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MOBILITY CAN'T TAKE A DAY OFF

People living with late-onset Pompe disease (LOPD) face obstacles that may challenge their well-being and livelihood. A 2011 Dutch survey of LOPD patients showed[1,2]:

40% (n=32/80) stopped working due to their disease

85% required support from more than 1 caregiver to help with household tasks such as cleaning and grocery shopping

As Pompe disease progresses, it can lead to irreversible loss of mobility, respiratory function, and ability to perform daily activities, as well as premature death.[3,4] In a 2007 international study[5]*:

42% of patients with LOPD depended on a wheelchair

46% required respiratory support

Regular evaluation is recommended in patients with Pompe disease to assess for disease progression and to understand the impact on daily activities and lifestyles.[3]

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*Mean disease duration of patients studied was 11 years.

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A cross-sectional study of memory and executive functions in patients with sporadic inclusion body myositis

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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BHR has received honoraria from Bial and Merck Group unrelated to this manuscript.

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ABSTRACT

Introduction: Sporadic inclusion body myositis (IBM) is a degenerative and inflammatory acquired myopathy characterised by muscle deposition of various proteins typically associated with Alzheimer’s disease and other neurodegenerative diseases. While cognitive impairment is not noted as a clinical feature of IBM, evidence is lacking. We aimed to investigate whether cognitive performance of patients with IBM differs from population norms, focussing on cognitive domains affected in early Alzheimer’s disease (memory, executive function), and to test whether disease duration and the level of disability of IBM are associated with cognitive function.

Methods: Twenty-four patients with IBM (mean [SD] age 62.0 [7.2] years; disease duration 9.6 [4.8] years) were assessed cross-sectionally on neuropsychological tests covering multiple cognitive domains, including the Preclinical Alzheimer Cognitive Composite (PACC). Performance was compared to published normative data adjusted for age, sex and education (National Alzheimer's Coordinating Center; N=3,268). Associations were examined between PACC score, disease duration and level of disability (assessed using the IBM Functional Rating Scale [IBMFRS]).

Results: Across all cognitive tests, group performance was within ±1SD of the normative mean. There was no evidence of associations between PACC score and either disease duration (ρ=-0.04, *p*=0.87) or IBMFRS total score (ρ=0.14, *p*=0.52).

Discussion: Memory and executive function in patients with IBM did not differ from normative data, and we observed no evidence of associations between the cognitive composite and disease duration or level of disability. This addresses a question frequently asked by patients, and will be of value for clinicians and patients alike.

Keywords: Inclusion Body Myositis; Neuromuscular; Muscle disease; Cognition; Neuropsychology

INTRODUCTION

Sporadic inclusion body myositis (IBM) is the commonest acquired myopathy in individuals over 50 years old[1]. It presents as an insidious onset of slowly progressive, often asymmetric, muscle weakness particularly affecting finger flexors and/or knee extensors, and may cause dysphagia. Muscle biopsy samples reveal inflammatory

and myopathic features as well as accumulation of various proteins typically associated with neurodegenerative diseases, such as β-amyloid$_{1-42}$, phospho-Tau, sequestosome-1 (p62) and TAR DNA-binding protein 43 (TDP-43). Such proteins are present in brain parenchyma of patients with Alzheimer's disease and frontotemporal dementia. In sporadic Alzheimer's disease, β-amyloid deposition is estimated to occur 1-2 decades before dementia onset[2].

IBM has been referred to as "Alzheimer's disease of the muscle"[3], based on the common aetiology of IBM and Alzheimer's disease in terms of the pathological proteins. There are two reported cases of simultaneous coexistence of IBM and Alzheimer's disease[4,5], raising the question of whether individuals with IBM are at increased risk of Alzheimer's disease. However, there was no pathological confirmation of Alzheimer's disease in either case, hence there remains uncertainty regarding the accuracy of the diagnosis, and the co-occurrence of IBM and Alzheimer's disease may be coincidental. Statistically, one may expect a prevalence of coexisting IBM and Alzheimer's disease of 0.1 per million. Cognitive impairment has not been documented as a clinical feature of IBM.

We aimed to investigate whether cognitive performance of patients with IBM differs from population norms, focussing on memory and executive functions as these are cognitive domains affected early in Alzheimer's disease[6,7], and to test whether disease duration and the level of disability of IBM are associated with cognitive function.

METHODS

Study Design

Participants were recruited from the longitudinal study "Natural History of Inclusion Body Myositis", for which the inclusion criteria were a diagnosis of IBM made by a neuromuscular expert and the fulfilment of established IBM classification criteria[8]. Invitations for an optional neuropsychological assessment at University College London (UCL) Centre for Neuromuscular Diseases were issued sequentially when patients attended clinic appointments and the neuropsychometrist was available. As this was a pilot study, the sample size was determined based on feasibility. All patients who declined to participate did so because of time constraints. The study was approved by the London – Bromley Research Ethics Committee (Reference:10/HO721/28). All participants provided written informed consent.

Physical disability assessment

IBM disease duration (since onset of symptoms) at the time of assessment was estimated based on clinical notes and patient reports.

The IBM Functional Rating Scale (IBMFRS)[9] was used to quantify the level of disability. This involves rating performance on ten daily activities from 0-4, where 0 represents severe disability and 4 represents normal functioning. Thus, lower IBMFRS score indicates greater disability (range of total score from 0 to 40).

Neuropsychological assessment

Participants completed a neuropsychological battery, administered by experienced neuropsychometrists, and based on the one used in the Alzheimer's Disease Neuroimaging Initiative[10]. See Supplemental material for a list of assessments included in the battery.

Data analysis

For all neuropsychological tests except the Rey Auditory and Verbal Learning Test (RAVLT), raw scores were converted to z-scores adjusted for age, sex, and education, using a normative calculator based on 3268 cognitively-normal older adults from the National Alzheimer's Coordinating Center[11]. For RAVLT, raw scores were converted to z-scores adjusted for age and sex, using a calculator based on published normative data (http://www.beaumont.ie/index.jsp?p=273&n=659). For each test, we examined the number of participants performing below the fifth percentile (a standard cut-off indicative of possible impairment on neuropsychological tests).

Preclinical Alzheimer Cognitive Composite (PACC) scores were calculated as the mean of four z-scores: Mini Mental State Examination (MMSE), Digit Symbol Substitution, Logical Memory Delayed, and RAVLT (total trials 1-5). The PACC captures cognitive performance across multiple domains in a single score that is sensitive to subtle cognitive deficits seen in preclinical Alzheimer's disease[6,12,13].

Spearman's correlation coefficient was used to test whether cognition (PACC score) was associated with disease duration and disability (total IBMFRS score). This non-parametric test was appropriate because of the skewed distributions of disease duration and disability. The PACC was selected for these correlation tests as we

considered it more appropriate to use a single composite measure rather than examining many correlations with multiple cognitive sub-tests, given the absence of evidence for a hypothesis about specific IBM-related deficits in any particular cognitive domain(s).

RESULTS

Of 35 patients invited, 27 accepted and were assessed between August 2016 and January 2020, of whom 3 were excluded from this analysis due to non-fluent level of English language which could affect the validity of neuropsychology scores. Participant (n = 24) demographic and clinical characteristics are reported in Table 1. Neuropsychology scores are presented in Table 1 and Figure 1.

Across the tested cognitive domains, scores were generally in the normal range with group mean adjusted z-scores within ±1 SD of the normative mean. The number of patients performing below the fifth percentile on each test was approximately as expected based on the sample size. Conversely, a number of participants scored above the ninety-fifth percentile on Digit Span backwards and Category Fluency. Out of the sixteen cognitive measures (listed in table 1), no individual performed below the fifth percentile on more than two of them (the numbers of participants with 0, 1 and 2 scores below the fifth percentile were 12, 5 and 7 respectively).

There were no statistically significant correlations between PACC and disease duration (Figure 2A) nor IBMFRS total score (Figure 2B).

DISCUSSION

Overall, we did not find evidence of cognitive impairment in people with IBM as group performance did not differ from normative data. Although there were some occasional low scores, this was not unexpected considering the number of different tests used. Four participants scored below the fifth percentile on the MMSE; however, due to the ceiling effect on this test, the fifth percentile cut-off does not correspond to a low raw score: for a 62-year-old male with 15 years of education (the average demographics of our sample), an MMSE score of ≤26/30 falls below the fifth percentile according to the normative data[11]. A commonly-used cut-off for normal cognitive function on this test is ≥24[14], and all of our participants scored above this threshold (minimum score 25). Furthermore, a number of participants demonstrated performance within or exceeding the high average range. Moreover, we found no evidence that longer IBM disease duration or greater disability were associated with poorer cognition.

There are several limitations of this study. The sample size (n=24) is relatively small, limited by the rarity of this condition[15]. We did not screen for depression[16] nor sleep disorders (which seem to be prevalent in IBM[17]); these may be confounding variables affecting cognitive performance and should be accounted for in future studies. While we did not correct for motor slowness, it was reassuring to observe that there were no correlations between the "handwriting" item from IBMFRS and performance on cognitive tasks with writing or drawing components (data not shown). As this is a convenience sample, there is a selection bias towards patients who are motivated to be proactively involved in research. As the current study was cross-sectional it might have missed the possibility of later development of cognitive impairment in the course of IBM, particularly in view of the younger mean age of onset in IBM relative

to Alzheimer's disease. However, the lack of association between IBM disease duration or physical disability and cognitive performance supports the absence of delayed onset of cognitive impairment. While the current study included a range of memory and executive function tests, it is possible that the test battery might have missed subtle deficits in other cognitive domains, so future studies would be beneficial to investigate any potential link between IBM and other cognitive domains that are affected in Alzheimer's disease and other dementias (e.g. visuoperception and social cognition).

CONCLUSION

This study did not elicit any evidence of significant cognitive deficits in the domains of memory or executive function in patients with IBM. Further longitudinal studies with larger sample sizes will be needed to consolidate the findings of this study.

ABBREVIATIONS

IBM = sporadic inclusion body myositis; IBMFRS = IBM Functional Rating Scale; MMSE = Mini Mental State Examination; PACC = Preclinical Alzheimer Cognitive Composite; RAVLT = Rey Auditory and Verbal Learning Test; TDP-43 = TAR DNA-binding protein 43 (TDP-43); UCL = University College London.

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FIGURE LEGENDS

Figure 1. Cognitive test scores in 24 patients with inclusion body myositis.

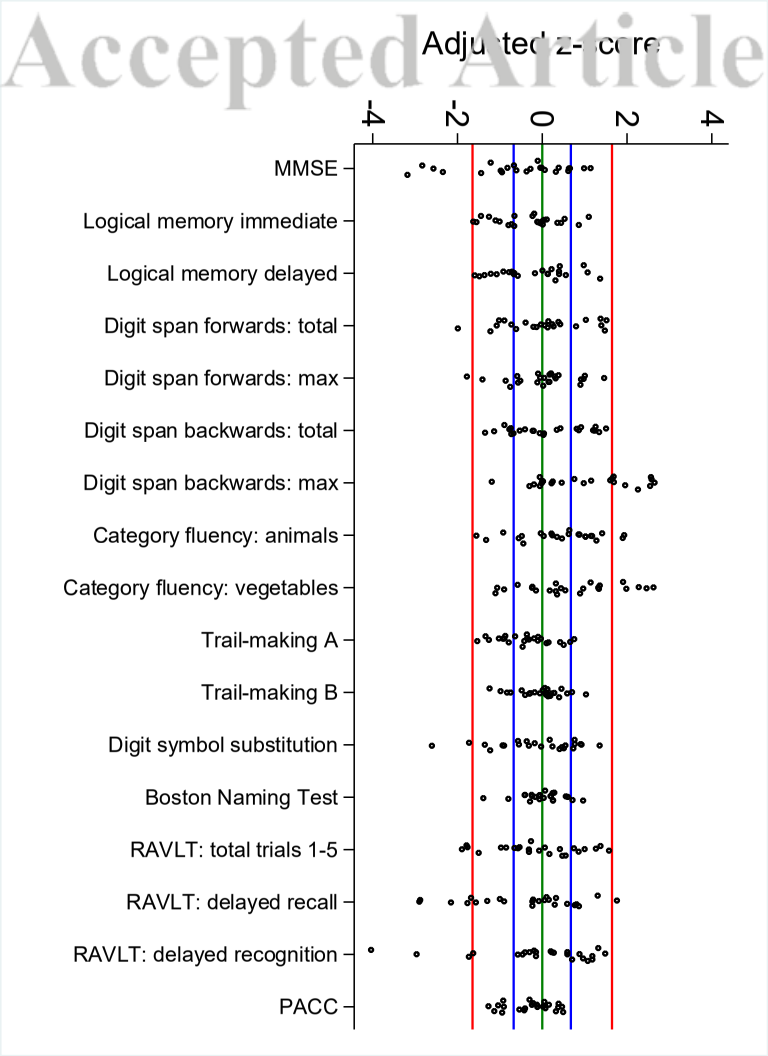
Markers show individual participants' scores for each test. Coloured lines correspond to the fifth and ninety-fifth percentiles (red), lower and upper quartiles (blue), and median (green) based on the published normative data.

MMSE = Mini Mental State Examination; PACC = Preclinical Alzheimer Cognitive Composite; RAVLT – Rey Auditory Verbal Learning Test

Figure 2. Associations between disease duration, clinical disability and cognition in 24 patients with inclusion body myositis.

Associations between (A) disease duration and cognition (PACC score) (ρ = -0.04, p = 0.87); (B) disability and cognition (ρ = 0.14, p = 0.52).

IBMFRS = IBM Functional Rating Scale; PACC = Preclinical Alzheimer Cognitive Composite



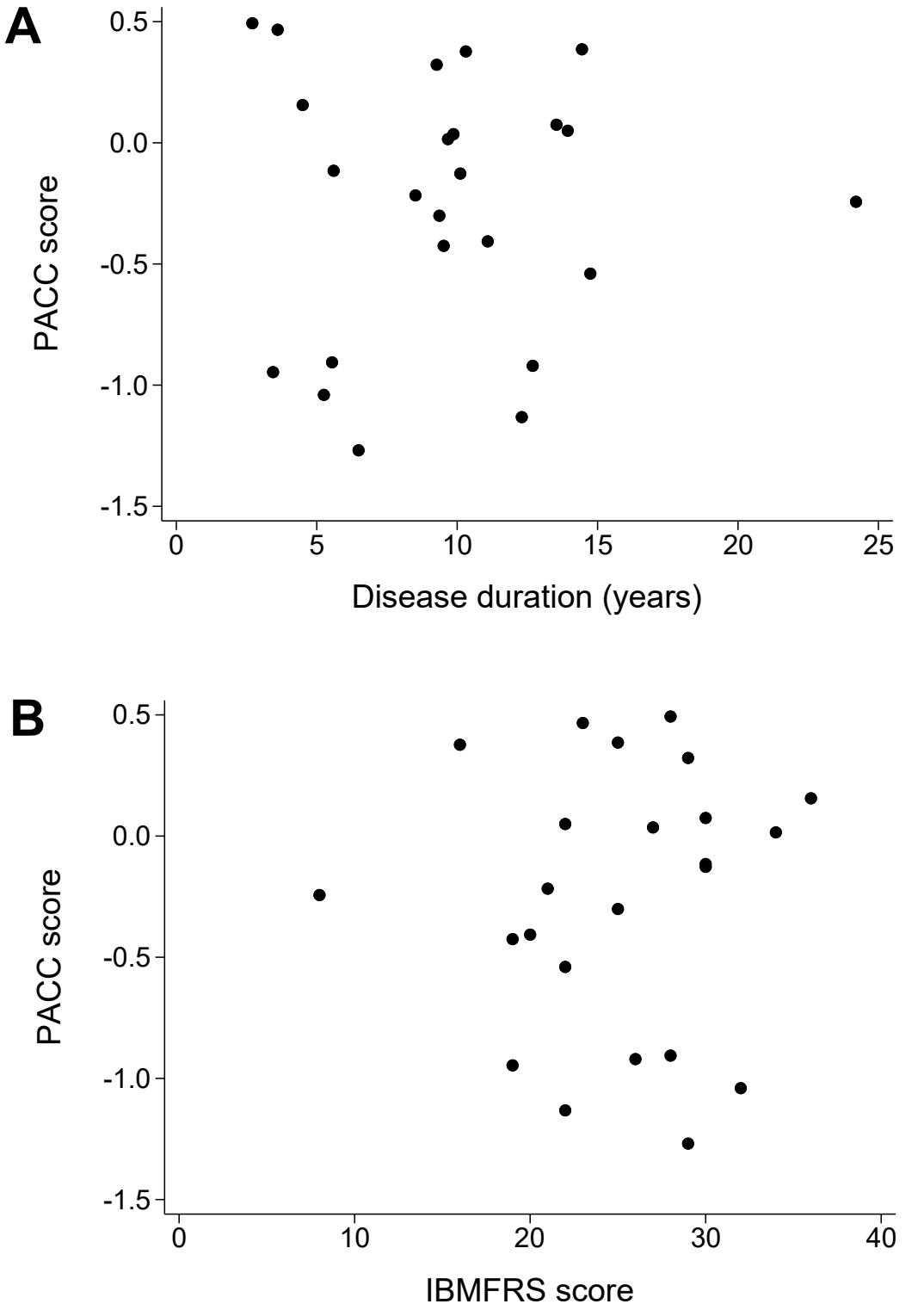

A
0.5
0.0
-0.5
-1.0
-1.5
PACC score
0
5
10
15
20
25
Disease duration (years)
B
0.5
0.0
-0.5
-1.0
-1.5
PACC score
0
10
20
30
40
IBMFRS score

Table 1. Participant characteristics and neuropsychological test scores (n = 24)

DEMOGRAPHIC AND CLINICAL VARIABLES			
Sex: m:f	16:8		
Handedness: right:left	19:5		
Years of education: mean (SD), *range*	14.7 (2.4), *11 – 18*		
Age at onset (years): mean (SD), *range*	52.4 (7.6), *42 – 68*		
Age at assessment (years): mean (SD), *range*	62.0 (7.2), *49 – 72*		
Disease duration (years): mean (SD), *range*	9.6 (4.8), *2 – 24*		
IBMFRS score: mean (SD), *range*	25.0 (6.2), *8 – 36*		
NEUROPSYCHOLOGICAL TEST SCORES: mean (SD), *range*			
	Raw score	**Adjusted *z*-score ***	**n below 5th percentile**
MMSE (/30)	27.9 (1.4), *25 – 30*	-0.6 (1.2), *-3.2 – 1.1*	4
Logical Memory Immediate (/25)	11.4 (2.9), *6 – 17*	-0.3 (0.8), *-1.6 – 1.1*	0
Logical Memory Delayed (/25)	10.3 (3.45), *5 – 17*	-0.2 (0.8), *-1.6 – 1.4*	0
Digit Span Forward (total correct) (/14)	8.9 (2.0), *5 – 12*	0.0 (0.9), *-2.0 – 1.5*	1
Digit Span Forward (max length)	6.8 (0.9), *5 – 8*	0.0 (0.8), *-1.8 – 1.5*	1
Digit Span Backward (total correct) (/12)	7.0 (2.0), *4 – 10*	0.1 (0.9), *-1.3 – 1.5*	0
Digit Span Backward (max length)	5.1 (1.2), *3 – 7*	1.0 (1.1), *-1.2 – 2.6*	0
Category Fluency (animals)	23.1 (5.4), *13 – 33*	0.4 (0.9), *-1.6 – 1.9*	0
Category Fluency (vegetables)	15.2 (3.7), *9 – 21*	0.7 (1.1), *-1.1 – 2.6*	0
Trail-Making A (time in seconds)	34.3 (7.7), *22 – 51*	-0.4 (0.6), *-1.5 – 0.8*	0
Trail-Making B (time in seconds)	75.3 (19.4), *49 – 126*	-0.0 (0.5), *-1.2 – 1.0*	0
Digit Symbol Substitution (/93)	47.6 (8.4), *27 – 64*	-0.1 (1.0), *-2.6 – 1.4*	2
Boston Naming Test (/30)	28.1 (1.5), *24 – 30*	0.0 (0.5), *-1.4 – 1.0*	0
RAVLT (total trials 1-5) (/75)	42.0 (8.5), *30 – 61*	-0.1 (1.0), *-1.9 – 1.6*	3
RAVLT (delayed recall) (/15)	6.9 (3.6), *0 – 12*	-0.4 (1.3), *-2.9 – 1.8*	5

RAVLT (delayed recognition) (/15)	11.3 (3.6), *1 – 15*	-0.1 (1.4), *-4.0 – 1.5*	3
PACC (mean of z-scores)	-0.3 (0.5), *-1.3 – 0.5*	N/A	N/A

* Adjusted for age, sex and education (except RAVLT which is adjusted for age and sex only) – see details in Methods. IBMFRS = Inclusion Body Myositis Functional Rating Scale; PACC = Preclinical Alzheimer Cognitive Composite; RAVLT = Rey Auditory Verbal Learning Test.