A Modern Hypothesis: The Distinct Pathologies of Dementia Associated with Parkinson’s Disease versus Alzheimer’s Disease

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Introduction

Parkinson’s disease (PD) has traditionally been regarded primarily as a motor disorder, but dementia is a common associated feature. Dementia becomes more common as PD advances, with the most significant risk factors and associated features being increased age, early occurrence of levodopa-related psychosis, increased duration of PD, more severe motor symptoms and depression [1]. It has been commonly thought that dementia in PD is caused by Alzheimer’s disease (AD) pathology, but accumulating evidence reviewed here suggests that PD dementia (PDD) is more closely associated with Lewy body pathology. Patients with PD have an almost 6-fold increased risk of developing dementia compared with age-matched individuals without PD [2]. About 10% of people aged over 65 years have probable AD [3], while the prevalence of dementia in older (mean age 73 years) PD patients may be as high as 80% [4]. If this high prevalence cannot be accounted for by AD, the increased occurrence of dementia in PD patients represents an excess that must be attributable to PD.

The profiles of PDD and AD are clinically distinct. The prototype of PDD is a dysexecutive syndrome in which impairment of executive and attentional functions are the initial and early prominent cognitive features, while AD is characteristically an amnestic disorder [1]. There are also multiple early behavioural and personality abnormalities in patients with PDD, occurring more frequently than typically seen in AD patients [1]. Visual hal-
lucinations are much more frequent in PDD patients, having been reported in as many as 70% of this population, compared with 25% of AD patients.

Early clinicopathological research in PDD was hampered by methodological difficulties such as referral biases in autopsy studies, clinical challenges in defining the illness [e.g., differentiation from dementia with Lewy bodies (DLB) and other syndromes], absence of stains specific to relevant pathology and differences among neuropathologists in their approaches to characterizing the pathology. Several older studies showed an association between AD-type pathology and dementia in PD [5–8]. Many of the reported changes are also evident in normal aging, and the original work was based largely on findings of haematoxylin-eosin and silver impregnation techniques that underestimated cortical Lewy bodies. The advent of ubiquitin and α-synuclein (SCNA) immunohistochemical techniques has improved and sharpened diagnosis by allowing more specific and sensitive detection of Lewy body pathology.

In these first few years of the 21st century, our understanding of disease mechanisms in PDD has been revolutionized at a basic level by these enhanced molecular and immunochemical techniques, and at a clinical level by improved methodology and new data from neuroimaging studies. Both have provided support for the concept of PDD as an entity that is separate from AD. Here, we review evidence indicating that PDD involves pathological processes and neurological substrates in the brain that are distinct from AD. Our viewpoint is that the current, widely accepted theory that AD and PDD are different manifestations of the same disease process may not be correct, at least in a proportion of patients, and we present evidence for this argument. It is our intention to stimulate discussion and further research on this topic, with the ultimate objective of understanding the complex pathologies of dementia.

Methods

A literature search was performed in April 2007 using PubMed to identify relevant English-language articles that had been published since January 1, 2001. The search words ‘pathology’, ‘Parkinson’s disease’ and ‘dementia’ were used to source original research reports of PDD pathology in human subjects. Earlier work (before 2001) was not included as the research described in these articles was more likely to have been limited by the methodological difficulties described above.

The Neuropathology of PDD

Senile plaques are frequently present in PD cases with advanced dementia, but the burden of plaque pathology is typically no greater than that found in non-demented controls and plaques are absent in PD cases with mild cognitive impairment [9, 10]. Lewy bodies are abundant in the cortices of patients with PDD. A post-mortem examination of 12 PD patients with dementia suggested that the average SCNA-stained Lewy body counts were increased nearly 10-fold in the neocortex and limbic areas, compared with 9 PD patients without dementia (p < 0.002) [11]. If plaques and neurofibrillary tangles (NFTs) are present, dementia is nearly always also present, but many cases of dementia occur without plaques and NFTs. Lewy body pathology is both sensitive and specific for the diagnosis of PDD, while plaques and tangles are specific but lack sensitivity. Dementia is rare in the absence of cortical Lewy bodies [9, 12].

Lewy bodies are specific pathological markers for PDD and their presence, as detected using modern techniques such as SCNA staining (fig. 1), is the most consistent pathological correlate of dementia in this population [9–14]. Matilla et al. [13] showed that the presence of Lewy bodies in the frontal cortex was significantly correlated with cognitive impairment, as evaluated retrospectively from Global Deterioration Scale (an overall staging of dementia severity) scores in hospital records of 27 PDD patients (r = 0.41, p = 0.037). Similarly, Hurtig et al. [9] performed a comprehensive assessment of histopathological markers of neuropathological change in the setting of PD and showed that a moderate intensity of cortical Lewy body pathology (a count of 2–4 bodies per randomly selected ×100 microscopic field) was the single best correlate for dementia, with an odds ratio of 31.5. The sensitivity of correlation to dementia was 100% for cortical Lewy bodies, compared with only 63.9% for NFTs or senile plaques, in 22 PDD and 20 PD (without dementia) patients [9].

Aarsland et al. [15] described autopsy results from 22 subjects drawn from a large longitudinal community-based study of 245 Parkinson’s patients in Norway. Eighteen of these subjects had dementia, 1 had questionable dementia with a Mini-Mental State Examination (MMSE; a 30-point scale) score of 20 and 3 were without dementia having MMSE scores of 26, 27 and 27, at last assessments, respectively. None fulfilled Braak and Braak or Reagan Institute Criteria for AD. All had significant limbic or neocortical Lewy body disease and the Lewy body score was significantly associated with the rate of cognitive decline.
Colosimo et al. [16] suggested that the presence of Lewy bodies might not always predict dementia. Using a brain bank of 276 PD patients, 38 were reported to have no or very late cognitive impairment before dying. The clinical diagnosis at death was PDD in 11 of these patients and PD (with no dementia) in 27. Of the 27 patients in which dementia was not reported, 17 revealed limbic Lewy body pathology and 9 neocortical Lewy body pathology. In these cases, clinical assessments were not rigorously confirmed in late-onset patients and the presence of dementia may have been underestimated. In addition, regional abundance of Lewy bodies may be critical in determining which patients exhibit dementia, and this type of regional quantification is still methodologically being developed.

Kövari et al. [12] performed a clinicopathological analysis of 22 elderly PDD patients. Dementia was assessed using the Clinical Dementia Rating scale and assessments of Lewy body pathology, NFTs and senile plaques in the cortex were performed at autopsy. There was a highly significant correlation between Clinical Dementia Rating scores and regional Lewy body scores in the entorhinal cortex and anterior cingulate cortex. In multivariate models, only Lewy body densities (not plaques or NFTs) in these 2 regions correlated significantly with Clinical Dementia Rating scores. The results implied that Lewy body pathology in limbic areas is critical for the development of PDD [12]. These findings were supported by Kraybill et al. [17], who took a ‘reverse approach’ by first looking at brain pathology and then referring to patient records to identify the predominant clinical phenotype. The authors reviewed 135 subjects for whom autopsy and brain tissues were available. Neuropathological tests confirmed that 48 patients had ‘pure’ AD and 22 had ‘pure’ Lewy body pathology [17]. Records showed that Lewy body pathology alone was associated with more severe executive dysfunction (a prominent feature in PD and PDD [1]), while AD pathology was associated with a more amnestic clinical profile.

**Relationship between PDD and DLB**

Sixty-five patients in the study by Kraybill et al. [17] had mixed AD and Lewy body pathologies. Like the ‘pure AD’ patients, these patients had a more amnestic type of dementia than patients with Lewy body pathology alone. DLB is distinguished from PDD on a temporal basis: in PDD motor symptoms precede dementia, whilst in DLB dementia precedes the motor symptoms [18]. PDD and DLB are indistinguishable in pathologic terms.
Evolution of Lewy Body Pathology over the Course of PDD

Recent studies have staged the involvement of cerebral structures in patients with advancing PD and provided a framework for understanding the emergence of dementia during the course of the condition. Braak et al. [14] performed a thorough investigation of the evolution of Lewy body pathology in an autopsy study of 168 human brains: 41 from individuals with a clinical diagnosis of PD, 69 from individuals with no clinical diagnosis of PD but with CNS Lewy neurites or Lewy bodies, and 58 age- and gender-matched control individuals with no records of neurological or psychiatric disease and with no evidence of Lewy bodies or Lewy neurites. SCNA immunohistochemical techniques were used to optimize the sensitivity and specificity for visualizing cortical Lewy bodies. Six stages of PD pathology were identified using statistical methods to determine whether a proposed stage in the evolution of the PD-related pathology differed from a preceding one by virtue of a significant shift in the frequency with which given brain structures, regarded as characteristically affected at that stage, were involved. The results showed that Lewy changes initially found in the lower brain stem and in the olfactory bulb gradually ascend to involve limbic and neocortical areas (fig. 2; table 1) [14]. These findings may explain why cognitive changes and dementia usually appear relatively later in the course of patients with classic PD.

Braak et al. [10] subsequently studied the association between the clinical stage of dementia and neuropathological staging in 88 patients with sporadic PD and mild to severe dementia. All patients were assigned to 1 of the 6 PD stages defined by the group’s previous work [14]. Of the 88 patients included in this second study, none had PD stages 1 or 2, 14 had PD stage 3, 36 stage 4, 32 stage 5 and 6 stage 6. Cognition was assessed using the MMSE to grade the severity of cognitive impairment. The study authors stratified patients as having intact or marginally

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**Table 1. Stages in the evolution of PD-related Lewy body pathology and cognitive impairment recorded at each stage [10, 14]**

<table>
<thead>
<tr>
<th>PD stage</th>
<th>Location of Lewy body pathology</th>
<th>Patients</th>
<th>Cognitive status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>– Dorsal IX/X motor nucleus</td>
<td>0</td>
<td>normal</td>
</tr>
<tr>
<td></td>
<td>– Intermediate reticular zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Stage 1 plus:</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Caudal raphe nuclei</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>– Gigantocellular reticular nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Coeruleus-subcoeruleus complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Stage 2 plus:</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Midbrain, in particular pars compacta of the substantia nigra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Stage 3 plus:</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Prosencephalic lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Stage 4 plus:</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Higher-order sensory association areas of the neocortex and prefrontal cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Stage 5 plus:</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– First-order sensory association areas of the neocortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Premotor areas</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients = Numbers of patients for whom disease staging and MMSE scores were evaluated [10].

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Dement Geriatr Cogn Disord 2008;25:301–308

Farlow/Cummings
impaired cognition (MMSE scores 25–30), mildly impaired cognition (MMSE scores 21–24), moderate cognitive impairment (MMSE scores 11–20) or severe cognitive decline (MMSE scores 0–10). They demonstrated that more severe cognitive impairment on the MMSE correlated significantly with more advanced neuropathological staging (p < 0.005; table 1). At stage 3, 65% of these patients still had intact, marginally or mildly impaired cognition, but by stage 4, 67% had moderate to severe cognitive decline. By stage 5, 94% of the patients had moderate to severe cognitive decline, and 100% of the patients with stage 6 PD pathology had moderate to severe cognitive decline. Cognitive status was also correlated with PD progression on Hoehn and Yahr PD staging criteria (p < 0.0005). The burden of AD pathology was generally low, with only 2 patients diagnosed as having mixed AD and PD pathologies [10].

**Neurochemistry of PDD**

Neurotransmitter deficits may contribute to the cognitive and neuropsychiatric symptoms of PDD. Dopaminergic (nigro-striatal and extra-striatal), noradrenergic (locus coeruleus) and serotonergic (raphe nuclei) deficits associated with the illness may impact on cognition and emotion [19–21]. A differentiating pathological feature of PDD compared with AD is marked nigro-striatal dopaminergic neuronal degeneration. Compared with D3 binding in the caudal striatum of control subjects, Piggott et al. [20] reported a 13% decrease in PD patients with or without dementia and a 20% increase in AD patients. Cell loss in the medial substantia nigra has been associated with the presence of dementia in PDD [19].

Cholinergic involvement in PDD has been interpreted previously as evidence to support the importance of AD pathology in the illness, because cholinergic deficits are prominent in AD-type dementia [22]. PDD patients have cholinergic deficits that are greater in magnitude and are more widespread throughout the brain than those reported in patients with AD [23–25]. Using in vivo positron emission tomographic techniques, Bohnen et al. [25] showed the mean cortical acetylcholinesterase (AChE) activity in 14 PDD patients to be about 20% below ‘normal’ (as assessed in 10 age-matched healthy control subjects), compared with 9% below normal in 12 AD patients. The mean reductions in AChE activity were consistently greater in the PDD patients than in the AD patients in the cortex, amygdala, hippocampus, inferior temporal, superior temporal, parietal and frontal regions [25]. The same research group separately reported cognitive correlates of cortical AChE activity in patients with PDD, PD without dementia and normal controls [26]. Scores on the WAIS-III Digit Span, a test of working memory and attention, had the most robust correlation with cortical AChE activity (p < 0.005). There were also significant correlations between cortical AChE activity and other tests of attentional and executive functions, such as the Trail Making and Stroop Color Word tests. However, there was no correlation between cortical AChE activity and duration of motor disease or severity of Parkinsonian motor symptoms. The authors concluded that cortical cholinergic denervation in PD and PDD is associated with decreased performance on tests of attentional and executive functioning – core clinical features of PDD.

Two major subcortical cholinergic pathways are affected in PD; one is the basal forebrain pathway that extends from the nucleus basalis of Meynert [27] and is the principal source of cholinergic innervation to the cortex, and the second is a brain stem pathway comprised of various brain stem nuclei [28]. The degree of neuronal loss in the nucleus basalis of Meynert has been shown to correlate with the severity of cognitive deficit in PD patients [23, 29]. In contrast to AD, PDD is also associated with cholinergic neuronal loss in the striatum and pedunculopontine pathways that project to the thalamus [28] and comprises the brain stem cholinergic system.

**Overlapping PDD and AD Pathology**

It is an indubitable fact that many patients have mixed PDD and AD pathologies. Sixty-five patients (48%) in the study by Kraybill et al. [17] had mixed AD and Lewy body pathologies. Similarly, in the study by Braak et al. [10] that mapped cognitive decline against the neuropathologic stages of PD, the authors reported that the majority of patients had at least mild (stages I or II) concomitant AD changes in the brain. In brain bank study of PD patients by Colosimo et al. [16], 19 patients were excluded from their analysis because of ‘coexistent features of advanced Alzheimer’s disease changes’, compared with 11 diagnoses of PDD.

Overlapping PDD and AD pathologies are common, and perhaps these overlaps have contributed to the sustained belief that AD and PDD are caused by the same underlying pathology. However, it is the authors’ opinion that such patients suffer from a combination of 2 separate
types of pathology that can occur independently of each other to produce ‘pure’ AD or PDD clinical profiles, or together to produce a diagnosis of mixed pathology. Patients with mixed AD and Lewy body pathologies appear to decline more rapidly than those with pure AD or pure Lewy body pathology [17]. It seems that, when they occur together, the 2 types of pathology may result in a greater clinical consequence.

**Genetics of PDD**

No genetic mutations have been identified that regularly cause both AD and PDD. Deposition of SCNA has been associated with neurodegenerative diseases, and this protein is the principal component of Lewy bodies. It exists physiologically in unstructured soluble and α-helical membrane-bound conformations. The physiological function of SCNA appears to require conversion between these conformations, and abnormal processing may lead to pathological changes in its binding properties and function [30]. Increased expression of SCNA protein alone can result in PD-associated dementia. Some genetic forms of PD are associated with increased deposition of SCNA [30–32]. PD can be seen with additional copies of the normal SCNA gene and, as the gene load increases, the likelihood of developing PDD (but not AD) increases [33–36].

The results of apolipoprotein E (APOE) genotyping also differentiate PDD and AD. Huang et al. [37] performed a systematic review and meta-analysis of results from 22 studies that provided clear clinical or pathological criteria for PD (with or without dementia) and that reported APOE genotype frequencies. The estimated odds ratio for 1 or more copies of each APOE allele was 1.2 for APOE ε2 and 0.99 for APOE ε4. Similarly, Camicioli et al. [38] genotyped brain tissue from 47 autopsy-confirmed cases of PDD patients, 7 of whom had concomitant AD-type pathology. In Cox regression models, adjusting for age of onset and duration of treatment, APOE ε4 was not associated with an increased risk of dementia or psychosis; inclusion of Alzheimer-type pathology did not change the result. Thus, unlike AD, for which the APOE ε4 allele increases the prevalence and the APOE ε2 allele is protective, the APOE ε2 allele has been shown to be mildly associated with sporadic PD, and the APOE ε4 allele appears to have no significant association with PDD [37, 38].

**Neuroimaging Studies in PDD**

Relatively few neuroimaging studies have been reported in patients with PDD. However, available evidence suggests both structural and functional differences between PDD and AD.

Magnetic resonance imaging (MRI) using voxel-based morphometry has shown that whereas temporal lobe atrophy including the hippocampus and parahippocampal gyrus is more severe in AD patients, there is more prominent atrophy of the thalamus and occipital lobe in PDD. Burton et al. [39] performed 1 such study to establish the pattern of cerebral atrophy on MRI in 31 PDD, 34 PD (without dementia), 35 AD and 20 DLB patients, and 39 healthy elderly controls. Whole-brain T1-weighted 3-dimensional datasets were acquired in the coronal plane, yielding 124 contiguous slices through the head. Compared with control subjects, the PDD patients’ grey matter volume was reduced in the temporal lobe, hippocampus, parahippocampal gyrus, occipital lobe, right frontal lobe, left parietal lobe and some subcortical regions. These patients had more grey matter atrophy in the occipital lobe, compared with PD patients without dementia, but less temporal lobe atrophy than AD patients [39]. Similarly, another recent voxel-based morphometry study reported different areas of cortical atrophy in patients with PDD (n = 16) or PD with no dementia (n = 20) [40]. Grey matter reductions were found in frontal and temporal lobes in PD patients with or without dementia, but those with PDD had additional reductions in parietal and limbic regions of the brain.

Tam et al. [41] performed MRI studies in 31 PDD, 33 PD, 31 AD, and 25 DLB patients, and 39 control subjects, all of whom were community-dwelling and had comparable ages, education and (for those with dementia) similar dementia durations. Medial temporal lobe atrophy was less severe in control subjects than in any of the dementia patients (all p < 0.05 vs. controls), and within the dementia patients, medial temporal atrophy was less severe in PD or PDD than in AD patients.

Wiltshire et al. [42] performed MRI studies to evaluate callosal atrophy as a marker for cortical pathology in 25 patients with PDD, 24 with PD, 16 with AD and 27 healthy controls. They found that AD patients had a significant loss of callosal area compared with controls, whereas PD and PDD patients did not show significant callosal atrophy. Moreover, dementia severity was correlated with total callosal atrophy in AD but not PDD patients. These results suggested that anatomic structures other than the
cortex and/or medial temporal lobe are predominantly implicated in PDD.

White matter hyperintensities do not appear to change differentially in different dementia types. A recent study using fluid-attenuated inversion recovery images in 13 PDD, 23 AD and 14 DLB patients, and 33 healthy elderly control subjects evaluated white matter hyperintensity volume at baseline and after 1 year [43]. Severity of baseline white matter lesions, rather than specific diagnosis or severity of dementia at baseline, was a significant factor in lesion progression.

**Conclusions**

There is clear evidence that, in some patients at least, AD and PDD pathologies overlap. Both result in cholinergic deficiencies and ‘brain failure’, and the common, conventional viewpoint that the 2 diseases share the same underlying changes at many pathological and clinical levels is easy to comprehend. However, modern research using specific stains and imaging techniques appears to suggest that this viewpoint should now be challenged. PDD can be distinguished from AD at the neuropathological, clinical, genetic and radiologic level (table 2). Current neuropathological evidence supports the hypothesis that Lewy-body-related α-synucleinopathy is the underlying pathology causing the dementia syndrome associated with PD and that the predominant neuropathologies of PDD and AD differ. The studies reviewed here have probably not yet revealed a full understanding of these 2 disease entities. Researchers should be encouraged to continue to establish the distinctions between AD and PDD, fully elucidate the pathological processes underlying each condition and consider how they may act together in patients with mixed dementia to contribute to a more rapid disease course [17]. This may offer potential for the future development of therapies targeting protein mis-folding, metabolism and/or elimination of the SCNA protein.

**Acknowledgements and Disclosures**

This report was supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation, USA. J.C. receives support from a National Institute of Aging, Alzheimer’s Disease Research Grant (P50 AG16570), an Alzheimer’s Research Centers of California grant and the Sidell-Kagan Foundation, and has acted as consultant to Eisai, Forest, Janssen, Novartis and Pfizer. M.R.F. receives research support from a National Institute of Aging, Alzheimer’s Disease Center Grant (P30 AG10133), and also from Eli Lilly & Co., Novartis Pharm, Ono/Pharmanet, Elian and Pfizer, is on speaker bureau for Forest Labs, Pfizer Inc., Eisai Inc. and Novartis, and consultant for Abbott Labs, Accera, Adamas, Cephalon Inc., Eisai, GlaxoSmithKline, Medivation, Memory Pharm., Merck Res Labs, Neurochem, Novartis, Octapharma, Takeda, Toyama and Worldwide Clinical Trials.

**References**


