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The association of vagal atrophy with parameters of autonomic function in multiple system atrophy and progressive supranuclear palsy

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Abstract

Background: Vagal atrophy is a hallmark of Parkinson's disease (PD) and has been found to be associated with autonomic dysfunction, while analyses of the vagus nerve (VN) in atypical Parkinsonian syndromes (APS) have not yet been performed. We here investigate the characteristics of the VN in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) and, in a second step, its potential as a possible biomarker for orthostatic dysregulation.

Objectives: The aim was to compare the VN pathology in MSA and PSP with healthy individuals and patients with PD as a differentiating factor and to further analyse the correlation of the VN with clinical parameters and cardiovascular response.

Design: We conducted a monocentric, cross-sectional cohort study in 41 APS patients and compared nerve ultrasound (NUS) parameters with 90 PD patients and 39 healthy controls.

Methods: In addition to a detailed neurological history and examination, several clinical severity and motor scores were obtained. Autonomic symptoms were reported in the Scales for Outcomes in Parkinson's Disease – Autonomic questionnaire. Further scores were used to detect other non-motor symptoms, quality of life and cognition. Additionally, we performed a head up tilt test (HUTT) and NUS of the VN. We conducted correlation analyses of the VN cross-sectional area (CSA) with clinical scores and the heart rate and blood pressure variability parameters of the HUTT.

Results: The examination demonstrated a high prevalence of abnormal autonomic response in both MSA (90%) and PSP (80%). The VN CSA correlated with spectral parameters of the HUTT, which are associated with sympatho-vagal imbalance. In addition, the CSA of the VN in patients with PD and PSP were significantly smaller than in healthy controls. In MSA, however, there was no marked vagal atrophy in comparison.

Conclusion: The occurrence of autonomic dysfunction was high in MSA and PSP, which underlines its impact on these syndromes. Our findings indicate a connection between vagal pathology and autonomic dysfunction and might contribute to a better comprehension of APS. To further evaluate the clinical relevance and the VN as a possible marker of autonomic dysfunction in APS, prospective longitudinal observations are necessary.

Keywords: autonomous nervous system, atypical Parkinsonian syndromes, head-up tilt test, multiple system atrophy, nerve ultrasound, orthostatic dysfunction, Parkinson's disease, peripheral neuropathy, progressive supranuclear palsy, vagus nerve

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Introduction

Parkinsonian syndromes belong to the group of extrapyramidal motor movement disorders and are defined by a variety of symptoms such as brady- or hypokinesia, rigour, tremor and postural instability.[1]

In addition, atypical Parkinsonian syndromes (APS) are characterized by a range of additional motor and non-motor symptoms. These can be further categorized as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia (LBD) and corticobasal degeneration (CBD). Overall, patients with APS show a rapid disease progression, a poorer dopaminergic treatment response[2] and can be further subdivided based on their underlying neuropathology.[1]

The α-synucleinopathies include Parkinson's disease (PD), MSA and LBD, while the tauopathies are represented by PSP and CBD. The abnormal protein deposits are found in different cell types in each disease. In α-synucleinopathies, deposits are found not only in neurons in all three types but also in oligodendrocytes in MSA. Tauopathies affect neurons as well as oligodendrocytes and astrocytes. In this work, we focused on the atypical syndromes MSA and PSP.

As mentioned above, MSA is characterized by the deposition of aggregated α-synuclein, particularly in the cytoplasm of oligodendrocytes. This leads to the appearance of glial cytoplasmic inclusions (GCI), which are characteristic for the disease and affect different regions of the brain at different densities.[3] A higher density of GCIs is associated with neurodegeneration.[4]

As the name suggests, MSA affects many systems and regions of the brain. In particular, a distinction is made between striatonigral and olivopontocerebellar atrophy, which leads to the Parkinson's type (MSA-P) and cerebellar type (MSA-C) subtypes[5] with different predominant motor syndromes.[6] Furthermore, MSA presents with pronounced autonomic dysfunction in the sense of orthostatic hypotension (OH), bladder dysfunction and erectile dysfunction. Pathological protein deposits in preganglionic neurons are discussed as a correlate of the frequently occurring OH, which is also used for diagnostic criteria.[7,8]

In PSP, as in CBD, tau is found as the underlying pathological protein deposition.[9] Tau becomes hyperphosphorylated, which inhibits its proteolytic degradation.[10] This leads to its accumulation in various areas of the brain, particularly the basal ganglia (more specifically the pallidum, substantia nigra and subthalamic nucleus), brainstem and diencephalon.[11]

There are different subtypes of PSP, characterized by a wide range of phenotypic symptoms. These in turn correlate with a different neuropathological distribution. The subtypes PSP-Richardson and PSP-Parkinson are considered to be the most common clinical presentations. Patients with PSP show oculomotor disturbances, speech and language disorders and early postural instability in addition to the hypokinetic-rigid syndrome. Autonomic symptoms such as constipation or cardiovascular dysfunction also occur,[12] but they are less frequent than in the synucleinopathies. According to the criteria of Höglinger et al.,[13] severe OH even contradicts the diagnosis of PSP.

The diagnosis of APS is challenging, as there is a large overlap of a broad spectrum of symptoms with other diseases. These include not only the various forms of Parkinson but also other neurodegenerative diseases. Diagnosis is particularly difficult in the early phase of the disease, despite the pathophysiological differences, as some symptoms only become apparent as the disease proceeds and the course of the disease can be a decisive feature in the assessment.

Biomarkers can contribute to a better understanding of the disease and highlight commonalities within the syndromes. This will make patients eligible for trials and possibly disease-modifying therapies and will help predict the course of the disease.

In addition, the disease can present with a wide range of symptoms that can also be easily overlooked as they are not always recognized as being associated with the disease. With better biomarkers, these can be better identified and treated, and patients can be provided with improved information and awareness.

There are certain current approaches which focus on the detection of new biomarkers. One of the

promising approaches includes α-synuclein seed amplification assays from different biological tissues[14,15] in PD and APS. However, meta-analyses show that the selectivity, for example, between the respective synucleinopathies, varies considerably depending on the study.

There have also been studies of imaging in patients with Parkinson's. Differentiation between the syndromes is not always possible and is influenced by the clinical stage of the disease, which means that the accuracy differs. In the early stages of the disease, neuroimaging can also be completely unremarkable.[16] The choice of imaging technique is also important. It is a tool that appears to be inadequate without the addition of further parameters.[17]

Another approach is the analysis of extracellular vesicles. α-Synuclein from the central nervous system could be stored in these vesicles and analysed in different body fluids. However, the results published so far have been heterogeneous and not always reproducible. A meta-analysis has also shown that it is not sufficient to distinguish between atypical syndromes.[18,19]

Pathological protein deposits in the context of Parkinson's syndromes also affect the peripheral nervous system (PNS) and can be associated with axonal polyneuropathy. This was also evident in patients with MSA and PSP in our own preliminary work.[20] An atrophy of the vagus nerve (VN) in patients with PD is reported[21] but not yet well understood, whereas studies in APS are limited.

The VN, as part of the PNS, is significantly involved in the parasympathetic regulation of the circulatory system and orthostatic functions are regulated from the interaction of the sympathetic and VNs. Since the autonomic nervous system (ANS) and VN pathology is implicated in the pathophysiology of PD, it is of particular interest to understand its functions properly.[22,23]

With the nerve ultrasound (NUS) it is possible to achieve precise images of the nerval morphology mostly in the diagnostic of polyneuropathies,[24,25] especially in inflammatory types like Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy.[26,27] A widely used measure is the cross-sectional area (CSA) in mm^2, which can indicate nerval enlargements due to not only demyelination and inflammation[28] but also atrophy. Vagal atrophy has already been discussed in recent publications as a sign of parasympathetic dysfunction.[25]

In PD, the value of NUS is discussed more controversially, as there was found a significant CSA reduction[21,29–32] as well as no difference to controls.[33] For APS, on the other hand, studies are scarce.

Studies investigating the CSA of the VN in NUS in patients with idiopathic PD show a vagal atrophy mostly of the right vagal nerve.[21,29,30] Similar studies on APS are needed.

To date, there have been few correlation analyses of VN with other parameters, which will be crucial for a deeper understanding of vagus pathology in the future. In our own preceding work,[28] we were able to show for the first time an association of vagus pathology with spectral analysis parameters in head up tilt test (HUTT).

Based on our preliminary data on vagal atrophy, which we analysed in a cohort of patients with PD, we decided to investigate NUS in two representatives of APS. This included not only the characteristics of the VN but also the correlation with the orthostatic components measured on the tilt table. It was appropriate to examine MSA more closely due to the aspect of autonomic dysfunction characterizing the disease. On the one hand, the PSP provides a comparative cohort of a Parkinson's syndrome with primary tauopathy for comparison with the other groups. Furthermore, there are published studies suggesting an influence of VN on autonomic symptoms in patients with PSP.

In this study we investigate the functional significance of ultrasound imaging of the VN in MSA and PSP in relation to tilt table parameters and clinical data. We will also compare the CSA of the VN with patients with PD and healthy controls. The aim is to find out whether vagal atrophy develops in patients with MSA and PSP and whether this can be helpful in detecting the disease pattern but also correlates with other important symptoms and allows inferences to be made about orthostatic regulation.

Methods

Inclusion of patients and controls

We conducted a monocentric, cohort study at St. Josef-Hospital in Bochum, Germany, including patients who fulfilled either the clinical criteria for MSA according to Gilman et al.[7] or PSP according to Höglinger et al.[13] We recruited patients who presented to the outpatient or inpatient neurological department and were treated by movement disorder specialists. In addition, we considered the further clinical course and examination parameters of longitudinal examinations as well as additional available patient data such as imaging of the brain.

Our study involved patients diagnosed with PD according to the criteria of the United Kingdom Parkinson's Society Brain Bank[34] and the Movement Disorders Society.[35] Individuals affected by other recognized causes of neuropathy (including diabetes mellitus and a history of alcohol abuse) were excluded from the study.

We retrospectively utilized a control group ($n = 39$, female = 18, male = 21) that had undergone sonographic examination in our clinic for reasons unrelated to polyneuropathy. For this control group, we excluded all acknowledged causes of polyneuropathy.

The study is listed in the German clinical trials registry (DRKS-ID: DRKS00020752, https://drks.de/search/de/trial/DRKS00020752), and our study protocol was approved by the local university ethics committee (Medical Faculty of Ruhr University Bochum, Reg. Nr. 18-6360). We obtained written consent from all examined patients. The study was implemented in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and its subsequent amendments.

Exclusion criteria were polyneuropathy-associated diseases such as insulin-dependent diabetes mellitus, drug or alcohol dependence in the last 6 months, stereotactic surgery, electroconvulsive therapy in the last 180 days, severe depression with suicidality or severe dementia (Mini-Mental State Exam < 10).

In total, we included 41 patients with APS between 10/2018 and 09/2021, eventually being able to perform a HUTT with 20 patients affected by MSA and 10 affected by PSP due to disease severity (Supplemental Figure 1 gives an overview of the inclusion process).

Clinical parameters

All patients received a detailed medical history and clinical examination.

Demographic data were collected in the form of patient age, age at onset of the disease, duration of the disease and the levodopa equivalent dose and gender.

Furthermore, important clinical scores validated for Parkinson were collected.

Disease severity and motor examination were recorded in the modified Hoehn and Yahr (H&Y) scale,[36] the MDS-Unified Parkinson's Disease Rating Scale (UPDRS I–IV)[37] and disease-specific either the MDS-Unified Multiple System Atrophy Rating Scale[38] or Progressive Supranuclear Palsy Rating Scale.[39]

Autonomic symptoms were detected using the Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction (SCOPA-AUT).[40,41] Quality of life and non-motor symptoms were assessed using the Parkinson's Disease Questionnaire (PDQ-39)[42] and Non-motor Symptoms-Score (NMS-Quest).[43] For cognition testing, a Montreal Cognitive Assessment[44] was performed. Neuropathic scores were also determined with the Neuropathy Deficit score and Neuropathy Symptom score.[45]

Nerve ultrasound

In our study, NUS was conducted under the supervision of KP with at least 10 years of neuromuscular ultrasound experience (performed by LS, SH). All our patients were examined with an Affinity® 70G ultrasound system (Philips, Hamburg, Germany), using an 18-MHz linear array transducer. The investigation was always conducted in supine position. To avoid artificial compression of the nerve in the image, it was crucial not to apply more force than the weight of the transducer at the site. Measurements of the CSA were performed at the inner border of the thin hyperechoic epineural rim by continuous tracing. This procedure is widely described in previous studies.[43,46]

To guarantee reliable CSA values and to ensure a reliable isotropy the transducer was kept vertical to the nerve. We measured the VN on both sides at the level of the carotid bulb between the common carotid artery and the internal jugular vein.

Head up tilt test

A Task Force® Monitor system 3040i (CN System, Graz, Austria) was used for the HUTT. The test was performed at least 2 h later than meals.

After 5 min in resting position, the tilt table was raised to 70 degrees so that the patients had to stand for 10 min. Patients who had previously experienced severe complications such as dizziness or who experienced pain while standing were examined for a shorter duration. The follow-up time in the supine position was again at least 3 min.

During the whole time, heart rate (HR) and systolic and diastolic blood pressure (sBP, dBP) were continuously recorded as well as parameters for HR (HRV) and blood pressure variability (BPV).

For this purpose, different frequency bands were determined by means of spectral analysis. Power spectral analysis (PSD) includes all frequency bands up to 0.4 Hz. Other frequency bands include high frequency (HF, 0.15–0.4 Hz), low frequency (LF, 0.04–0.15 Hz) and very low frequency (VLF, 0.003–0.05 Hz). These values were also expressed as normalized units (nu).

Furthermore, an LF/HF ratio is calculated. The frequency bands are subject to various autonomous influences of the ANS.

Based on HR and blood pressure measurements, patients were either classified into a group with a physiological orthostatic response or subdivided into different pathological groups. Therefore, OH with a drop in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic during standing was considered pathological.[47] Chronotropic incompetence (as a possible precursor of orthostatic dysregulation)[48] was defined as a failure to increase HR by at least 10% or 10 bpm while standing.

Statistics

For data collection, statistical analysis and graphs we used the programmes Microsoft Excel and IBM SPSS Statistics 27. The Shapiro–Wilk test was used to test the values for normal distribution. Group comparisons for significance were made with the Cohen's *d* test or the analysis of variance (ANOVA) test. Correlations were made with Pearson or Spearman depending in either normally or non-normally distributed data. We considered all p values ≤ 0.05 to be significant.

Results

Clinical data and prevalence of abnormal orthostatic response

The cohort of patients, who received a tilt table examination showed the following characteristics (shown in Tables 1 and 2). In the group of MSA patients, 35% were female. The mean age at examination was 71.4 ± 8.4 with a disease duration of 2.9 ± 2.4 years. The median H&Y score, which reflects disease severity, was 3. The motoric outcome in the MDS-UPDRS III was 42.1 ± 12.9. Autonomic symptoms, that were reported in the SCOPA-AUT, showed an average score of 20 ± 11.2 and the PDQ-39, evaluating the quality of life, 34.2 ± 17.1. Non-motoric symptoms were detected with the NMS-Quest with an average score of 10.53 ± 4.98.

Overall, there was a high prevalence of orthostatic dysfunction (OD) in MSA at assessment. More specifically, 55% had OH and 35% CI (Figure 1). Patients with OD, consisting of either OH or CI, showed a significant worse motor examination in the MDS-UPDRS III ($p = 0.015$) in comparison with patients without an OD.

Autonomic symptoms that were evaluated in the SCOPA-AUT were significantly associated with a higher burden of disease in our MSA cohort, both motoric in the MDS-UPDRS III ($p = 0.015$) and in quality of life measured in the PDQ-39 ($p = 0.017$) (data shown in Supplemental Figure 4).

In our PSP cohort, 40% of the patients were women. The mean age at examination was 71.6 ± 8 and the duration of disease 3.2 ± 3.4 years. Disease severity in the H&Y scale showed a median of 3.5. The motoric examination in the MDS-UPDRS III was 38.4 ± 13.4 points. In the SCOPA-AUT score, we measured an average of 17.1 ± 9.7 and the PDQ-39-score was 31 ± 18.5. The NMS-Quest showed 9 ± 4.88 points.

Table 1. Demographical and clinical data shown as mean value ± standard deviation (SD), p-value, standard error (SE) and effect strength (r) calculated with Cohen's d Test, compared for patients without orthostatic dysregulation (OD) and with OD in form of orthostatic hypotension (OH) or chronotropic incompetence (CI) in multiple system atrophy (MSA).

Demographical and clinical data	MSA without OD ($n=2$)		MSA with OH or CI ($n=18$)		p	r
	Mean ± SD	SE	Mean ± SD	SE		
Age (years)	65.0 ± 11.3	8.0	72 ± 8.1	1.9	0.268	8.29
Disease duration (years)	2.5 ± 2.1	1.5	2.9 ± 2.5	0.6	0.835	2.48
LED	646 ± 161.2	114	555.8 ± 309.4	72.9	0.694	303.08
H&Y median (IQR)	3.25		3 (1)			
MDS-UPDRS III	19 ± 9.9	7.0	43.4 ± 12.3	2.9	**0.015***	**12.16**
SCOPA-AUT	11.5 ± 3.5	2.5	19.4 ± 9.8	2.5	0.288	9.56
PDQ-39	51 ± 31	9.8	58.6 ± 34.5	4.8	0.777	19.74
NMS-Quest	4.5 ± 0.7	0.5	11.3 ± 4.7	1.2	0.066	4.57
CSA right VN (mm^2)	2.77 ± 0.02	0.02	2.34 ± 0.68	0.18	0.402	0.66
CSA left VN (mm^2)	2.4 ± 0.52	0.37	1.96 ± 0.45	0.12	0.223	0.46

Bold values indicate significant results.
CI, chronotropic incompetence; CSA, cross-sectional area; H&Y, Hoehn and Yahr scale; IQR, interquartile range; LED, levodopa-equivalent dose; MDS-UPDRS III, MDS-Unified Parkinson's Disease Rating Scale; MSA, multiple system atrophy; NMS-Quest, non-motor symptoms questionnaire; OD, orthostatic dysfunction; OH, orthostatic hypotension; PDQ, Parkinson's Disease Questionnaire; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; SD, standard deviation; SE, standard error; VN, vagus nerve.
*$p < 0.05$.

A total of 80% of the PSP patients revealed abnormal autonomic response in HUTT in total. Thirty percent featured an OH and 50% CI (Figure 2). Patients with either OH or CI had a higher score in the NMS-Quest ($p=0.041$) in comparison to those without an OD (Tables 1 and 2).

Also in the PSP cohort, autonomic symptoms in the SCOPA-AUT correlated significantly with the MDS-UPDRS III ($p=0.044$) as well as the PDQ-39 ($p=0.011$)) (data shown in Supplemental Figure 5).

Tables 1 and 2 provides an overview of the collected demographic and clinical data as well as the average values of the CSA from the VN. We differentiated between MSA and PSP and compared patients with and without OD.

Figure 1(a) and (b) shows the distribution of the different orthostatic regulation disturbances of MSA and PSP.

Sonomorphological data of the VN

Furthermore, we compared the vagus CSA values of all examined patients with controls. Thereby we also included these without tilt table examination and patients with the diagnosis of PD (Tables 3–5 and Figure 3(a)–(c)).

The VN CSA of all patient cohorts were smaller compared to the control group, whereas there was only a significant difference between the VN CSA at both sides of the PD sample (right $p=0.02$; left $p=0.05$), both VN CSA of the PSP group (right $p=0.008$; left $p=0.044$) and the controls (Figure 2). Compared to each other via ANOVA test, it

Table 2. Demographical and clinical data shown as mean value ± standard deviation (SD), p-value, standard error (SE) and effect strength (r) calculated with Cohen's d Test, compared for patients without orthostatic dysregulation (OD) and with OD in form of orthostatic hypotension (OH) or chronotropic incompetence (CI) in progressive supranuclear palsy (PSP).

Demographical and clinical data	PSP without OD ($n=2$)		PSP with OH or CI ($n=8$)		p	r
	Mean ± SD	SE	Mean ± SD	SE		
Age (years)	78 ± 11.3	8	69.9 ± 7	2.5	0.218	7.69
Disease duration (years)	1 ± 1.4	1	3.6 ± 3.5	1.2	0.351	3.35
LED	325 ± 247.5	175	435 ± 364.4 ($n=7$)	137.7	0.707	350
H&Y median (IQR)	**3.5**		3 (1)			
MDS-UPDRS III	37 ± 5.7	4	37.9 ± 13.9 ($n=7$)	5.2	0.937	13.01
SCOPA-AUT	16.5 ± 9.2	6.5	16 ± 8.9	3.1	0.945	8.89
PDQ-39	95.5 ± 20.5	14.5	48.6 ± 31.7	11.2	0.088	30.57
NMS-Quest	13.5 ± 0.7	0.5	7.3 ± 3.5	1.2	**0.041***	**3.24**
CSA right VN (mm^2)	2.23 ± 0.02	0.02	2.09 ± 0.45	0.18	0.692	0.43
CSA left VN (mm^2)	2.34 ± 0.11	0.37	1.74 ± 0.41	0.12	0.085	0.38

Bold values indicate significant results.
CI, chronotropic incompetence; CSA, cross-sectional area; H&Y, Hoehn and Yahr scale; IQR, interquartile range; LED, levodopa-equivalent dose; MDS-UPDRS III, MDS-Unified Parkinson's Disease Rating Scale; NMS-Quest, non-motor symptoms questionnaire; OD, orthostatic dysfunction; OH, orthostatic hypotension; PDQ, Parkinson's Disease Questionnaire; PSP, progressive supranuclear palsy; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; SD, standard deviation; SE, standard error; VN, vagus nerve.
*$p < 0.05$.

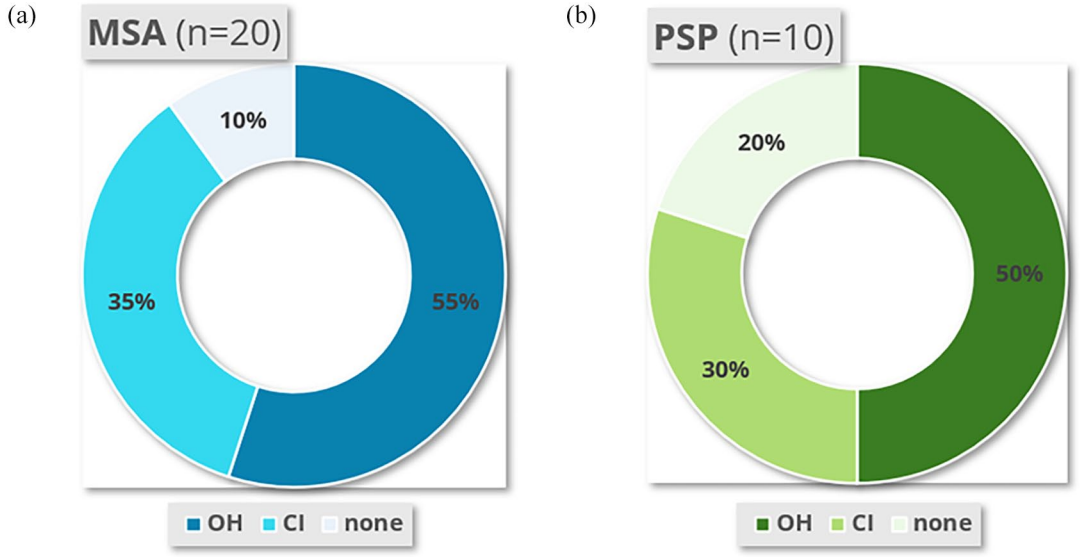

Figure 1. Prevalence of of abnormal hemodynamic response in head up tilt testing (HUTT) in multiple system atrophy (MSA) (a) and progressive supranuclear palsy (PSP) (b).
CI, chronotropic incompetence; n, number of subjects included; OH, orthostatic hypotension;.

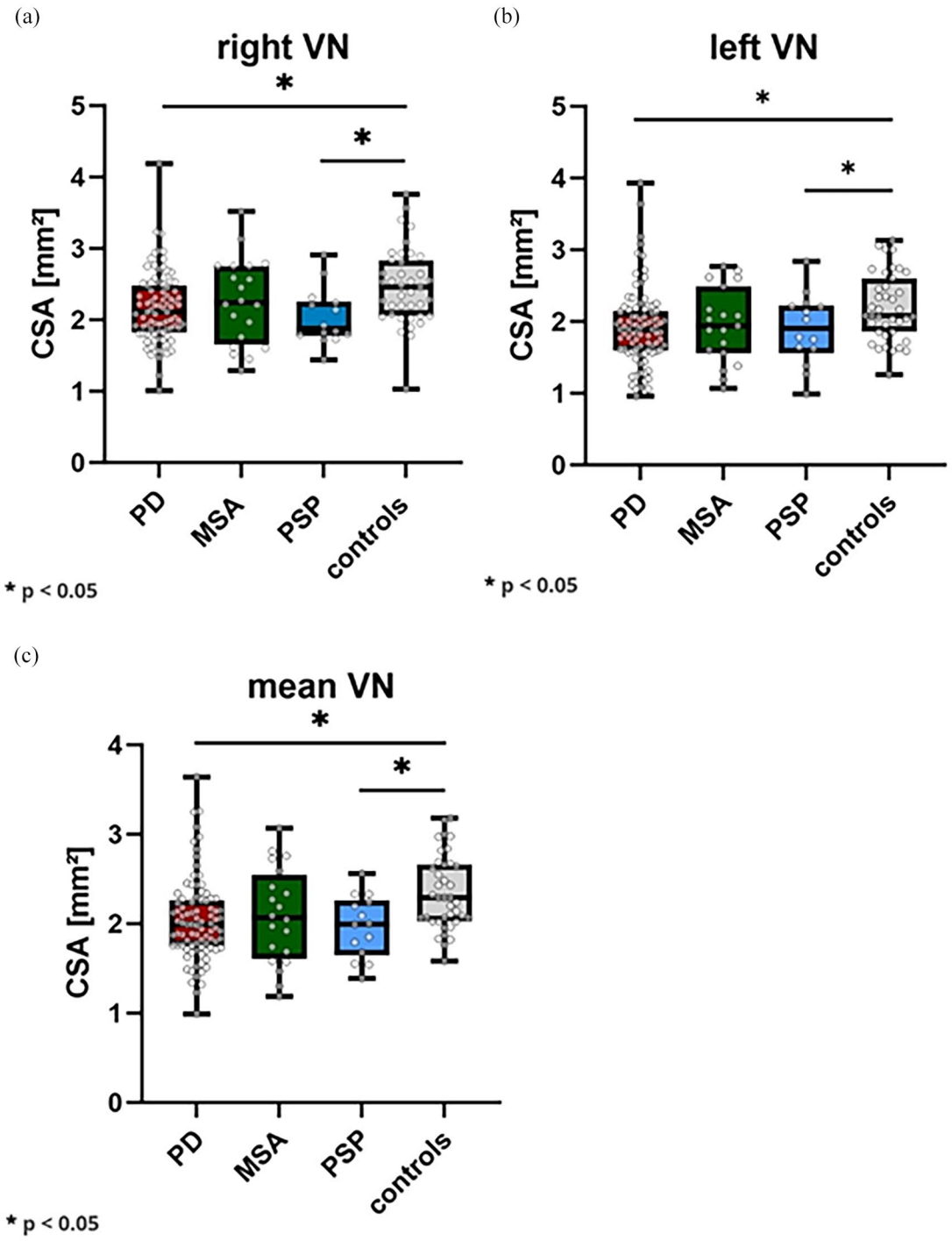

Figure 2. Values of the right (a), left (b) and mean (c) vagus nerve (VN) cross-sectional area (CSA) in all subjects.
The right (p=0.02) and left (p=0.05) VN of the PD group are significantly smaller compared with controls. The right (p=0.08) and the left (p=0.046) VN is significantly smaller in the PSP cohort compared to controls.
There were no statistically significant differences between the groups.
CSA, cross-sectional area; MSA, multiple system atrophy; PD, Parkinson's Disease, PSP, progressive supranuclear palsy; VN, vagus nerve;

Table 3. Demographical data and cross-sectional area (CSA) values of the vagal nerve (VN) in subjects with Parkinson's Disease (PD) compared to controls. Shown are mean values ± standard deviations (SD), standard error (SE), p-value and effect sizes (r) calculated with Cohen's d test.

Demographical and VN data	Controls ($n = 39$)	SE	PD ($n = 90$)	SE	p	r
Sex (m:f)	21:18		49:41			
Mean age (years)	66.8 ± 10.7	1.7	69.5 ± 10.2	1.1	0.173	10.4
CSA right VN ± SD (mm^2)	2.47 ± 0.54	0.09	2.16 ± 0.49	0.05	**0.002***	**0.51**
CSA left VN ± SD (mm^2)	2.2 ± 0.47	0.08	1.91 ± 0.54	0.06	**0.005***	**0.52**
CSA mean VN ± SD (mm^2)	2.34 ± 0.41	0.07	2.04 ± 0.46	0.05	**<0.001***	**0.45**

Bold values indicate significant results.
*$p < 0.05$.

Table 4. Demographical data and cross-sectional area (CSA) values of the vagal nerve (VN) in subjects with multiple system atrophy (MSA) compared to controls. Shown are mean values ± standard deviations (SD), standard error (SE), p-value and effect sizes (r) calculated with Cohen's d test.

Demographical and VN data	Controls ($n = 39$)	SE	MSA ($n = 20$)	SE	p	r
Sex (m:f)	21:18		10:10			
Mean age (years)	66.8 ± 10.7	1.7	69.4 ± 9.8	2.1	0.380	10.4
CSA right VN ± SD (mm^2)	2.47 ± 0.54	0.09	2.26 ± 0.61	0.14	0.185	0.56
CSA left VN ± SD (mm^2)	2.2 ± 0.47	0.08	1.95 ± 0.52	0.12	0.073	0.49
CSA mean VN ± SD (mm^2)	2.34 ± 0.41	0.07	2.09 ± 0.54	0.12	0.053	0.46

CSA, cross-sectional area; MSA, multiple system atrophy; SD, standard deviation; SE, standard error; VN, vagus nerve.
*$p < 0.05$.

Table 5. Demographical data and cross-sectional area (CSA) values of the vagal nerve (VN) in subjects with progressive supranuclear palsy (PSP) compared to controls. Shown are mean values ± standard deviations (SD), standard error (SE), p-value and effect sizes (r) calculated with Cohen's d test.

Demographical and VN data	Controls ($n = 39$)	SE	PSP ($n = 14$)	SE	p	r
Sex (m:f)	21:18		8:6			
Mean age (years)	66.8 ± 10.7	1.7	70.07 ± 7.8	2.1	0.303	10.0
CSA right VN ± SD (mm^2)	2.47 ± 0.54	0.09	2.04 ± 0.4	0.11	**0.008***	**0.51**
CSA left VN ± SD (mm^2)	2.2 ± 0.47	0.08	1.89 ± 0.5	0.13	**0.044***	**0.48**
CSA mean VN ± SD (mm^2)	2.34 ± 0.41	0.07	1.97 ± 0.35	0.09	**0.004***	**0.40**

Bold values indicate significant results.
CSA, cross-sectional area; PSP, progressive supranuclear palsy; SD, standard deviation; SE, standard error; VN, vagus nerve.
*$p < 0.05$.

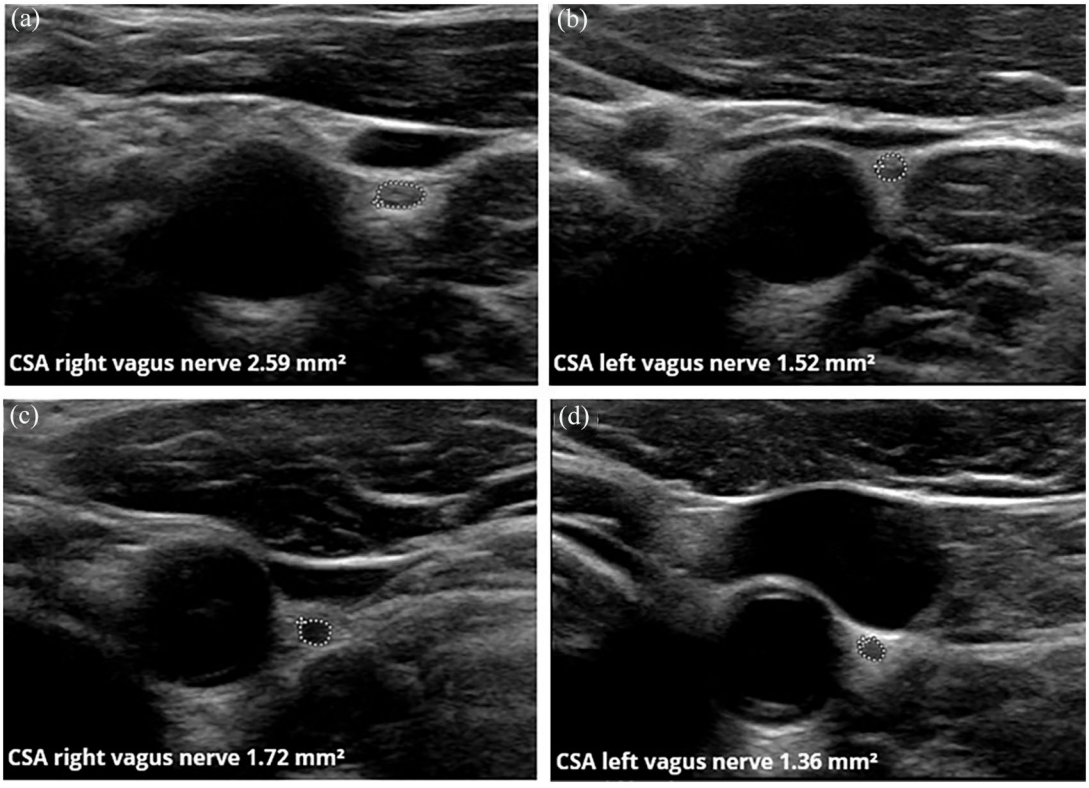

Figure 3. Representative nerve ultrasound (NUS) images of the vagus nerve (VN) in a patient with MSA (a, b) and with PSP (c, d). The nerve is located between the carotid artery and the jugular vein.
CSA, cross-sectional area; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

did not appear any significant difference between the pathologies (data shown in Supplemental Table 5).

NUS data of the VN could be collected from 90 patients with PD, 20 with MSA, 14 with PSP and 39 healthy controls. The sample size is larger here because NUS could also be performed on patients whose autonomous functions were too severely affected for the tilt table.

As shown in Tables 3–5, NUS revealed a side dependent difference of the VN CSA (mm^2) in MSA with a larger CSA on the right side compared to the left side. The VN CSA was $2.26 \pm 0.61\,mm^2$ on the right and $1.95 \pm 0.52\,mm^2$ on the left, which was significantly smaller ($p = 0.008$). For PD ($p < 0.001$) and healthy controls ($p = 0.005$), the comparison was as well significant. In our PSP cohort, the VN CSA showed $2.04 \pm 0.4\,mm^2$ on the right and $1.89 \pm 0.5\,mm^2$ on the left. The side-dependent difference was not significant in this group.

Furthermore, we found no statistically significant difference in the CSA of the VN between the different subtypes (data shown in the Supplemental Tables 2–4).

Figure 3 shows representative ultrasound VN images of a patients with MSA ((a) and (b)) and PSP ((c) and (d)).

Correlations

We performed correlation analyses of the VN CSA with clinical scores and the HRV and BPV parameters of the HUTT in the MSA and PSP group. In both cohorts, the VN CSA did not correlate significantly with age or disease duration (data shown in the Supplemental Table 1, Supplemental Figures 2 and 3).

However, the VN showed a correlation with several autonomic parameters measured in the HUTT study that were different in MSA and PSP. Tables 6 and 7 provide an overview of the significant correlations, which are shown graphically in Figure 4.

Table 6. Correlational analysis of the vagus nerve (VN) cross-sectional area (CSA) with head up tilt test (HUTT) parameters in patients with multiple system atrophy (MSA). Correlations were performed using Pearson unless otherwise stated.

HUTT parameters	Vagus right		Vagus left		Vagus mean	
	r	*p*	*r*	*p*	*r*	*p*
LF/HF-sBP						
LF/HF-sBP rest	**−0.663**	**0.007***	**−0.376**	**0.017***	**−0.603**	**0.017***
LF/HF-sBP upright	**−0.654**	**0.008***	−0.381	0.179	**−0.601**	**0.018***
LF/HF-sBP supine	**−0.668**	**0.018***	−0.324	0.331	**−0.584**	**0.046***
LF/HF-dBP						
LF/HF-dBP rest	−0.325	0.219	0.067	0.811	−0.173	0.522
LF/HF-dBP upright	−0.349	0.186	0.138	0.624	−0.154	0.569
LF/HF-dBP supine	**−0.584**	**0.036***	−0.227	0.479	−0.495	0.086
Lfnu-sBP						
Lfnu-sBP rest	−0.494	0.061	−0.102	0.728	−0.352	0.199
Lfnu-sBP upright	**−0.708**	**0.003***	−0.219	0.451	**−0.545**	**0.036***
Lfnu-sBP supine	**−0.716**	**0.004***	−0.319	0.288	**−0.601**	**0.023***
Lfnu-dBP						
Lfnu-dBP rest	−0.467	0.068	−0.105	0.711	−0.338	0.201
Lfnu-dBP upright	**−0.653**	**0.006***	−0.243	0.383	**−0.527**	**0.036***
Lfnu-dBP supine	−0.416	0.139	0.049	0.873	−0.227	0.434

Bold values indicate significant results.
LF/HF-sBP, low frequency to high frequency ratio of the systolic blood pressure; LF/HF-dBP, low frequency to high frequency ratio of the diastolic blood pressure; LFnu-sBP, low frequency band of the systolic blood pressure in normalized units; LFnu-dBP, low frequency band of the diastolic blood pressure in normalized units; r, correlation coefficient.
*$p < 0.05$.

In patients with MSA, the CSA value of the right VN correlated inversely with the LF/HF-sBP ratio in the resting ($r = -0.663$; $p = 0.007$) (Figure 4(a)), upright ($r = -0.654$; $p = 0.008$) (Figure 4(b)) and supine position ($r = -0.668$; $p = 0.018$) (Figure 4(c)), the LF/HF-dBP ratio in the supine ($r = -0.584$; $p = 0.036$) position, the Lfnu-sBP in upright ($r = -0.708$; $p = 0.003$) (Figure 4(d)) and supine ($r = -0.716$; $p = 0.004$) (Figure 4(e)) position and the Lfnu-dBP in upright ($r = -0.653$; $p = 0.006$) position (Table 6). The left VN only correlated with LF/HF-sBP at rest ($r = -0.376$; $p = 0.017$) (Table 6).

In the PSP cohort, we found a significant inverse correlation of the left VN with PSD-dBP in upright ($r_S = -0.75$; $p = 0.02$) (Figure 4(g)) and supine position ($r_S = -0.762$; $p = 0.017$) (Figure 4(h), Table 7). The left VN also correlated inversely with HF-dBP ($r_S = -0.812$; $p = 0.008$) in supine position (Table 7). There were also correlations of the CSA of the right VN with PSD-dBP in the upright ($r_S = -0.667$; $p = 0.05$) (Figure 4(f)) and HF-dBP in supine position ($r_S = -0.72$; $p = 0.029$), such as the VLF-RRI in resting position ($r_S = -0.685$; $p = 0.029$) (Table 7).

Discussion

Clinical data and autonomic dysfunction

The prevalence of OD was high in both groups in our study. Furthermore, autonomic symptoms in

Table 7. Correlational analysis of the vagus nerve (VN) cross-sectional area CSA with head up tilt test (HUTT) parameters in patients with progressive supranuclear palsy (PSP). Correlations were performed using Pearson unless otherwise stated. (a): Spearman-rho correlation used.

HUTT parameters	Vagus right		Vagus left		Vagus mean	
	r	*p*	*r*	*p*	*r*	*p*
PSD-dBP						
PSD-dBP rest	−0.489	0.152	−0.391	0.263	−0.502	0.139
PSD-dBP upright (a)	**−0.667**	**0.050***	**−0.750**	**0.020***	**−0.733**	**0.025***
PSD-dBP supine (a)	−0.636	0.066	**−0.762**	**0.017***	**−0.695**	**0.038***
HF-dBP						
HF-dBP rest	−0.426	0.220	−0.425	0.221	−0.488	0.153
HF-dBP upright	−0.536	0.137	−0.643	0.062	−0.66	0.053
HF-dBP supine (a)	**−0.720**	**0.029***	**−0.812**	**0.008***	**−0.762**	**0.017***
VLF-RRI						
VLF-RRI rest (a)	**−0.685**	**0.029***	−0.285	0.425	−0.612	0.06
VLF-RRI upright	0.069	0.849	0.443	0.199	0.304	0.394
VLF-RRI supine	0.252	0.585	0.382	0.398	0.366	0.420

Bold values indicate significant results.
PSD-dBP, power spectrum density of the diastolic blood pressure; HF-dBP, high frequency band of the diastolic blood pressure; VLF-RRI, very low frequency band of the heart rate interval; r, correlation coefficient.
*$p < 0.05$.

the SCOPA-AUT were significantly associated with a higher burden of disease, which underlines the essential impact of autonomic dysfunction on Parkinsonian syndromes.

However, patients affected by MSA showed a more severe expression which is consistent with the predominance of autonomic dysfunction in MSA. A total of 90% showed at least a CI. Fifty-five percent had an OH. These findings substantiate the important role of orthostatic dysbalance as a key feature of the disease.

In the case of PSP, autonomic dysfunction in the literature is generally reported with varying degrees of occurrence, but less frequently.[49] OH was never severe in PSP, which would even be a clinical exclusion criterion.[13] This has also been described by other authors.[50] However, our cohort still presented a high number of mild-to-moderate orthostatic regulation disorders, so we hypothesize that this can be a recurring feature of PSP. Seventy percent of the patients with PSP had a CI and showed an insufficient increase in HR during standing, which has already been described in the literature.[51] Three of them also had prolonged OH after 10 min of standing. OH has already been reported in PSP with very variable occurrence[49] between 0[52] and 45%.[53] It has already been shown that cardiovascular autonomic dysfunction may be associated with a worse outcome in PSP[54,55] and is often overlooked as it is not the main focus in PSP. Nevertheless, OD does occur and should be further characterized.

Correlations of the VN CSA data

In our patient population, there was no correlation with height, age or disease duration (data shown in the Supplemental Table 1, Supplemental Figures 2 and 3).

The side-dependent difference of the VN CSA, we found in subjects with PD and MSA, had been previously reported by many authors[28,56] and

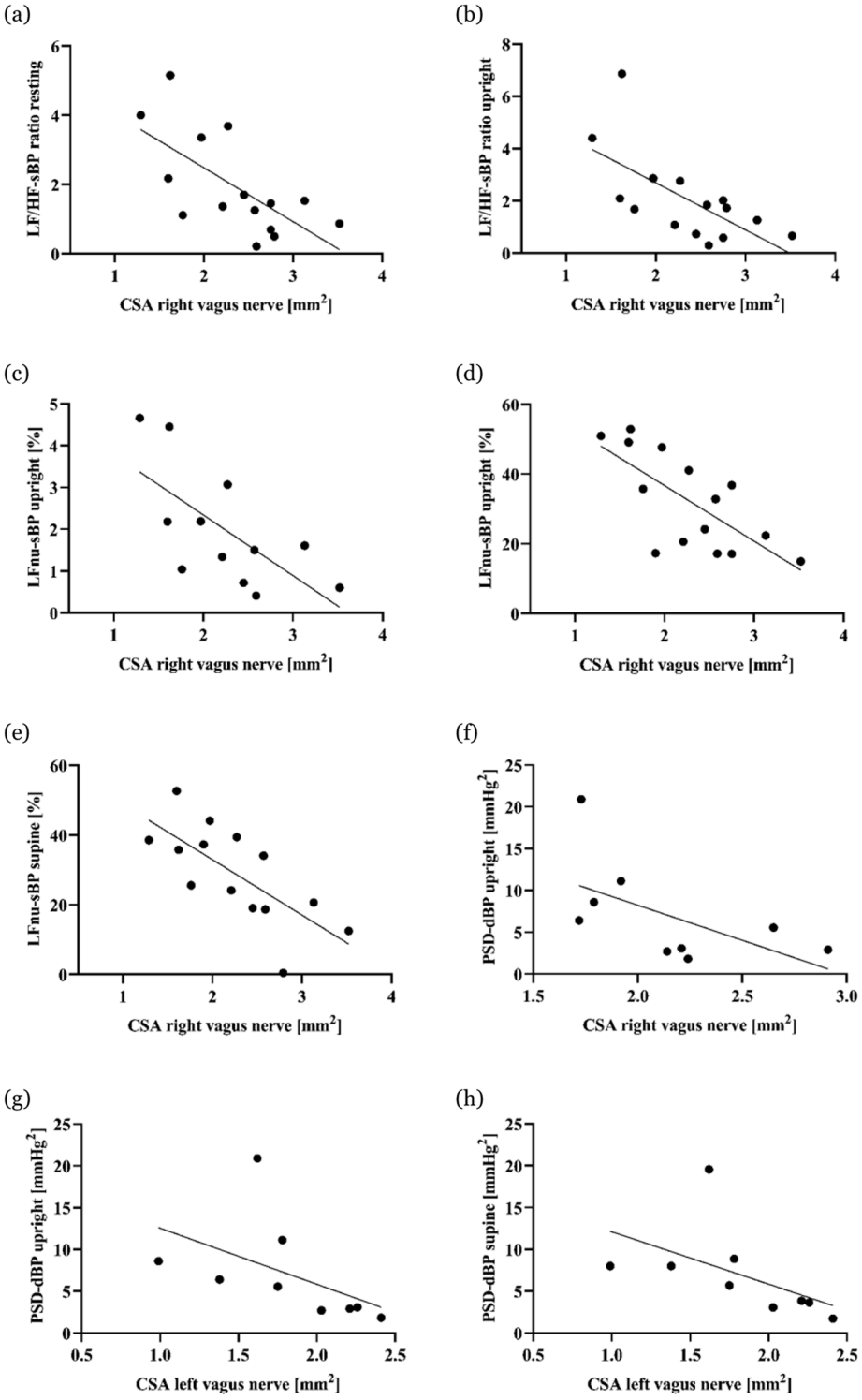

Figure 4. Correlations of the cross-sectional area (CSA) of the vagus nerve (VN) with different parameters of the spectral analysis in multiple system atrophy (MSA) (a-e) and progressive supranuclear palsy (PSP) (f-h).
(a) CSA right VN in relation to LF/HF-sBP ratio in resting position (n=15; r=-0.663; p=0.007). (b) CSA right VN in relation to LF/HF-sBP ratio in upright position (n=15; r=-0.654; p=0.008). (c) CSA right VN in relation to LF/HF-sBP ratio in supine position (n=12; r=-0.688; p=0.018). (d) CSA right VN in relation to LFnu-sBP in upright position (n=15; r=-0.708; p=0.003). (e) CSA right VN in relation to LFnu-sBP in supine position (n=14; r=-0.716; p=0.004). (f) CSA right VN in relation to PSD-dBP in upright position (n=9; r=-0.667; p=0.05). (g) CSA left VN in relation to PSD-dBP in upright position (n=9; r=-0.750; p=0.02). (h) CSA left VN in relation to PSD-dBP in supine position (n=9; r=-0.762; p=0.017).
LF/HF-sBP, low frequency to high frequency ratio of the systolic blood pressure.

seems to reflect a different functional anatomy, depending on asymmetric location of vagal nuclei and innervation of the non-paired abdominal organs.[20] In addition, the right VN innervates the sinus node.[57] We attribute the absence of a significant difference in PSP to the small study sample.

The observation of a significant smaller VN CSA in PD and PSP compared to controls, which were not significant in the MSA cohort, could result partly from the small group size. In all groups, we saw outliers, which we cannot explain so far. Another explanation for this observation could lie in the different pathogenesis of the diseases.

Particularly in PD, VN has already received much attention in circumstances of its pathogenesis. Pathological protein deposits in the nerve suggest the hypothesis that the disease could also begin in the intestine and spread prion-like towards the brain.[22] There is also retrospective data on patients with vagotomy who showed a significant risk reduction for PD.[58]

The pathogenesis of MSA is currently not fully understood. Research focuses on different models involving α-Synuclein accumulation, mitochondrial dysfunction or inflammation with activation of microglia.[59] In addition, there is the hypothesis that the spread of α-Synuclein in MSA may originate from the urogenital tract.[60] It is also discussed that neuronal damage only occurs secondarily and that oligodendrocytes are involved first.[59]

Although autonomic dysfunction appears to be more severe and occurs earlier in MSA, the VN was not smaller in our cohort than in PD. In MSA, the neuropathological pattern seems to be particularly extensive, affecting every part of the nervous system.[61] We hypothesize that VN therefore accounts for a greater proportion of orthostatic symptoms in PD than in MSA. Nevertheless, protein aggregates have been detected in nuclei of the VN, particularly in the dorsal motor nucleus and the ambiguous nucleus, which contain visceromotor fibres.[62,63]

Overall, we consider it possible that the VN is not smaller in MSA than in PD or in comparison with the other groups because it might be affected less early and is less relevant for the pathogenesis of the disease. In PD, on the other hand, we saw a tendency towards more pronounced atrophy, which on the one hand could be due to the larger cohort, and on the other hand could possibly be indicative of the longer prodromal phase with earlier involvement of the VN.

In PSP, autonomic dysfunction is discussed controversially but should be addressed as many authors have shown that it occurs and neuropathological studies demonstrated that different autonomic nuclei can be affected.[64–66] The role of VN remains unclear, yet we were able to show for the first time in a small cohort that atrophy is present on both sides compared to healthy controls. There are few objective studies on the function of the VN in PSP. However, a significantly prolonged colonic passage time of the right colon, which is supplied by the VN, has already been demonstrated, so to assume a pathological involvement.[67]

Correlations of CSA and HUTT data

We found numerous correlations between the VN and HUTT parameters, but they varied within the syndromes. This illustrates the diverse aetiology and neuropathogenesis of MSA and PSP and postulates a differently characterized autonomic disorder of the diseases.

HUTT data provide parameters, which are influenced by the ANS and can sometimes be assigned to more parasympathetic or sympathetic inputs. These are not yet uniformly defined in the research literature but could prospectively contribute to a further comprehension of orthostatic regulation mechanisms.

It was discussed, that the LF-component of the BPV reflects sympathetic modulation of the vascular tone and could be induced by the baroreflex.[68] The LF/HF ratio of the sBP indicates an autonomic dysregulation, respectively, a sympatho-vagal imbalance.[69] As our results in MSA patients demonstrate an inverse correlation of the vagal CSA value with the LF/HF-sBP in all positions, there could be a connection between vagal atrophy and a sympathetic overweight in the blood pressure regulation. At least the results suggest an autonomic imbalance, which could be

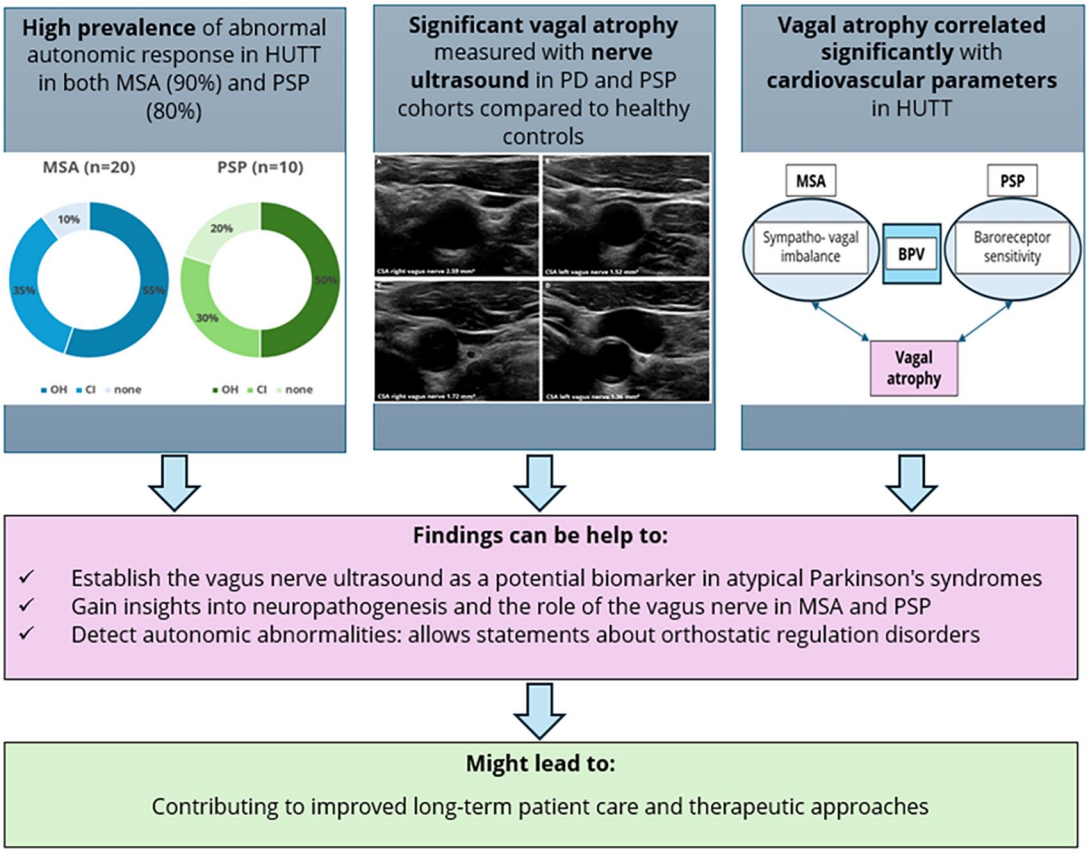

Figure 5. Clinical implications and results of the study.
BPV, blood pressure variability; CI, chronotropic incompetence; HUTT, head-up tilt testing; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; PD, Parkinson's Disease; OH, orthostatic hypotension.

also explained by functional lesions in central nervous locations.[70]

In the smaller group of PSP patients, the analysis of VN with tilt table parameters was different from those with MSA. The correlations primarily between the VN and PSD-dBP that we observed, might suggest an association of vagal atrophy and baroreceptor sensitivity impairment.[71] PSD-dBP is a parameter that includes all frequencies of diastolic blood pressure. An elevated value could be an expression of increased BPV and thus lower baroreceptor sensitivity which correlated with a smaller CSA of the VN in the PSP cohort. Decreased baroreceptor sensitivity has also been reported in cohorts with PD and Alzheimer's disease.[72] This could also be related to increased cardiovascular mortality.[73]

No further significant correlation was found between CSA of the VN and clinical autonomic parameters.

Clinical implications

To our knowledge, this is the first study to analyse the morphology of VN in MSA and PSP in such detail. It is the first study to use NUS as a possible additional tool for the analysis of these syndromes. Furthermore, the combination with several clinical parameters and the possibility to correlate with the spectral bands of the tilt table examination are novel.

The NUS is a readily available, inexpensive and non-invasive parameter. In addition, studies have shown it to be reproducible. Examination of the VN can help to better characterize autonomic dysfunction and identify the risk of orthostatic dysregulation in APS, which are currently difficult to treat. In particular, in patients who cannot be studied on a tilt table, the ANS could be better understood in general, as it remains available even in very severely affected individuals. This could contribute to a better understanding of patients and also help to prevent the consequences of orthostatic

dysregulation in everyday life, such as falls, as the literature has shown a correlation between autonomic cardiovascular parameters and postural instability in patients with PD.[74] Figure 5 provides a graphical overview of the clinical implications.

Limitations

This study has some limitations, such as the small study sample. Aside from that, it was often not possible to perform tilt table examinations on patients with APS who were very severely affected early on, both in MSA and in PSP. For these patients, an investigation of the VN could be even more important, as it may be a marker for autonomic dysfunction, as already postulated in other studies on PD.[28]

Additionally, we included clinically probable and possible patients based on the criteria, which are not as accurate as neuropathological examinations.

A further limitation of the study is that it was not possible to perform subtype analysis, as no statistical differentiation was possible due to the small number of cases.

No power analysis was performed to calculate the sample size; we conducted an interim analysis of a register study on PD, MSA and PSP.

Furthermore, it would be important to study people already in the prodromal phase of the disease and longitudinally to better understand the value of the NUS from the VN as a potential biomarker. Even if the value as a biomarker for single individuals still seems limited at first, due to frequently observed 'outliers'. In addition, neuropathological studies that also involve the VN would be important.

Moreover, knowledge about HUTT parameters is still limited so far and we suggest that an affiliated control group also performing tilt table examinations for comparison with VN are necessary for a better comprehension.

Conclusion

To our knowledge, yet this is the largest published study on VN NUS in MSA and PSP. For the first time, despite a small study sample, we were able to show an association of vagal atrophy with important circulatory parameters indicating autonomic dysfunction in APS. This might be useful to better understand the underlying pathology.

To further evaluate the clinical relevance of OD and the role of the VN as a possible biomarker in Parkinsonian syndromes, prospective longitudinal observations with a larger cohort are necessary, to identify characteristics possibly present in patients with larger or smaller VN CSA in a second step.

Declarations

Ethics approval and consent to participate

Our study protocol was approved by the Institutional Review Board of the Medical Faculty of the Ruhr University Bochum (Reg. No. 18-6360) and is listed in the German Clinical Trials Register (DRKS-ID DRKS00020752, https://drks.de/search/de/trial/DRKS00020752). The patients were recruited from the inpatient and outpatient clinic of St Josef Hospital, Bochum. All patients signed informed consent to participate. The study was conducted in accordance with the ethical standards laid down in the declaration of Helsinki of 1964 and its later amendments.

Consent for publication

All patients signed informed consent to publication of the data collected.

Author contributions

Teresa Kleinz: Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Leonard Scholz: Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Sophie Huckemann: Formal analysis; Investigation; Methodology; Writing – review & editing.

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Christiane Schneider-Gold: Methodology; Writing – review & editing.

Ralf Gold: Conceptualization; Writing – review & editing.

Eun Hae Kwon: Methodology; Writing – review & editing.

Lars Tönges: Conceptualization; Methodology; Supervision; Writing – review & editing.

Kalliopi Pitarokoili: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Competing interests

RG is the Editor-in-Chief of Therapeutic Advances in Neurological Disorders; therefore, the peer review process was managed by alternative members of the Board and the submitting Editor was not involved in the decision-making process. The other authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials

All data were raised by our group in St. Josef-Hospital Bochum. Demographic data as well as examinations results are saved on local data devices. The data can be made available to other researchers upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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