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The impact of white matter lesions on the cognitive outcome of subthalamic nucleus deep brain stimulation in Parkinson's disease

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ABSTRACT

Objectives: White Matter lesions (WML) are a risk factor for cognitive impairment in Parkinson's disease. There is no clear evidence of reduced general cognitive function after DBS. However, a subgroup of patients develops dementia rapidly after DBS despite careful patient selection processes. The aim of this study was to evaluate the load of WML as a possible risk factor for cognitive decline following STN DBS.

Patients and methods: 40 PD-patients receiving bilateral STN-DBS were followed at least three years after surgery to detect dementia. All patients underwent comprehensive neuropsychological assessment and MRI before surgery. The extent of WML was assessed using an automated approach. WML volume was correlated to the onset of dementia and the decline of a cognitive composite score retrospectively.

Results: Patients with a rapid onset of dementia within one, respective three following DBS showed significant higher WML volumes compared to cognitive normal and MCI patients (55.8 cm^3 ± 18.836 vs. 9.3 cm^3 ± 12.2; $p = 0.002$). The same significant association was found in a multivariable model, including the covariables age, gender and PD disease duration ($p = 0.01$). WML volume was associated to the rate of decline in cognitive composite score within three years after DBS surgery ($p = 0.006$; $R^2 = 0.40$) after correction for age.

Conclusions: Damaged white matter may lead to a reduced compensation of disconnections in cognitive circuits caused by the implantation of the DBS electrodes or by chronic stimulation.

The role of WML as a prognostic factor for the cognitive outcome after DBS may be underestimated. The WML burden should be taken seriously in preoperative risk stratification.

1. Introduction

Cognitive decline is a common symptom of Parkinson's disease (PD). Mild Cognitive Impairment (MCI) affects about a third of PD patients within the first five years after diagnosis [1]. In the Movement Society Task Force Criteria, PD-MCI is defined as a cognitive decline in the context of PD which is not sufficient to interfere with functional independence [2]. Pure frontal deficits in executive functions may not be generally associated with a higher risk for dementia [3]. Instead, reduced semantic fluency and narrowed visual-constructive functioning indicate the progression from MCI to dementia in PD (PD-D) [4]. The transition to PD-D, defined as cognitive deficits severe enough to cause dependency in the activities of daily living, has a prevalence of 70–80% during the disease course [5] with a conversion rate of up to 11% per year [6]. PD-D increases morbidity and decreases quality of life in PD patients [7].

White Matter lesions (WML) on magnetic resonance imaging (MRI) scans are frequent among older adults [8]. Although the exact pathogenesis is not completely understood yet, the typical cerebrovascular risk factors, e.g. hypertension, diabetes and smoking are causative [9]. While single lesions are an unspecific sign of aging to some extent, a high WML burden with confluent lesions is a risk factor for functional and cognitive decline in the healthy elderly [10]. WML in PD patients are predominantly found in frontotemporal regions compared to healthy controls and are correlated to executive dysfunction [11]. A recent review of the literature outlined that most of the present studies demonstrated an inverse relationship between cognitive function and WML burden [12]. In a comparison between PD-MCI and cognitive normal (CN) PD patients, WML were identified as a risk factor for PD-MCI [13]. The WML burden may also predict the conversion from PD-MCI to PD-D [14].

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus

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(STN) is a well-established symptomatic therapy option in advanced PD [15]. Dementia is a contraindication to DBS since the positive effect of DBS on the quality of life may be offset by the progressing cognitive decline [16].

The influence of DBS on cognition has been topic of many studies. The sole consistent finding about DBS-related cognitive deficits is reduced verbal fluency which may be a transient effect of the surgery itself [17]. Additionally, a recent *meta*-analysis of controlled trials showed evidence of decreased executive functioning after STN DBS [18]. There is conflicting data whether preoperative MCI deteriorates the cognitive outcome of DBS [19,20]. Overall, there is no clear evidence for a general cognitive decline or an increased risk for PD-D. Dementia tends to be interpreted as the natural evolution of PD rather than a direct effect of DBS [21]. Nevertheless, a subset of patients develops PD-D rapidly after DBS surgery [22]. Therefore, the aim of this study was to evaluate the load of WML as a risk factor for cognitive decline following STN DBS.

2. Patients and methods

2.1. Patients

Data of 40 consecutive PD patients (Table 1) were analyzed retrospectively after bilateral STN DBS between 2004 and 2012. All patients fulfilled the inclusion criteria for DBS, having a functional disability in daily life due to severe motor fluctuations or disabling tremor with a significant improvement of Unified Parkinson's Disease Rating Scale part III (UPDRS III) in a standardized levodopa challenge. Exclusion criteria were age older than 75 years, active psychiatric diseases and dementia. Patients were included to this analysis only if no adverse effect of the surgery itself occurred and if they were treated in our outpatient clinic at least once a year during a follow up period of at least three years after DBS surgery. The vascular risk factors at baseline, e.g. diabetes, hypertension, hypercholesterinemia, coronary heart disease and peripheral arterial disease were gathered from the medical reports. It is noteworthy that no information was available about smoking and alcohol consumption. This retrospective study was approved by the Ethical Committee of the University Regensburg.

Table 1
Baseline characteristics and comparison of PD-D to NC and PD-MCI patients.

	All (n = 40)	PD-D after 3 years (n = 10)	NC or MCI after 3 years (n = 30)	p
age (years)	61.8 ± 6.7	**65.8 ± 6.5**	**60,5 ± 5.8**	**0.03**[a]
disease duration (years)	12.5 ± 4.5	12.2 ± 4.4	13.2 ± 4.7	0.6[a]
UPDRS III ON (of 108)	12.2 ± 6.6	12.5 ± 6.6	11.2 ± 6.4	0.08[a]
UPDRS III OFF (of 108)	33.6 ± 10.7	34.8 ± 11.3	30.2 ± 7.8	0.7[a]
WML volume (cm^3)	14.0 ± 19.0	**29.6 ± 25.7**	**8.8 ± 12.2**	**0.009**[b]
WML/whole brain volume	0.008	**0.018**	**0.005**	**0.01**[b]
male//female	30//10	7//3	23//7	0.7[d]
T//AR//mixed	5//14//21	0//6//4	5//8//17	0.3[d]
no CVRF//CVRF	17//23	3//7	15//15	0.5[d]
CN//MCI	14//26	2//8	12//18	0.4[d]

CN = cognitive normal, CVRF = cerebrovascular risk factor, MCI = mild cognitive impairment, WML = white matter lesions, T = tremor dominant type, AR = akinetic-rigid type

Significant differences between the PD-D and the NC / MCI groups in bold.

[a] *T*-test.

[b] Mann-Whitney *U* test.

[d] Fisher's exact test.

2.2. Neuropsychological assessment

All patients were assessed prior to DBS surgery in ON medication state. The neuropsychological assessment included two tests for each of the neuropsychological domains, attention (Trail Making Test A, Symbol Digit Modalities Test), executive functions (Trail Making Test B, Similarities Test of Wechsler Adult Intelligence Scale), language (Semantic Verbal Fluency, Controlled Oral Word Association Test), memory (Rey Complex Figure Retention, Logical Memory Scale 1 and 2 of Wechsler Memory Scale) and visual-constructive function (Rey Complex Figure Copy, Block Design Test of Wechsler Adult Intelligence Scale). 17 patients had a follow-up assessment within three years (mean 21 months) after the first testing. MCI and PD-D were diagnosed using the Movement Disorders Society Task Force Criteria level 2 [2,23]. A performance below two SD compared to the age-matched reference group was defined as pathological [24].

To correlate cognitive decline to the WML burden, we created a cognitive composite score (CCS): All test results were first transformed to z scores. The mean z score of both tests for each of the five domains were summed and divided by five. These individual CCS for both neuropsychological assessments were subtracted to quantify the cognitive decline.

2.3. Imaging

All patients were scanned with the same MR scanner (Magnetom Sonata, 1.5T, Siemens, Erlangen, Germany) prior to DBS implantation. The fluid attenuated inversion recovery (FLAIR) sequence (SL: 30.50; ST: 5.00; Res: 256 × 192; TR/TE: 7530.00/110.00 ms; FOV: 230.00 × 172.50 mm) was used for the semi-automated rating of the WML. The DICOM images were converted to NIFTI format for brain extraction by the dcm2nii tool [25]. With BET (Brain Extraction Tool, FMRIB Software Library, FSL, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK) non-brain tissue from the images of the whole head were deleted. The resulting images were transferred to the iPlan stereotaxy software (Brainlab, Feldkirchen, Germany) via the Amira® format converter (NIFTI to DICOM, Amira®, FEI™, Hillsboro, Oregon, USA). Using the iPLAN software, WML were segmented according to intensity values and afterwards each axial FLAIR slice was examined by a single rater to correct the WML contouring.

To reduce the influence of different brain sizes, the absolute WML volume was also stated as percentage of the whole brain volume. Hereby no additional or deviant information was added with respect to absolute WML volume. Therefore, only the results calculated with absolute WML volume are reported here.

2.4. Statistics

Between group comparisons were performed using *T*-test for normally distributed variables and Mann-Whitney-*U* test if normal distribution was not significantly probable. Fisher's exact test was used for nonparametric data.

Pearson correlation was used to correlate quantitative variables. We performed a multivariable linear regression to test for an association between the postoperative diagnosis of PD-D and WML volume, including the covariables age, PD disease duration and gender.

In the second model to explore the association of WML volume and change of cognitive composite score, we included only age as a covariable to avoid bias because of the small sample (n = 17). Results are presented as mean and standard deviation and significance level was established at $p < 0.05$.