Parkinsonism and Related Disorders 66 (2019) 68–73

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Third ventricular width assessed by transcranial ultrasound correlates with cognitive performance in Parkinson's disease

Stefanie Behnke[a,1,*], Andrea Pilotto[b,c,1], Inga Liepelt-Scarfone[b,d], Rezzak Yilmaz[e], Christoph Pausch[a], Svea Dieterich[f], Jan Bürmann[a], Jörg Spiegel[a], Ulrich Dillmann[a], Marcus Unger[a], Ina Posner[b], Daniela Berg[e,b]

[a] Department of Neurology, Saarland University Hospital, Homburg Saar, Germany
[b] Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany
[c] Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy and Parkinson's Disease Rehabilitation Centre, FERB ONLUS S. Isidoro Hospital, Trescore Balneario, BG, Italy
[d] German Center for Neurodegenerative Diseases, Tuebingen, Germany
[e] Department of Neurology, Christian-Albrechts-University, Kiel, Germany
[f] Department of Psychiatry, Saarland University Hospital, Homburg Saar, Germany

ARTICLE INFO

Keywords:
Parkinson's disease
Cognition
Brain atrophy
Transcranial ultrasound

ABSTRACT

Introduction: Cognitive impairment and dementia are common in PD; however, no stable marker of cognitive dysfunction is available. Transcranial sonography can evaluate global and focal brain atrophy and has been widely used in the differential diagnosis of parkinsonism.

Methods: 225 consecutive PD patients were recruited in a two-center cross sectional study and underwent a standardized sonographic protocol assessing the third ventricle's width and substantia nigra hyperechogenicity. All subjects were evaluated with an extensive motor and cognitive battery.

Results: 222 PD patients were included and classified as PD with normal cognition (PDNC; n = 130), mild cognitive impairment (PD-MCI; n = 61) and dementia (PDD; n = 31). Ventricular width correlated strongly with cognitive performance in all cognitive domains ($p < 0.001$) while SN size did not. PDD patients had significantly wider ventricles than PD patients without dementia ($p < 0.001$) while differences between PD-MCI and PDNC or PDD were less strong ($p < 0.05$). There were no group differences in SN size.

ROC analyses resulted in age-related cut-offs of third ventricular diameter for the prediction of PDD (6.0 and 7.5 mm for subjects $<$ and ≥ 70 years of age, respectively). These cut-offs significantly differentiated PDD from PDNC ($p < 0.001$) and from all patients without dementia (PDNC + PD-MCI; $p < 0.001$).

Conclusions: The third ventricular diameter correlated with cognitive performance in all domains and was able to differentiate PDD patients from those without dementia. Longitudinal studies are warranted to evaluate whether transcranial sonography could identify PD patients at risk for a rapid cognitive decline.

1. Introduction

Cognitive impairment is a common non-motor finding in Parkinson's disease (PD). Up to 42% of patients are already affected at the time of diagnosis [1]. Eighty percent of PD patients experiencing a disease course of more than 20 years will proceed towards dementia [2]. Dementia in PD (PDD) has an enormous impact on the individual prognosis with substantial increase of dependency on caregivers, re-settlement into nursing homes, and doubling of mortality [3]. Biomarkers indicating cognitive impairment or the risk for upcoming cognitive decline would be of great value in the individual care of the patient.

Transcranial ultrasound has proven its efficacy in assessing global and focal brain atrophy in equal accuracy to magnetic resonance imaging [4]. Further, it has been widely used in the differential diagnosis of Parkinsonian syndromes [5].

We here present the results of extensive neuropsychological testing and transcranial ultrasound examination in a cohort of 225 PD patients. Objective of the study was to evaluate the role of transcranial sonography in discriminating PD patients with normal cognition from those

* Corresponding author. Saarland University Hospital, Department of Neurology, Kirrberger Str., 66421, Homburg Saar, Germany.
E-mail address: stefanie.behnke@uks.eu (S. Behnke).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.parkreldis.2019.07.005
Received 22 January 2019; Received in revised form 8 May 2019; Accepted 6 July 2019

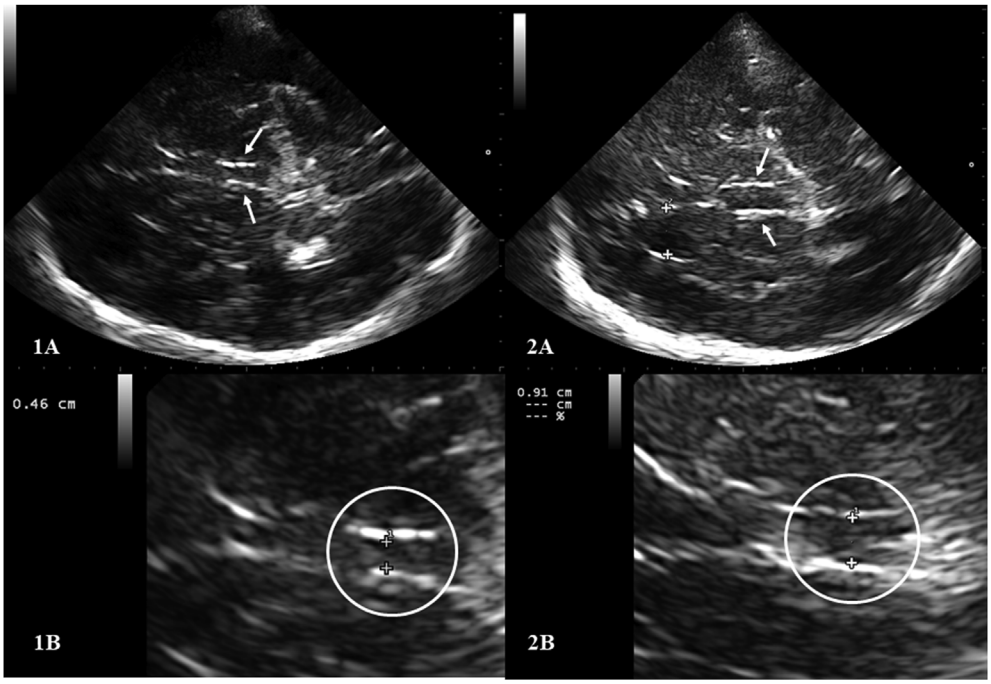

Fig. 1. Sonographic assessment of the third ventricular width in two examples. 1A and 1B show a normal width of 4.6 mm 1A = imaging of both hyperechogenic transition lines between ependyme and cerebrospinal fluid in the center of the image (arrows) being the sonographic aspect of the third ventricle. 1B = measurement of the distance between the inner boundaries after enlarging the sonographic image of the third ventricle (circle) with the zoom-function. 2A and 2B show an enlarged third ventricle with a width of 9.1 mm in the overview (2A) and in the zoomed image (2B).

with cognitive impairment up to dementia.

2. Methods

The study was performed at two different centres: The Neurological departments of the University hospitals of Tuebingen and Homburg, Germany. The local Ethical committees approved the study at both sites. All participants gave written informed consent according to the declaration of Helsinki.

2.1. Subjects

PD patients were recruited consecutively in the outpatients' clinics for movement disorders of both centres. All of them had to fulfil clinical diagnostic criteria for PD. Patients with cognitive decline prior to onset of motor impairment were not enrolled into the study to exclude cases of possible dementia with Lewy bodies (DLB).

2.2. Anamnestic data

For each patient, the following personal data were recorded: sex, age, symptom onset and year of diagnosis, medications, self-reported and relative- or caregiver-reported cognitive decline or impairment of daily life, years of school and professional education.

2.3. Neuropsychological assessments

Neuropsychological performance was assessed based on the German version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-plus) consisting of the subtests: Boston Naming Test (BNT), semantic and phonemic fluency tests, Mini Mental State Examination (MMSE), a ten-word list learning, recognition and delayed recall, a test for drawing and recall of complex geometric figures, Trail making test A and B (TMT) [6]. Furthermore, the Montreal Cognitive Assessment (MOCA) [7], and the digit-symbol-test, similarities and letter-number-sequencing from the Wechsler Adult Intelligence Scale (WAIS-IV) were applied [8].

Depressive symptoms were quantified using the Becks depression inventory (BDI) [9].

2.4. Motor assessment

All patients were thoroughly examined by a clinician experienced in movement disorders. During the examinations, patients were in "ON" motor state. Motor signs were documented using the MDS-UPDRS part III (motor examination) [10]. Disease stages were quantified according to the Hoehn and Yahr scale (H&Y).

2.5. Transcranial ultrasound

Sonographers were blinded for the results of the neuropsychological test battery. Transcranial sonography was performed following consensus criteria [11]. In brief, an ultrasound device (Esaote Mylab Gold 25) equipped with a transducer of low emitting frequency (2.5 MHz) was used at both study sites. The brain was insonated through the preauricular transtemporal bone window with an examination depth of 15–16 cm and a dynamic range of 45 dB. In the brainstem plane, the butterfly-shaped mesencephalon was displayed. At its anatomic region, hyperechogenic signals of the substantia nigra (SN) were identified at their largest extent; the image was frozen, magnified with the zoom function two-to fourfold and measured planimetrically by encircling the hyperechogenic area manually. Following consensus criteria, SN hyperechogenicity was stated if the hyperechogenic area was equal or above the 90th percentile of a norm collective examined in each ultrasound laboratory and if this finding was present at least unilaterally [11].

By tilting the probe upwards about 10° the ventricular plane was visualized. In the center of the image the third ventricle could be identified as two parallel hyperechogenic lines where the ultrasound beam meets the transition between ependyme and cerebrospinal fluid, orthogonal to the probe. The minimal distance between both lines was measured from their inner boundaries according to consensus guidelines (Fig. 1). A third ventricular width of > 7 mm at the age of < 60 years as well as a width of > 10 mm at the age of > 60 years was stated separately since it is suggestible for progressive supranuclear palsy [11].

In the ventricular plane, the third ventricle and the anterior and posterior horns of the lateral ventricles surround the basal ganglia with a homogenously iso/hypoechogenic aspect of the different nuclei.

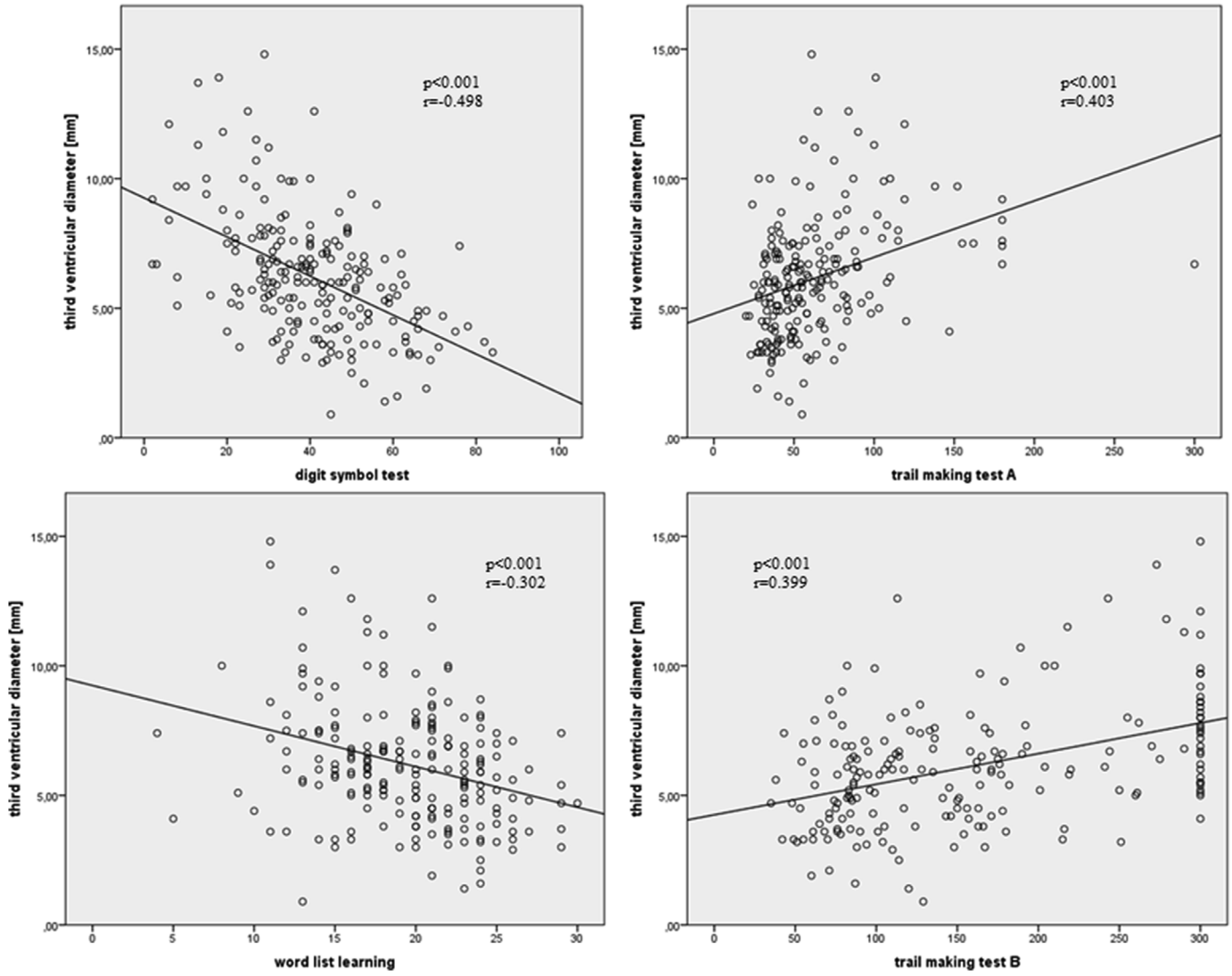

Fig. 2. Correlation between third ventricular diameter and neuropsychological subtests, statistical significance and Spearman correlation coefficient.

Specific hyperechogenic signals in the anatomic region of the lenticular nucleus (LN) were documented as hyperechogenic LN if they were not connected to the ventricle wall [11].

To further substantiate the exclusion of patients with DLB, the sonographic "onset index" proposed by Walter and colleagues was applied [12]:

Onset index = (age at disease onset * sum of bilateral SN hyperechogenic area size)/asymmetry index. The asymmetry index can be calculated dividing the larger hyperechogenic area size by the smaller one [12]. An onset index of > 35.5 in case of bilateral marked SN hyperechogenicity ($\geq 0.25\ cm^2$) has been found to be suggestive for DLB [12]. Patients in our two cohorts with an onset index > 35.5 and fulfilling level I MDS criteria for dementia (MMSE < 26) were excluded from further analysis.

2.6. Statistics

Normal distribution of data was assessed based on the Kolmogorov-Smirnov-Test. Since all variables were non-normally distributed, descriptive data are given as median and upper and lower quartile. Mann-Whitney-U and Kruskal-Wallis tests were used for group comparisons in case of quantitative data, chi square test and Fisher's exact test for categorical variables. For correlation, Spearman correlation coefficient and partial correlations were applied. Linear and logistic regression models were calculated to assess influence of multiple variables. Receiver operating characteristics (ROC) were calculated to define a cut-off value of third ventricular diameter predicting dementia with highest sensitivity and specificity.

3. Results

3.1. Sonographic criteria for DLB

17 out of 225 patients fulfilled the sonographic criterion of an onset index of > 35.5 suggestive for DLB (Homburg n = 10; Tuebingen n = 7). Among these patients were three individuals fulfilling MDS level I criteria for dementia [13]. In the following analysis these three patients were excluded.

3.2. Cohorts

Both cohorts did not differ regarding sex, educational and professional levels. Significant differences were found in the two centres for mean age, disease duration (as assessed by time since symptom onset) and severity (H&Y, MDS-UPDRS III), with the Homburg patients being older and having a longer disease duration and clinically a more severe presentation (table A; supplementary material).

Since neuropsychological, neurological and sonographic

assessments were identical at both sites, analysis of findings was performed for the complete cohort (n = 222).

3.3. Descriptive statistics

The study population of 222 PD patients consisted of 138 men and 84 women. Median age was 69 years (62; 74). Median years of education were 12 years (11; 15). Women had significantly less years of education than men ($p < 0.001$).

Median disease duration was 6.4 years (3; 10) and median age at diagnosis was 61.2 years (54; 68.5). 39 patients were classified as H&Y 1, 113 patients as H&Y 2, 46 patients as H&Y 3, and 19 as H&Y 4. Five patients were categorized as H&Y stage 5 due to their inability to walk because of postural instability. Disease severity as defined by median MDS-UPDRS motor score (part III) was 28.5 points (21; 38).

Assessment of the third ventricle using transcranial sonography (TCS) was possible in all but nine patients who had an insufficient bone window (4%). Median ventricular width was 6.0 mm (4.5; 7.5). No significant difference was detected between men and women. Twelve patients (5.6%) displayed a third ventricular width of > 7 mm (in the age group of < 60 years) or > 10 mm (age > 60 years), two of them showed uni- or bilateral hyperechogenicity of the lenticular nucleus. Another five patients exhibited LN hyperechogenicity but no enlargement of the third ventricle. 173 patients (88.3%) showed SN hyperechogenicity (n = 27 insufficient temporal bone window).

3.4. Correlations

3.4.1. Ventricular width

There was a significant positive correlation between the width of the third ventricle and age ($p < 0.001$; $r = 0.502$). No significant correlation was found between ventricular width and disease duration or disease severity (MDS-UPDRS III, H&Y).

Ventricular width correlated with cognitive performance in all cognitive domains with wider third ventricles resulting in poorer performance (Fig. 2). There was no correlation with the extent of depressive symptoms.

Partial correlations showed a minor influence of disease duration and education with all correlations remaining significant when these factors are taken into account. Age had a substantial influence on the correlation between cognition and ventricular width in most cognitive domains limiting significant correlations to visuoconstruction and some tests of executive and attentional functions (TMT A and B). Detailed correlation of ventricular width and the neuropsychological subtests with partial correlations are given in Table 1.

3.4.2. Neuropsychological tests

No gender differences occurred regarding cognitive testing apart from visuoconstruction ($p = 0.002$; median: women 11; men 10).

Neuropsychological performance correlated inversely with age (all subtests $p < 0.001$) and positively with years of education (all $p < 0.001$). A moderate correlation with disease duration was found regarding some subtests for executive function, memory and MOCA (each < 0.05) but not for language, visuoconstruction, learning, or MMSE. Neuropsychological performance worsened significantly with advancing H&Y disease stages though statistical significance varied between cognitive domains. Language dominated subtests showed no statistically significant influence of disease stages. Severity of motor impairment (MDS-UPDRS III) correlated inversely with all neuropsychological subtests but the similarities. The magnitude of depressive symptoms correlated inversely with most neuropsychological test results.

Detailed tabular information is given in the supplementary material (table B).

3.4.3. Linear regression model of multiple variables

In the linear regression model including influencing factors of neuropsychological performance (sex, age, education, disease duration, MDS-UPDRS III, H&Y, depression, ventricular width) with MMSE as dependent variable, only ventricular width had a significant impact ($p < 0.05$).

Linear regression models using other test results of single or combined cognitive domains as dependent variables revealed that third ventricular width had a significant impact on some tests of executive (TMT B; $p < 0.05$) and attentional function (TMT A, digit symbol test; $p < 0.01$) and visuoconstruction ($p < 0.05$). No impact was found for semantic and phonemic fluency, BNT, similarities, word list, letter number sequencing, or the MOCA test as dependent variables. Regarding other included influencing factors, significant impact could be shown in case of varying dependent variables especially for age, education, motor deficits, and depressive symptoms.

3.4.4. Group differences

31 patients fulfilled MDS level II criteria for PDD, 61 patients fulfilled MDS criteria level II for PD-MCI, and 130 patients showed normal cognition (PDNC).

PDD patients had significantly wider third ventricles than PD patients without dementia (PDNC + PD-MCI; $p < 0.001$). This significance persisted in a logistic regression model including the following covariates: age, age at diagnosis, years of education, disease duration, severity of motor impairment (as assessed by MDS-UPDRS III), depressive symptoms and sex (ventricular width $p = 0.006$; other variables not significant).

There was a significant group difference in ventricular width between PD-MCI patients and PDNC patients (PD-MCI: median 6.5 mm versus PDNC: median 5.8 mm; $p < 0.05$). This significance did not persist in a logistic regression model taking into account the above mentioned variables out of which only motor performance (MDS-UPDRS III) turned out to be significantly worse in PD-MCI compared to PDNC patients ($p < 0.05$).

Excluding PD-MCI patients, PDD patients exhibited significantly wider third ventricles than PDNC patients (PDD: median 7.6 mm; $p < 0.001$). A logistic regression model for the differentiation between PDNC and PDD listed ventricular width as the most significant variable ($p = 0.006$) distinguishing these two conditions, followed by MDS-UPDRS-III ($p = 0.05$) while other variables were not significant.

3.4.5. Cut-off values of ventricular width regarding the differentiation between PDD and PD without dementia

Based on ROC curves, cut-off values for the width of the third ventricle were defined in order to predict the presence of PDD among the whole cohort of PD patients with the highest diagnostic accuracy. In order to consider the effect of age on brain atrophy and ventricular width, the cut-off ROC calculations were separately done for patients < 70 years and patients ≥70 years.

In the age group of ≥70 years (n = 103; PDD n = 21), a ventricular width of ≥7.5 mm predicted PDD with a sensitivity of 67% and a specificity of 72% (AUC 0.662).

In the age group < 70 years (n = 119; PDD n = 10) a threshold of ≥6.0 mm was most likely to predict PDD with a sensitivity of 80% and a specificity of 64% (AUC 0.721).

Based on these age-relatedly defined normative values, there were significantly more PDD cases presenting with a „pathological“ ventricular width ($p < 0.001$) with a fivefold increased risk for PDD (OR 5.1; 95%CI 2.2–11.7; sensitivity 71%, specificity 68%, positive predictive value 0.27, negative predictive value 0.93).

We repeated the calculation of ROC curves-based threshold values for the prediction of PDD in our cohort after the exclusion of PD-MCI patients (potentially at risk of PDD development). This resulted in the same values of ≥7.5 mm for patients ≥70 years (AUC 0.700; sensitivity 67%, specificity 77%) and ≥6.0 mm for patients < 70 years (AUC

Table 1
Correlation between width of III. ventricle, assessed by transcranial ultrasound, and performance in neuropsychological tests. Partial correlation taking into account the influence of disease duration, education, and age on the correlation between ventricular width and cognitive tests.

Neuropsycho-logical test	Statistical significance and Spearman correlation coefficient	Partial correlation with disease duration	Partial correlation with education	Partial correlation with age
SF (animals)	$p < 0.001$; r = -0.263	$p < 0.05$; r = -0.183	p = 0.007; r = -0.196	ns
BNT	$p < 0.001$; r = -0.257	$p < 0.05$; r = -0.187	$p < 0.05$; r = -0.161	ns
WL learning	$p < 0.001$; r = -0.302	p = 0.001; r = -0.252	p = 0.001; r = -0.239	ns
WL recall	$p < 0.001$; r = -0.285	$p < 0.001$; r = -0.255	$p < 0.001$; r = -0.259	ns
VC	$p < 0.001$; r = -0.310	$p < 0.001$; r = -0.310	p = 0.001;r = -0.237	$p < 0.05$; r = -0.154
VC recall	$p < 0.001$; r = -0.248	$p < 0.001$; r = -0.259	$p < 0.001$; r = -0.265	$p < 0.05$; r = -0.171
PF (s-words)	p = 0.001; r = -0.232	$p < 0.05$; r = -0.167	$p < 0.05$; r = -0.177	Statistical trend (p = 0.07; r = -0.130)
TMT A	$p < 0.001$; r = 0.403	$p < 0.001$; r = 0.340	$p < 0.001$; r = 0.318	$p < 0.05$; r = 0.170
TMT B	$p < 0.001$; r = 0.399	$p < 0.001$; r = 0.413	$p < 0.001$; r = 0.385	p = 0.007; r = 0.197
TMT A/B	p = 0.012; r = 0.179	ns	ns	ns
DST	$p < 0.001$; r = -0.498	$p < 0.001$; r = -0.461	$p < 0.001$; r = -0.435	ns
SIM	p = 0.005; r = -0.193	p = 0.002; r = -0.227	p = 0.004; r = -0.209	Statistical trend (p = 0.06; r = -0.135)
LNS	$p < 0.001$;r = -0.247	p = 0.002; r = -0.220	p = 0.006; r = -0.201	ns
MOCA	$p < 0.001$; r = -0.261	p = 0.005; r = -0.206	p = 0.001; r = -0.239	ns
MMSE	$p < 0.001$; r = -0.261	p = 0.004; r = -0.207	p = 0.007; r = -0.199	Statistical trend (p = 0.07; r = -0.133)

ns = not significant, SF = semantic fluency, BNT = Boston naming test, WL = word list, VC = visuoconstruction, PF = phonematic fluency, TMT = trail making test, DST = digit symbol test, SIM = similarities, LNS = letter number sequencing, MOCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination.

0.751; sensitivity 80%, specificity 68%). Patients with a pathological third ventricular width had a sixfold increased risk for PDD (OR 6.2; 95%CI 2.6–14.8; $p < 0.001$; sensitivity 71%, specificity 72%, positive predictive value 0.39, negative predictive value 0.91).

3.4.6. Sonographic assessment of substantia nigra hyperechogenicity and cognition

No statistically significant difference was found between the groups of PDD, PD-MCI and PDNC patients regarding the proportion of patients with SN hyperechogenicity. Retesting the groups with regard to right-sided, left-sided, and dominant hyperechogenic SN area (representing the larger area of bilateral examination), asymmetry or onset index did not disclose a significant group difference.

4. Discussion

The main goal of our study was to determine the value of transcranial ultrasound as diagnostic tool for cognitive impairment and dementia in PD. We could show an inverse correlation between the width of the third ventricle assessed by transcranial ultrasound and cognitive performance in PD patients in all cognitive domains. Cognitive performance correlated with a number of other co-variables, too, as there were the known risk factors age, education, depression, extent of motor impairment, disease duration and advanced disease stage. These factors do influence cognition in PD and have an impact on the correlation between neuropsychological impairment and ventricular width that has to be taken into account. Among these, age seems to be the most important factor influencing both, cognition and ventricular width. Although the only factor distinguishing PDD patients from PD patients without dementia was ventricular width, age-related cut-off values of the ventricular diameter predicted PDD in our cohort with only moderate diagnostic accuracy. Our findings support the hypothesis that TCS-assessed third ventricular width may help to identify PD patients with cognitive decline up to dementia although diagnostic accuracy seems not sufficient for being a biomarker, and influencing co-factors limit the value in clinical routine when used alone. However, rather than being a sole imaging marker diagnosing PDD, it must be considered as a screening instrument and an assessment tool of value in increasing the prediction power when combined with other markers.

Biomarkers suggested for cognitive impairment in PD include genetic markers, wet biomarkers in cerebrospinal fluid (CSF) or blood, electrophysiological findings, and functional and structural neuroimaging changes [14]. Structural neuroimaging based on magnetic resonance imaging (MRI) and voxel-based morphometry are heterogeneous in findings, showing atrophy in temporal, parietal, and frontal cortices but also gray matter loss in hippocampus, parahippocampus, and anterior and posterior cingulate [14]. Whole brain atrophy rates based on serial MRI scans showed a more rapid rate in PDD patients compared to PDNC patients and controls [15].

Using transcranial sonography, we demonstrated that the third ventricular diameter constitutes a parameter for global cerebral atrophy at a single-subject level. Our findings are in line with several MRI studies correlating cognitive decline in PD and enlargement of ventricular spaces [16,17]. PDD patients had larger ventricles than controls or PDNC patients [18,19]. Several MRI studies also showed a ventricular enlargement in PD-MCI suggesting this alteration as possible early marker of incident dementia [19–21]. Among patients with MCI due to different pathologies, dilatation of the third ventricle was most pronounced in PD-MCI [20]. In serial MRI studies, the progression of ventricular enlargement correlated with the extent of cognitive deterioration over time [19].

Sonography-based assessment of ventricular width has additional strengths that need to be considered: Image resolution of deep brain structures has been shown to be comparable to that of MRI [22]. The clear advantages of ultrasound-based techniques in neuroimaging are their non-invasiveness, short examination time, wide availability, and low cost. The third ventricle constitutes a cerebral structure that is most easy to examine. In the vast majority of our patients (96%) it was sufficiently displayable to measure its diameter even in patients with suboptimal temporal bone window.

Pathomorphological correlates of cognitive deficits in PD may be heterogenous and are not completely understood. With limbic and neocortical spreading of cerebral Lewy body and Lewy neurites (LB/LN) pathology, the risk for dementia increases substantially [23]. However, Braak found one third of cases in the earlier stage 3 having been demented, too, although no cortical LB were present [24]. Accordingly, Halliday highlighted the presence of different pathological substrates underlying dementia and cognitive impairment in PD like cerebrovascular disease and cerebral amyloid angiopathy [25]. Particularly, co-occurring Alzheimer's disease (AD) pathology may be seen in PDD cases [25]. This was recently supported by a single subject FDG-PET study [26] that indicated different patterns of cortical hypometabolism

(resembling that of AD, LBD, or frontotemporal dementia) in PD patients who developed dementia at four years of follow-up. Additional evaluation of hippocampal atrophy in PD patients by using TCS could be of interest in order to evaluate potential co-pathology or to increase the value of third ventricle measures [27].

Global atrophy with enlargement of ventricular spaces is an unspecific finding in PDD that occurs in vascular and AD, too, and can even be found in MCI [23]. In an unselected cohort of PD patients this might be a strength of the ultrasound method presented in this manuscript. The individual neurobiological mechanisms of cognitive decline do not influence the presence of the main pathological finding on TCS – enlargement of the third ventricle. Therefore, TCS could help to identify PD patients at risk for cognitive impairment irrespective of an underlying heterogenous pathology.

Longitudinal studies may disclose whether TCS could additionally help identifying those PD patients at risk for a further rapid cognitive decline. Since ultrasound is repeatable, serial examinations may reveal different dynamics of progressing atrophy indicative for a high or low probability of preserved neuropsychological performance or an earlier development of PDD, respectively.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.005.

References

[1] A.J. Yarnall, D.P. Breen, G.W. Duncan, T.K. Khoo, S.Y. Coleman, M.J. Firbank, C. Nombela, S. Winder-Rhodes, J.R. Evans, J.B. Rowe, B. Mollenhauer, N. Kruse, G. Hudson, P.F. Chinnery, J.T. O'Brien, T.W. Robbins, K. Wesnes, D.J. Brooks, R.A. Barker, D.J. Burn, Characterizing mild cognitive impairment in incident Parkinson disease. The ICICLE-PD Study, Neurology 82 (2014) 308–316.

[2] M.A. Hely, W.G.J. Reid, M.A. Adena, G.M. Halliday, J.G.L. Morris, The sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years, Mov. Disord. 23 (2008) 837–844.

[3] G. Levy, M.X. Tang, E.D. Louis, L.J. Côté, B. Alfaro, H. Mejia, Y. Stern, K. Marder, The association of incident dementia with mortality in PD, Neurology 59 (2002) 1708–1713.

[4] B.A. Kallmann, J. Sauer, M. Schliesser, M. Warmuth-Metz, P. Flachenecker, G. Becker Dagger, P. Rieckmann, M. Mäurer, Determination of ventricular diameters in multiple sclerosis patients with transcranial sonography (TCS) - a two year follow-up study, J. Neurol. 251 (2004) 30–34.

[5] A. Pilotto, R. Yilmaz, D. Berg, Developments in the role of transcranial sonography for the differential diagnosis of parkinsonism, Curr. Neurol. Neurosci. Rep. 15 (2015) 43.

[6] N.S. Schmid, M.M. Ehrensberger, M. Berres, I.R. Beck, A.U. Monsch, The extension of the German CERAD neuropsychological assessment Battery with tests assessing subcortical, executive and frontal functions improves accuracy in Dementia diagnosis, Dement. Geriatr. Cognit. Dis. Extra 4 (2014) 322–334.

[7] D.J. Gill, A. Freshman, J.A. Blender, B. Ravina, The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease, Mov. Disord. 23 (2008) 1043–1046.

[8] D.E. Hartman, Wechsler Adult intelligence scale IV (WAIS IV): return of the gold standard, Appl. Neuropsychol. 16 (2009) 85–87.

[9] A.T. Beck, A. Beamesderfer, Assessment of depression: the depression inventory, Mod. Probl. Pharmacopsychiatr. 7 (1974) 151–169.

[10] C.G. Goetz, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, G.T. Stebbins, M.B. Stern, B.C. Tilley, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. Van Hilten, N. LaPelle, Movement disorders society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan, Mov. Disord. 22 (2007) 41–47.

[11] U. Walter, D. Skoloudik, Transcranial sonography (TCS) of brain parenchyma in movement disorders: quality standards, diagnostic applications and novel technologies, Ultraschall der Med. 35 (2014) 322–331.

[12] U. Walter, D. Dressler, A. Wolters, M. Wittstock, B. Greim, R. Benecke, Sonographic discrimination of dementia with Levy bodies and Parkinson's disease with dementia, J. Neurol. 253 (2006) 448–454.

[13] B. Dubois, D. Burn, C. Goetz, D. Aarsland, R.G. Brown, G.A. Broe, D. Dickson, C. Duyckaerts, J. Cummings, S. Gauthier, A. Korczyn, A. Lees, R. Levy, I. Litvan, Y. Mizuno, I.G. McKeith, C.W. Olanow, W. Poewe, C. Sampaio, E. Tolosa, M. Emre, Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force, Mov. Disord. 22 (2007) 2314–2324.

[14] B. Mollenhauer, L. Rochester, A. Chen-Plotkin, D. Brooks, What can Biomarkers tell us about cognition in Parkinson's disease? Mov. Disord. 29 (2014) 622–633.

[15] E.J. Burton, I.G. McKeith, D.J. Burn, J.T. O'Brien, Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging, Mov. Disord. 20 (2005) 1571–1576.

[16] M. Alegret, C. Junqué, R. Pueyo, F. Valldeoriola, P. Vendrell, E. Tolosa, J.M. Mercader, MRI atrophy parameters related to cognitive and motor impairment in Parkinson's disease, Neurologia 16 (2001) 63–69.

[17] T.O. Dalaker, R. Zivadinov, D.P. Ramasamy, M.K. Beyer, G. Alves, K.S. Bronnick, O.B. Tysnes, D. Aarsland, J.P. Larsen, Ventricular enlargement and mild cognitive impairment in early Parkinson's disease, Mov. Disord. 26 (2011) 297–301.

[18] L.G. Apostolova, M. Beyer, A.E. Green, K.S. Hwang, J.H. Morra, Y.Y. Chou, C. Avedissian, D. Aarsland, C.C. Janvin, J.P. Larsen, J.L. Cummings, P.M. Thompson, Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia, Mov. Disord. 25 (2010) 687–695.

[19] R. Camicioli, J. Sabino, M. Gee, T. Bouchard, N. Fisher, C. Hanstock, D. Emery, W.R. Martin, Ventricular dilatation and brain atrophy in patients with Parkinson's disease with incipient dementia, Mov. Disord. 26 (2011) 1443–1450.

[20] J.S. Meyer, J. Huang, M.H. Chowdhury, MRI confirms mild cognitive impairment prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementia, J. Neurol. Sci. 257 (2007) 97–104.

[21] B. Segura, H.C. Baggio, M.J. Marti, F. Valldeoriola, Y. Compta, A.I. Garcia-Diaz, P. Vendrell, N. Bargallo, E. Tolosa E, C. Junque, Cortical thinning associated with mild cognitive impairment in Parkinson's disease, Mov. Disord. 29 (2014) 1495–1503.

[22] U. Walter, M. Kanowski, J. Kaufmann, A. Grossmann, R. Benecke, L. Niehaus, Contemporary ultrasound systems allow high-resolution transcranial imaiging of small echogenic deep intracranial structures similarly as MRI: a phantom study, Neuroimage 40 (2008) 551–558.

[23] D.J. Irwin, M.T. White, J.B. Toledo, S.X. Xie, J.L. Robinson, V. Van Deerlin, V.M. Lee, J.B. Leverenz, T.J. Montine, J.E. Duda, H.I. Hurtig, J.Q. Trojanowski, Neuropathologic substrates of Parkinsondisease dementia, Ann. Neurol. 72 (2012) 587–598.

[24] H. Braak, U. Rüb, E.N.H. Jansen Steur, K. Del Tredici, R.A.I. de Vos RAI, Cognitive status correlates with neuropathologic stage in Parkinson's disease, Neurology 64 (2005) 1404–1410.

[25] G.M. Halliday, J.B. Leverenz, J.S. Schneider, C.H. Adler, The neurobiological basis of cognitive impairment in Parkinson's disease, Mov. Disord. 29 (2014) 634–650.

[26] A. Pilotto, E. Premi, S. Paola Caminiti, L. Presotto, R. Turrone, A. Alberici, B. Paghera, B. Borroni, A. Padovani, D. Perani, Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease, Neurology 90 (2018) e1029–1037.

[27] R. Yilmaz, A. Pilotto, B. Roeben, O. Preiche, U. Suenkel, S. Heinzel, F.G. Metzger, C. Laske, W. Maetzler, D. Berg, Structural ultrasound of the medial temporal lobe in alzheimer's disease, Ultraschall der Med. 38 (2017) 294–300.