Parkinson’s Disease with Dementia, Lewy-Body Disorders and Alpha-Synuclein: Recent Advances and a Case Report

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Abstract-
The advance in research on the dementia syndrome associated with Parkinson’s disease recently gains momentum in part because Parkinson’s disease inevitably causes declined cognition and then lead to poor quality of life. More importantly, dementia of Lewy bodies, now known as the second most common neurodegenerative disorder, shares the common neuropathological hallmark with Parkinson’s disease and yet exhibits a unique clinical syndrome. Recent genetic, neurochemical and neuropsychological experiments robustly confirm a link between dementia associated with Parkinson’s disease and dementia with Lewy bodies. Meanwhile, controversial issues regarding diagnostic criteria and proper treatments remain unresolved. Here I review milestone research conclusions and report a typical case with pathological data in order to clarify different aspects of these two dementia disorders.

Key Words: dementia, dopaminergic, executive, visuospatial; Parkinson, Lewy body, alpha-synuclein, cholinergic, cholinesterase inhibitor, gene mutation

INTRODUCTION

1. Historical views

James Parkinson (1755-1824), while describing the distinctive motor features, did not think Parkinson’s disease (PD) affected brain functions. In his famous text, he stated “by the absence of any injury to the senses and to the intellect that the morbid state does not extend to the encephalon”(1). In fact, he did not have autopsy data to support his points of view. Nevertheless, even in the early twentieth century, several keen researchers already reported mental changes and dementia of patients with idiopathic PD(2). Friedrich Heinrich Lewy not only discovered the pathological hallmark of PD - Lewy bodies (LBs), but also he did describe significant mental dysfunction in PD patients (3). Before the remarkable efficacy of dopaminergic treatments was available to PD patients in the 60s, both dementia and motor debilitation were deemed unavoidable as PD severely progressed(2).

In the 70s and 80s, dopaminergic treatments were proven to effectively improve motor functions of PD patients. Neurologists began to be specialized at diagnosing and treating PD and other movement disorders. Meanwhile, “subcortical dementia” was proposed to denote the core features of cognitive dysfunction and behavioral issues observed in various parkinsonian dis-
orders, including PD, progressive supranuclear palsy and Huntington’s disease. The idea of “subcortical dementia” was simple: pathologies affecting subcortical ganglia of the human brain can cause a particular dementia syndrome rather different from the type of dementia caused by pathologies primarily affecting cortical functions, like language, memory and perception. In the recent years, however, the use of “subcortical dementia” diagnosis is mostly abandoned. The main reason is that anatomic-pathological research has revealed the same pathological findings can be found in both cerebral cortices and subcortical structures. Moreover, thoughtfully-designed neuropsychological experiments further allow us to understand specific cognitive dysfunctions of PD patients. Either cortical or subcortical-nuclear pathologies can contribute to the PD associated cognitive disorder. In the brain of PD with dementia (PDD), the LBs can distribute in both cortical and subcortical regions. It is nearly impossible to explain the dementia syndrome exclusively by the PD subcortical pathologies.

In the 90s, while making tremendous efforts in improving motor functions of PD, neurologists have begun to pay attention to the burden of cognitive disorder and dementia in PD patients. Meanwhile, dementia with Lewy bodies (DLB) and other disorders linked with LBs have been discovered and continuously redefined by many clinical and pathological correlation studies. There are controversial issues concerning a variety of Lewy-body disorders (LBDs); they will probably remain in the years to come. Most excitingly, the discovery of alpha-synuclein gene mutations causing familial PD and DLB has opened up a new era of research and will likely promise new therapeutic strategies in the foreseeable future.

2. Dementia and impaired cognition of Parkinson’s disease

For decades, clinicians note PD patients constantly display slowness in mental processing speed – so-called “bradyphrenia”. Despite dopaminergic treatments, cognitive capacity as well as motor functions progressively deteriorate. As a result, dementia is inevitable. Early on, one popular explanation for dementia in PD patients has been thought to be related to the pharmacological interventions. Careful observations clearly indicate the drug-induced dementia in PD can be closely linked with the anti-cholinergic treatments. By contrast, there still is no consensus with regard to whether or not the dopaminergic treatments can worsen cognitive function of PD patients. Some studies have shown levodopa treatment improved performance on cognitive tasks. Others however have reported dopaminergic treatments either failed to restore or could not influence cognitive function in PD.

In the 80s, while researchers were still debating the nature of dementia in PD, the pathological research on PDD repeatedly demonstrated the superimposed Alzheimer’s pathology in the cerebral cortex could be the culprit of severe dementia known in the advanced PD patients. Therefore, initially PDD was thought to develop only in the late stage of PD. Yet, the recent research results suggest to the other direction. Analyzing data of the U.K. Parkinson’s Disease Society Brain Bank, a group of researchers found PD patients, no matter whether they responded to dopaminergic treatments during the early stage of PD, all experienced cognitive impairment to a certain degree. Although more than half of the studied subjects displayed a small amount of Alzheimer pathology in their brains, this degree of Alzheimer pathology however has been deemed insufficient to explain cognitive dysfunction. And yet, the distributions of Lewy body pathology alone can be correlated with severity of dementia. Taken together, these research data indicate PDD can be caused either by the load of Lewy body pathology or by the underlying mixed AD pathology in certain PD patients.

In order to understand cognitive dysfunction of PD, many neuropsychologists have applied experimental paradigms to clarify disturbed brain functional systems and to discover measurable cognitive changes. Recently, we can draw the following conclusions from these studies: First, due to the dopaminergic deficiency, the fronto-striatal circuits are profoundly disrupted in PD, leading to executive dysfunction. Secondly, although less known to clinicians, visuospatial and visuoperceptual dysfunction also has been documented in PD.
Thirdly, both explicit and implicit memory systems in PD patients are defective. Applying the neuropsychological battery, clinicians now can even detect the changes of cognitive function in the early stage of PD. In order to predict the risk of developing PDD in a large, community-based cohort of PD subjects, researchers utilize different neuropsychological batteries that have been tested in the laboratory settings. First, several longitudinal, prospective follow-up studies show both dementia and cognitive impairment are prevalent in PD patients. Secondly, for the study period of three and a half years, researchers recorded at least ten percent of PD patients have already become demented. Strikingly, more than sixty percent of the cohort’s PD patients have significant cognitive impairment that can be detected by the neuropsychological battery. Thirdly, there are several identifiable risk factors for developing cognitive dysfunction. One such risk factor is the age of onset of PD. Another is that PD patients who initially present the non-tremor motor dysfunction are prone to developing dementia in the following years. Finally, regarding the annual rate of cognitive decline that is recorded based on the Folstein’s Mini-Mental Status Examination (MMSE) over the eight-year study period, one study reports that PDD patients progress in the way similar to the decline observed in Alzheimer patients (an annual decline of 2.3 points per year on the MMSE).

To predict dementia developing in PD patients at the early stage, efforts have been made to define the specific “mild cognitive impairment (MCI)” syndrome of nondemented PD patients. The longitudinal, prospective follow-up studies have been launched to delineate the cognitive dysfunction in the mild PD (the Hoehn and Yahr scale score less than 3). One of these studies recently reported mild PD patients with the MCI syndrome on average show a lower MMSE score at the baseline visit, compared with PD patients without MCI (the mean score of PD with MCI vs. the mean score of PD without MCI: 26.5 vs. 28.2 respectively). Two cognitive tests seem to be particularly useful in terms of early presentation of the cognitive dysfunction of mild PD patients. A longitudinal follow-up study has found, among mild PD patients, poor performance on two tasks (the semantic fluency test and the intercepted pentagon copying test) could be important predictors of PDD.

3. Lewy-body disorders

While the existence of LBs within the substantial nigra is widely considered as the pathological hallmark of idiopathic PD, the fact that LBs can be discovered in the other brain regions has not received deserved attention. At first, the LBs in the cerebral cortex were reported as the incidental finding and thought to be of no clinical relevance. Not until Okazaki, et al first reported two cases in 1962, did we learn that LBs diffusely distributed in cortical regions can be linked to dementia and psychiatric issues. Later on, Kosaka and his colleagues made enormous efforts to link cortical Lewy bodies with dementia and named the dementia syndrome as “diffuse Lewy-body disease” (DLBD). In the 1990s, further research contributed to the dementia syndrome of Lewy-body type (DLB) in two areas. First was that clinical-pathological studies noted pathological hallmarks of Alzheimer’s disease (AD), amyloid plaques and neurofibrillary tangles, can be found in majority of the DLB brains. The clinical and pathological features of these patients can be grouped as an independent clinical entity, named “Lewy-Body Variant of Alzheimer’s disease” (LBV). The second area was regarding specific psychotic and behavioral disorders of these patients described and emphasized by geriatric psychiatrists. Many elderly patients with late-onset psychosis have fulfilled the clinical diagnosis of DLBD. In 2005, the report of most recent international conference has incorporated important findings of these two areas of research and has formed the consensus of diagnostic criteria of DLB. Rarely, patients who have only Lewy body pathology and absolutely do not have evidence of Alzheimer pathology are labeled as the “pure diffuse Lewy-body disease” (PDLD).

The questions about nomenclature of these disorders, based on distributions of Lewy bodies and distinct clinical syndromes, grow over the past decade, suggesting the diversity of phenotypes collectively called “Lewy-body disorders”. Idiopathic PD is at the one
end of the spectrum of LBDs because its motor disorders typically respond to dopaminergic treatments whereas the PDLBD, at the other end, primarily presents cognitive and psychotic disorders\(^{(48)}\). Meanwhile, the controversy about the distinction between dementia of Lewy bodies (DLB) and Lewy-body variant (LBV) remains a heated debate. For patients with DLB, it is almost not possible to determine the degree of Alzheimer pathology attributed to the cognitive impairment of DLB\(^{(49)}\). Many Alzheimer patients can also exhibit mild Parkinsonism and psychiatric symptoms. Therefore, the accuracy of DLB diagnosis based on the published consensus criteria is not very satisfied based on the pathological examination data\(^{(49)}\). Rare research studies have provided useful insights into this important issue. For example, comparing the clinical features of pathologically-proven DLB to those of AD, Tiraboschi et al pointed out that visual hallucination and visuospatial/constructional dysfunction could be the best predictors for DLB\(^{(50)}\). Recent neuroimaging data has shown that outstanding dysfunction of the parietal-occipital perceptual network system could be the underlying pathophysiology of visual hallucinations in DLB\(^{(50)}\).

4. Contributions of alpha-synuclein research

Neurogenetics research of alpha-synuclein (SNA)

After years of epidemiological and genetic research, the most important breakthrough was announced in 1997. The first mutated gene which can cause autosomal dominant PD has been identified at the chromosome 4q21-23; the gene product, alpha-synuclein (SCNA), has been proven to be the key protein component of LBs\(^{(52)}\). Most strikingly, DLB as well as PDD can also be caused by one particular mutation of the SCNA gene\(^{(53)}\). After all only three point mutations (miss-sense mutation) the alpha-synuclein gene were discovered - A53T, A30P and E46K\(^{(52-54)}\). Detailed clinical research on one mutation of the SCNA gene (A30P) has shown that the cardinal features of motor symptomatology of this dominantly inherited PD are indistinguishable from the sporadic idiopathic PD; nevertheless, a response to the dopaminergic treatments is expected. The age of disease onset can be ranging from 54 to 76 years. The striatal presynaptic dopaminergic dysfunction can be demonstrated by the PET study; neuropsychological assessment of all the A30P mutation carriers revealed impairment in visuospatial/constructional functions\(^{(55)}\). With regard to the A53T mutation, the patients presented an early age onset and a more rapid progression from PD characteristics to dementia\(^{(55)}\). Most importantly, the patients with E46K mutation particularly presented DLB\(^{(55)}\). Overall, these findings indicate alpha synuclein truly plays a central role of all Lewy-body disorders - PD, PDD, LBD and PDLBD (Fig 1).

The second crucial breakthrough of the PD genetic research is regarding multiplication of the SCNA gene\(^{(56-57)}\). A survey of many more dominantly inherited PD families has failed to demonstrate additional mutations of the SCNA gene. Instead, duplications and even triplications of the SCNA gene are discovered by several researchers. Patients with duplications of the SCNA gene more often present the cardinal features of PD and develop cognitive impairment in the later stage, whereas patients with triplications of the SCNA gene are prone to progressing dementia mimicking DLB\(^{(58-59)}\). These studies further indicate that dosage of SCNA gene can influence the phenotypic presentations of familial PD and that alpha synuclein mutations alone indeed can result in the dementia disorder - DLB.
Neuropathological staging of alpha-synuclein-positive Lewy bodies:

In 2003, Braak et al utilized the alpha-synuclein immunohistochemistry to classify the Parkinson pathology into six stages based on the degree of presence of alpha-synuclein-positive Lewy pathology\(^{(60)}\). Braak stage 1 and 2 designed the involvement of nuclei of the lower brain stem as well as the olfactory system. When the disease progresses the distribution of Lewy bodies begins to emerge in the upper brain stem and forebrain structures. At Braak stage 3, the substantial nigral Lewy bodies are abundant, loss of dopaminergic neurons is evident and the forebrain cholinergic system is also involved with Lewy body pathology. This is the stage when the typical features of Parkinson’s disease start to manifest. The Braak stage 4 is used specifically to describe that the limbic system is plagued by the Lewy body pathology. The advanced stages, 5 and 6, denote the wide distribution of Lewy bodies throughout the entire neocortex. By matching the cognitive function with different pathological stages of PD, Braak et al also demonstrate that the cognitive dysfunction correlates with severity of Lewy body pathology\(^{(62)}\).

This classification system of Parkinson pathology should be use cautiously to infer the chronological progression of Parkinson’s disease and its relationship with dementia with Lewy bodies. Since this is a cross-section study, whether or not every Parkinson patient should develop the disease progression from stage 1 to stage 6 remains uncertain. From case-study research, we learned LDB or DLB patients can first present cognitive dysfunction with psychosis and later manifest Parkinsonian symptoms and signs. Nevertheless, this pathological classification system broadens our view of Parkinson’s disease as the “whole-brain” neurodegenerative disorder.

Neurochemistry of PDD and DLB - focusing on the cholinergic system:

While the cholinergic hypothesis has been proposed for Alzheimer’s disease, researchers also had demonstrated evident cholinergic deficit and thus postulated cholinergic dysfunction as the basis of cognitive disorder in PD\(^{(65)}\). First of all, the loss of cholinergic neurons in PD brains is the convincing evidence\(^{(64)}\). Secondly, as we have learned from the Braak Parkinson pathology staging research, the basal forebrain cholinergic system is overwhelmingly affected by Lewy body pathology (LBs and Lewy neurites) as early as at the stage 3 of PD pathology\(^{(60)}\). Thirdly, measuring the synthetic enzyme choline acetyltransferase (ChAT) of the cholinergic neurotransmitter acetylcholine, researchers have found significant reduction of this enzyme in either DLB or PDD, suggesting that Lewy body pathology disrupts the cholinergic neurotransmission at the cortical regions\(^{(60)}\). Moreover, compared with Alzheimer brains, DLB brains display even more severe depletion of cholinergic neurons and ChAT\(^{(7)}\). Using a double-transgenic rodent model that overexpresses both the mutated human SCNA gene and amyloid precursor protein (APP) gene, Masliah et al elegantly have shown that this particular model exhibits the characteristic DLB pathology, has learning deficiency on the water maze task and displays cholinergic deficits much worse than the transgenic rodent models of PD and AD\(^{(65)}\). Taken together, these results suggest that cholinergic enhancement therapy can be utilized to treat cognitive dysfunction of both PDD and DLB.

5. A clinician’s approach to Parkinson’s disease with dementia and dementia with Lewy bodies

The application of current knowledge to diagnosis and treatment of PDD and DLB can be quite puzzling. Recently, a position paper has been published by the DLB/PDD study group organized by international experts in order to form the consensus and to promote further research\(^{(9)}\). The bottom line is that it is almost impossible to distinguish PDD from DLB based on the pathological features. And applying the consensus diagnostic criteria of DLB, even expert clinicians are found to have low sensitivity in their ability to diagnose DLB\(^{(66)}\). Knowing that Alzheimer pathology often exits in PDD and DLB brains, clinicians often find lacking confidence in making the diagnosis and experience frustrations in providing care for PDD and DLB patients. There are so far no reliable diagnostic tools and useful biomarkers of PDD and DLB\(^{(66)}\). Clinicians still should rely...
on clinical judgment to make diagnosis and provide proper care. At the present time, the evidence of marked cholinergic deficits provides the pharmacological basis of cholinesterase inhibitors for PDD and DLB. Yet, only one cholinesterase inhibitor rivastigmine has been tested by a large-scale, placebo-controlled study and the study has demonstrated modestly improved cognitive function among the rivastigmine-treated PPD patients. Rivastigmine has gained the approval for the indication of treating PDD from the US Food and Drug Administration (FDA).

The following case presentation is to illustrate the clinical course and pathological data of a PDD subject:

This was an 82-year-old right-handed Caucasian woman (M.J.) with a high school diploma who had a ten-year history of Parkinson’s disease. She brought to the Memory clinic for consultation regarding cognitive dysfunction and behavioral problems. She first noted bradykinesia, cogwheel rigidity and resting tremor on her left upper extremity; then Parkinsonian features spread to her legs and right hand within one year. After diagnosed with Parkinson’s disease by one movement disorder specialist, she began to receive treatment with levodopa. In the initial five years, she responded to the treatments very well; she can live independently and drive. Then resting tremor and bradykinesia were worsening. A dopaminergic agonist pramipexole was used for a while; yet she quit this drug due to developing orthostatic hypotension and severe dizziness. Subsequently, a COMT inhibitor entacapone was added; her tremor and rigidity were better controlled. However, in the recent two years, she developed marked anxiety and cognitive difficulties. She became forgetful and unable to manage her medications. She sometimes overly took levodopa to control her tremor of both hands. She cannot manage household chores and gave up driving. Lately, she frequently reported visual hallucinations - seeing people and animal in the evening. Her MMSE score was 21. She cannot lay out numbers and place the hand on the clock-drawing test. A neuropsychological assessment demonstrated impaired executive functions, naming ability and memory. These presentations and test results were consistent with a diagnosis of dementia. The patient died of pulmonary embolism and respiratory failure at age 83. An autopsy was performed. The brain examination revealed characteristic loss of pigmented dopaminergic neurons and existence of Lewy bodies in the substantial nigra region by using the H&E method (Fig 2). Lewy bodies were also found in the nucleus basalis of Meynert where the cholinergic neurons (hyperchromic magnocellular neurons labeled by a mark) exist (Fig 3). Extracellular Lewy bodies also were shown in this figure. Interestingly, few amyloid plaques and tau-immunoreactive neurofibrillary tangles and neurites were also detected in the neocortex (Fig 4 A, B). Lewy bodies can be observed in the large pyramidal neu-
Figure 4.

A: Amyloid Plaques (H & E stain)

B: Tangles, dystrophic neurites (AT8 IHC)

C: Lewy bodies (H & E stain)

D: Neocortex of the mid-frontal lobe

Figure 5.

Figure 6.

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ron and the small cortical interneuron in the frontal neocortex (Fig 4 C, D). Using either ubiquitin or alpha-synuclein immunohistochemistry (IHC), Lewy bodies or Lewy neurites are demonstrated in the hippocampal formation (Fig 5), the substantial nigra region (Fig 6) and the neocortex (Fig 7).

6. Future challenges

Lewy-body disorders (namely, PD, PDD and DLB) are quite diverse both phenotypically and genetically. Alpha-synuclein-positive Lewy body is the important pathognomonic marker of all these disorders. The most crucial step in the future is to improve the accuracy of diagnosis by developing reliable biomarkers and genetic information. Secondly, targeting at the alpha-synuclein/Lewy-body pathology, we need to investigate the disease-modifying therapies to at least delay the neurodegenerative process of DLB and PDD. Thirdly, we shall study in depth the pathogenesis of psychotic and behavioral issues so that more effective treatments can be discovered.

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