REVIEWARTICLE

PROGRESS IN CLINICAL NEUROSCIENCES: Parkinson's Disease with Dementia and Dementia with Lewy Bodies

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ABSTRACT: Dementia occurs in up to 30% of people with Parkinson's disease and is a major cause of disability. Pathologically, Parkinson's dementia, where dementia follows the onset of parkinsonism by at least one year, overlaps with dementia with Lewy bodies. We review the functional impact, definitions, neuropsychology, epidemiology and pathophysiology of Parkinson's dementia, dementia with Lewy bodies and their overlap. Associated psychiatric and imaging findings are also considered. Lastly, current and emerging approaches to assessment and treatment in patients with these Lewy body associated dementias are presented.

RÉSUMÉ: Maladie de Parkinson avec démence et démence à corps de Lewy. La démence est présente chez plus de 30% des patients atteints de la maladie de Parkinson et constitue une cause importante d'invalidité. Au point de vue anatomopathologique, la démence de la maladie de Parkinson (DMP) apparaissant au moins un an après le début de la maladie chevauche la démence à corps de Lewy (DCL). Nous révisons l'impact fonctionnel, les définitions, la neuropsychologie, l'épidémiologie et la physiopathologie de la DMP et de la DCL et leur chevauchement. Les manifestations psychiatriques et l'imagerie sont également discutées. Finalement, les approches actuelles et émergentes d'évaluation et de traitement chez les patients porteurs de ces démences à corps de Lewy sont présentées.

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting about 0.5-5% of the population older than age 65, both in European and non-European populations.[1,2] The prevalence of PD increases with age in most studies from less than 1% in people aged 65-69 years to 2-3% or more in people older than age 90. The prevalence might decrease in the very elderly, possibly reflecting diagnostic uncertainty, overlap with other diseases, a disproportionate effect on survival in the oldest old with PD or inadequate sample sizes in studies of the oldest old (greater than age 85 years).[3,4] At a societal level, PD increases health care utilization and costs.[5,6]

Parkinson's disease is a progressive disorder associated with acquired parkinsonism and the loss of substantia nigra neurons in the presence of Lewy bodies (http://www.ICDNS.org). Parkinsonism is defined by the presence of two cardinal signs among resting tremor, rigidity, bradykinesia and postural or gait impairment, and can be caused by disorders other than idiopathic PD. Lewy bodies are eosinophilic inclusions that stain with antibodies directed against alpha-synuclein, a ubiquitous synaptic protein evident in a number of neurodegenerative disorders.[7] Clinical features that make a diagnosis of idiopathic PD more likely include asymmetrical onset, resting tremor, and a favorable response to levodopa.[8] Good accuracy (approximately 90% positive predictive value) and sensitivity (90%) can now be achieved.[9,10] Nevertheless in the general medical setting parkinsonism is often not diagnosed and specific diagnoses may be inaccurate.[11]

PARKINSONISM AND DEMENTIA

Both PD and other disorders causing parkinsonism can be associated with dementia and cognitive impairment (Table 1). Dementia can be defined by the presence of an acquired cognitive disorder, affecting two cognitive domains (i.e., among memory, language, praxis, visuospatial function and executive function), leading to a decline in activities of daily living.[12,13] Nevertheless, definitions differ between studies (see Definition of Dementia, below). The population prevalence of PD, parkinsonism and the degree of accompanying cognitive impairment vary depending on study methods (methods for case-ascertainment and diagnostic definitions) and the age of the

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Table 1: Causes of parkinsonism associated with dementia in older adults.

Lewy Bodies Disorders
Parkinson's disease
Dementia with Lewy bodies
Other Movement Disorders
Progressive supranuclear palsy
Corticobasal degeneration
Multiple system atrophy
Huntington disease
Primary Dementias
Frontotemporal dementia
Alzheimer's disease
Other Disorders
Cerebrovascular disease
Normal pressure hydrocephalus
ALS-PD-Dementia Complex of Guam
HIV Dementia
Creutzfeld-Jakob Disease

population under study. In most studies the prevalence of dementia associated with PD is 20-40% with an incidence of 2.6-9.5 cases per 100 patient-years of observation.[4,11,14-27] The recent recognition of Dementia with Lewy bodies (DLB), wherein dementia and parkinsonism may occur within one year of each other and are accompanied by cognitive fluctuations and hallucinations, has both complicated and illuminated our understanding of the role of Lewy body pathology in causing dementia with parkinsonism. Although a number of studies have addressed the epidemiology of Parkinson's dementia (PDD), the epidemiology of DLB is not as clear.[28,29]

Impact on Quality of Life, Autonomy and Mortality

The effect of PD on quality of life correlates with progression of symptoms and is most closely related to depression, disability, postural impairment and cognitive impairment.[30,31] The degree of cognitive impairment affecting executive function in patients with PD is associated with impaired decision making capacity.[32] Moreover, PD is associated with long term care placement in Canada.[33] Independent risk factors for nursing home placement among patients with PD include older age, functional impairment, cognitive impairment and hallucinations.[34,35]

In addition to affecting independence, and despite the availability of effective treatments for PD, PD and parkinsonism are associated with increased mortality.[36-39] Parkinson's dementia confers an increased risk of mortality regardless of whether the patient is living in the community[40] or in a nursing home.[41] Given the potential impact of cognitive deficits on meaningful clinical outcomes, its early identification in PD and of PDD and related conditions is important for future planning.

Definitions of Dementia (Table 2)

Several different classification systems are used to diagnose dementia in PD (see Table 2). Among these are the criteria of Cummings and Benson,[42] International Classification for Disease (ICD)-9,[43] ICD-10,[44] the Diagnostic and Statistical Manual (DSM)-III,[45] DSM-III-R,[46] and the DSM-IV.[47] It is clear from examination of Table 2 that a patient could fulfill the criteria for one diagnostic system yet not another. For example, many patients without functional decline and/or memory impairment might meet Cummings and Benson criteria, but would not meet the DSM criteria. The ICD-9 criteria imply that executive dysfunction and memory impairment are both mandatory for the diagnosis. The ICD-10 criteria are vague with respect to whether memory impairment and functional decline are required. Psychiatric etiologies of cognitive disturbance are not specifically excluded in the Cummings and Benson criteria, but are exclusionary in the DSM systems. The variability in definitions used in research contributes to the wide range of PDD prevalence rates, and the inconsistencies reported between studies examining cognition in PD versus PDD.

It could be argued that none of the above diagnostic systems is adequate with respect to PDD. Functional decline related to cognitive decline, as required by the DSM criteria, is often difficult to discern in the PD population due to motor difficulties. None of the above systems classify subtypes of the disorder. Furthermore, no operational criteria specific to PDD are available. A consensus conference should be held to produce operational guidelines outlining specific systematic research criteria for diagnosing dementia in PD (i.e., akin to the NINCDS-ADRDA Work Group for Alzheimer's disease (AD),[48] and the Consensus guidelines for diagnosis of DLB[49]).

Neuropsychological Distinction of Cortical versus Subcortical Dementia

Dementia in PD is commonly labeled "subcortical", entailing slowing of cognitive and motor skills, poor free recall of information in the context of relatively preserved recognition memory (i.e., suggesting a memory retrieval deficit), executive dysfunction (e.g., loss of cognitive flexibility) and mood disturbance (e.g., depression).[50,51] Aphasia, apraxia, agnosia and severe amnesia are uncommon.[42] This is in contrast to a "cortical" dementia picture (e.g., AD) which involves deficits in language and visuospatial functioning and a memory pattern categorized by impaired learning, and rapid forgetting (i.e., no benefit from recognition trials).

Many neuropsychological studies support this distinction.[52,53] For example, although both AD and PD patients have impaired learning and recall, PD patients show evidence of a primacy effect with relative sparing of recognition memory on word list tasks, compared to AD patients who show a reduced primacy effect and poor recognition memory.[54] This suggests a retrieval deficit in PD as opposed to a storage deficit in AD, and corresponds to a subcortical (i.e., frontal-subcortical) pattern of memory disruption in PD as opposed to a cortical deficit in AD (i.e., temporal-hippocampal).

The utility of the cortical-subcortical dementia distinction has been questioned as simplistic and inaccurate. In PD, frontal-subcortical circuitry is affected, implicating disruption of both

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Table 2: Definitions of Dementia

Diagnostic System	MI Required	Other Cognitive Impairment Required	Functional Decline (ADL/IADL)	Other
DSM-III	Y	at least one of: impaired abstract thinking; impaired judgment; aphasia, apraxia, or agnosia; constructional difficulty; personality change	interferes with social or occupational functioning	Evidence of organic factor judged to be etiologically related or an organic etiologic factor can be presumed if conditions other than organic mental disorders have been ruled out and if behavioural change represents cognitive impairment in a variety of areas
DSM-III-R	Y (STM and LTM)	at least one of: impaired abstract thinking; impaired judgment; aphasia, apraxia, or agnosia; constructional difficulty; personality change	interferes with work or usual social activities or relationships with others	Evidence of organic factor judged to be etiologically related or an organic etiologic factor can be presumed if there is no psychiatric disorder that could account for the cognitive impairment
DSM-IV	Y (impaired ability to learn new info. or to recall previously learned info.)	at least one of: aphasia; agnosia; apraxia; disturbance of executive functioning	cognitive deficits cause significant impairment in social or occupational functioning and represent a decline from previous level of functioning	PD dementia characterized by cognitive and motor slowing, executive dysfunction and memory retrieval problems; not better accounted for by psychiatric disorder
ICD-9	Y	impairment of memory and abstract thinking, the ability to learn new skills, problem-solving, and judgment	interferes with occupational and/or social performance	Cognitive impairment often accompanied by personality change or impaired impulse control
ICD-10	?	disturbance of multiple higher cortical functions including memory, thinking, orientation, comprehension, calculations, learning capacity, language and judgment	N	Cognitive impairment often accompanied by or preceded by decreased emotional control, social behaviour or motivation; “no particular distinguishing clinical features of PD dementia have yet been demonstrated”
Cummings and Benson (1992)	N	acquired deficits in at least 3 of the following: language; memory; visuospatial skills; emotional; personality; calculation; abstraction; judgment; executive function	N	Includes psychiatric, structural, metabolic and toxic etiologies

ADL = Activities of Daily Living
IADL= Instrumental Activities of Daily Living
LTM = Long-term Memory
MI = Memory Impairment
STM = Short Term Memory
Y = Yes; N = No

systems.[55] Furthermore, cortical changes occur in PD[56,57] and in DLB[58] and there is evidence of subcortical in addition to cortical degeneration in AD.[59,60] Moreover, damage to subcortical structures (e.g., thalamus and basal ganglia) can cause "cortical" symptoms such as aphasia, and visuospatial difficulties have been reported in subcortical dementias.[55] If these limitations are recognized, as a general scheme for differentiating clinical cognitive deficit patterns or behavioral syndromes, the cortical-subcortical distinction can be helpful.[50,61] The term "frontal-subcortical" has been used increasingly to describe PD and other "subcortical" dementias while the relative contributions of "cortical" and "subcortical" changes remain to be fully elucidated.

Psychometric measures in PD, PDD and DLB

Some researchers classify patients as demented or non-demented on the basis of scores on psychometric rating scales or mental status examinations. Cut-off scores of less than 123 on the Mattis Dementia Rating Scale[62] or less than 24 on the Mini Mental State Examination[63] have been used in this manner, and represent performance two standard deviations below the normative mean. These measures do not account for age and education and have several psychometric weaknesses.[64] They are more useful for staging progress/severity rather than for diagnostic classification.

Specific and unique cognitive patterns have been identified for PD, PDD, and DLB by investigators employing comprehensive standardized neuropsychological batteries. Identification of distinct cognitive profiles contrasting PD and PDD supports a subtype model rather than a simple progression model.[65,66] There has also been a suggestion of distinct neuropsychological profiles based on etiology of PD (e.g., sporadic versus familial).[67] In this small study, patients in both groups (who did not differ with regard to several indicators of disease severity) demonstrated impaired executive functioning, but only those with sporadic PD showed explicit memory recall impairment.

Parkinson's Disease

Parkinson's disease patients without dementia often have impairments on standardized cognitive tests.[68] Many studies are limited by low statistical power, however, and this has led to inconsistencies in the literature.[69] Other factors contributing to these inconsistencies include differing criteria for ruling out dementia, heterogeneous PD samples, variations in methodologies and measures utilized, differences in duration of illness, and varying degrees of control regarding medication regimens. Generalities from better designed studies are reviewed here.

In PD without dementia, simple verbal attentional skills (e.g., Digit Span) are typically preserved.[70-75] Mild impairment on visual attention span tasks has been reported by some authors[76] but not others.[73] Working memory is reduced, notably on more complex measures with dual-task properties.[71,75,77] Learning efficiency and free recall is generally mildly reduced compared to normal controls[73,77-79] although a few studies do not report declines.[80] Recognition memory is typically intact[72,78-80] although this may be impaired in patients who are taking anti-Parkinsonian medication.[69] Long-term (i.e., semantic) memory[65] and remote memory[72] are spared. Psychomotor slowing and increased response latencies are commonly observed[76,78,81] and may account for deficits observed on tasks of higher order cognitive processing, which require a certain minimal speed of processing.[82] Some investigators have reported impairments on language measures while others have not.[70,83,84] A meta-analysis suggested relative sparing of verbal skills.[72] Some investigators report specific visuospatial declines among PD patients without dementia,[70,73,85] but others do not.[78,85] These differences may, in part, relate to primary decreases in psychomotor speed or motor control, abilities often required on visual (e.g., timed) tasks. Zakzanis and Freedman[72] in their meta-analysis, found visuo-spatial tasks to be minimally affected. Impairment of executive function is most consistently reported in the literature and is often the earliest detectable area of cognitive decline. This includes performance on problem-solving tasks, such as the Wisconsin Card Sorting Test and the Odd-Man-Out task, that require concept formation, spontaneous generation of efficient strategies, set-shifting and the use of feedback to modify response patterns.[73,77,78,86]

Parkinson's Disease with Dementia

The dementia of PD may exhibit a "frontal-subcortical" pattern with deficits in problem-solving, speed of processing, learning efficiency, and recall (with relative sparing of recognition memory).[51] Compared to nondemented PD patients, some studies report that PDD patients perform worse on measures of learning efficiency and long delay free word-list recall but not on recognition trials.[83] Others report that PDD patients perform worse on recognition trials compared to both PD patients and normals.[87] A recent meta-analysis suggested that PDD patients exhibit impairment on recognition measures relative to controls, and that they perform worse than non-demented PD patients.[69] Many studies of PDD patients report relative sparing of recognition memory compared to other types of demented patients (e.g., Alzheimer's patients), yet significantly lower performances compared to normals.[54]

Long-term semantic recall is typically spared in PDD[65,88,89] as is simple attention span.[90] Parkinson's dementia patients show mild deficits on verbal measures.[72] For example, PDD patients are impaired compared to normals and PD patients on letter, category and verb production (i.e., action word fluency) tasks.[83,87] In one study, PDD patients performed significantly worse than PD patients on the Boston Naming Test.[83] Zakzanis and Freedman[72] reported that category (i.e., semantic) fluency, WAIS-R Performance IQ, and Purdue Pegboard scores were capable of discriminating PDD patients from normal controls (i.e., less than 5% overlap in test score distributions). Patients with PDD are impaired on problem-solving tasks involving concept formation, hypothesis testing and set-shifting.[89] Psychomotor slowing is also evident in PDD and decision-making time on choice reaction time tasks is substantially worse compared to nondemented PD patients.[81]

Dementia with Lewy Bodies

Lewy body disease may present as a combined cortical-subcortical picture[61,91] that includes deficits in memory, visuospatial function, language, executive function, attention and psychomotor speed. The neuropsychological DLB literature

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is marked by small sample sizes and variability in terms of how DLB is defined (e.g., neuropathological evidence of DLB+AD (i.e., Lewy body variant of AD), neuropathologically pure DLB (i.e., without AD), use of DLB clinical criteria only). Visuospatial/visuoconstructional performance (e.g., Block Design, copy tasks, shape detection, fragmented letter tasks, etc.) is disproportionally and more severely impaired than typically observed among AD patients.[91-100] On the clock drawing/copying task, patients with DLB do not improve on the copy portion of the task, as do patients with PD and AD.[94,101] Psychomotor speed is reduced compared with AD patients.[94,95,98]

Impairment on verbal fluency (FAS, Category) tasks has also been consistently reported.[91-94,101] As well, there is consistent evidence of equivalently impaired semantic memory/knowledge accessibility in AD and LBD.[91,92,95] Hansen et al[91] and Galasko et al[95] reported equivalent impairment of AD and DLB patients on the Boston Naming Test and Category fluency tasks, yet disproportionate impairment by the DLB group on letter fluency. This is in contrast to the commonly observed AD verbal fluency pattern of letter fluency > category fluency.[102] Lambon et al[93] report similar findings, noting naming and verbal fluency impairments in DLB. Also, whereas the DLB group was equally impaired on the two tasks, this group's letter fluency was significantly inferior to that of the AD group. Calderon et al[92] reported equally impaired naming, category fluency and letter fluency between groups of DLB and AD patients, and a trend toward inferior performance on letter fluency by DLB patients.

Patients with DLB are significantly impaired on attentional tasks including Digit Span, vigilance, sustained attention, divided attention, selective attention, and reaction time tasks.[91,92,103,104] There is a suggestion that attentional deficits are more widespread and severe than seen in AD (e.g., see Calderon et al[92]). Comparison with AD samples with regard to Digit Span has produced inconsistent reports (see Lambon et al[93] for review). Fluctuating attention/cognition is characteristic of the LBD syndrome.[103,105,106] This can be assessed using observational methods amenable to clinical practice.[107,108] Recent data suggest that cognitive fluctuation may also occur in PDD, blurring the distinction from DLB.[109]

Patients with DLB may be better oriented than AD patients.[98,110] More severe memory loss than normally seen in PD is common, including impairments on recognition memory tasks.[92,93,98] Episodic memory impairment is generally less severe than in AD[92,94,98,100,110] although a few authors report memory impairment equal to that seen in AD.[91,95] The finding of equally severe memory impairment in LBD and AD groups by Hansen et al[91] and Galasko et al[95] may be related to the fact that their Lewy body groups showed mixed neuropathology (AD+LBD). In neuropathologically pure DLB patients, Salmon et al[94] found significant impairments on all aspects of a verbal learning and recall task (i.e., California Verbal Learning Test), without the typical pattern or severity of losses observed in AD. For example, recognition memory was not exceptionally impaired, and their group did not show an increased propensity for intrusion errors when cued.

Dementia with Lewy bodies patients generally have difficulty in executive function compared to matched controls (e.g., Trails B, Similarities, card sorting tests).[91,94,99,101] Because the initial clinical presentation of DLB can be very similar to AD (with memory complaints and only minimal extrapyramidal signs), referral to a neuropsychologist for detailed assessment may be useful diagnostically.

Incidence Studies of PDD

Incidence studies offer many advantages over cross-sectional prevalence studies including the prospective identification of risk factors for disease and outcomes such as mortality (Table 3). Because of differential mortality,[39,40] prevalence studies do not reflect the true impact of dementia in PD.[111] Incidence rates in recent studies range from as low as approximately 2.1 per 100 patient years of observation in an earlier clinic based sample[21] with a mean age of 56 years to as high as 9.5 per 100 patient years in a recent population-based study that had a mean age of 70 years.[26] In general, participants who are older and more cognitively impaired are less likely to participate and more likely to withdraw from studies.[112] Patients referred to clinics may differ from those in population-based studies. For example, movement disorder clinics might be referred younger or more complicated patients. In contrast to PDD there are no current incidence studies of DLB, reflecting the difficulty in separating the onsets of cognitive and motor impairment, and its more recent definition.

Risk factors for PDD (Table 3)

A case control study of risk factors for PDD identified education (less than high school), motor severity and an older age of onset as predictors.[113] Incidence studies have identified similar factors. Older age, worse motor function, and axial motor impairment are associated with dementia.[24-26] While global cognitive impairment is associated with dementia risk, specific

Table 3: Risk factors for dementia in Parkinson's disease

Demographic	
	Older age[21,24-26]
	Older age at onset[22,23,113]
	Longer disease duration[26]
	Male gender[25]
	Education[25,113]
Motor impairment	
	Worse motor impairment[21,22,24,26]
	Axial motor impairment and bradykinesia[25]
Cognitive	
	Worse global cognitive function[21,26]
	Auditory verbal learning and nonverbal reasoning[22]
	Picture completion, Stroop interference, verbal fluency[23]
	Verbal fluency[114]
	Executive function and verbal learning[115]
Psychiatric	
	Psychosis[26]
Environmental	
	Smoking[16,116]
	Estrogen use as protective[117]

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aspects of cognitive function that have been identified include measures of verbal fluency,[114] verbal memory and executive function.[115] One study showed impairment on the Picture Completion subtest of the WAIS-R, raising the possibility that aspects of visuospatial function may be predictive.[23] A study that examined shared risk factors between AD and PDD found that smoking history predicted dementia in PD while head injury, hypertension and diabetes were not associated with PDD.[116] Estrogen use was a protective factor in some studies.[117,118]

Genetic Risks and PDD

The role of genetic factors in PDD is supported by the increased risk of dementia (including AD) in family members of patients with PDD.[119,120] The effect of polymorphisms associated with an increased risk of AD on the risk of dementia in PD is not clear. One recent study,[121] but not the majority,[122,123] showed an association between the Apolipoprotein E epsilon 4 (Apo E ε4) allele and increased dementia risk in PD. In another, the Apo E e2 allele increased the risk of PDD.[124] Differences between studies might reflect pathological heterogeneity in PDD; for example, PD patients with coexistent AD pathology might have an overrepresentation of the Apo E ε4 allele,[125,126] but this has not been confirmed.[127] The Apo E ε4 may be a shared risk factor for these disorders.[128,129] Dipeptidyl-carboxypeptidase 1 was found to be associated with PD with coexistent AD pathology while butyrylcholinesterase and estrogen receptor polymorphisms were not.[130,131] One study found an association with PDD and estrogen receptor gene polymorphisms in a Japanese population.[132] Mitochondrial genes have been implicated in both AD and PD.[133]

Cases of familial DLB have been described.[134-136] Studies of DLB generally show an association with Apo E ε4.[137-139] Other genes associated with AD that have been examined in relation to DLB include polymorphisms in the amyloid precursor protein,[140] alpha2-macroglobulin,[141] presenilin 1,[142] and alpha-1 anti-chymotrypsin[143] with no clear association. A gene associated with peripheral dopamine metabolism, CYP2D6, has been associated with DLB in some[144] but not all studies.[145] Age-dependent changes in prevalence of alleles, as exemplified by the CYP2D6 allele, might affect results.[146] Mitochondrial genes,[147] and monoamine oxidase polymorphisms,[148] have been examined with conflicting results.

An association between PD and the tau gene, including polymorphisms associated with progressive supranuclear palsy and corticobasal degeneration, has been described in some studies[149,150] but was not confirmed in a pathologically proven sample[151] and the relationship between tau polymorphism and dementia risk has not been examined.[152] Other loci may be involved in PD.[153] The association between tau mutations and frontotemporal dementia, often with parkinsonism (but without Lewy bodies) makes this an important candidate gene for PDD.

Dementia has been observed in autosomal dominant familial PD.[154,155] In a study that examined cognitive function in patients with familial PD, deficits were observed among family members,[156] consistent with a study where family members of PD patients showed motor deficits.[157]

Psychosis and Parkinsonism: PD, PDD, DLB and their overlap

Hallucinations are common in PD and are included in the core criteria for DLB. There is debate as to whether or not these constitute two separable disorders.[158] Dementia with Lewy bodies is defined as a dementia occurring in association with two signs or symptoms among parkinsonism, visual hallucinations and cognitive fluctuations[29] (see Table 4 contrasting PDD and DLB). Patients may have additional manifestations including frequent falls, syncope and additional psychiatric symptoms.[29,159-161] Hallucinations and delusions occur in PD, PDD and DLB with increasing frequency, while depression may be equally frequent in each of these disorders.[162,163] By the original convention, dementia and parkinsonism occur within one year of each other in DLB; however, DLB overlaps pathologically with PD. Recent studies have specified that clinical parkinsonism should have been present for at least two years to assure that PD patients have clear onset of motor signs prior to dementia.[164] Cognitive fluctuations, thought to be suggestive of DLB, also occur in PD.[109] Pathologic changes of AD, specifically amyloid plaques, may or may not coexist with Lewy bodies that are diffusely distributed throughout the neocortex.[158,165] Patients with PD who develop early hallucinations (within one year of treatment) are likely to have a premorbid psychotic illness or DLB.[166] One key clinical feature in DLB is the presence of dramatic neuroleptic sensitivity to conventional and even some atypical neuroleptics in many patients.[167] The recognition of DLB has allowed more prudent treatment of these patients with specific atypical neuroleptics such as clozapine or quetiapine, agents that are also effective for psychosis in PD. The basis of hallucinations in DLB and PD is not known, but neurochemical heterogeneity[168] or specific pathological involvement; for example, involvement of the temporal lobe, may be implicated.[169] It has been suggested that REM sleep behavior disorder may be characteristic of Lewy body disorders and other synucleinopathies[170] and that such problems may contribute to hallucinations.[171] A comparison of extrapyramidal signs in DLB and PD, revealed more severe action tremor, axial symptoms and rigidity in DLB.[172]

Table 4: Contrasting the classic features of Parkinson's disease with dementia (PDD) with Dementia with Lewy Bodies (DLB).

	PDD	DLB
Parkinsonism	More than 1 year	Less than 1 year
Motor Signs	Fluctuating	Milder
Cognition	Stable	Fluctuating
Hallucinations	Drug Related	Independent of drugs
LB Pathology	LB/DLB	DLB
AD Pathology	Yes	Yes
Apo E ε4 risk	?Onset	Association

Pathophysiologic relationship between PDD, DLB and Alzheimer's disease

Pathology

Although the pathologic basis for PDD remains to be fully delineated, increasing evidence supports the notion that it is heterogeneous and that there may be progressive cortical involvement.[173] Coexistent cortical Alzheimer pathology may contribute to decline in PD.[174] However, such changes are not present to a sufficient degree to warrant a diagnosis of coexistent AD in most cases.[165] Cortical Lewy bodies have been better recognized since the introduction of ubiquitin and alpha-synuclein staining. Lewy body densities are significantly associated with cognitive impairment, independent of Alzheimer-type pathology.[175,176] On the other hand many patients with PD without dementia have diffuse Lewy bodies[177] and the presence of cortical Lewy bodies does not distinguish between DLB and PDD. While parahippocampal Lewy bodies were readily identified in one study, regardless of the designation DLB or PDD, DLB patients had more coexistent plaque pathology.[58] Others have found weak correlations between cortical Lewy bodies and dementia.[178,179] In addition to Lewy bodies, Lewy neurites are associated with dementia in both DLB and PDD, but can be found in cases of PD without dementia. Moreover, it is evident that alpha-synuclein staining can also be observed in AD and multiple system atrophy.[7,161] The relationship with AD may be related to interactions between amyloid and alpha-synuclein toxicity that have been observed in model studies.[180]

Neurochemistry

The dopaminergic deficit in PD has been known since the 1960s.[181] However, additional changes have been noted in cholinergic,[182] noradrenergic[183] and serotonergic systems.[184] Cholinergic deficits, reflected in decreased frontal choline-acetyl transferase (ChAT) have been associated with cognitive impairment and dementia in PD.[185] Similar changes have been found in DLB patients who died with mild impairment.[186] Nicotinic changes may occur in PDD and DLB.[187] Measures of serotonin turnover (5-HIAA/5-HT) relative to cholinergic function (5-HIAA/ChAT) may be associated with hallucinations in DLB, in contrast to decreased serotonin turnover in PD.[188]

Cognitive dysfunction has been related to diminished dopamine D1 and D3 receptor binding in PD and PDD.[185,189] An impaired ability to compensate for loss of dopaminergic transmission may be suggested in DLB.[190] The loss of D3 binding, reflecting mesolimbic dopaminergic neurons, might be associated with dopamine non-responsive symptoms.[191]

Neuroimaging

Deficiencies in [^{18}F] fluoro-dihydroxyphenylalanine by positron emssion tomography have been noted in PDD patients in the caudate, ventral striatum and anterior cingulate.[192] Dementia with Lewy bodies can be differentiated from AD and PD on the basis of decreased dopamine transporter binding using [^{123}I]-beta-carbomethoxy-3-beta-(4-iodophenyl)-nortropane, a pre-synaptic dopamine transporter marker: both PD and DLB show decreased transporter binding, which may be more severe in DLB, in keeping with the autopsy-based neurochemical studies.[193,194]

Changes in blood flow may correlate with frontal and global cognitive dysfunction in PD patients.[195-197] Others have not been able to distinguish PDD from AD using [^{18F}]fluorodeoxyglucose positron emission tomography.[198-203] Decreases in perfusion or glucose metabolism in PDD compared to PD have been shown.[204,205] Compared with matched AD patients, PDD patients show a greater decrease in occipital glucose metabolism, with sparing of medial temporal metabolism,[206] findings reminiscent of DLB.[207] Cholinergic binding is reduced in PDD as in AD.[208] One study showed that DLB, PD and AD could be distinguished by the pattern blood flow measured by 99mTc hexamethylpropylenamineoxime SPECT: DLB showed greater hypoperfusion compared to PD, except in the frontal and occipital regions, and frontal perfusion was lower in DLB compared to AD.[209] In DLB more occipital hypoperfusion may be evident,[210-212] and temporoparietal hypoperfusion may correlate with cognitive function.[213] In another study, decreased blood flow using 99mTc hexamethylpropylenamineoxime SPECT in LBD did not correlate with cognitive function, but was similar to that seen in AD patients.[214]

Structural imaging (e.g., CT, MRI) has been applied to the evaluation of dementia in PD. Atrophy on MRI is associated with cognitive decline in PD.[215,216] Hippocampal atrophy can be seen in PD with and without dementia,[217] a finding that was not replicated in another study,[218] but shown in a study of older PD patients.[219] Patients with DLB similarly show medial temporal atrophy,[220] but to a lesser degree than in AD. This pattern in DLB, with sparing of medial temporal structures compared to AD, has been confirmed by other investigators.[221-223] Atrophy in the substantia inominata has likewise been observed in AD and other dementias, including PDD.[224] Patients with DLB have a rate of brain atrophy similar to that observed in AD.[225] Volumetric change of the basal ganglia or occipital lobe has not been seen in DLB, but white matter changes may be observed.[226-228]

Changes on MR spectroscopy in cortical N-acetyl aspartate/creatine[229] are correlated with cognitive change, and are associated with dementia in PD[87] - findings that offer the potential of a widely available dynamic biomarker for dementia in parkinsonian syndromes. Similarly, MR spectroscopy findings have been reported in DLB.[230] In the future, developments in imaging promise to further advance the development of MRI as a biomarker in neurodegenerative disease as well as a differential diagnostic tool.[231]

Impact of Functional Neurosurgery on Cognition

Although a complete review of cognitive consequences of stereotactic surgery for movement disorders is beyond the scope of this article, neuropsychological evaluation is considered a standard part of the presurgical work-up.[232] This process allows for determination of whether the candidate has dementia or cognitive impairment, which increases risk for postoperative cognitive decline. Specific aspects of cognition may be affected by surgery.[233] It is important to establish the person's cognitive capability to understand the decision to have surgery including the risks involved, to provide informed consent and to assess their ability to remain cooperative and alert during the procedure. Evaluation of depression, anxiety and psychiatric disturbance that could interfere with surgery, or be exacerbated by the surgical process, is also important.

Evaluation and Treatment of PDD

Evaluation

Guidelines for the evaluation of people with dementia in the general population have been published, however it is unclear if these apply to PD patients who develop dementia.[13,234-236] Since dementia is part of the natural history of PD, one might argue that blood work and neuroimaging might not be routinely necessary.[237] In the community, even though it is unusual to identify completely reversible causes of dementia, it is more common to identify factors that might contribute to cognitive impairment.[238] The greatest benefit is expected when reversible factors are treated and when patients have mild cognitive impairment. It would, therefore, seem prudent to identify dementia and cognitive impairment as it appears in PD patients and to tailor investigations based on clinical assessment, but not to deny patients an evaluation that might reveal occult contributors to cognitive decline.

Assessment of dementia in the patient with parkinsonism includes a careful history (e.g., focusing on the nature of the deficit, onset i.e., gradual vs. sudden and course, etc.) and examination. A review of systems and medications is important. Mental status evaluation using standardized instruments such as the Mini-Mental State Examination may be helpful, especially if a clear decline is documented.[239] On the other hand the Mini-Mental State Examination is not sensitive to deficits in executive dysfunction, common in PD.[240] The development of brief instruments sensitive to frontal dysfunction, such as the Frontal Assessment Battery and other, related instruments[241,242] may partially fill this void. Nevertheless, it remains important to assess various aspects of individual cognitive domains, including memory, visuospatial function, language and praxis in patients with movement disorders in whom cognitive impairment is of concern. Referral to a neuropsychologist may be helpful in patients in whom cognitive dysfunction is of concern.

A psychiatric history addressing psychotic and depressive symptoms is important, given the prevalence of psychosis and depression in PD.[243] Depression can be associated with impaired cognition.[244] Assessment instruments that can be helpful for grading the degree of depressive symptoms are available. These include the Beck,[245] Hamilton,[246] Geriatric[247] and Cornell[248] Depression Scales. The physical examination of patients with PDD should focus on the identification of potential medical conditions that might exacerbate cognitive dysfunction, including postural hypotension and illnesses unrelated to PD (e.g., pneumonia, congestive heart failure, malignancy, diabetes). New focal neurological signs may suggest cerebrovascular disease. One should also reevaluate the diagnosis, looking specifically for autonomic dysfunction, gaze abnormalities, dysmetria, pyramidal signs, neuropathy, and gait ataxia.

Laboratory testing for occult illness includes complete blood count, glucose, electrolytes, urea, creatinine, liver function tests, thyroid stimulating hormone, and a vitamin B12 level. If there is an acute change, suggesting a delirium, a work-up for infection should be included, along with metabolic studies and other assessments targeted by the history and physical examination. A rapid progression, focal signs, and prominent gait impairment raise the concern of additional intracranial pathology, motivating imaging.

Treatment

Reversible causes should be treated. In particular, medications that might be contributing to cognitive dysfunction should be discontinued. Anticholinergic medications are important to eliminate because they are associated with cognitive impairment.[249-253] Psychosis can improve with reduction and elimination of some medications, particularly selegeline, amantadine and dopamine agonists. In some patients levodopa might have to be decreased. It is not as clear whether reducing antiparkinsonian medications improve cognition, but simplification of medication regimens is reasonable if cognitive impairment is identified. Changes in medication should be undertaken with caution due to the possibility of drug withdrawal delirium, as has been observed with amantadine[254,255] and the risk of inducing neuroleptic malignant syndrome.[256-259]

Currently there are no approved cognition-enhancing drugs for patients with PD. Depression can be treated with counseling and medications. Psychosis that does not reverse with medication changes, or elimination of identifiable triggers can be treated with atypical antipsychotic medications.[260] These include clozapine, quetiapine and olanzapine. Typical neuroleptics predictably worsen parkinsonism.[261] Clozapine is the only agent that has been subject to a double blind placebo-controlled study for psychosis in PD,[262] but must be monitored with weekly or two-weekly blood tests to monitor for agranulocytosis. A placebo-controlled trial that was designed to compare clozapine to olanzapine[263] revealed worsened motor function with olanzapine. Another study found that olanzapine did not improve psychosis.[264,265] Similar concerns apply in DLB.[266] Quetiapine is an atypical antipsychotic that appears effective in open label experience, possibly with less (but not without) potential to exacerbate parkinsonism.[267,268] The propensity for improving psychosis without extrapyramidal effects may relate to the kinetics of drug binding to D2 dopamine receptors, whose blockade leads to parkinsonism.[269] Blockade of serotonergic recepters (5-HT2A) or subtypes of dopaminergic recepters may also be relevant.

Given the profound cholinergic deficits in PD and PDD, cholinergic enhancing medications are under evaluation in PDD. Nevertheless there remain concerns regarding the possibility of exacerbating motor symptoms.[270,271] Aplacebo-controlled trial of rivastigmine, a cholinesterase inhibitor, has demonstrated cognitive and behavioral improvement in DLB.[272] Open label experience with rivastigmine has been published for patients with PDD and has shown improvement of psychotic symptoms, sleep disturbance and caregiver distress.[273,274] Improved psychosis has been similarly shown with donepezil.[275,276] Recently, a placebo-controlled crossover study demonstrated significant improvement in PDD patients treated with donepezil.[277] Open label benefits in cognitive function has also been reported for PDD with donepezil[278] and tacrine.[279] Medications that directly affect the nicotinergic system may have promise in PDD.[280-282] Modulation of other neurotransmitter systems in treating cognitive decline has not been as extensively examined.

Competency and advance directives

Because of the cognitive declines often noted among PD patients, decision-making competence is sometimes called into question. For example, capacity to consent to medical treatment

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may be reduced by impaired executive function. Recent research on cognitively impaired PD patients reported impaired consent capacity under four different legal standards, particularly with regard to comprehension of treatment information (including risks and benefits) and the provision of rational/logical reasons for a treatment choice.[32] Furthermore, performance on cognitive tests predicted performance on measures of three of the four legal competence standards.[32] Neuropsychological assessment is often conducted to assist with competency assessment.

Even if the patient is cognitively competent, planning for the future is at issue in any progressive neurological condition. That is, it is important to plan for future health care and personal affairs. It is recommended that individuals prepare personal directive and enduring power of attorney documents at a time when they are cognitively competent, as a safeguard, in case cognitive difficulties progress. These documents vary in nature by jurisdiction. Typically, however, the personal/advanced directive allows for designation of an agent to make decisions on one's behalf should one become mentally/cognitively incompetent. Information covered includes not only the name of the individual to whom this decision-making power is designated, but also an outline of the individual's health care wishes. The Enduring Power of Attorney also names an agent, but this document is typically concerned only with management of the individual's financial affairs should they become cognitively incompetent. Declaration of incompetence by two health care professionals is typically required for activation of these documents. In most states/provinces, if an individual does not have a personal directive and Enduring Power of Attorney and has lost capacity, guardianship/trusteeship are sought (i.e., person is no longer capable of assigning an agent for a personal directive or power of attorney).

Summary

Cognitive impairment is common in PD and is a major cause of disability. While clinical and psychological risk factors are continuing to be defined, it is likely that imaging and genetic predictors will soon be identified. This will provide insight into the pathophysiology of dementia in addition to predictive potential. Such studies will then need to be coupled with pathological investigations of well-defined, longitudinally assessed, cohorts of patients, as has been done in AD. This approach will allow the border-zone between Lewy body disorders and other age related disorders to be clarified. Clearly the future hope is to develop treatments that can accompany supportive management with the goal of preventing dementia.

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