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Cognitive and Neuropsychiatric Profile of the Synucleinopathies: Parkinson's Disease, Dementia with Lewy Bodies and Multiple System Atrophy

Aimee W. Kao, MD, PhD, **Caroline A. Racine, PhD**, **Lovingly C. Quitania, MA**, **Joel H. Kramer, PsyD**, **Chadwick W. Christine, MD**, and **Bruce L. Miller, MD**
Department of Neurology, University of California San Francisco, San Francisco, CA

Abstract

Parkinson's Disease (PD), multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB) share α-synuclein immunoreactivity [1]. These “synucleinopathies” have overlapping signs and symptoms, but less is known about similarities and differences in their cognitive and neuropsychiatric profiles. We compared the cognitive and neuropsychiatric profiles of individuals with PD, MSA and DLB. Overall, the DLB group showed the most cognitive impairment, the MSA group demonstrated milder impairment and the PD group was the least cognitively impaired. The DLB and MSA groups showed worse executive function and visuospatial skills than PD, while DLB showed impaired memory relative to both PD and MSA. On the neuropsychiatric screening, all groups endorsed depression and anxiety; the DLB group alone endorsed delusions and disinhibition. Consistent with their greater level of cognitive and neuropsychiatric impairment, the DLB group showed the greatest amount of functional impairment on a measure of instrumental ADLs (FAQ). We found that MSA subjects had cognitive difficulties that fell between the mild deficits of the PD group and the more severe deficits of the DLB group. PD, MSA and DLB groups have similar neuropsychiatric profiles of increased depression and anxiety. Similar underlying α-synuclein pathology may contribute to these shared features.

Keywords

Parkinson's Disease; Dementia with Lewy Bodies; multiple system atrophy; dementia; alpha-synuclein

INTRODUCTION

Parkinson's Disease (PD), multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB) share overlapping clinical features of parkinsonism and underlying α-synuclein immunoreactivity [1]. Collectively, these diseases are known as the “synucleinopathies.” Shared α-synuclein inclusions suggests that modifications in this potentially toxic protein could contribute to disease pathogenesis. Despite their molecular similarities, the synucleinopathies manifest clinically in distinctive ways. Of the three, PD is felt to be the closest to a pure motor syndrome with the cardinal features of resting tremor, rigidity and bradykinesia [2]. MSA patients develop early autonomic symptoms, pyramidal signs and poor response to dopaminergic agents and can be further sub-divided into individuals with a preponderance of parkinsonian signs

Corresponding Author: Aimee W. Kao, M.D., Ph.D. UCSF Memory and Aging Center 350 Parnassus Ave. Suite 706 San Francisco, CA 94143 Ph: (415) 713-0145 Fax: (415) 476-4800 akao@memory.ucsf.edu.

Non-standard character key: α-synuclein—alpha-synuclein

(MSA-P) and those with primarily cerebellar signs (MSA-C) [3]. DLB is characterized by fluctuating cognitive impairment, parkinsonian features and hallucinations [4]. REM sleep behavior disorder is recognized as being common to all three of these synucleinopathies [5].

Multiple factors likely contribute to the differences in clinical symptomatology seen between PD, DLB and MSA. Despite the fact that PD, DLB and MSA patients all exhibit α-synuclein pathology in the brain, the regions and structures that are affected vary markedly between the disorders, especially early in disease. In PD, Lewy bodies and neurites are found early in the deep brainstem and substantia nigra [6]. Conversely, paralimbic and neocortical structures are affected early in DLB [7]. Finally, in MSA deep brainstem, cerebellar nuclei, striatal and basal ganglia regions show α-synuclein staining [8, 9]. In addition, the primary cell type with α-synuclein immunoreactivity differs between the synucleinopathies. Neurons are affected in PD and DLB while in MSA both neuronal intranuclear inclusions and glial cytoplasmic inclusions are found [10].

As a result of this regional variability, one would expect distinctive patterns of cognitive impairment in the synucleinopathies. Indeed, all three have been shown in neuropsychological batteries to have varying degrees of cognitive dysfunction localized primarily to the executive and visuospatial domains [11, 12]. Recognition of the patterns of cognitive and neuropsychiatric dysfunction in these diseases could contribute to increased diagnostic accuracy and improved targeting of symptoms for treatment.

METHODS

Subjects

Twelve MSA patients were recruited through either the University of California San Francisco (UCSF) Movement Disorders Clinic or the UCSF Memory and Aging Center from November 2004 through November 2006. They were then matched for age, gender, education and disease duration (from time of first motor or cognitive symptom) with fourteen PD and fourteen DLB patients. A neurologist administered a detailed history and neurological exam to each subject. At least two neurologists reviewed each case to determine if consensus criteria were met prior to entry into the study. Probable PD, DLB or MSA was diagnosed according to established criteria [3, 4, 13, 14]. Informed consent was obtained from all subjects.

Neuropsychological testing

General intellectual function was assessed using the Mini-Mental State Exam (MMSE) [15]. Tests of executive function include the modified Trails B, a visuomotor set shifting and sequencing task [16, 17], the Stroop interference task [18] which assesses response inhibition, and trial 1 of the Design Fluency subtest of the Delis-Kaplan Executive Functions Scale [19]. The modified Trails B task required participants to draw lines switching back and forth between numbers and days of the week (i.e. 1-Sunday-2-Monday...) as quickly as possible [17]. Backward digit span was used to assess working memory. Ability to perform five written arithmetic calculations was also assessed. The M's and N's task was used to assess perseverative tendencies [17]. Participants were required to write a series of ‘m n m n...’ in cursive across an 8.5 × 11 inch page with the score reflecting the number of perseverations within the series (i.e. 0=none, 1=1 perseveration). The California Verbal Learning Test—SF [20 21] was used to evaluate verbal episodic memory and a modified (simpler) version of the Rey-Osterrieth complex figure with a 10 minute free-recall delay trial was used to evaluate non-verbal episodic memory [17]. Language assessment included the abbreviated (15 item) Boston Naming Test [22], repetition, semantic fluency (animals in one minute) and phonemic fluency (D-words in one minute). Visuospatial testing included copying the modified Rey-Osterrieth figure and localizing numbers on the visual object and spatial perception battery (VOSP) [23, 24]. Mood was assessed

using the Geriatric Depression Scale [25]. The Functional Activities Questionnaire (FAQ) was used to score degree of independence in activities of daily living [26] and the neuropsychiatric inventory (NPI) was used to assess behavioral and psychiatric symptoms [27]. The FAQ and NPI were completed by the patient's spouse or primary caregiver.

Statistical Analysis

Due to non-normal distribution of all neuropsychological variables and small numbers of subjects, we elected to use non-parametric statistical analysis to compare diagnostic groups. We compared all neuropsychological variables (Table II) between groups using Kruskal-Wallis tests. We identified significant group differences, controlling for multiple tests, using the false discovery rate (FDR) method [28]. Significant group effects were then examined further with post-hoc Mann-Whitney tests. For the NPI (Table III), the effect of diagnosis on the presence or absence of symptoms was examined using Chi-Square tests. Specific statistical results are presented in Tables II and III.

RESULTS

Demographics

Study subjects were matched for age, gender, education, disease duration (from first symptom to the time of neuropsychological evaluation). Subjects were selected with MMSE scores >23 in order to recruit a DLB cohort with more mild cognitive difficulties. Eleven of the 14 DLB patients met criteria for dementia based on the DSM-IV [29]. None of the PD or MSA patients met DMS-IV criteria for dementia. Characteristics of subjects are shown in Table 1. Ten of fourteen PD patients, two of twelve MSA patients and nine of fourteen DLB patients were receiving dopaminergic medications (levodopa and/or a dopamine agonists). One PD and one MSA patient were being treated with a cholinesterase inhibitor while nine of the DLB patients were treated with this class of medication. Five from each disease grouping were on a selective serotonin reuptake inhibitor. One MSA patient and three DLB patients were being treated with an atypical anti-psychotic drug. Two PD patients were being treated with anti-cholinergic agents.

Clinical Neuropsychological Tests

The means and standard deviations for results of the cognitive battery administered to subjects are presented in Table II and detailed below. A sub-group analysis was performed on MSA subjects and no significant differences were found between those classified as MSA-P (N=7) versus MSA-C (N=5) (data not shown.)

Executive function—Across all executive function tasks, the DLB group tended to show the most impairment, the PD group showed the least impairment, and the MSA group fell between DLB and PD subjects. On the modified Trails task, the MSA and DLB subjects took longer to complete the task and made more errors than the PD subjects. For PD patients, there was no significant difference in scores on the modified Trails task between those individuals that were receiving treatment with a dopaminergic agent and those that were not. The DLB subjects showed a reduced number of correct lines relative to the other groups. On a task of design fluency, MSA and DLB subjects both showed a reduction in the number of correct designs relative to PD subjects; however there was no significant difference in the number of errors between the groups. Although the pattern of DLB<MSA<PD was also apparent on a response inhibition task (Stroop Interference), only DLB subjects showed significantly worse performance relative to MSA and PD subjects. Both the MSA and DLB group tended to make more perseverations on the “m's and n's” task relative to the PD group. There were no significant group differences on a working memory test (Backwards Digit Span).

Visuospatial function—On a test of visuospatial abilities, the MSA and DLB group again performed significantly worse than those with PD as evidenced by scores for copying the modified Rey figure. Although DLB subjects had a tendency to perform more poorly than MSA and PD subjects on a spatial location task (VOSP: number location), this was not significantly different after correction for multiple comparisons.

Language—Consistent with previous reports suggesting only mild language impairment in PD, MSA and DLB subjects [30, 31], the groups performed equally well on tests of sentence repetition, object naming (15 item Boston Naming Test) and lexical fluency (D word generation.) However, both MSA and DLB groups exhibited decreased semantic fluency (animals generation) compared to PD.

Memory—The California Verbal Learning Test (CVLT-SF) was used to assess verbal learning. The DLB group performed worse than PD and MSA groups on ability to encode words over 4 learning trials and also recalled fewer words after 10 minutes. There was also a trend for the DLB subjects to have worse recall at 30 seconds compared to the other groups. Recognition did not differ between the groups for number of words correctly recognized, however the DLB subjects endorsed more false positives than MSA or PD subjects. There was no statistical difference between groups in visuospatial learning as assessed by recall of the modified Rey figure. In summary, DLB subjects showed relatively greater memory impairment in comparison to MSA and PD subjects, with decreased verbal learning and recall and a tendency to make false positive responses during a recognition task.

Other—On the FAQ, DLB subjects demonstrated the most functional impairment relative to MSA and PD subjects. On the GDS, all groups demonstrated depressive symptoms with no difference between groups.

Neuropsychiatric Symptoms

The prevalence of symptoms from the neuropsychiatric inventory (NPI) when administered to subjects' caregivers are presented in Table III and detailed below. Overall, DLB showed the most evidence of neuropsychiatric disturbance on the NPI, with the exception of numerically higher rates of anxiety and sleep disturbance in PD subjects. Consistent with the GDS findings, all groups showed high rates of depression; however, there was a trend for depression to be more frequent in PD (87.5%) and DLB (91.7%) relative to MSA (50%). Those with DLB (41.7%) showed significantly higher rates of disinhibition relative to those with MSA (10%) and PD (0%). Only individuals with DLB showed symptoms of delusions (41.7%). Some individuals in all groups had hallucinations. Although these were most frequent in DLB (41.7%), the group differences were not significant (MSA: 20%; PD: 12.5%). Anxiety was quite high across all groups (DLB: 58.3%, MSA: 33.3%, PD: 62.5%). Other symptoms that were elevated across all groups included agitation, apathy, irritability, repetitive motor behavior, sleep disturbance and eating changes (see table III).

DISCUSSION

Differentiation between PD, DLB and MSA continues to be a problematic diagnostic dilemma. This study compared these groups based upon their neuropsychological and neuropsychiatric profiles. Overall, on test of cognitive ability, the PD subjects demonstrated the least impairment and the DLB subjects exhibited the most impairment. Despite the perception that MSA tends to spare cognition, the MSA group consistently performed in an intermediate level between the PD and DLB group.

Significant differences between groups were found in tests of executive function. In particular, the DLB and MSA subjects performed worse than PD subjects on tasks that rely heavily on visuospatial processing functions (modified Trails and design fluency). DLB subjects also demonstrated slower processing speed, decreased generation and increased errors relative to both MSA and PD, consistent with previous research suggesting that DLB subjects show significant impairment in frontal-subcortical executive abilities [32, 33]. Tests of executive function on which there were no significant differences between PD, MSA and DLB (backward digit span and letter fluency) tended to involve language, rather than visuospatial frontal cortical and subcortical systems.

Results from language testing were notable for relative sparing of sentence repetition and object naming across all groups. However, both DLB and MSA subjects showed decreased semantic fluency relative to PD subjects. Consistent with previous research suggesting that DLB is associated with specific impairment in visuospatial skills [34], we found that DLB subjects had more difficulty copying a complex figure and on a spatial location task. Again, the MSA group tended to show scores between PD and DLB groups on visuospatial tasks.

Interestingly, some of the most significant cognitive discrepancies were found on tasks of memory. Although all groups demonstrated reductions in visuospatial memory, DLB tended to have the worst performance. Additionally, on a verbal learning task, the DLB group had greater impairment both encoding and retrieving information and made more false positive responses on a recognition task. These findings are not unexpected given that Lewy bodies and neurites have been found in the hippocampus at pathology in DLB [35, 36]. Furthermore, Alzheimer's Disease (AD) and DLB pathology frequently occur together and memory is further impaired in individuals with combined pathology [34]. Not surprisingly, the degree of functional impairment was most severe in DLB and least severe in PD, which is consistent with the higher observed rates of cognitive impairment and of some neuropsychiatric symptoms in DLB.

DLB is known to manifest with neuropsychiatric symptoms, particularly hallucinations and delusions [4]. Depression is associated with PD and DLB [12]. In our study, caregivers reported high rates of depression on the GDS in all three groups (PD = 87.5%, MSA = 50% and DLB = 91.7%). Prominent anxiety was also notable across all groups. Anxiety is known to be found in PD [12, 37]; we show that it is also seen in MSA and DLB. Although less frequent, other neuropsychiatric symptoms, including apathy, irritability, sleep disturbance, and eating problems were also present across all three groups. Although limited by low numbers of subjects, the GDS and NPI results suggest that these α-synuclein disorders share similar neuropsychiatric features, most notably depression and anxiety, which suggests that these symptoms should be monitored and targeted interventions applied when clinically warranted. Future studies are needed to understand whether similar underlying α-synuclein pathology is responsible for the depression and anxiety observed in all three groups and how differential pathology may contribute to the hallucinations and delusions of DLB.

Unfortunately, we did not collect UPDRS data for the DLB or MSA patients in our study at the time of enrollment. However, subjects were excluded if the examiner felt the neuropsychological data collected was unreliable because of motor slowing. The PD patients would be most likely to have lower test scores due to motor impairment. However, on the Trails, Design Fluency and Rey copy tests, which require relatively more motor coordination, they scored the best compared to other groups. This is consistent with the findings on many of the other tests in which inter-group differences were noted.

Lack of pathological confirmation of the clinical diagnosis represents a potential limitation of this study. However, we employed the most recent clinical consensus criteria available at the time of the study for each disorder which, in autopsy series, are estimated to have an accuracy

of seventy to ninety-five percent [38, 39]. New consensus criteria have since been published for MSA [14]. A review of the MSA patients using the new criteria did not result in any change of classification. The most likely confounding factor is the presence of two neurodegenerative conditions, such as DLB and AD, occurring simultaneously in the same subject. Since concurrent AD would tend to lower MMSE scores, we have tried to minimize this possibility by selecting DLB subjects with relatively high MMSE scores compared to the general population of DLB patients. Nonetheless, pathological verification of the clinical diagnosis is important for definitive classification of disease characteristics, thus the participants of this study will be followed to autopsy. Additional confounds that could drive inter-group differences include medication treatment (differential use of dopaminergic agents, cholinesterase inhibitors, anti-psychotics), gender, disease duration, and differences in numbers of patients meeting criteria for dementia based on the DSM-IV. An inability to detect differences between MSA-P and MSA-C subgroups may be due to low numbers of test subjects. Although group differences remained significant after corrections for multiple comparisons, we acknowledge that our sample is small and use of FDR correction can result in Type I error. Thus, our findings deserve additional study and replication.

Despite sharing α-synuclein immunoreactivity in the brain, PD, MSA and DLB exhibit distinctive profiles of cognitive impairment that are may be related to differential regional sensitivity to the toxic effects of α-synuclein or some other factor. Some scientists now believe that formation of pathological inclusions such as Lewy Bodies represents a protective mechanism that cells use to sequester away toxic proteins [40]. Thus, it may be soluble forms of α-synuclein, that are not easily visualized on autopsy samples, are responsible for the differences found in this study. Mutations in α-synuclein are responsible for some forms of familial PD [41]; whether changes in α-synuclein will be found to causal for sporadic PD, DLB and MSA remains to be seen. However, their distinctive clinical signs and cognitive profiles in the setting of common α-synuclein immunoreactivity suggests further avenues in which to study the intriguing problem of selective neuronal vulnerability.

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Table I

Characteristics of subjects with Parkinsons Disease (PD), multiple system atrophy (MSA) or dementia with Lewy Bodies (DLB). Values are expressed as mean +/- standard deviation where applicable. P –values are shown for those characteristics by which subjects were matched.

	PD	MSA	DLB	P-value
N	14	12	14	
Sex (F/M)	4/10	5/7	4/10	0.12
Age (years)	65 ± 6.7	66.9 ± 11.3	70 ± 7.5	0.34
Education (years)	17.9 ± 2.8	15.9 ±2.8	16.6 ± 2.8	0.34
Disease duration (years)	4.1 ± 3.5	5.4 ± 3.6	5.7 ± 3.5	0.54
Handedness (R/L)	11/2	12/0	14/0	
Dopaminergic agent total (n)	10	2	9	
L-DOPA	9	2	8	
Dopamine Receptor agonist	8	1	1	
Amantadine	1	0	1	
Cholinesterase inhibitor (n)	1	1	9	
Anti-depressant (n)	5	5	5	
Anti-psychotic (n)	0	1	3	
Anti-cholinergic agent	2	0	0	

Table II

Results of cognitive testing comparing PD, MSA and DLB groups. Values shown are mean +/- standard deviation. Maximum score is shown in ( ) where applicable. Tests with significant group differences have p-value shown. (n.s. not significant). Post-hoc tests were performed after correction for multiple comparisons (*p<.05; **p<.01; ***p<.001). # The VOSP number location test scores were not significantly different between groups after correction for multiple comparisons.

	PD	MSA	DLB	Group effect	Posthoc tests
MMSE (30)	28.8 ± 1.4	27.3 ± 2.5	27.0 ± 1.7	p =.027	DLB<PD*
ModTrails: Time (120”)	50.3” ± 19.7	85.5” ± 25.3	100.3” ± 35.2	p =.001	MSA>PD***, DLB>PD***
ModTrails: # Correct (14)	14.0 ± 0.0	12.1 ± 4.0	7.6 ± 5.7	p =.002	DLB<MSA*; DLB<PD***
ModTrails: # Errors	0.3 ± 0.5	1.3 ± 1.1	1.4 ± 1.2	p =.023	MSA>PD*; DLB>PD*
Design Fluency: # Correct	10.3 ± 3.6	7.1 ± 2.0	5.1 ± 2.8	p =.003	MSA<PD*; DLB<PD***
Design Fluency: # Errors	2.6 ± 2.8	2.3 ± 1.9	1.4 ± 1.3	n.s.	
Stroop Interference: # Correct	44.5 ± 14.6	31.9 ± 11.1	20.5 ± 14.3	p =.001	DLB<MSA*; DLB<PD***
Stroop Interference: # Errors	1.1 ± 1.4	1.1 ± 2.2	2.3 ± 2.5	n.s.	
Digits Backward (Span)	4.7 ± 1.2	4.1 ± 1.5	3.9 ± 1.4	n.s.	
CVLT-SF: Learning (36)	24.9 ± 6.9	24.1 ± 3.8	17.3 ± 4.8	p =.006	DLB<MSA***; DLB<PD*
CVLT-SF: 30” Recall (9)	6.0 ± 2.2	6.4 ± 2.0	4.3 ± 2.2	n.s.	
CVLT-SF: 10’ Recall (9)	5.9 ± 2.3	5.5 ± 2.2	3.4 ± 1.7	p =.015	DLB<MSA*; DLB<PD*
CVLT-SF: Recog. (9)	8.3 ± 0.8	8.1 ± 1.0	7.6 ± 1.9	n.s.	
CVLT-SF: Recog. False +	0.6 ± 0.8	0.4 ± 0.8	2.6 ± 2.3	p =.007	MSA<DLB***; PD<DLB*
ModRey: Copy (17)	15.6 ± 1.0	13.4 ± 2.1	13.9 ± 2.3	p =.014	MSA<PD***; DLB<PD*
ModRey: Recall (17)	9.2 ± 4.4	8.7 ± 2.4	6.8 ± 3.6	n.s.	
VOSP: Number Location	9.0 ± 0.9	8.6 ± 2.8	7.4 ± 2.8	p =.043#	
M's & N's (2)	0.5 ± 0.9	1.3 ± 0.9	1.5 ± 0.9	p =.020	MSA>PD*; DLB>PD*
Sentence Repetition (3)	2.5 ± 1.0	3.0 ± 0.8	2.7 ± 0.6	n.s.	
D words: # Correct	14.9 ± 6.7	10.0 ± 3.5	10.1 ± 5.5	n.s.	
Animals: # Correct	19.2 ± 5.8	12.9 ± 4.7	11.1 ± 5.4	p =.003	MSA<PD***; DLB<PD***
15-Item BNT: # Correct	14.2 ± 1.2	13.5 ± 1.6	14.1 ± 1.1	n.s.	
FAQ	3.8 ± 4.1	7.0 ± 5.2	16.9 ± 7.9	p =.001	MSA<DLB***;PD<DLB***
GDS	11.9 ± 7.4	14.9 ± 5.7	11.3 ± 7.6	n.s.	

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Table III

Neuropsychiatric Profile of PD, MSA and DLB subjects. Results are expressed as percent of subjects that endorsed a particular symptoms. Mean total score is expressed as an absolute value out of a total of 144 +/- standard deviation.

	PD (n=8)	MSA (n=10)	DLB (n=12)	Results
Delusions	0	0	41.7	$\chi^2(2)=9.0$ (p=0.01)
Hallucinations	12.5	20	41.7	$\chi^2(2)=2.4$ (p=0.28)
Agitation	25	10	50	$\chi^2(2)=4.3$ (p=0.12)
Depression	87.5	50	91.7	$\chi^2(2)=6.0$ (p=.05)
Anxiety	62.5	33.3	58.3	$\chi^2(2)=1.8$ (p=0.41)
Euphoria	0	0	0	n/a
Apathy	37.5	40	66.7	$\chi^2(2)=2.2$ (p=0.33)
Disinhibition	0	10	41.7	$\chi^2(2)=6.2$ (p=0.05)
Irritability	37.5	20	50	$\chi^2(2)=2.1$ (p=0.35)
Motor	25	20	25	$\chi^2(2)=0.1$ (p=0.95)
Sleep	62.5	40	50	$\chi^2(2)=0.9$ (p=0.64)
Eating	37.5	30	50	$\chi^2(2)=0.9$ (p=0.63)