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Parkinson's disease dementia – A diminished role for the Lewy body

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Abstract

The literature currently views Lewy bodies as central in the pathogenesis of Parkinson's disease dementia (PDD) when Alzheimer's disease (AD) or vascular pathology is not present. Because the neuropathology of PDD is not well understood, the pathological features of PDD were characterized in eighteen PD brain specimens using published criteria for AD, Diffuse Lewy Body Disease (DLBD), and Vascular Disease as a framework. Among the PD dementia ($n = 16$) subjects, 3 (19%) did not have LBs outside of the brain stem, nor AD or vascular pathology. In two additional cases, one did have rare LBs in the neocortex and cingulate gyrus. However, these two cases did not meet the diagnostic criteria for DLBD. Beyond these 5 cases, the remaining PD dementia subjects fitted a classical pathological profile consistent with AD (38%), vascular disease (12.5%), DLBD (6%), or a combination of these pathologies (12.5%). The findings from this study do not support the hypothesis that LBs are the main substrate for dementia in PD. More research with a larger sample size is needed to determine whether the LB may be a secondary phenomenon and/or an “innocent-bystander”. The entire role of the LB in PD dementia is again brought into question.

Keywords

Parkinson's disease; Dementia; Neuropathology; Alpha-synuclein; Lewy bodies

Parkinson's disease (PD) is a neurodegenerative disorder with a powerful impact on the motor system accompanied by alterations in movement such as tremor, bradykinesia, rigidity, and postural abnormalities. In addition, PD is associated with affective [1] and cognitive symptoms which occur frequently, especially when the motor illness has a late life onset. Indeed, approximately 75% of older PD patients develop dementia within eight years

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of the onset of their motor symptoms [2]. The prevalence of dementia in PD is significantly greater than what is typically found in age and gender matched controls [3,4], indicating that in selected patients, dementia is an integral part of the PD syndrome. Dementia places PD patients at greater risk for increased functional disability and, it is not surprising that dementia in PD is receiving much attention in the literature [5–8].

At present, several disease states have been reported as contributing factors to dementia in PD. Among those are Alzheimer's (AD) disease [9], diffuse Lewy body (DLBD) dementia [10,11], and vascular (VADM) dementia [12]. Although the literature generally views Lewy bodies (LBs) as central in the pathogenesis of PD dementia [8], widespread LBs have been observed in PD patients “without” dementia [13]. Moreover, PD patients with dementia may not have widespread LBs, vascular, and/or AD pathology [14]. On this note, previous research from our laboratory using the ubiquitin staining procedure revealed that LBs had an apparently modest or perhaps no role at all in many cases of dementia of PD [15]. Similarly, another post-mortem study observed that 8 out of 34 (24%) PD dementia cases had brain-stem LBs without “sufficient” cortical amyloid, tau, or synuclein pathology to meet criteria for AD or DLBD [16]. However, each of these eight cases (without “sufficient” AD or DLBD pathology) only had questionable/mild dementia [16]. The researchers suggested that had these eight PD patients lived longer it is possible that they too would have developed AD or DLBD pathology [16].

We now seek to confirm and update these initial observations [15,16] with the more LB sensitive alpha-synuclein immuno-staining procedure and within a group of PD patients with definite Parkinson's disease and definite clinical dementia. It is hypothesized that a unique and atypical neuropathology without neocortical LBs and without, amyloid, tau, vascular, and/or alpha-synuclein will emerge among a series of demented PD cases.

1. Methods

1.1. Subject

All brain tissue specimens with a clinical–pathological diagnosis of PD were utilized in this study, deriving from our autopsy program between the years 1985–2006. This 21 year time-span represents the interval of the autopsy program at the Jewish Home and Hospital (JHH) in collaboration with the brain bank of the Mount Sinai School of Medicine (MSSM). As a result, we were able to identify a total of 18 PD brain specimens that met the CERAD-Diagnostic Criteria for Definite PD [17,18]. The majority of subjects had been residents of the Jewish Home and Hospital (83%). All autopsies were performed by the Mount Sinai School of Medicine Department of Pathology after receiving consent for autopsy from each subject's legal next-of-kin. The neuropathological study of these specimens was approved by both the Mount Sinai School of Medicine and Jewish Home and Hospital Institutional Review Boards for the protection of human subjects' of research protocols. The demographic/clinic characteristics of the subjects within this study can be seen in Table 1.

1.2. Materials and procedure

Assessment of dementia—The cognitive changes accompanying PD were judged as primary dementia according to DSM-IV criteria. The Clinical Dementia Rating (CDR) Scale was also used to document the presence and severity of dementia in all subjects in the study as part of the formal review of the post-mortem charts, and as described previously [18,19]. These reviews were conducted in all cases that underwent autopsy. For each subject, a CDR score was obtained for the 6 months prior to death using a review of all information contained within each patient's chart, including admitting diagnoses, nurse's notes, social work records, psychiatric and neurological consultation results, medication histories, results

of mental status testing, all other medical records and laboratory studies, and informant interviews when possible. The CDR scores were expressed numerically with increasing grades of cognitive impairment as follows: 0, cognitively intact; 0.5, minimal impairment; 1, mild impairment; 2, moderate impairment; 3, severe impairment; 4, profound impairment; and 5, terminal state of cognitive impairment [18,19].

Neuropathological assessment—We characterized the pathological features of dementia in PD using published criteria for AD [17], DLB [20], and VADM [21] as a framework. The tissue sampling protocols were those recommend by CERAD [17], and used in previous research [1,18,19]. Representative blocks were examined selectively in the substantia nigra pars compacta, locus cereulus, nucleus basalis of Meynert, dorsal raphe nuclei, dorsal vagus nucleus, amygdala, hippocampus, entorhinal cortex, cingulated gyrus and neocortex, including middle frontal gyrus (Brodmann area 9), Orbital frontal cortex (Brodmann area 45), superior temporal gyrus (Brodmann area 22) and inferior parietal lobule (Brodmann area 7).

Histological sections from paraffin-embedded blocks of formalin fixed specimens were stained using hematoxylin–eosin, modified Bielschowsky, thioflavin S, and immunohistochemistry procedures for anti-β-amyloid (*Dako, Carpinteria, Ca, dilution 1:50*), anti-τ (TG3, donated by Dr. Peter Davis, dilution 1:100) and alpha-synuclein (Santa Cruz Biotech., Santa Cruz, CA; dilution 1:500). The immunohistochemical method used was an avidin–biotin staining procedure with diaminobenzidine detection. Neurohistological assessment was carried out blind to clinical information for the density of LBs and neurodegenerative changes (neuronal loss and gliosis). The following histopathological criteria for a PD diagnosis derived from the CERAD-Diagnostic Criteria for Definite PD [17] were employed: 1) substantial depletion of pigmented neurons and gliosis from the substantia nigra; 2) at least one Lewy body in the substantia nigra; 3) no pathological evidence for other diseases such as supranuclear palsy, corticobasal degeneration, and multiple system atrophy; and 4) clinical history of Parkinsonism. Through retrospective chart review, all patients had received a clinical diagnosis of PD by movement disorder specialists, neurologists, and/or geriatricians. Retrospective chart review also revealed that 94% of these PD patients received anti-parkinsonian medications while residing at the JHH.

2. Results

As seen in Table 1, 88% of the PD patients (Age: 83.06 ± 8.31; Female: 56%, Male: 44%) exhibited primary clinical dementia according to DSM-IV criteria. In Table 2, we note that among the PD dementia subjects, 3 out of 16 present a brain neuropathological profile which shows no LBs outside of the brain stem. Moreover, these 3 cases were neither AD nor VADM. Retrospective chart review revealed that 1 of the 3 cases was medically diagnosed at age 94 as possible vitamin B12 deficiency. His vitamin B12 level at age 92 was normal (345 Pg; Pg normal range is 200–900). At age 93, two years before his death, he was noted to be intermittently confused and noted for the first time to have a dementia. A normal, though lower serum level of B12 (261 Pg) was observed at about the time he was clinically diagnosed with dementia. The senior geriatric psychiatrist at the program evaluated the patient and described the “dementia as likely secondary to Parkinson's disease”. The serum methylmalonic acid level was elevated (517 nmol/l; normal range is 73–271) at the time of this low normal B12 level and this suggested a B12 deficiency. The patient also had chronic renal insufficiency which is known to be one cause of elevated serum methylmalonic acid [22].

Nevertheless, the patient was given B12 injections for several months on the presumption of a true B12 deficiency, but there was no clinical evidence noted in the medical record of a

reversal of his cognitive impairment. Neuropathological review of this one case revealed significant brain-stem pathology. The substantia nigra showed a moderate degree of neuronal depletion, gliosis, and pigment incontinence. Several distinct LBs were present in the pigmented neurons of the substantia nigra. The locus cereulus was similarly affected. This case also showed moderate neuronal depletion in the nucleus basalis of Meynert. It is important to note that this one possible B12 deficient patient showed a similar pattern of brain-stem pathology relative to the other two cases who also were without LBs outside of the brain stem. Due to the consistent pattern of brain-stem neuropathology (e.g., substantia nigra, nucleus basalis, and locus cereulus) among the three cases, and that the B12 deficiency was speculative, the clinical–neuropathological consensus team assessed the case as dementia of PD.

The mean severity of dementia among our Pure Parkinson's Disease Dementia subjects (CDR = 3.66) was greater than those PD subjects with DLBD (CDR = 2.5), AD (CDR = 2.8), or VADM (CDR = 3.0) pathology.

3. Discussion

This clinical–neuropathological study demonstrated an absence of LBs outside of the brain stem in 3 out of 16 patients with advanced dementia and definite PD both by clinical and neuropathological criteria. In addition to the absence of LBs in the neocortex, these 3 cases did not meet neuropathological criteria for AD, VADM, or DLBD. Although we have emphasized our conservative classification in limiting our Pure Parkinson's Disease Dementia group to the 3 aforementioned cases, it is important to reemphasize that two additional cases of advanced dementia and definite PD (which would have brought the total of these Pure Parkinson's Disease Dementia group to 5) also did not meet the diagnostic criteria for DLBD, AD, or VADM, and one of these two cases had only few LBs in the cingulate gyrus. Others have reported the significant impact of cingulate gyrus LBs on worsening cognition in Alzheimer's disease [23]. However, there is no evidence in the literature that cingulate gyrus LBs in PD brains without Alzheimer disease pathology have any linkage to dementia. Nonetheless, we only consider the 3 cases without LBs outside of the brain stem and without AD, DLBD or VADM as belonging to the Pure Parkinson's Disease Dementia group. Our findings are consistent with previous literature [16].

Galvin et al. [16] also observed that 8 out of 34 (24%) PD cases with questionable dementia did not have “sufficient” LBs outside of the brain stem to meet diagnostic criteria for DLBD. However, our 3 Pure Parkinson's Disease Dementia cases had severe dementia and were not “possible cases of dementia” as described in Galvin's paper. Thus, it is not likely that our 3 cases with already advanced dementia (CDR = 3.5) would have evolved over time to DLBD or AD had they lived longer. However, the patients in our study were not followed prospectively, and it cannot be ruled out that delirium due to medical or drug-related factors contributed to their advanced CDR scores. Despite the retrospective nature of this study, the clinical picture of these three cases appears to be of chronic advanced dementia and that LBs (outside of the brain stem) may not be central to the development of the PD dementias excluding possibly those cases with classic DLBD. Additionally, we emphasize here that our research does not negate the DLBD entity as a dementia producing disorder [20]. Future research with larger samples of PD dementia cases is needed to further validate our study's findings.

The pilot findings from our study could be viewed as contrary to consensus group statements and guidelines [20]. These guidelines reflect international workshop groups which emphasize the importance of the LB in the dementias of Parkinson's disease. The concept “Lewy Body disorders” has been adopted as an umbrella-like term to cover the

neuropathologies of PD, PDD, and DLB [8]. Based on our findings, it is possible to conclude that with regard to Pure Parkinson's Disease Dementia, of the non-DLBD type, excessive emphasis is being placed on the LB. Our consideration of the LB as a finding not specific to PD dementia is further supported by the presence of LBs in other neurological diseases including ataxia telangiectasia and neuroaxonal dystrophy, pantothenate kinase-associated neurodegeneration and Down's Syndrome. Some have even suggested that the traditional view of the LB as responsible for major pathology in PD may be erroneous [24]. The initial findings reported in this study and from the LB presence in diseases other than PD support the view that the “LB” may not be specific to the dementia syndrome of PD.

Interestingly, our findings also suggest that AD changes (β-amyloid plaques and neurofibrillary tangles) often accompany the dementia in PD as 6 out of 16 PD dementia cases (38%) contained significant AD plaques and tangles. Recent studies in the literature emphasize the frequent co-occurrence of Alzheimer's disease and Parkinson's disease in patients with dementia. For instance, it has been observed that 30–43% of PD patients fulfill CERAD criteria for a pathological diagnosis of AD [25]. Moreover, in-vitro evidence also suggests an interaction between AD type (i.e., tau) and PD-type (alpha-synuclein) pathology at the biochemical level with both proteins undergoing similar post-translational modifications including hyperphosphorylation, nitration, and ubiquitination [26]. However a positron emission tomography (PET) study using the Pittsburgh Compound B found considerable β-amyloid present only in living DLBD and not PD dementia patients [27]. Because of the differences found in neuropathological and brain imaging studies, future research is needed to examine the relative role of Alzheimer's disease in the dementia of PD.

Several important limitations in our study need to be addressed as we cannot exclude that other factors contributed to dementia in the 3 cases without cortical/neocortical LBs. A recent neuropathological study on DLBD patients found a high number of small presynaptic alpha-synuclein aggregates and only few LB inclusions when utilizing paraffin-embedded tissue blot (PET) and protein aggregate filtration (PAF) assays [28]. Thus, it is plausible that even in cases such as ours (without cortical/neocortical LBs), undetected presynaptic alpha-synuclein aggregates may be a contributing factor to dementia in PD. Future research utilizing the more sensitive PET and PAF staining methods are needed to better support our view that cortical/neocortical alpha-synuclein pathology may not be specific to the dementia syndrome of PD. Additionally, our study does not address whether there are important subcortical changes in our PDD brains. Several neuropathological studies have produced mixed results with respect to the locus coeruleus being implicated in PD dementia [29]. Moreover, it has been observed that cholinergic and not monoaminergic deficits are related to dementia in PD [7]. The findings from our qualitative study reveal that all 3 cases did indeed have monoaminergic and cholinergic pathology in brain-stem nuclei. Thus, future research should examine differences in brain-stem pathology among the PD dementia entities (e.g., AD, DLBD, and Pure Parkinson's Dementia) with a “more robust” sample size and with “quantitative data” (e.g., frequency and severity of neuronal loss, gliosis, and LBs). Moreover, despite rigorous employment of current diagnostic standards (e.g., CERAD) in the present study, the diagnostic accuracy of our groups may be limited due to the retrospective nature of this study. Ideally, future prospective research would have to employ more adequate assessment for both the cognitive and motor evaluations in this elderly PD population.

Another limitation to our study is that a possible B12 deficiency (without abnormal levels of serum B12) was found in one of our Pure Parkinson's Dementia cases. However, B12 deficiencies are quite common even in non-demented elderly individuals. Moreover, there is no evidence in the literature that B12 deficiency has any linkage to lesions in the brain stem as observed in all 3 of our cases. A recent brain-imagining study observed that unlike folate

serum levels, B12 was not related to neuropathology in key regions related to cognition and depression (e.g., hippocampus and amygdala) in geropsychiatric inpatients [30]. For these reasons, we believe that maintaining this one case as part of our Pure Parkinson's dementia grouping is justified based on the available clinical and neuropathological evidence. However, we acknowledge that B12 deficiency can produce dementia through metabolic and not neuropathological lesions related to PD. For this reason, we interpret our preliminary findings which derive from a small sample with caution but it must be reemphasized that the main finding from this study is that the majority of PD dementia cases did “not” have cortical and neocortical LBs.

4. Conclusions

The LB is not present in the neocortex in 3 out of 16 of our PD dementia elderly patients. Thus, it is concluded that the findings from this study do not support the hypothesis that LBs are the main substrate for dementia in PD. More research with a more robust sample of patients is needed to determine whether the LB may be a secondary phenomenon and/or an “innocent-bystander”. The entire role of the LB in dementias is brought into question.

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Table 1

Demographic and clinical characteristics of our elderly PD subjects.

Sample Size	18
Male/Female	8/10
Age, years Mean (S.D.)	83.06 (8.31)
% Taking Anti-parkinsonian Medication	94%
Hoehn & Yahr-stage Mean (S.D.)	3.40 (1.78)
Estimated PD duration (years)	10–15 years
Clinical Dementia Rating Scale Median (range)	3.00 (4.50)
% Demented	88% (n = 16)

Table 2

Prevalence of dementia-types in Parkinson's disease – according to clinical and neuropathological criteria.

Clinical-Pathological diagnosis Among PD Dementia (*n* = 16) Cases	Prevalence
Absence of LBs, AD, and VDM Pathology outside of brain stem	19% (*n* = 3)
AD pathology (Plaques and Tangles)	38% (*n* = 6)
DLBD pathology (LBs in brain stem, limbic system, and/or cerebral cortex)	6% (*n* = 1)
AD+DLBD (Mixed) pathology	12.5% (*n* = 2)
Vascular Pathology (VDM)	12.5% (*n* = 2)
Total cases not meeting diagnostic criteria for DLBD, AD, or VADM[a]	31% (*n* = 5)

[a]The 5 cases not meeting the diagnostic criteria for DLBD, AD, or VADM consisted of the 3 cases without LBs AD, and VDM pathology outside of the brain stem, 1 subject with only few LBs in the cingulate gyrus, and 1 subject with mild LBs in the cingulate gyrus and neocortex. All of these cases did have brain-stem LBs.