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Neurological, Cognitive, and Clinical Biomarkers of Lewy Body Dementia Subtypes: A Literature Review

Muhammad A. Ansar, HBSc Student [1]†, Tanveer S. Soni, HBSc Student [2]†*

[1] Department of Psychology, University of Toronto Scarborough, Scarborough, Ontario, Canada M1C 1A4
[2] Department of Biological Sciences, University of Toronto Scarborough, Scarborough, Ontario, Canada M1C 1A4
† These authors contributed equally to this work.

*Corresponding Author: tanveer.soni@mail.utoronto.ca

Abstract

Introduction: Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are two subtypes of Lewy body dementia (LBD) that share many clinical features such as visual hallucinations, cognitive impairment, and parkinsonism. Despite these similarities, both DLB and PDD can vary in the severity, frequency and onset of these symptoms. Therefore, a differential diagnosis between the two subtypes is needed to optimize symptom management and patient care. Today, the fundamental difference between DLB and PDD is based upon the chronological sequence of motor and cognitive deficits and their onset. In DLB, cognitive deficits precede parkinsonian motor symptoms by one year, whereas PDD is diagnosed when cognitive deficits develop after motor impairments (known as the "1-year rule"). Besides this "1-year rule", current research has shown subtle, yet unclear, differences that could help distinguish between these two subtypes. Therefore, this literature review will examine and summarize neurological, cognitive, and clinical differences between DLB and PDD.

Methods: Informed by three databases, a literature search for peer-reviewed, empirical studies was conducted. In total, eight articles were examined for this review that directly compared a DLB clinical group with a PDD group.

Results: Neuroanatomical differences in cortical atrophy, cerebral angiopathy, functional connectivity, fluid biomarkers overlapping with Alzheimer's disease, and alpha-synuclein were observed. Clinical and cognitive differences include frequent delusions and hallucinations, more severe dementia symptoms and poorer independent functioning for DLB. In contrast, people with PDD tend to have more tremors, but better orientation and visual memory.

Discussion: Despite these neurological, cognitive, and clinical differences between the two subtypes, no reliable or valid biomarker has been shown to confidently and accurately distinguish DLB from PDD. However, the synthesis of this research will be helpful to clinicians in conducting differential diagnoses by considering the potential underlying differences between PDD and DLB. As well, this literature review will be beneficial for researchers looking to further study these two LBD subtypes.

Conclusion: Given the heterogeneous nature of different types of dementia, further research is needed to validate these clinical differences to determine the prognosis of PDD relative to DLB, and to determine specific biomarkers for a definitive differential diagnosis.

Keywords: Parkinsonism; Parkinson's disease dementia; dementia with Lewy bodies; Parkinson's disease; neurodegenerative disorders; Lewy body dementia

Introduction

Parkinsonism is an umbrella term that refers to the signs and symptoms often seen in neurological disorders, mainly in Parkinson's disease (PD). These include bradykinesia (slowed movements), rigidity, tremors, and postural instability [1]. Research has shown that 680,000 Americans over the age of 45 were living with PD in 2010 and that this number is expected to increase to 1,238,000 Americans by 2030 [2]. Additionally, it has been shown that men are twice as likely to develop PD than women, but that women tend to have a higher mortality rate [3]. The incidence of PD increases with age [2], and the mean onset age for PD diagnosis is in the 60s for most individuals [4-6].

Of note, the observation of parkinsonism can be more apparent when these individuals with PD show cognitive impairment due to neurodegeneration, as in the caseLewy body dementia (LBD) Research has shown that LBD is characterized by the accumulation of aggregated alpha-synuclein (α-syn) which is a neuronal protein that plays a key role in the regulation of synaptic vesicle trafficking and subsequent neurotransmitter release. This abnormal aggregation of alpha-synuclein in the brain forms Lewy

bodies [7]. Within LBD, clinicians have suggested two subtypes: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) [8]. The main agreed-upon difference between PDD and DLB subtypes are the onset of cognitive and motor symptoms (i.e. dementia and parkinsonism), also known as the "1 year rule". If the onset of dementia occurs one year after the onset of parkinsonism (and in the setting of established PD), then this would qualify for a PDD diagnosis. On the other hand, if the onset of dementia precedes, or if dementia occurs concurrently or within a year after the onset of parkinsonism, this would qualify for a diagnosis of DLB [9].

As PDD and DLB fall under the same umbrella, they share similarities in both clinical, cognitive, and neurological domains. Recent studies have shown that DLB leads to a decline in cognitive abilities and independent functioning in day-to-day activities. Along with the previously described symptoms of parkinsonism, it may also have other characteristics like spontaneous changes in attention and alertness, frequent visual hallucinations, and sleep problems (such as REM sleep behaviour disorder, or RBD) [10]. Similarly, PDD has been linked to a decline in cognitive abilities. However, people with DLB have been shown to have less frequent tremors as well as poorer verbal memory compared to those with PDD. Furthermore, people with DLB tend to have more frequent visual hallucinations and poorer motor performance compared to people with PDD. In addition the visual hallucinations associated with DLB tend to be spontaneous, whereas those associated with PDD occur after conventional drug treatment for parkinsonism [7].

In addition to these motor and cognitive deficits, they both also show neuropathological lesions that are associated with characteristics of Alzheimer's disease (AD): amyloid plaques and tau tangles [11]. Because of these overlaps in clinical features of PDD and DLB, and alongside overlaps with other dementias, an important line of research is determining the extent to which both PDD and DLB represent the same disorder, or if they represent two different disorders and etiologies that are categorized by very similar features and symptoms (i.e., the syndrome). Therefore, this literature review will critically examine peer-reviewed articles to determine similarities and dissimilarities between PDD and DLB based on neuroanatomical differences, cognitive and clinical features, and differences in fluid biomarkers.

Methods

A literature review informed by three academic databases searches - PubMed, Google Scholar, and Web of Science – was conducted and eight empirical articles studies were selected for review. As this review focused on cognitive, neurological, and clinical differences between DLB and PDD, keywords that were used in this initial search are as follows: "Genetic OR cognitive OR clinical OR neurological OR neurophysiological" AND "Lewy body dementia OR dementia with Lewy bodies OR Parkinson's disease dementia OR Parkinson's dementia".

The articles were excluded if they conducted animal or cell culture studies, and/or if they did not directly compare between DLB and PDD. Preprints (e.g., bioRxiv, medRxiv), review articles, meta-analyses, and case studies were excluded from this literature review. All the selected articles were peer-reviewed, empirical articles that were written in English and published within the last 22 years (i.e. after January 2000). The articles further underwent a preliminary screening process to ensure that they directly compared a DLB participant group with a PDD group. Some of these studies included healthy controls as well that were used to test for any significant deviations from the two clinical groups.

Results

Neurological and Neuroanatomical Differences

Several research studies have found neuroanatomical differences between people with PDD and DLB, despite their significant overlapping features. In one particular empirical study, 74 participants (DLB: n = 18, PDD: n = 15, AD: n = 21, controls: n = 20) were scanned using structural MRI and images were analysed for cortical atrophy among the DLB and PDD groups [12]. Results from this study showed significant differences in atrophy among these two groups. In particular, these researchers found more cortical atrophy in people with DLB compared to those with PDD. Specifically, these changes in atrophy were found bilaterally in the inferior parietal lobule and in the precuneus (which plays a critical role in visuospatial imagery and memory). Some of this increased cortical atrophy seen in people with DLB compared to PDD was only shown in one hemisphere. For instance, brain regions with increased atrophy in the right hemisphere in participants with DLB included the insula, inferior temporal gyrus, and the lentiform nucleus (a part of the basal ganglia), whereas in the left hemisphere, these brain regions included the angular gyrus, cuneus, and in the superior occipital gyrus.

Furthermore, other research has shown that cerebral amyloid angiopathy (CAA), a condition where amyloid protein builds up on the walls of cerebral arteries and increases the risk for dementia and stroke, is more frequently seen in people with DLB relative to those who have PDD (100% vs 63.5%, respectively) [13]. Additionally, the severity of CAA in the parietal and occipital lobes of people with DLB was observed to be much greater than in PDD. Furthermore, the researchers observed worse prognosis in individuals with DLB, as they reached each of its clinical milestones (e.g., time to regular falls, wheelchair dependence, and residential care placement) sooner than PDD. Moreover, another study showed that the claustrum, a gray matter structure connecting prefrontal and thalamic brain regions, has been implicated in both PDD and DLB, but to different extents [14]. Critically, a significantly higher alpha-synuclein deposition in the claustrum was found in people with DLB compared to PDD.

Clinical and Cognitive Differences

Several research studies have found clinical and cognitive differences between people with PDD and DLB. Researchers found that participants with PDD more commonly experienced tremors (88% of their sample) than participants with DLB participants (19%) [15]. In contrast, people with DLB more commonly had orthostatic hypotension (78%), a measure of autonomic disturbance, than PDD participants (7%). The DLB group also had higher rates of delusions (78%), hallucinations (17%), and floating sensations (65%) than the PDD group (13%, 6%, and 2%, respectively). PDD participants had similar scores on the Mini-Mental State Exam (MMSE), a measure of cognitive status, but worse scores on the Hierarchic Dementia Scale-Revised (HDS-R), a dementia screening tool, than DLB participants. When compared to PDD participants, DLB individuals only had lower scores on the "orientation to place" subscale of the MMSE and HDS-R. In contrast, scores on the Frontal Assessment Battery (FAB), which assesses front-temporal dementia, were significantly higher in PDD than DLB participants. Specifically, participants with DLB had worse scores on three FAB subscales: “similarities”, “conflicting instructions”, and “go/no-go” than PDD participants. On measures of affective functioning, DLB participants had more frequent symptoms of depression and agitation than in PDD participants. In terms of functional independence, the PDD group had poorer scores on the Activities of Daily Living (ADL) scale than the DLB group.

Using structural MRI, the same researchers also observed a slight decrease in frontal lobe cerebral blood flow (CBF) in the PDD group, but similar CBF in both posterior lobes was observed [15]. Also, the contrast between two clinical groups showed higher CBF in the cingulate gyrus in DLB than in the PDD group. Furthermore, there was less CBF in the precuneus area in DLB compared to PDD. Furthermore, the researchers suggested that PDD participants’ lower scores for “repetition” (MMSE), “recent memory” (HDS-R), and “lexical fluency” (FAB) were related to lower CBF in the cingulate gyrus than in DLB. In contrast, DLB participants’ poorer subscale scores of “orientation to place” (MMSE) and “similarities”, “conflicting instructions”, and “go-no go” (FAB) tasks were related to lower CBF in the precuneus in DLB than PDD.

In another study, researchers found significant differences between DLB and PDD clinical groups in visual object recognition memory and working memory tasks [16]. The DLB group was observed to have poorer performance in orientation, and tests of processing speed including Trail Making Test A and color-naming task in the Stroop Test, compared to the PDD group. In addition, the DLB group also had lower scores for visual object recognition memory in both short- and long-term recognition.

Differences in Fluid Biomarkers

Several studies have found differences in fluid biomarkers between people with PDD and DLB. One empirical study looked at the incidence of aberrant cerebrospinal fluid (CSF) AD biomarkers across the range of LBD in a large multicenter cohort [17]. They also looked into whether changes in DLB's demographics and clinical characteristics were related to an AD biomarker profile. The sample comprising 375 DLB participants, 55 PDD participants, 164 PD participants without dementia, from 10 centers was scanned for their AD biomarkers such as CSF amyloid-beta 42, t-tau, and p-tau values and dichotomized as abnormal or normal according to locally available cut-offs. Results from this study showed that a substantial proportion of DLB participants had abnormal values for CSF amyloid-beta42 (49%), t-tau (28%), and p-tau (32%), and the values were far lower in the PDD group (amyloid-beta 42: 12%; t-tau: 4%; p-tau: 7%). The DLB and PDD groups differed in overlap of AD biomarkers - amyloid-beta 42, t-tau, and p-tau - where a CSF AD profile was observed in 25% of DLB participants, compared with only 9% of PDD participants.

Similarly, another set of researchers examined AD CSF levels of markers such as amyloid-beta 1-42, t-tau, and clusterin in 96 participants (DLB group: n = 14, PDD group: n = 14, AD group: n = 17, PD group without dementia: n = 27, controls: n = 24) [18]. Results showed that in all of the clinical groups, amyloid-beta 1-42 levels were decreasing in the order of PD>PDD>DLB>AD, whereas t-tau and the tau/amyloid-beta 1-42 index were increasing in the same order (PD<PDD<AD), except for DLB. The paired group comparisons showed higher levels of clusterin in PD participants and PDD participants compared to the control group. Another study was conducted to analyze the levels of Chromogranin A (CgA, a general marker of gut endocrine cells, as part of the “gut-brain axis” in PD) in the CSF serum from 54 participants (DLB: n = 24, PDD: n = 17, AD: n = 17, PD: n = 13, controls: n = 14) [19]. The results showed a positive correlation between CSF and serum CgA levels. The CgA values in CSF and serum were highest in DLB, with a significant difference in CgA between DLB and PDD. The control group had lower serum CgA levels compared to DLB. Notably, serum levels from PD increased gradually in comparison to both PDD and DLB. In addition to the above findings, increased CSF levels of CgA were correlated with lower amyloid-beta42.

Discussion

Based on these findings, no definitive differentiation between the two conditions known as DLB and PDD has been made, other than the arbitrary timing of the onset of cognitive and motor impairments (1-year rule). While there is some consensus that the two entities may merge or may become the same disease, the research discussed in this review says otherwise. Moreover, as cognitive loss has been documented to begin as early as 6 years prior to PD

diagnosis, the 1-year time frame might not be the best way for diagnosing the two conditions [20].

Despite considerable overlap between DLB and PDD, recent studies reveal significant differences in their neurological and neuroanatomical features. In particular, people with DLB have greater bilateral cortical atrophy in brain regions such as the inferior parietal lobule and the precuneus along with other regions [12]. The affected brain regions are known to play a critical role in visuospatial imagery and memory, and the impairment in these regions would lead to clinical impairments in orientation and visual hallucinations. Since hallucinations are a key symptom in the clinical diagnosis of LBD, the claustrum is the target of many studies. It is known that this region has functional connectivity with limbic structures such as hippocampus, thalamus, amygdala, and caudate nucleus/putamen to facilitate the processing of sensory information [21]. As previously mentioned, the claustrum in DLB has higher levels of alpha-synuclein deposition compared to PDD [14], which in turn disrupts the underlying connections between claustrum and other brain regions. However, the difference in the intensity of cognitive impairment is not enough to make a differential diagnosis on PDD and DLB. Further research must be conducted to understand which specific connections between claustrum and other brain areas contribute to the different levels of alpha-synuclein deposition in this region and in critical limbic structures affected by parkinsonism, such as the basal ganglia.

Another prominent neuropathological difference is the CAA pathology, which is more severe in DLB compared to PDD, in brain regions such as the parietal lobe and the occipital lobe [13]. Past findings report that CAA is part of the AD profile, as it is also commonly seen in people with AD [22]. Since the neuropathology of AD is more commonly observed in DLB than in PDD, CAA could be a potential factor in distinguishing DLB from PDD. Research findings also suggest that DLB has worse prognosis than PDD and that it reaches its clinical milestones faster than PDD [13]. However, it should be stated that a definitive diagnosis of CAA can only be done through a post-mortem examination of the brain, and clinicians may only make probable CAA diagnoses. Despite these findings, CAA diagnosis as a differential for PDD and DLB is not very practical as this can only be confirmed with an autopsy.

The clinical features of DLB are in many aspects similar to those seen in PDD, which typically include, but are not limited to: rigidity, akinesia (absence of movement), RBD, hallucinations, as well as cognitive, motor, language and visual impairments. However, although DLB and PDD might share these symptoms, they are distinguished by their levels of intensities. For instance, DLB is associated with greater orthostatic hypotension, more frequent delusions, hallucinations, floating sensations, depression, and agitation. DLB is also characterized by scoring higher on dementia rating scales and has less independent functioning [15]. On the other hand, PDD is associated with greater intensity and frequency of tremors, better orientation to place (possibly due to preserved activity of the precuneus compared to DLB), processing speed, and visual object recognition memory [15,16].

Lastly, an AD biomarker profile is observed more frequently in people with DLB compared to PDD. As stated in the literature, DLB is associated with higher values for CSF biomarkers which include amyloid-beta42, t-tau, and p-tau. In other words, a CSF AD profile was observed in more cases of DLB than in PDD [17]. On the contrary, it has also been shown that DLB is associated with lower levels of amyloid-beta 1-42 (or amyloid-beta42) compared to PDD [18]. Apart from the usual biomarkers of AD pathology, a novel biomarker called clusterin has been extensively studied in the past few years and it has been linked to DLB and PDD, as well PD without dementia. The literature found that PDD and PD have higher levels of CSF clusterin compared to DLB and AD [18]. Another possible biomarker for differential diagnosis was found to be CgA. CgA levels in CSF and in serum were found to be higher in DLB than in PDD [19]. It was also observed that DLB, which had high CSF CgA levels, also had low levels of amyloid-beta42 [19]. Low amyloid-beta 42 has also been shown to predict cognitive decline in DLB, strengthening this finding [23]. This inconsistency of amyloid-beta42 levels could be due to the difference in sample sizes between the studies discussed above. Moreover, it can also be reasoned that the greater the extent of an AD pathology, the less likely for a presentation of the DLB clinical syndrome [24]. There may also be variations in the way CSF is acquired, processed, and analysed as well as contamination (e.g., blood). This variability may also be explained by different stages of amyloid deposition and the varying degrees of AD pathology; however, this has yet to be researched. Overall, these findings pave the way to the development of blood-based parameters for the differential diagnosis, which needs to be confirmed by extensive research.

Conclusions

In summary, there are several distinguishable features of DLB and PDD including neuroanatomical, clinical, and cognitive differences as well as variations in fluid biomarkers. These subtle differences, alongside the 1-year rule of cognitive and motor symptom onset, clearly supports the notion that DLB and PDD are two different disorders that are characterized by very similar features. However, these differences alone are not enough for clinicians to use to make a definitive differential diagnosis between PDD and DLB. Even though these differences may be subtle and/or require elaborate testing, future research can further evaluate their clinical utility and therapies to help alleviate symptoms. Further studies are needed to solidify what contributes to differences observed in levels of fluid biomarkers in PDD and DLB. Moreover, the exact role of the claustrum (and its inputs and outputs) in relation

to PDD and DLB is still unknown. Future studies could examine the relationship between Lewy bodies in the claustrum and cognition and sensorimotor functioning, and whether alpha-synuclein deposition in this region is necessary or sufficient for a differential diagnosis between DLB and PDD.

List of Abbreviations Used
AD: Alzheimer's disease
ADL Scale: activities of daily living scale
CAA: cerebral amyloid angiopathy
CBF: cerebral blood flow
CgA: chromogranin A
CSF: cerebrospinal fluid
DLB: dementia with Lewy bodies
FAB: frontal assessment battery
HDS-R: hierarchic dementia scale-revised
LBD: Lewy body dementia
MMSE: mini-mental state exam
PD: Parkinson's disease
PDD: Parkinson's disease dementia
RBD: REM behavior disorder
VBM: voxel-based morphometry
α-syn: alpha-synuclein

Conflicts of Interest
The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
The study did not require any ethics approval and/or participant consent because this was a literature review.

Authors' Contributions
TSS: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.
MAA: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

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