Short communication

Cognitive impairment in REM-sleep behaviour disorder and individuals at risk of Parkinson's disease

A.V. Nagy [a], G. Leschziner [b], S.H. Eriksson [c], A. Lees [d], A.J. Noyce [e,1], A. Schrag [a,*,1]

[a] Department of Clinical and Behavioural Neurosciences, University College London Queen Square Institute of Neurology, United Kingdom
[b] Sleep Disorders Centre and Department of Neurology, Guy's and St Thomas' NHS Foundation Trust, Dept of Basic and Clinical Neuroscience, Institute of Psychology, Psychiatry and Neuroscience, King's College London, United Kingdom
[c] National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, United Kingdom
[d] Rita Lila Weston Institute of Neurological Studies, University College London Queen Square Institute of Neurology, United Kingdom
[e] Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, United Kingdom

ABSTRACT

Background: Mild cognitive impairment (MCI) is commonly present at the time of Parkinson's Disease (PD) diagnosis, but its prevalence amongst individuals at increased risk of PD is unclear.
Methods: Cognition was assessed using the Montreal Cognitive Assessment (MoCA) in 208 participants in the PREDICT-PD study, and 25 participants with REM-sleep behaviour disorder (RBD). Prevalence of MCI level I was determined in all participants, and level II MCI in the RBD sub-group.
Results: Total MoCA scores were worse in the higher risk than the lower risk group defined as those below the 15th percentile of risk (p = 0.009), and in the RBD group compared to all healthy participants (p < 0.001). The prevalence of MCI level I was 12.8% in the lower-risk, 21.9% in the higher-risk (within the highest 15th percentile) and 64% in RBD participants; 66% of RBD participants had MCI level II with multi-domain MCI, but particularly attention and memory deficits.
Conclusions: Cognitive impairment is increased in different groups at higher risk of PD, particularly in the sub-group formally diagnosed with RBD.

1. Background

Cognition is affected early in Parkinson's Disease (PD) with prevalence of mild cognitive impairment (MCI) in incident cases estimated to be 15–43% [1,2]; the main determinant is age at diagnosis. The cognitive profile in this group shows executive function, visuospatial and memory deficits with visuospatial and fluency-cortical tasks thought to be predictive of future dementia [3]. In groups at-risk for PD, cognitive dysfunction is also more likely to be detected, particularly in executive function and memory (verbal and non-verbal) domains [4]. A large case-control study suggested that patients with later diagnosis of PD presented to their general practitioner with memory complaints more frequently than controls and up to 2–5 years before diagnosis of PD [5, 6]. Longitudinal studies show that there is measurable impairment on neuropsychological tests up to 6 years before diagnosis [7].

MCI in PD is classified using Movement Disorder Society (MDS) guidelines [8]. Level I (brief) diagnosis requires impairment in a global test of cognitive function such as the Montreal Cognitive Assessment (MoCA). Level II diagnosis requires that cognition is measured using at least 2 tests for each of the 5 domains. MCI is defined as being impairment (between 1 and 2 standard deviations below age-adjusted normative values) in at least 2 tests. Whilst not all patients with MCI progress to develop dementia, MCI is an important prognostic marker. We present work here which describes cognitive function according to this framework in different groups at increased risk of PD.

2. Methods

PREDICT-PD is a cohort study which has quantified PD risk in healthy participants aged between 60 and 80 years, recruited from the UK general population [9]. In the pilot phase, 1,323 healthy participants without neurodegenerative disease had their PD risk calculated using an

* Corresponding author.
  E-mail address: a.schrag@ucl.ac.uk (A. Schrag).
[1] equal contribution.

evidence-based algorithm incorporating known risk factors ascertained online [10]. The PREDICT-PD algorithm calculates risk of PD by age and risk and prodromal factors based on data in the literature, such as smoking and family history, depression and autonomic symptoms, comorbidities, head injury, consumption of coffee and alcohol, and medications. It provides similar results to the MDS research criteria for prodromal PD [11] but includes clinical features only and uses continuous variables. Additionally, patients with RBD were recruited from specialist centres following formal diagnosis from a sleep specialist using International Classification of Sleep Disorders 3rd edition (ICSD-3) criteria and overnight polysomnography.

208 PREDICT-PD participants were randomly selected to be seen in person and underwent brief cognitive testing using the MoCA. 25 participants with PSG-confirmed RBD were also seen in person and assessed with the MoCA. Comparisons were made between a) lower risk vs. higher risk, defined as being below the lowest and within the highest 15th percentiles of risk, respectively, and b) RBD vs. all PREDICT-PD participants from the general population (irrespective of risk score). Proportions of participants with level I MCI were compared using the chi-squared test and MoCA scores are compared using the Wilcoxon rank-sum test, as data were non-parametric. RBD participants additionally underwent comprehensive 5-domain neuropsychometry, allowing categorisation of level II MCI. The battery included 12 individual tests (supplementary data 1) with at least two in each cognitive domain. For each individual cognitive task, performance is corrected for age and education using published normative data to calculate z-scores in place of each test score. The individual test z-scores are summed up for each of the 5 cognitive domains for every individual and mean group z-scores are then calculated for each domain. The cognitive profile in RBD participants with and without level II MCI is presented descriptively.

Ethics approval was granted by the Central London Research Ethics Committee 3 and all patients provided informed consent.

3. Results

Demographic and cognitive testing results for the different groups are shown in Table 1. Compared to the higher risk group, the lower risk group was more likely to be female and younger age, in keeping with characteristics used in the risk algorithm. Compared to PREDICT-PD participants, the RBD group was more likely to be male.

3.1. Level I MCI in high-risk, low-risk and RBD participants

Total MoCA scores were worse in the higher risk group compared to lower risk group (p = 0.009) and in the RBD group compared to PREDICT-PD participants (p < 0.001). Rates of MCI level I were 12.8% in the lower-risk, 21.9% in the higher-risk and 64% in RBD participants (p = 0.12 for lower risk vs higher risk and p < 0.001 for RBD vs PREDICT-PD participants).

Amongst the cognitive sub-domains of the MoCA, most domains were worse in the RBD group compared to PREDICT-PD participants using Bonferroni correction for multiple comparisons (p-values ≤0.001 for all domains except naming, p = 0.24 with p < 0.006 considered significant). Between lower and higher risk participants, only memory scores differed (p = 0.002)

3.2. Level II MCI in RBD participants

RBD participants showed high rates of level II MCI with 15/25 (60%) fulfilling MDS level II diagnostic criteria. In comparing those participants with MCI and those without, they were older, had poorer smell (UPSIT score) and increased motor disability (UPDRS-III) but on direct comparison none of these differences were significant.

Table 1

Demographic characteristics and cognitive results for Lower Risk, Higher Risk and RBD participants with further analysis by cognitive domain for RBD participants with and without level II cognitive impairment.

Risk Group	Lower risk (<15th centile)	Higher risk (≥ 15th centile)	RBD	RBD with Level II MCI	RBD with NC
N	117	91	25	15	10
Male gender N (%)	32 (27)^	77 (85)^	20 (80)^^	11 (73)	9 (90)
Age Mean (SD)	66.1 (4.0)^	72.8 (5.0)^	70.2 (7.6)	72.0 (7.9)	67.9 (7.0)
MOCA median (IQR)	28 (26–29)^	27 (26–28)^	24 (21–26)^^	22 (19–25)	25.5 (24–27)
Level I MCI N (%)	15 (12.8)	20 (21.9)	16 (64.0)	11 (73.3)	5 (50.0)
MOCA sub-sections					
Visuospatial/ executive median (IQR)	5 (4–5)	5 (4–5)	4 (3–5)**	4 (2–4)	5 (3–5)
Naming median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
Memory median (IQR)	4 (3–5)*	3 (2–4)*	2 (0–3)**	1 (0–2)	3 (2–4)
Attention median (IQR)	6 (6–6)	6 (6–6)	6 (5–6)**	5 (4–6)	5.5 (5–6)
Language median (IQR)	3 (2–3)	3 (2–3)	2 (1–2)**	2 (1–3)	2 (2–2)
Abstraction median (IQR)	2 (2–2)	2 (2–2)	2 (1–2)**	1 (1–2)	2 (2–2)
Orientation median (IQR)	6 (6–6)	6 (6–6)	6 (5–6)**	6 (5–6)	6 (6–6)
Verbal fluency mean (SD)	17.5 (6.0)	16.0 (4.9)	12.6 (5.7)**	9 (4.9)	15 (5.6)
Cognitive results by domain					
Memory domain mean z-score	–	–	−0.49	−0.77	−0.08
Executive domain mean z-score	–	–	−0.25	−0.67	0.37
Attention domain mean z-score	–	–	−0.93	−1.40	−0.21
Visuospatial domain mean z-score	–	–	−0.21	−0.68	0.49
Language domain mean z-score	–	–	0.15	−0.08	0.49

^significant difference between lower and higher risk groups at p < 0.05 ^^significant difference between RBD and PREDICT-PD participants at p < 0.05 *significant difference between low and high risk groups at p < 0.006 **significant difference between RBD and PREDICT-PD participants at p < 0.006 (IQR = Interquartile Range, MCI = Mild Cognitive Impairment, MOCA = Montreal Cognitive Assessment, NC = Normal Cognition RBD = Rapid Eye Movement Sleep Behaviour Disorder, SD = Standard Deviation, UPDRS = United Parkinson's Disease Rating Scale, UPSIT = University of Pennsylvania Smell Identification Test).

3.3. Cognitive profiles

In those RBD participants with level II cognitive impairment, 15/15 (100%) had multi-domain cognitive impairment (93% attention, 87% memory, 67% executive function, 47% visuospatial and 13% language). At the group level, RBD patients were most impaired in attention and memory domains (mean z-score −0.93 and −0.49 respectively). In those without level II MCI, only attention and, subtly, memory were reduced, whereas in those with MCI, scores across all domains were reduced, particularly attention, with relative preservation of language. Individual cognitive profiles, the overall group profile and profiles for those with and without MCI are shown in Fig. 1. This figure uses z-scores calculated using age and education-adjusted normative values for individual
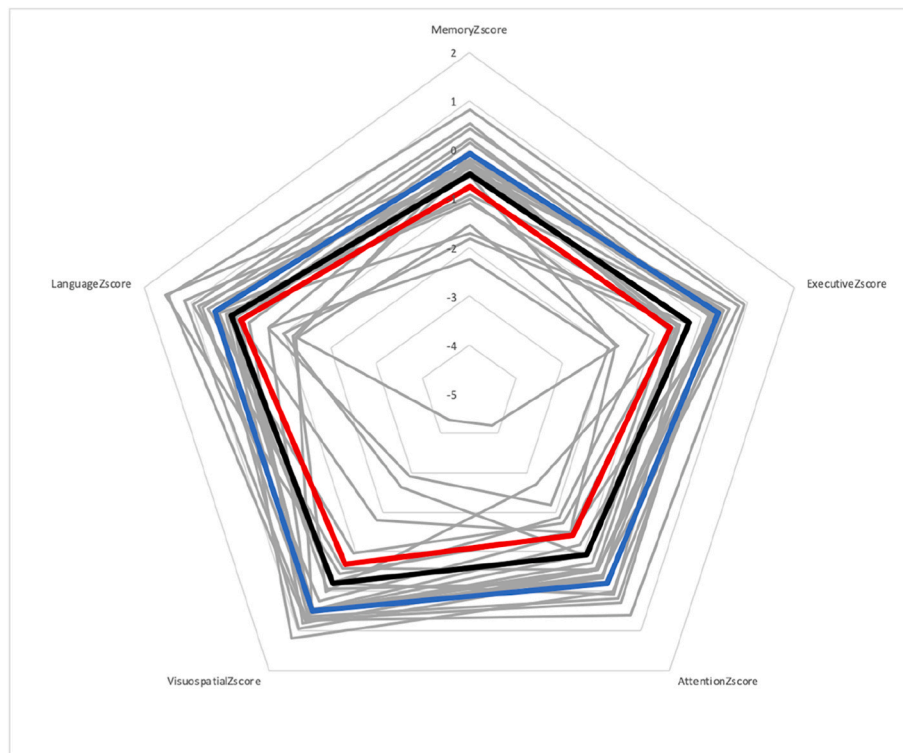
Fig. 1. Cognitive profile in RBD participants, illustrating the reduction (lower z-scores) particularly in the attention domain (total RBD group in black, level II MCI group in red, no MCI group in blue, individual participants in grey). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cognitive tests, 0 being a score at the mean and −1 being a score at 1 standard deviation below the mean.

4. Discussion

In the present study, we found evidence that cognitive function is impaired in groups at higher risk of developing PD. Rates of MCI were 21.9% in the higher risk group compared to 12.8% in the lower risk group. Median MoCA scores differed significantly but slightly suggesting that these differences may be useful as a part of an algorithm but not on an individual level in the general population. Patients with RBD however had a particularly high prevalence of cognitive impairment with 64% in RBD patients classified as having MCI, similar to that reported in a previous study [12], using Level I MDS criteria. On comprehensive neuropsychological testing, RBD patients were most affected in attention and more subtly memory, suggesting early involvement of these domains. In RBD patients who already met the definition of MCI, particularly attention but also other domains including visuospatial function and executive function domains were affected. This may suggest that visuospatial and executive functions deteriorate later in the course of the disease.

This is the first study to quantify rates of cognitive impairment using the MDS MCI criteria in different at-risk groups. Our results are however in keeping with the literature in established PD, showing that there is higher cognitive burden in those who also have RBD than those who do not [13]. In previous studies that have longitudinally followed community-based participants to the point of PD diagnosis, executive function [15], divided attention [16], language and working memory have been shown to differ at pre-morbid assessments between those that are later diagnosed with PD ('converters') and healthy controls. In RBD, patients who convert to neurodegenerative disease show poorer performance in tests of attention and executive function before diagnosis [17]. The pre-morbid RBD group as a whole has poorer verbal memory and visuo-spatial abilities than controls [18].

5. Limitations

RBD symptoms are unlikely to be reported at diagnosis but may be found on polysomnography. For example, of 159 de novo PD patients screened using polysomnography in one study, none had sought medical advice for abnormal behaviours in sleep. In this group a prevalence rate for ISCD-2 diagnosis of RBD of 25% is reported [14]. Therefore, patients formally diagnosed with RBD prior to PD diagnosis are likely to represent only a small number of future PD patients with RBD.

It is not known whether all our at-risk participants will develop future PD, and how many of the patients with RBD will convert to PD. A proportion of patients with RBD develop other neurodegenerative conditions, notably Dementia with Lewy Bodies and Multiple System Atrophy. Whilst the semiological classification of patients with early cognitive impairment in PD remains controversial, it is likely that at least a proportion of those with MCI in the RBD group will develop Dementia with Lewy Bodies [19].

Overall, this study demonstrates early cognitive changes in prodromal PD, and confirms the importance of attentional and memory deficits in RBD patients, but also suggests that cognitive problems evolve to involve executive and visuospatial deficits as patients develop MCI. RBD may represent a specific pathway to PD, with high levels of cognitive impairment and a specific cognitive profile. Further work is needed to define rates of level II MCI in pre-diagnostic cohorts without RBD (for example, our higher risk cohort) and to longitudinally follow up all cohorts to define the specific tests most predictive of neurodegenerative disease in all pre-diagnostic patients.

Author roles

ANa: data collection, analysis and writing of the first draft; SE: editing of the final version of the manuscript; GL: editing of the final version of manuscript; AL: editing of the final version of manuscript; ANo: design, editing of the final version of the manuscript; AS: design, editing of the final version of manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105312.

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