Clinical short communication

Identifying parkinsonism in mild cognitive impairment

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ABSTRACT

Introduction: Clinical parkinsonism is a core diagnostic feature for mild cognitive impairment with Lewy bodies (MCI-LB) but can be challenging to identify. A five-item scale derived from the Unified Parkinson's Disease Rating Scale (UPDRS) has been recommended for the assessment of parkinsonism in dementia. This study aimed to determine whether the five-item scale is effective to identify parkinsonism in MCI.

Methods: Participants with MCI from two cohorts (n = 146) had a physical examination including the UPDRS and [123I]-FP-CIT SPECT striatal dopaminergic imaging. Participants were classified as having clinical parkinsonism (P+) or no parkinsonism (P-), and with abnormal striatal dopaminergic imaging (D+) or normal imaging (D-). The five-item scale was the sum of UPDRS tremor at rest, bradykinesia, action tremor, facial expression, and rigidity scores. The ability of the scale to differentiate P+D+ and P-D- participants was examined.

Results: The five-item scale had an AUROC of 0.92 in Cohort 1, but the 7/8 cut-off defined for dementia had low sensitivity to identify P+D+ participants (sensitivity 25%, specificity 100%). Optimal sensitivity and specificity was obtained at a 3/4 cut-off (sensitivity 83%, specificity 88%).

In Cohort 2, the five-item scale had an AUROC of 0.97, and the 3/4 cut-off derived from Cohort 1 showed sensitivity of 100% and a specificity of 82% to differentiate P+D+ from P-D- participants. The five-item scale was not effective in differentiating D+ from D- participants.

Conclusions: The five-item scale is effective to identify parkinsonism in MCI, but a lower threshold must be used in MCI compared with dementia.

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia. The presence of parkinsonism is a core clinical feature for the diagnosis of DLB and mild cognitive impairment with Lewy bodies (MCI-LB) [1]. The clinical diagnosis of MCI-LB is challenging, as symptoms are less frequent and less severe at this early disease stage [2]. Clinical parkinsonism is one of the most common core clinical features of MCI-LB, and is present in around two thirds of cases [2], though parkinsonism may develop later in females than males [3]. Therefore, the accurate identification of clinical parkinsonism in MCI-LB is of vital importance for research and clinical practice.

Previously, a scale derived from the Unified Parkinson's Disease Rating Scale (UPDRS) was developed to help clinicians identify parkinsonism in dementia. Using five features (tremor at rest, bradykinesia, action tremor, facial expression, rigidity), a cut-off of 7.5 had a sensitivity of 85% and a specificity of 100% to identify clinical parkinsonism [4]. This scale has been recommended in diagnostic toolkits for DLB [5]. The aim of this manuscript was to determine whether this scale could be used to identify parkinsonism in mild cognitive impairment.

1. Methods

1.1. Participants

Participants from two research cohorts were analysed. The details of participant recruitment and the characteristics of Cohort 1 (LewyPro) [6] and Cohort 2 (SUPErB) [7] have been published previously. Briefly, participants ≥60 years old with MCI were recruited from memory clinics, older people's medicine clinics and neurology clinics in the Northeast of England and Cumbria. Participants were excluded if they had dementia, a Mini-Mental State Examination (MMSE) score < 20, a CDR score of >0.5, parkinsonism that developed >1 year prior to cognitive impairment or evidence of clinical stroke or a serious neurological or medical condition that would affect their performance in study assessments.

All participants with capacity gave their written and informed consent to take part in this study.

The study received ethical approval from the National Research Ethics Service Committee North East–Newcastle & North Tyneside 2 (Research Ethics Committee identification numbers 15/NE/0420, 12/NE/0290).

1.2. Clinical assessment

Participants underwent a comprehensive clinical and cognitive assessment, including a full neurological examination, Hoehn and Yahr scale and the Movement Disorders Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) Motor Sub-scale. A three person expert consensus clinical panel reviewed all of the clinical assessment data to confirm whether the patients had parkinsonism, defined as one or more of the cardinal features of bradykinesia, rest tremor or rigidity [1], independent of the results of the dopaminergic imaging.

A five-item parkinsonism score was calculated as previously described [4]. The scores for five features (tremor at rest, bradykinesia, action tremor, facial expression, rigidity), each rated 0–4, were added to give a total score. The scale was initially devised using a previous version of the UPDRS, therefore a single score was used for each feature (e.g. the score for 'tremor at rest' was the highest score for tremor at rest in the MDS-UPDRS either in one of the upper or lower limbs, or in the lip/jaw).

1.3. Imaging

Striatal dopaminergic imaging ([123I]FP-CIT SPECT 2β-Carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane SPECT) was carried out at baseline as previously described [8]. Images were classed as normal or abnormal based on consensus visual rating by a five-person panel, blind to any clinical data.

1.4. Classification of groups

Participants were classified as having parkinsonism (P+) or no parkinsonism (P-) and with abnormal striatal dopaminergic imaging (D+) or normal imaging (D-). In the primary analysis, we compared P+D+ and P-D- groups. Participants with discordant findings (P+D- or P-D+) were excluded from the primary analysis but included in the secondary analysis, based solely on striatal dopaminergic imaging. P+D- participants were presumed to have non-neurodegenerative features mimicking parkinsonism, such as vascular disease, arthritis and essential tremor [9]. P-D+ participants were presumed to have nigrostriatal dopaminergic loss that was insufficient to cause clinical signs [10].

1.5. Statistics

Statistical analysis was carried out using IBM SPSS Statistics, version 29. Demographics and clinical data were compared using *t*-tests, Mann-Whitney *U* tests, Chi-Square tests and Fisher's Exact tests as appropriate. Area under the receiver operating characteristic (AUROC) was plotted to quantify discriminant ability. A cut-off for optimal sensitivity and specificity was calculated in Cohort 1 and tested in Cohort 2.

2. Results

2.1. Demographics

The group demographics for both cohorts are displayed in Table 1 and Supplementary Table 1. There were 146 participants ($n = 22$ P+D+, $n = 86$ P-D-, $n = 33$ P-D+ and $n = 5$ P+D-). P+D+ participants were more likely to be male (Table 1).

2.2. Discriminant ability of five-item scale

The five-item scale had an AUROC of 0.92 (95% Confidence Interval (CI) 0.85–1) to discriminate P+D+ from P-D- in Cohort 1. However, few participants reached the 7.5 cut-off previously published for dementia (sensitivity 25%, specificity 100%, Fig. 1). Optimal sensitivity and specificity was obtained at a 3.5 cut-off with a sensitivity of 83% and a specificity of 88%.

This finding was tested in an independent sample, Cohort 2. The AUROC was 0.97 (95% CI 0.93–1). The 3.5 cut-off demonstrated a sensitivity of 100% and a specificity of 82% (Fig. 1).

Raters were not blind to MDS-UPDRS scores when assigning the presence or absence of parkinsonism. To avoid circularity, the 3.5 threshold derived from Cohort 1 was tested against FP-CIT SPECT result only in Cohort 2. 12/20 (60%) of those scoring above the 3.5 threshold were D+, compared with 14/51 (28%) of those scoring below the 3.5 threshold ($p = .01$).

Table 1
Cohort 1 & Cohort 2 - Demographics.

	Cohort 1			Cohort 2		
	P-D-	P+D+	p	P-D-	P+D+	p
N	41	12		45	10	
Age, mean (SD)	76.0 (8.3)	76.8 (7.9)	0.775	73.5 (7.3)	76.1 (4.5)	0.290
Sex, n (% male)	19 (46%)	11 (92%)	0.005	20 (44%)	10 (100%)	0.001
Years education, median (IQR)	10 (3)	11 (4)	0.518	11 (5)	11 (4)	0.927
MMSE Total, median (IQR)	26 (3)	27 (3)	0.940	27 (3)	26.5 (5)	0.741
CIRS-G Total, mean (SD)	10.2 (4.7)	8.8 (3.5)	0.358	7.4 (4.1)	7.9 (4.5)	0.711
MDS-UPDRS total, median (IQR)	14 (14)	39 (21)	<0.001	12 (19)	37.5 (13)	<0.001
5-item score (max 20), median (IQR)	1 (2)	4.5 (4)	<0.001	2 (2)	7 (3)	<0.001
Facial expression, median (IQR)	0 (0)	1 (2)	<0.001	0 (0.5)	2 (2)	<0.001
Rigidity, median (IQR)	0 (0)	1 (1.75)	<0.001	1 (1)	3 (1.25)	<0.001
Rest tremor, median (IQR)	0 (1)	1 (1.75)	0.068	0 (1)	0.5 (1)	0.242
Action tremor, median (IQR)	1 (0)	1 (0)	0.020	0 (1)	1 (1)	0.429
Bradykinesia, median (IQR)	0 (0)	1 (1)	<0.001	0 (0)	1 (1)	<0.001

P-D-: no clinical parkinsonism and normal [123I]FP-CIT SPECT. P+D+: clinical parkinsonism and abnormal [123I]FP-CIT SPECT. MMSE: Mini Mental State Examination. CIRS-G: Cumulative Illness Rating Scale for Geriatrics. MDS-UPDRS: Movement Disorders Society Unified Parkinson's disease Rating Scale Motor Sub-scale.
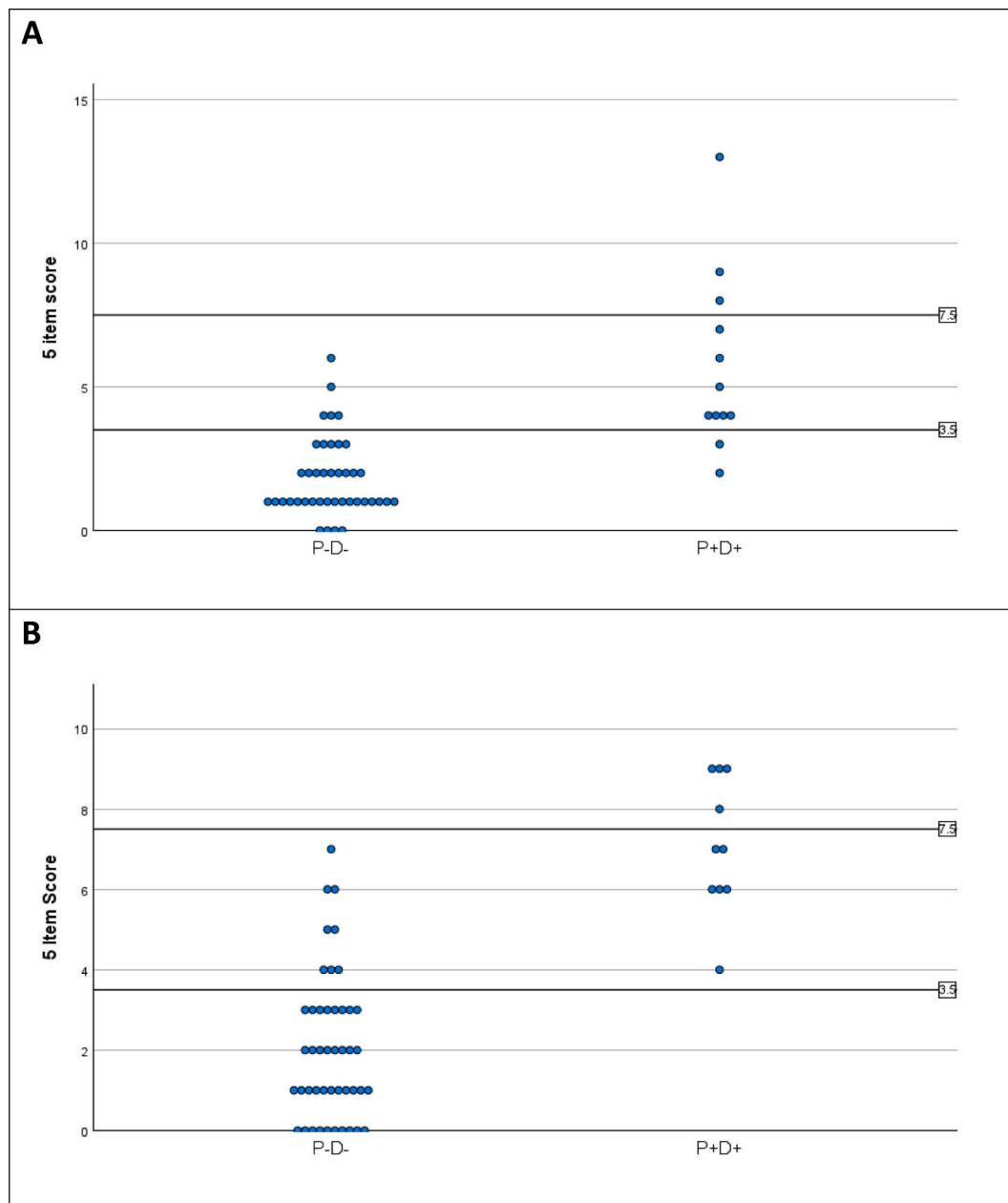
Fig. 1. Dot plots of five-item UPDRS scores in P+D+ and P—D— groups in Cohort 1 (A) and Cohort 2 (B). Reference lines of 3.5 and 7.5 added for illustration.

2.3. Secondary analysis

The demographics for the D+ and D- groups are displayed in Supplementary Table 1. The D+ group were more likely to be male. The five-item scale had an AUROC of 0.61 (95% CI 0.48–0.74) in Cohort 1 and an AUROC of 0.66 (95% CI 0.52–0.80) in Cohort 2 to differentiate D+ from D- participants. The 3.5 cut-off had a sensitivity of 42% and a specificity of 82% to identify D+ participants in both cohorts combined (Supplementary Fig. 1).

Given the poor discriminant ability of the five-item scale to discriminate between D+ and D- participants, a post-hoc analysis was carried out to investigate whether other UPDRS features could identify D+ participants. The AUROCs of all MDS-UPDRS items to identify D+ participants in Cohort 1 are displayed Supplementary Table 2. The five items with the highest AUROC were combined to make a sum score, to compare with the original five-item scale, these were: upper limb rigidity, finger tapping, pronation-supination movements, toe tapping

and global spontaneity of movement (Supplementary Table 2). The sum score of these five variables was tested in Cohort 2 to discriminate D+ from D- participants, but this sum score had a similar performance to the original five-item scale (AUROC 0.63, 95% CI 0.49–0.78).

2.4. Sex differences

Males were more likely than females to have an abnormal FP-CIT SPECT scan across both cohorts (Cohort 1: 23/42 (55%) v 6/33 (18%), $p = .001$; Cohort 2: 25/45 (56%) v 1/26 (4%), $p < .001$). Seven females had an abnormal FP-CIT SPECT across both cohorts, of which only one had clinically identified parkinsonism and none scored above the 3.5 cut-off on the five-item scale.

3. Discussion

This paper presents one of few cohorts worldwide in MCI with a

combination of standardised assessment for parkinsonian features, expert clinician determination of the presence or absence of parkinsonism and striatal dopaminergic imaging. We have demonstrated that a previously described five-item scale for parkinsonism in dementia can identify the presence of parkinsonism in MCI, but that parkinsonian signs are much milder in MCI and therefore a lower threshold is necessary at this disease stage.

The identification of early clinical parkinsonism is challenging in MCI. Mild motor signs, which may be suggestive of parkinsonism, are present in up to 46% of older adults, and this prevalence increases with age [9]. From our findings, there are two important points that should be considered by clinicians and researchers. Firstly, parkinsonism in MCI-LB is mild, as few participants with P+D+ met the previously described 7.5 threshold on the five-item scale. Secondly, patients without parkinsonism can have relatively high scores on the MDS-UPDRS, with median scores of 12 and 14 in the two cohorts in this study. The clinical and research implications of these findings are considered below.

3.1. Clinical implications

The five-item scale is not intended to replace clinical judgement. However, these five features may be useful to aid in the identification of parkinsonism in people with MCI in the clinic, where the full MDS-UPDRS is unlikely to be undertaken. In particular, in addition to the cardinal features of parkinsonism, the features of reduced facial expression and intention tremor should be considered by clinicians. Where patients score over the threshold of 3.5, further investigation could be considered if clinically indicated. In Cohort 2, 12/20 (60%) of those with a score over 3.5 had abnormal striatal dopaminergic imaging.

3.2. Research implications

Large-scale cohort studies have sought to identify parkinsonism based on the presence of features measured by the UPDRS [11]. This has led to relatively high estimates of parkinsonism in control groups. Features that may be associated with mild motor signs include vascular disease, diabetes, arthritis and essential tremor [9]. The 3.5 cut-off for the five-item scale had a specificity of >80%, which may be satisfactory for clinical populations, where the prior probability of parkinsonism is relatively high. However, for populations where the prior probability of parkinsonism is low (e.g. community populations), a higher threshold for inferring the presence of parkinsonism may be required. The limitations of this method in comparison to expert clinical judgement must be recognised.

3.3. Sex differences

Females were less likely to have a positive dopaminergic imaging and the vast majority of the P+D+ group was male. This is in keeping with higher rates of parkinsonism in males than females with DLB in a pathologically confirmed cohort [12], and later presentation of parkinsonism in females than males in DLB [3]. However, in the small number of females with reduced nigrostriatal dopaminergic innervation demonstrated by FP-CIT SPECT, clinical parkinsonism was generally not identified. This raises the possibility that the classical signs of parkinsonism are less likely to be present in females than males, even in the presence of neuronal loss in the nigrostriatal dopaminergic neurones. Few conclusions can be drawn from our data, due to the small number of females with abnormal FP-CIT SPECT scans, but this issue requires further research attention.

3.4. Strengths and limitations

This paper reports data from a well-characterised cohort with a comprehensive clinical assessment and striatal dopaminergic imaging.

Post-mortem cohorts represent the gold standard for validating clinical assessment, but there are few post-mortem cohorts in MCI-LB and these have small numbers of participants [2]. The original paper describing the five-item scale in dementia used a previous version of the UPDRS, but it was possible to extrapolate sores in the original scale from the MDS-UPDRS.

There is a degree of circularity in this analysis, as the UPDRS was considered when assigning the presence or absence of clinical parkinsonism. However, a key strength of the study is that the groups had biomarker confirmation of the presence or absence of striatal dopaminergic degeneration. As a secondary analysis, we investigated the effectiveness of the scale to identify participants with abnormal striatal dopaminergic imaging, without considering clinical parkinsonism. The five-item scale was less effective to discriminate between these groups and a post hoc analysis using all MDS-UPDRS items was unable to identify a set of features that could accurately discriminate between D+ and D- participants. However, this was expected, as it has been demonstrated that clinical symptoms of parkinsonism do not manifest until after there has been a significant amount of nigrostriatal dopaminergic degeneration, exceeding the amount of degeneration required for an abnormal striatal dopaminergic scan [10]. This is demonstrated by high rates of abnormal scans in cohorts of idiopathic REM sleep behaviour disorder without clinical parkinsonism [13]. As such, the D+ group would be expected to include participants without clinical parkinsonism. Neither the five-item scale or the wider UPDRS appear effective to identify subtle motor signs that may be present these participants.

These studies excluded people with clinical stroke, therefore, care must be used when considering if parkinsonism could be due to vascular disease.

4. Conclusion

Clinicians and researchers should be aware that parkinsonian signs are mild in MCI-LB. A five-item scale developed in dementia is effective to identify parkinsonism in MCI, but a lower threshold must be used in MCI compared with dementia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.122941.

CRediT authorship contribution statement

Rishira Fernando: Formal analysis, Writing – original draft, Investigation, Methodology, Writing – review & editing. **Alan J. Thomas:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Calum A. Hamilton:** Formal analysis, Investigation, Writing – review & editing. **Rory Durcan:** Investigation, Writing – review & editing. **Sally Barker:** Investigation, Writing – review & editing. **Joanna Ciafone:** Investigation, Writing – review & editing. **Nicola Barnett:** Investigation, Writing – review & editing. **Kirsty Olsen:** Investigation, Writing – review & editing. **Michael Firbank:** Conceptualization, Writing – review & editing. **Gemma Roberts:** Investigation, Writing – review & editing. **Jim Lloyd:** Conceptualization, Writing – review & editing. **George Petrides:** Investigation, Writing – review & editing. **Sean Colloby:** Investigation, Writing – review & editing. **Louise M. Allan:** Conceptualization, Writing – review & editing. **Ian G. McKeith:** Investigation, Writing – review & editing. **John T. O'Brien:** Conceptualization, Writing – review & editing. **John-Paul Taylor:** Conceptualization, Writing – review & editing. **Paul C. Donaghy:** Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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