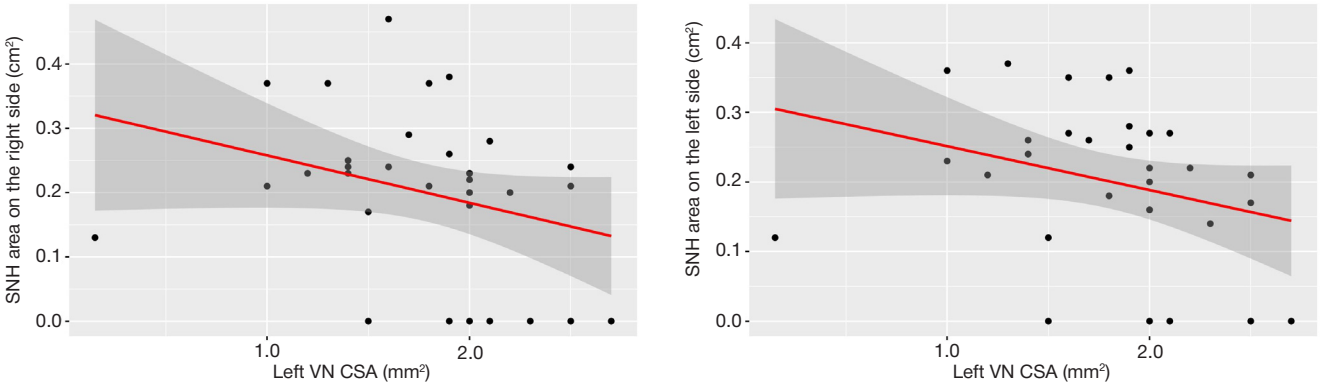

Fig. 3. The regression function graph for the association between the left VN CSA and SNH area on the right (**A**) and left (**B**). CSA — cross-sectional area; VN — vagus nerve; SNH — substantia nigra hyperechogenicity

Table 4. Ultrasonography findings in patients with PD

Reference study	Number of patients with PD/control	Number of men and women with PD	Transducer frequency	VN CSA on HR-US, (mm²) PD / control		Significant differences between PD and control groups
				Right VN	Left VN	
[16, 17]	19 / 21	6 / 13	12 MHz	1.58 / 2.35	1.45 / 1.91	yes
[18]	32 / 15	20 / 12	15 MHz	2.9 ± 0.7 / 2.7 ± 0.7	2.6 ± 0.7 / 2.4 ± 0.7	no
[19]	20 / 61	13 / 7	15 MHz	0.64 ± 0.17 / 1.04 ± 0.20	0.69 ± 0.18 / 0.87 ± 0.15	yes
[20]	35 / 35	19 / 16	15 MHz	2.1 ± 0.4 / 2.3 ± 0.5	1.5 ± 0.4 / 1.8 ± 0.4	yes
[21]	20 / 20	10 / 10	12 MHz	1.17 / 1.13#		no
[22] *	31 / 51	16 / 15	n/a	2.54 / 2.24	2.10 / 1.90	no
[23]	20 / 20	12 / 8	19 MHz	2.37 + 0.91 / 6.0 + 1.33	1.87 ± 1.35 / 5.6 ± 1.26	yes
[4]	63 / 56	43 / 20	12 MHz	2.23 / 2.37	1.89 / 1.97	no / yes¥
Our data	32 / 32	14 / 16	17 MHz	2.03 ± 0.50 / 2.21 ± 0.39	1.78 ± 0.52 / 2.11 ± 0.41	yes

Note: PD — Parkinson's disease; HR-US — high-resolution ultrasound; CSA — cross-sectional area; VN — vagus nerve; * preprint, not peer reviewed yet; # — average diameter (mm); ¥ — reduction of right VN CSA in the PD group corrected for sex.

While conducting literature analysis, we found a single report of a significant inverse correlation between right/left VN CSA and the severity of autonomic dysfunction in PD measured on the NMSQ scale (r = –0.46; p = 0.003) [19]. Besides, right (but not left) VN CSA was directly correlated with parasympathetic heart-rate variability (r = 0.58; p = 0.001) whereas left VN CSA was correlated with the severity of PD symptoms on the UPDRS-III scale (r = 0.58; p = 0.007). This inconsistency between our findings and the results of other studies might be explained by the applied study selection criteria: patients with comorbidities that could be associated with VN neuropathy were excluded.

In the course of the study, we investigated possible associations between VN CSA and SNH in the middle cerebral peduncles assessed by transcranial ultrasound. The analysis revealed a moderate inverse correlation between the left VN CSA and SNH area on both sides ($p < 0.04$). A similar correlation for the right VN was observed at the trend level. These findings seem to reflect the neurodegenerative process in the VN and dopaminergic neurons of the substantia nigra in patients with PD. Previously, we had demonstrated that SNH area (similar to VN CSA investigated in this study) did not correlate with the duration or severity of the disease. This marker stability suggests that changes can occur at the very early stages of the disease [23, 30].

CONCLUSIONS

HR-US of patients with PD has revealed atrophy of the VN and associations of VN CSA with the clinical form of PD and the changed echogenicity of the substantia nigra. However, the low sensitivity of the described VN assessment method prevents using HR-US as a diagnostic modality in wide clinical practice. Thus, VN CSA is not a reliable marker of VN damage.

References

1. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017; 3 (1): 1–21. DOI: 10.1038/nrdp.2017.13.
2. Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease–the gutbrain axis and environmental factors. Nat Rev Neurol. 2015. 11; 625–36. DOI: 10.1038/nrneurol.2015.197.
3. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dualhit hypothesis. Neuropathol Appl Neurobiol. 2007; 33: 599–614. DOI: 10.1111/j.1365-2990.2007.00874.x.
4. Horsager J, Walter U, Fedorova TD, Andersen KB, Skjærbæk C, Knudsen K, et al. Vagus Nerve Cross-Sectional Area in Patients With Parkinson's Disease-An Ultrasound Case-

Control Study. Front Neurol. 2021; 12: 681413. DOI: 10.3389/fneur.2021.681413.
5. Del Tredici K, Braak H. Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. Neuropathol Appl Neurobiol. 2016; 42: 33–50. DOI: 10.1111/nan.12298.
6. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015; 78: 522–29. DOI: 10.1002/ana.24448.
7. Liu B, Fang F, Pedersen NL, Tillander A, Ludvigsson JF, Ekbom A, et al. Vagotomy and Parkinson disease: a Swedish register-based matchedcohort study. Neurology. 2017; 88: 1996–2002. DOI: 10.1212/WNL.0000000000 003961.
8. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T., et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014; 128: 805–20. DOI: 10.1007/s00401-014-1343-6.
9. Mu L, Sobotka S, Chen J, Su H, Sanders I, Adler C, et al. Alphasynuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease. J Neuropathol Exp Neurol. 2013. 72; 119–29. DOI: 10.1097/NEN.0b013e3182 801cde.
10. Nakamura K, Mori F, Tanji K, Miki Y, Toyoshima Y, Kakita A, et al. α-Synuclein pathology in the cranial and spinal nerves in Lewy body disease. Neuropathology. 2016; 36: 262–69. DOI: 10.1111/neup. 12269.
11. Gjerloff T, Fedorova T, Knudsen K, Munk O, Nahimi A, Jacobsen S, et al. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. Brain. 2015; 138 (Pt 3): 653–63. DOI: 10.1093/brain/awu369.
12. Fedorova T, Seidelin L, Knudsen K, Schacht A, Geday J, Pavese N, et al. Decreased intestinal acetylcholinesterase in early Parkinson disease: An (11)C-donepezil PET study. Neurology. 2017. 88: 775–81. DOI: 10.1212/WNL.0000000000003633.
13. Grimm A, Décard B, Athanasopoulou I, Schweikert K, Sinnreich M, Axer H. Nerve ultrasound for differentiation between amyotrophic lateral sclerosis and multifocal motor neuropathy. J Neurol. 2015; 262: 870–80. DOI: 10.1007/s00415-015-7648-0.
14. Hong M, Baek J, Kim D, Ha E, Choi W, Choi Y, et al. Spinal accessory nerve: ultrasound findings and correlations with neck lymph node levels. Ultraschall Med. 2016; 37: 487–91. DOI: 10.1055/s-0034-1385673.
15. Tawfik E, Walker F, Cartwright M, El-Hilaly R. Diagnostic ultrasound of the vagus nerve in patients with diabetes. J Neuroimaging. 2017; 27: 589–93. DOI: 10.1111/jon.12452.
16. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, Suenaga T. Vagus nerve atrophy in Parkinson's disease detected by ultrasonography. Journal of the Neurological Sciences. 2017; 365, 129. DOI: 10.1016/j.jns.2017.08.391.
17. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, Suenaga T. The vagus nerve becomes smaller in patients with Parkinson's disease: a preliminary cross-sectional study using ultrasonography. Parkinsonism Relat Disord. 2018; 55: 148–49. DOI: 10.1016/j.parkreldis.2018.06.002.
18. Fedtke N, Witte O, Prell T. Ultrasonography of the vagus nerve in Parkinson's disease. Front Neurol. 2018; 9: 525. DOI: 10.3389/fneur.2018.00525.
19. Walter U, Tsiberidou P, Kersten M, Storch A, Lohle M. Atrophy of the vagus nerve in Parkinson's Disease revealed by high-resolution ultrasonography. Front Neurol. 2018; 9: 805. DOI: 10.3389/fneur.2018.00805.
20. Pelz J, Belau E, Fricke C, Classen J, Weise D. Axonal degeneration of the vagus nerve in Parkinson's disease-a high-resolution ultrasound study. Front Neurol. 2018; 9: 951. DOI: 10.3389/fneur.2018.00951.
21. Laucius O, Balnyte R, Petrikonis K, Matijosaitis V, Juceviciute N, Vanagas T, et al. Ultrasonography of the vagus nerve in the diagnosis of Parkinson's disease. Parkinsons Dis. 2020; 2020: 2627471. DOI: 10.1155/2020/2627471.
22. Sijben L, Mess W, Walter U, Janssen A, Kuijf M, Oosterloo M. The cross-sectional area of the vagus nerve is not reduced in Parkinson's Disease patients. medRxiv [Preprint]. 2020. DOI: 10.1101/2020.10.19.20214973.
23. Sartucci F, Bocci T, Santin M, Bongioanni P, Orlandi G. High-resolution ultrasound changes of the vagus nerve in idiopathic Parkinson's disease (IPD): a possible additional index of disease. Neurol Sci. 2021. DOI: 10.1007/s10072-021-05183-5.
24. Fedotova EYu, Chechetkin AO, Shadrina MI, Slominsky PA, Ivanova-Smolenskaya IA, Illarioshkin SN. Transcranial sonography in Parkinson's disease. Zh Nevrol Psikhiatr Im SS Korsakova. 2011; 1: 49–55.
25. Pelz J, Belau E, Henn P, Hammer N, Classen J, Weise D. Sonographic evaluation of the vagus nerves: protocol, reference values, and side-to-side differences. Muscle Nerve. 2018; 57 (5): 766–71. DOI: 10.1002/mus.25993.
26. Verlinden T, Rijkers K, Hoogland G, Herrler A. Morphology of the human cervical vagus nerve: implications for vagus nerve stimulation treatment. Acta Neurol Scand. 2016; 133: 173–82. DOI: 10.1111/ane.12462.
27. Hoffman H, Schnitzlein H. The numbers of nerve fibers in the vagus nerve of man. Anat Rec. 1961; 139: 429–35. DOI: 10.1002/ar.1091390312.
28. Cheng Z, Powley T, Schwaber J, Doyle F. Projections of the dorsal motor nucleus of the vagus to cardiac ganglia of rat atria: an anterograde tracing study. J Comp Neurol. 1999; 410: 320–41.
29. Braak H, Del Tredici K, Rub U, de Vos R, Steur J, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24: 197–211. DOI: 10.1016/S0197-4580(02)00065-9.
30. Fedotova EYu, Chechetkin AO, Abramycheva NYu, Chigaleychik LA, Baziyan BKh, Ponomareva TA, et al. Identification of people at the latent stage of Parkinson's disease (the PARKINLAR study): first results and an optimization of the algorithm. Zh Nevrol Psikhiatr Im S S Korsakova. 2015; 115 (6): 4–11. DOI: 10.17116/jnevro2015115614-11.

Литература

1. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017; 3 (1): 1–21. DOI: 10.1038/nrdp.2017.13.
2. Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease–the gutbrain axis and environmental factors. Nat Rev Neurol. 2015. 11; 625–36. DOI: 10.1038/nrneurol.2015.197.
3. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dualhit hypothesis. Neuropathol Appl Neurobiol. 2007; 33: 599–614. DOI: 10.1111/j.1365-2990.2007.00874.x.
4. Horsager J, Walter U, Fedorova TD, Andersen KB, Skjærbæk C, Knudsen K, et al. Vagus Nerve Cross-Sectional Area in Patients With Parkinson's Disease-An Ultrasound Case-Control Study. Front Neurol. 2021; 12: 681413. DOI: 10.3389/fneur.2021.681413.
5. Del Tredici K, Braak H. Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. Neuropathol Appl Neurobiol. 2016; 42: 33–50. DOI: 10.1111/nan.12298.
6. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015; 78: 522–29. DOI: 10.1002/ana.24448.
7. Liu B, Fang F, Pedersen NL, Tillander A, Ludvigsson JF, Ekbom A, et al. Vagotomy and Parkinson disease: a Swedish register-based matchedcohort study. Neurology. 2017; 88: 1996–2002. DOI: 10.1212/WNL.0000000000 003961.
8. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T., et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014; 128: 805–20. DOI: 10.1007/s00401-014-1343-6.

9. Mu L, Sobotka S, Chen J, Su H, Sanders I, Adler C, et al. Alphasynuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease. J Neuropathol Exp Neurol. 2013. 72; 119–29. DOI: 10.1097/NEN.0b013e3182 801cde.
10. Nakamura K, Mori F, Tanji K, Miki Y, Toyoshima Y, Kakita A, et al. α-Synuclein pathology in the cranial and spinal nerves in Lewy body disease. Neuropathology. 2016; 36: 262–69. DOI: 10.1111/neup. 12269.
11. Gjerloff T, Fedorova T, Knudsen K, Munk O, Nahimi A, Jacobsen S, et al. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. Brain. 2015; 138 (Pt 3): 653–63. DOI: 10.1093/brain/awu369.
12. Fedorova T, Seidelin L, Knudsen K, Schacht A, Geday J, Pavese N, et al. Decreased intestinal acetylcholinesterase in early Parkinson disease: An (11)C-donepezil PET study. Neurology. 2017. 88: 775–81. DOI: 10.1212/WNL.0000000000003633.
13. Grimm A, Décard B, Athanasopoulou I, Schweikert K, Sinnreich M, Axer H. Nerve ultrasound for differentiation between amyotrophic lateral sclerosis and multifocal motor neuropathy. J Neurol. 2015; 262: 870–80. DOI: 10.1007/s00415-015-7648-0.
14. Hong M, Baek J, Kim D, Ha E, Choi W, Choi Y, et al. Spinal accessory nerve: ultrasound findings and correlations with neck lymph node levels. Ultraschall Med. 2016; 37: 487–91. DOI: 10.1055/s-0034-1385673.
15. Tawfik E, Walker F, Cartwright M, El-Hilaly R. Diagnostic ultrasound of the vagus nerve in patients with diabetes. J Neuroimaging. 2017; 27: 589–93. DOI: 10.1111/jon.12452.
16. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, Suenaga T. Vagus nerve atrophy in Parkinson's disease detected by ultrasonography. Journal of the Neurological Sciences. 2017; 365, 129. DOI: 10.1016/j.jns.2017.08.391.
17. Tsukita K, Taguchi T, Sakamaki-Tsukita H, Tanaka K, Suenaga T. The vagus nerve becomes smaller in patients with Parkinson's disease: a preliminary cross-sectional study using ultrasonography. Parkinsonism Relat Disord. 2018; 55: 148–49. DOI: 10.1016/j.parkreldis.2018.06.002.
18. Fedtke N, Witte O, Prell T. Ultrasonography of the vagus nerve in Parkinson's disease. Front Neurol. 2018; 9: 525. DOI: 10.3389/fneur.2018.00525.
19. Walter U, Tsiberidou P, Kersten M, Storch A, Lohle M. Atrophy of the vagus nerve in Parkinson's Disease revealed by high-resolution ultrasonography. Front Neurol. 2018; 9: 805. DOI: 10.3389/fneur.2018.00805.
20. Pelz J, Belau E, Fricke C, Classen J, Weise D. Axonal degeneration of the vagus nerve in Parkinson's disease-a high-resolution ultrasound study. Front Neurol. 2018; 9: 951. DOI: 10.3389/fneur.2018.00951.
21. Laucius O, Balnyte R, Petrikonis K, Matijosaitis V, Juceviciute N, Vanagas T, et al. Ultrasonography of the vagus nerve in the diagnosis of Parkinson's disease. Parkinsons Dis. 2020; 2020: 2627471. DOI: 10.1155/2020/2627471.
22. Sijben L, Mess W, Walter U, Janssen A, Kuijf M, Oosterloo M. The cross-sectional area of the vagus nerve is not reduced in Parkinson's Disease patients. medRxiv [Preprint]. 2020. DOI: 10.1101/2020.10.19.20214973.
23. Sartucci F, Bocci T, Santin M, Bongioanni P, Orlandi G. High-resolution ultrasound changes of the vagus nerve in idiopathic Parkinson's disease (IPD): a possible additional index of disease. Neurol Sci. 2021. DOI: 10.1007/s10072-021-05183-5.
24. Fedotova EYu, Chechetkin AO, Shadrina MI, Slominsky PA, Ivanova-Smolenskaya IA, Illarioshkin SN. Transcranial sonography in Parkinson's disease. Zh Nevrol Psikhiatr Im SS Korsakova. 2011; 1: 49–55.
25. Pelz J, Belau E, Henn P, Hammer N, Classen J, Weise D. Sonographic evaluation of the vagus nerves: protocol, reference values, and side-to-side differences. Muscle Nerve. 2018; 57 (5): 766–71. DOI: 10.1002/mus.25993.
26. Verlinden T, Rijkers K, Hoogland G, Herrler A. Morphology of the human cervical vagus nerve: implications for vagus nerve stimulation treatment. Acta Neurol Scand. 2016; 133: 173–82. DOI: 10.1111/ane.12462.
27. Hoffman H, Schnitzlein H. The numbers of nerve fibers in the vagus nerve of man. Anat Rec. 1961; 139: 429–35. DOI: 10.1002/ar.1091390312.
28. Cheng Z, Powley T, Schwaber J, Doyle F. Projections of the dorsal motor nucleus of the vagus to cardiac ganglia of rat atria: an anterograde tracing study. J Comp Neurol. 1999; 410: 320–41.
29. Braak H, Del Tredici K, Rub U, de Vos R, Steur J, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24: 197–211. DOI: 10.1016/S0197-4580(02)00065-9.
30. Fedotova EYu, Chechetkin AO, Abramycheva NYu, Chigaleychik LA, Baziyan BKh, Ponomareva TA, et al. Identification of people at the latent stage of Parkinson's disease (the PARKINLAR study): first results and an optimization of the algorithm. Zh Nevrol Psikhiatr Im S S Korsakova. 2015; 115 (6): 4–11. DOI: 10.17116/jnevro2015115614-11.