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RESEARCH ARTICLE

Upper limb movements in dementia with Lewy body: a quantitative analysis

Laura Fadda[1] · Federica Corona[2] · Gianluca Floris[3] · Marcello Mario Mascia[3] · Barbara Cossa[3] · Tommaso Ercoli[1] · Massimiliano Pau[2] · Giovanni Defazio[1]

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Abstract

Dementia with Lewy body is a neurodegenerative disorder affecting both cognitive and motor domains. Motor impairment manifests predominantly as a symmetrical/mild asymmetrical parkinsonian syndrome that is only mildly responsive to Levodopa. To characterize motor dysfunction in dementia with Lewy body, we quantitatively assessed upper limb movements using a motion-capture system. Ten patients and ten healthy controls were tested while performing the hand-to-mouth movement of which speed, smoothness and accuracy features were measured. The results showed that individuals with dementia with Lewy body required a longer time to complete the task, particularly due to a prolonged duration of the adjusting phase (i.e., when approaching the target/mouth). The overall motor performance of dementia with Lewy body patients closely resembled what previously observed in patients affected by both Parkinson's disease and ataxia while performing the same task. Moreover, the severity of parkinsonian symptoms as assessed by the UPDRS-III scale impacted on the velocity of movement alone whereas impairment of executive functions correlated with variables related to the phase of targeting the mouth. This study provides new information about upper limb motor dysfunction in dementia with Lewy body.

Keywords Dementia with Lewy bodies · Upper limb assessment · Quantitative analysis · Cerebellum

Introduction

Dementia with Lewy body (DLB) is a neurodegenerative disorder characterized by the deposition of aggregates of misfolded α-synuclein (α-syn) in the amygdala, transentorhinal and cingulate cortex, temporal, frontal and parietal cortex, and in the brainstem (9th and 10th cranial nerve nuclei, locus ceruleus, and substantia nigra) (McKeith et al. 2005). Consistent with neuropathology, DLB typically affects both cognitive and motor domains. Cognitive impairment is characterized by visuo-spatial and executive function deficit and is frequently associated with visual hallucinations and fluctuating cognition. Motor impairment usually manifests as a symmetrical/mild asymmetrical rigid-akinetic parkinsonian syndrome (McKeith et al. 2017).

Characterization of motor dysfunction in clinical practice is usually performed by subjective clinical scales that are often unable to detect subtle motor signs.

Recently, kinematic analysis of movement based on the use of motion-capture systems has been proposed as an objective and highly sensitive tool allowing quantitative assessment of motor performance (Corona et al. 2018a, b). Furthermore, this tool allows the detection of even minimal (yet clinically meaningful) alterations in the spatio-temporal and kinematic features of a functional task (Corona et al. 2018a, b). Different functional tasks, such as grasping, pointing and reaching may be used to perform a kinematic analysis of upper limb (UL) movements. One of these tasks, the "hand-to-mouth" (HTM) task, is a standardized functional task that simulates feeding (Corona et al. 2018a, b; Menegoni et al. 2009) and was found suitable to characterize UL motor dysfunction in several neurologic conditions like stroke, Parkinson's disease (PD) and ataxia (Corona et al. 2018a, b; Menegoni et al. 2009; Caimmi et al. 2008).

✉ Laura Fadda
fadda_laura@yahoo.it

[1] Department of Medical Sciences and Public Health, Section of Neurology, University of Cagliari, ss.554 km 4.500 09042 Monserrato, Cagliari, Italy

[2] Department of Mechanical, Chemical and Materials Engineering, University of Cagliari, Cagliari, Italy

[3] Department of Neurology, University Hospital of Cagliari, Cagliari, Italy

In stroke patients, kinematic analysis of UL movement was also used to assess functional recovery following constraint-induced movement therapy (Caimmi et al. 2008). In PD patients, the HTM movement was significantly altered in terms of reduced velocity, reduced range of motion of elbow flexion–extension, and deviation from a physiologic pattern (Corona et al. 2018a, b). Finally, ataxic patients showed increased adjustment during the last phase of the HTM movement which was less smooth than that in controls (Menegoni et al. 2009).

In the present study, kinematic analysis of the HTM task was performed to evaluate UL motor dysfunctions in DLB patients to assess whether, in this condition, UL motor abnormalities could be exclusively attributable to the nigrostriatal system or to a widespread functional impairment of additional systems contributing to motor performance.

Materials and methods

Participants

Participants were recruited among consecutive patients with DLB attending the outpatient department of the Neurology Unit of the Department of Medical Sciences and Public Health of the University of Cagliari, Italy. We included patients with a diagnosis of probable DLB according with published criteria (McKeith et al. 2017) who were capable to learn and execute the HTM task. Global cognition, executive functions, and the overall severity of dementia were assessed by the Mini-Mental State Examination (MMSE) (Magni et al. 1996), the frontal assessment battery (FAB) (Appollonio et al. 2005), and the Clinical Dementia Rating Scale (Morris 1993) respectively. The severity of parkinsonian motor symptoms was measured in the on state by the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) (Movement Disorder Society 2003). Gender- and age (± 5 years)-matched healthy relatives of non-demented and non-parkinsonian outpatients were included in the healthy control (HC) group. Assessors were unblinded to the case–control status because it may be difficult to blind a DLB patient to a HC subject. However, assessors were unaware of study hypotheses. The study was approved by the local Ethics Committee and conducted according to the Declaration of Helsinki. All participants signed a written informed consent.

Kinematic analysis

Kinematic analysis of HTM movement was performed by means of a 8-cameras motion-capture system (SMART-D, BTS Bioengineering, Italy) set at 120 Hz frequency. According to the protocol described by Rab et al. (2002) 19 passive markers (14 mm diameter) were placed on the participant's skin at specific superficial bony landmarks to identify the following segments: head, thorax, right and left arm, forearm and hand (Fig. 1). Participants comfortably sat on a seatback chair positioned in front of a table with their hand palms on the table and the elbows flexed at approximately 90° (Menegoni et al. 2009; Caimmi et al. 2008; Corona et al. 2018a, b; Mackey et al. 2005; Cimolin et al. 2012). Then, they were instructed to perform the HTM movement as follows: starting from the hand palms down on the table, participants were asked to reach and touch their mouth and then return to the initial position (Fig. 1); the task was repeated at least six times for each arm at a self-selected pace (Menegoni et al. 2009). Subjects were not asked to perform the HTM task as fast as possible but to execute the movement accurately.

Raw kinematic data were processed with a custom code developed in the Smart Analyzer environment (BTS Bioengineering, Milan, Italy). According to previous studies, the HTM movement was segmented into three phases (Menegoni et al. 2009; Mackey et al. 2005; Cimolin et al. 2012; Rigoldi et al. 2012) namely: the going phase (GP), during which the hand is moved to the mouth; the adjusting

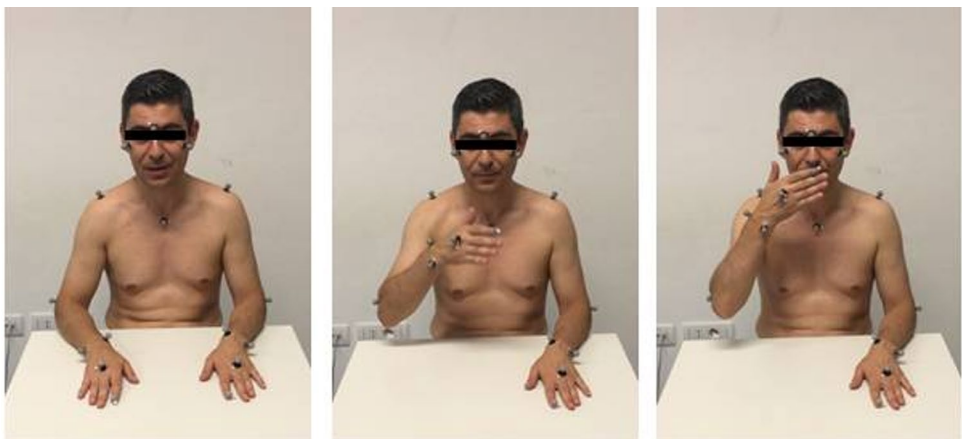

Fig. 1 Schematic representation of the hand-to-mouth movement task

phase (AP) during which the hand tries to precisely target the mouth; and the returning phase (RP), when the hand moves back to the initial position. The identification of the time events that differentiate the three phases was carried out on the basis of the fingernail marker velocity. In particular, the start of the GP was defined as point in time at which the linear velocity of the hand marker exceeded the 20% of the peak velocity (Carpinella et al. 2014) and, similarly, its end corresponded as the time in which the velocity dropped below 20% of the peak velocity. The same threshold was adopted to identify the RP so that the AP resulted as the time interval in which the fingernail marker velocity remained constantly below the 20% of the peak velocity value. The total time necessary to complete the HTM movement (expressed in s) as well as the duration of each phase (expressed as percentages of the total movement time) was computed. The accuracy of the movement in reaching the mouth was evaluated by calculating the adjusting sway (AS), which represents the 3D path length (expressed in mm) followed by the fingertip during the AP (Feng and Mak 1997; Quintern et al. 1999). A measure of the smoothness of the movement, namely the frequency of changes in direction of the hand trajectory (Hz), was also calculated (Menegoni et al. 2009; Quintern et al. 1999).

Statistical analysis

Data were expressed as mean and standard deviation (SD) unless otherwise indicated. Statistical analysis was performed using SPSS Statistics v.20 (IBM, Amonk, NY, USA). One-way multivariate analysis of variance (MANOVA) was used to detect possible differences between groups. The independent variable was the individual's status (DLB or HC), while the investigated kinematic parameters (i.e., total movement time, phases duration, adjusting sway, frequency of change in direction of the hand trajectory) were the dependent variables. The effect size was assessed using the eta-squared coefficient (η^2). For each dependent variable, follow-up analysis was performed using one-way ANOVA adjusting the level of significance by means of the Bonferroni correction. The existence of possible relationships between kinematic parameters of HTM task and UPDRS-III, MMSE and FAB scores were evaluated by Spearman's correlation analysis with a level of significance set at $p = 0.05$.

Results

Over an 8-month period, 10 DLB patients (7 men and 3 women aged 74.3 ± 3.5 years) and 10 HC subjects (7 men and 3 women aged 71.3 ± 7.6 years) were tested. The two groups did not significantly differ for sex and age. Two further DLB patients were excluded from the study because they were unable to perform the HTM task due to severe dementia (CDR = 4) and severe rheumatologic deformities in the UL. All subjects (DLB patients and HC) were right-handed.

Clinical characteristics of DLB patients are reported in Table 1. Parkinsonian signs were symmetric in five patients and mildly asymmetric in the remaining five cases. Mean UPDRS III total score was 33 (SD 12.3), and mean UPDRS III subscore summarizing the items related to bradykinesia (finger tapping, hand movements, rapid alternating movements of hands, and leg agility) was 13.1 (SD 5.50). As regard to general body bradykinesia and hypokinesia (item no. 31 of the UPDRS III), the mean values assigned to our DLB patients was 2.1 (SD 0.73). Mean MMSE score was 20.3 (SD 5.1), and mean FAB score was 7.2 (SD 3). Only

Table 1 Demographic and clinical characteristics of patients with Dementia with Lewy Bodies

Subject	Age (years)	Sex	Disease duration (years)	MMSE (adjusted for age and education)	FAB	CDR	UPDRS III total score	UPDRS III subscore for items 23–26	UPDRS III subscore for item 31	Levodopa treatment
S1	66	Men	4	15	6	2	30	13	3	Yes
S2	76	Women	3	22.3	11	2	34	16	2	Yes
S3	73	Men	10	24.4	8	2	21	8	2	Yes
S4	78	Men	4	27.3	11	2	21	10	2	No
S5	75	Men	2	16.7	1	2	27	14	2	No
S6	73	Women	2	23.4	8	2	61	26	3	No
S7	73	Men	5	22.7	9	1	25	14	1	Yes
S8	73	Women	3	13.3	6	2	29	14	2	No
S9	69	Men	2	13.9	4	2	16	6	1	Yes
S10	71	Men	5	24.6	8	2	29	10	3	Yes

MMSE mini-mental state examination, *FAB* frontal assessment battery, *CDR* clinical dementia rating, *UPDRS-III* Unified Parkinson's Disease Rating Scale—Part III, *UPDRS III subscores for item 23–26* items 23 (finger taps), item 24 (hand movement), item 25 (rapid alternating movements of hands), item 26 (leg agility); UPDRS III subscore for item 31: body bradykinesia and hypokinesia

6 out of 10 patients received levodopa (to which they were mildly responsive) at study time.

All participants successfully completed the HTM task as required. Table 2 summarizes the results of kinematic examination in DLB patients and HC subjects.

MANOVA revealed a significant main effect of the individual's status on HTM parameters [$F(7,32)=6.759$, $p<0.001$, Wilks $\lambda=0.403$, $\eta^2=0.597$]. In particular, follow-up analysis showed that individuals with DLB required a longer time than HC to complete either the HTM movement (2.5 ± 1 s vs. 1.3 ± 0.3 s, $p<0.001$) or each single phase (data not shown). Comparing GP, AP and RP in individuals with DLB yielded an increased duration of AP at the expenses of the other phases. Consistently, AS value was greater in DLB patients, thus suggesting that more adjustments were required to locate the target. By contrast, the frequency of directional changes did not significantly differ between DLB and HC groups (Table 2).

Table 2 Biomechanical parameters of the hand-to-mouth task in patients with Dementia with Lewy Bodies and healthy controls

	HC	DLB	*p* value
Total movement duration (s)	1.3 (0.3)	2.5 (1.0)	***< 0.001****
GP duration (%)	46.8 (3.2)	42.82 (8.6)	*0.063*
AP duration (%)	5.6 (5.2)	19.2 (8.9)	***< 0.001****
RP duration (%)	46.9 (4.6)	37.8 (6.7)	***< 0.001****
AS (mm)	2.2 (1.9)	17.2 (15.5)	***< 0.001****
Frequency of directional changes (Hz)	4.8 (1.2)	5.5 (0.7)	*0.025*

Values are expressed as mean (SD). The symbol "*" denotes significant difference vs. HC after Bonferroni correction ($p<0.007$)

HC healthy controls, *DLB* dementia with Lewy bodies, *GP* going phase, *AP* adjusting phase, *RP* returning phase, *AS* adjusting sway

Table 3 shows the results of correlation analysis performed between HTM parameters and clinical scores. Significant direct correlations were observed between total movement duration and UPDRS-III total score/UPDRS III subscore for item 31, between AS value and UPDRS III subscore for item 31, and between RP duration and MMSE score. Significant inverse correlations were found between FAB score and total movement duration, AP duration, and AS value.

Discussion

In this study we compared the performance of DLB patients and HC subjects in the HTM task, a standardized hand motor task typically performed during activities of daily living like feeding (Menegoni et al. 2009). The task was easy enough to be accomplished by all analyzed subjects and complex enough to highlight specific limitations from the pathology. Results showed that individuals with DLB required a longer time to complete the task. Segmentation of the movement's cycle into GP, AP and RP also revealed that DLB patients spent much more time during the AP of targeting the mouth, probably because they made more adjustments (as suggested by the greater AS value) and performed less smooth movement while reaching the mouth.

Overall, the kinematic profile showed by DLB patients was substantially similar to what previously described in cases of non-demented PD patients and in patients with cerebellar ataxia due to multiple sclerosis, spino-cerebellar ataxia and stroke while performing the HTM task (Corona et al. 2018a, b; Menegoni et al. 2009). This would suggest that shared brain abnormalities may account for the kinematic changes documented in these patients.

Table 3 Spearman's rank coefficients calculated for the correlation between HTM biomechanical parameters and clinical scores

	UPDRS-III	UPDRS III subscore for item 31	MMSE	FAB
Total movement duration (s)	**0.48**† ***p = 0.03***	**0.67**† **p = 0.001**	− 0.35 *p = 0.12*	**− 0.55**† ***p = 0.01***
GP duration (%)	− 0.10 *p = 0.66*	− 0.48 p = 0.048	− 0.38 *p = 0.09*	0.38 *p = 0.09*
AP duration (%)	0.05 *p = 0.81*	0.39 p = 0.08	0.11 *p = 0.64*	**− 0.49**† ***p = 0.02***
RP duration (%)	− 0.13 *p = 0.6*	− 0.10 p = 0.67	**0.48**† ***p = 0.03***	0.33 *p = 0.14*
AS (mm)	0.21 *p = 0.36*	**0.69** **p = 0.004**	− 0.13 p = 0.59	**− 0.64**† ***p = 0.002***
Frequency of directional changes (Hz)	− 0.004 *p = 0.98*	0.003 p = 0.99	0.31 p = 0,18	0.10 *p = 0.67*

Statistically significant correlations are in bold

UPDRS-III Unified Parkinson's Disease Rating Scale—Part III, *UPDRS III subscore for item no. 31* body bradykinesia and hypokinesia, *MMSE* mini-mental state examination, *FAB* frontal assessment battery, *GP* going phase, *AP* adjusting phase, *RP* returning phase, *AS* adjusting sway

The longer time required by our DLB patients to complete the task may well reflect the slowness of movement associated with parkinsonism. Even the difficulties in precisely locating the mouth might reflect dopamine depletion. Supporting this view, PD patients also spent more time than controls in performing the task (Corona et al. 2018a, b); moreover, when PD patients have to perform an accuracy task (as the precise localization of the mouth), they often show problems with implementation of precise motor commands (Alberts et al. 2000). However, the contribution of dopamine depletion secondary to disruption of the nigrostriatal system to the changes in the HTM task was not fully supported by correlation analysis showing that the severity of parkinsonian symptoms (as assessed by the UPDRS-III scale) in our DLB patients [and also in previously reported PD patients (Corona et al. 2018a, b)] significantly correlated with the velocity of movement but did not impact on variables related to the targeting phase of the HTM task (AP duration and AS value). The correlation we found between UPDRS III-item 31 subscore and AS value is reasonably justified by the general slowness and hesitancy of movement to which the item refers.

The results of correlation analysis raises the possibility of a role for abnormalities other than the disruption of the nigrostriatal system in the HTM task changes.

Troubles in regulating range, velocity, direction and rhythm of muscle contractions while reaching a target are typically associated with cerebellar ataxia due to multiple sclerosis, spino-cerebellar degeneration and stroke, conditions that displayed kinematic changes similar to those observed in DLB and PD patients (Menegoni et al. 2009) and that are usually associated with an intact nigrostriatal system. Indeed cerebellar manifestations may be common in conditions such as multiple system atrophy but have never been reported in other synucleinopathies like DLB and PD. Recently, however, the detection of α-syn pathology in the cerebellum of DLB and PD patients (Seidel et al. 2017), and the cerebellar involvement suggested by structural MRI investigations in DLB patients (Nakatsuka et al. 2013; Colloby et al. 2014) raised the possibility of a cerebellar contribution to the motor dysfunction characterizing DLB and PD patients.

Our analysis also revealed significant correlations between FAB score and both total movement duration and variables related to the phase of targeting the mouth (AP duration and AS value). This is a novel finding that, to date, has been assessed neither in PD nor in ataxic patients (Corona et al. 2018a, b; Menegoni et al. 2009). Providing specificity to the aforementioned observation, MMSE, a test assessing global cognition, did not correlate with most kinematic parameters. It is worth noting that the fronto-executive dysfunction revealed by FAB may be present in DLB and PD as well as in several forms of cerebellar ataxia (Lindsay and Storey 2017) and could, therefore, represent a shared abnormality that might account, at least in part, for the kinematic profile shared by these patients.

We could not exclude a possible influence of visuo-spatial deficits on motor performance in DLB patients. Visuo-spatial deficits, which are commonly reported in patients with DLB ad well as in PD and in subjects with cerebellar disorders, could affect the visual processing of the gesture. However, the HTM task was first explained verbally and then the subjects were asked to train it. This approach could have limited the influence of visuo-spatial deficits on motor performance.

Our study may have limitations. This was not a population-based study but recruiting criteria yielded a case series resembling the general population of cases in both demographic and clinical features. We included patients with relatively preserved cognitive and motor abilities and, therefore, our conclusions referred to non severe DLB. The results presented herein refer to a cross-sectional study carried out on a relatively small cohort of patients. Likewise, the lack of significant correlations between some kinematic parameters and motor/cognitive variables might merely reflect lack of statistical power. If so, then the strength of hypothetical associations would be lower than the strength of significant associations.

Despite the foregoing limitations, we were confident that our procedures probably yielded valid and accurate results and that this study provides new information about UL motor dysfunction in DLB patients raising the possibility of an intriguing contribution of cerebellum and fronto-executive function to DLB motor impairment. The relationship between executive dysfunction and motor performance in the HTM task is in line with a growing body of evidence suggesting that motor activities should no longer be considered as mere automated activities but as more complex tasks also requiring cognitive abilities (Amboni et al. 2013).

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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