Dementia associated with Parkinson's disease

Murat Emre

Dementia affects about 40% of patients with Parkinson's disease; the incidence of dementia in these patients is up to six times that in healthy people. Clinically, the prototype of dementia in PD is a dysexecutive syndrome. Loss of cholinergic, dopaminergic, and noradrenergic innervation has been suggested to be the underlying neurochemical deficits. Nigral pathology alone is probably not sufficient for the development of dementia. Although there is some controversy with regard to the site and type of pathology involved, dementia is likely to be associated with the spread of pathology to other subcortical nuclei, the limbic system, and the cerebral cortex. On the basis of more recent studies, the main pathology seems to be Lewy-body-type degeneration with associated cellular and synaptic loss in cortical and limbic structures. Alzheimer's disease-type pathology is commonly associated with dementia but less predictive. Recent evidence from small studies suggests that cholinesterase inhibitors may be effective in the treatment of dementia associated with PD.

Lancet Neurology 2003; **2:** 229–37

Idiopathic Parkinsons's disease (PD) is one of the most common neurodegenerative disorders. Contrary to the initial assumption that cognitive dysfunction is not an essential feature of the disease, it has become increasingly apparent that patients with PD can have impairment of certain cognitive functions and develop dementia. For practical purposes cognitive dysfunction in patients with PD can be classified as domain-specific cognitive impairments, not extensive or severe enough to qualify as dementia, and cognitive deficits severe and extensive enough to fulfil the DSM IV criteria[1] for the diagnosis of dementia. In this article I review research into dementia syndrome associated with PD: its epidemiology, clinical profile, associated neurochemical deficits, correlates in neuroimaging, clinicopathological correlations, diagnosis, and treatment.

Epidemiology

Prevalence

The prevalence of dementia in PD was reported to range from 2% in early-onset cases[2] to 81% in an unselected patient population.[3] In a review of 27 studies, Cummings and co-workers[4] found an average prevalence of 40%. The variation between different studies is probably due to the different methods of cognitive assessment, how dementia was defined, the study populations chosen, and the data collection methods. There have been several cross-sectional, population-based studies in which prevalance figures were calculated. Dementia was found in 29% of all identifiable patients with PD in southern Finland.[5] In a study conducted in the general population, the prevalance of dementia among patients with PD was 41%. An association with age was striking: the prevalance was zero in patients below age 50 years and 69% in patients above age 80 years.[6] Similarly, in a prospective observational study, Reid and colleagues[7] reported a prevalance of 37% versus 9% in patients whose disease had begun after or before age 70 years, respectively; after 5 years follow-up the prevalance of dementia had risen to 62% and 17%, respectively. In a community-based study of patients with probable PD 44% of the patients met DSM IV criteria for dementia.[8] In another community-based study of 220 000 inhabitants in Norway the prevalance was found to be 28%.[9]

Panel 1. Risk factors for dementia in patients with PD

- Advanced age
- Advanced age at onset of motor symptoms
- Early occurrence of levodopa related confusion or pscyhosis
- Presence of speech and axial involvement
- Severe motor symptoms, especially bradykinesia
- Poor cognitive (especially verbal fluency) test scores
- Depression
- Smoking

Incidence

Incidence studies may give a more accurate estimate of risk of dementia in PD because of their prospective nature and relative freedom from survival bias. Incidence of dementia was found to be consistently higher in patients with PD than in people without the disorder: Mindham and co-workers[10] found the number of patients with dementia to be four times higher than expected over a period of 3 years. Rajput and colleagues[11] reported an incidence nearly four times higher over 5 years; relative risk over 2 years follow-up was 1·7.[12] In a prospective study, incidence after 5 years was 69 per 1000 person-years, and by age 85 years the risk of dementia was 65%.[13] In another prospective study the incidence of dementia was six times higher in patients with

ME is at the Department of Neurology, Istanbul Faculty of Medicine, Istanbul, Turkey.

Correspondence: Prof Murat Emre, Istanbul Faculty of Medicine, Department of Neurology, Behavioral Neurology and Movement Disorders Unit, Istanbul University, 34390 Çapa Istanbul Turkey. Tel/fax +90 212 5338575; email muratemre@superonline.com

PD than in controls.[14] Finally, in a survey in which 83 patients and 50 controls, who were free of dementia at baseline, were followed over 10 years[15] and 14 years[16] the cumulative incidence was 38% and 53%, respectively.

Risk factors

Several features are consistently reported to be associated with prevalant dementia (panel 1). These risk factors include age at onset, age at the time of study, duration of the disease, akinetic-rigid syndrome,[2,6,9,17] depression, and atypical neurological features (such as early occurrence of autonomic failure, symmetrical disease presentation, and moderate response to dopaminergic treatment).[9] The ApoE 4 allele, which has been consistently shown to be associated with a higher risk of Alzheimer's disease (AD), does not constitute a risk factor for dementia in patients with PD.[18]

Several baseline characteristics have been reported to be associated with high risk of incident dementia. These include age at onset and at the entry to the study,[14,16,19] motor disability, cognitive scores,[11,13,18] confusion or pscyhosis while being treated with levodopa,[19] occurrence of early onset drug-related hallucinations,[20] motor features indicative of predominantly non-dopaminergic deficiency such as speech and axial impairment, severity of bradykinesia,[21] presence of depression,[12,19,22] and current—less so past—smoking.[23] Poor verbal fluency was found to be significantly and independently associated with incident dementia.[24] Older patients with a high severity of motor symptoms at baseline had a 9·7 times increased risk of incident dementia, compared with younger patients with lower motor-symptom severity, which suggests a combined effect of age and disease severity.[25]

Dementia is a major risk factor for nursing home placement and the risk of death in patients with PD is substantially higher for those with dementia than those without: the survival rate of patients with dementia was found to be significantly shorter compared with non-demented patients.[7,10,26,27]

In summary, up to 40% of patients with PD develop dementia, the incidence is up to six times higher than age matched controls; older age at onset and atypical features seem to be the main risk factors.

Clinical features of dementia associated with PD

The prototype of dementia associated with PD is a dysexecutive syndrome in which impairment of executive functions is the main feature.[28–30] The profile of dementia encompasses qualitatively the same type of deficits found in non-demented patients with PD,[31] but the impairments are more extensive and severe (panel 2). The changes in different cognitive domains have been extensively assessed in several studies and described in detail in a recent review.[32] Studies on the profile of cognitive deficits in demented patients with PD, as assessed by formal test batteries, are less extensive.

Attention and memory

Attention was found to be impaired in demented patients with PD,[30] as shown by measures of attention such as cognitive reaction time and vigilance. There was also evidence for fluctuations in attention[33] similar to those found in patients with dementia with Lewy bodies.

Memory—including working memory, long-term memory, visuospatial memory, and procedural learning—is impaired in demented patients with PD, but the impairment differs from the amnesia seen in patients with AD. Deficits in the learning of new information have been consistently reported, although these deficits are less severe than those seen in patients with AD.[29,34,35] Several studies have shown that demented patients with PD have impaired free recall, similar to that seen in AD, but that they benefit substantially from semantic cueing or probing (their recognition being better than free recall), which implies that new information was stored, but not readily accessed.[36,37] Non-demented patients with PD were also found to have impairments in learning and temporal sequencing, which was thought to be due to executive dysfunction.[38] In support of this assumption, memory in demented patients with PD was related to executive function test scores.[37] This suggests that amnesia is not of temporal-limbic type, because patients are able to store information, but is caused by difficulty with the accessing of memory traces, which may reflect a deficiency in internally cued search strageties (ie, patients' ability to spontaneously generate encoding and retrieval strategies) due to dysexecutive syndrome.[32,39]

Executive functions

Impairment of executive functions (defined as ability to plan, organise, and regulate goal-directed behaviour) constitutes the core feature of dementia in PD.[28,30] These deficits, which have been better elaborated in non-demented patients with PD, include impairment in concept formation and rule finding, problem solving, set elaboration and planning, set shifting, and set maintenance.[32] Patients have more difficulties with internally cued behaviour and they benefit substantially from external cues; difficulties are rather due to shifting attention to novel stimuli, whereas perseverative errors are less common.[40] Thus, the type of executive dysfunction in PD differs from that due to frontal cortical involvement.

Panel 2. Clinical features of dementia associated with PD

- Impaired attention with fluctuations
- Impaired executive functions
  - Concept formation
  - Problem solving
  - Set elaboration, shifting, and maintenance
  - Internally cued behaviour; benefit from external cues
- Impaired memory
  - Impaired free recall; benefit from external cues
  - Well preserved recognition
- Impaired visuospatial functions
- Language largely preserved, except for verbal fluency
- Praxis largely preserved
- Personality changes
- Multiple behavioural symptoms

Visuospatial dysfunction, with a progressive pattern of impairment,[41] was described in demented patients with PD.[29,31,35,42] Impairment was more severe in demented patients with PD than patients with AD with similar dementia severity.[35,42] Tasks that required visuospatial analysis and orientation were the most affected, which suggests visual perception was the most impaired function.[31] The visuoperceptive disabilities in a non-selected group of patients with PD were found to be independent of mental deterioration, where it was present.[43] Boller and co-workers[44] found impairments both in visuoperceptual and visuomotor tasks, which were independent of intellectual impairment; however, patients with the largest loss in motor function tended to show the greatest visuospatial impairment. In a review, Cummings and Huber[45] suggested that visuospatial impairment in PD is seen in all subcategories of visuospatial functioning without a specific pattern, except for spared visual sensory abilities and visual recognition. Impairment is especially evident in more complex tasks that require planning and sequencing of responses, or self generation of strategies. Thus, deficits in perceptual motor tasks may, in part, be due to problems in sequential organisation of behaviour.[46]

Language and praxis

Instrumental functions, such as language and praxis, are less impaired in demented patients with PD than in patients with AD.[42,47] Impaired verbal fluency is the main feature, reported to be more severe than that seen in patients with AD.[35,42] Other deficits such as naming difficulties, decreased information content of spontaneous speech, and impaired comprehension of complex sentences were all described in demented and non-demented patients with PD, albeit to a significantly lesser extent than patients with AD.[47–50] Similarly, apraxia is not a common feature of dementia in PD,[42] although impaired ideomotor praxis was described in an unselected population of patients with PD.[51] Many of the described language deficits (such as impaired verbal fluency and naming difficulty), however, may not reflect a true involvement of language functions, but may rather be related to the dysexecutive syndrome (ie, impaired self-generated search).[32,49]

Behavioural and personality changes

There are also multiple behavioural and personality changes in demented patients with PD. All demented patients with PD had evidence of change in personality[31] and depressive symptoms were found to be more common in demented patients with PD than in those with AD.[30,42] When minor forms were included visual hallucinations were found in 70% of demented patients with PD,[52] as opposed to 25% of patients with AD.[53] In a direct comparison of patients with dementia in PD and those with AD, 95% of patients with AD and 83% of those with PD were found to have at least one psychiatric symptom. Hallucinations were more severe in PD, but aberrant motor behaviour, agitation, disinhibition, irritability, euphoria, and apathy were more severe in AD.[54]

In addition to a dysexecutive syndrome in PD, some patients may develop another type of dementia, with a limbic or hippocampal type amnesia, which is sometimes associated with early impairment of language similar to that seen in patients with AD. These individuals may be patients in whom AD and PD coincide or in whom AD-type pathology significantly contributes to the clinical symptoms. Some researchers suggested that PD is associated with different types of dementia.[47,55,56]

Neurochemical deficits

Dopaminergic deficits

Dopaminergic deficit is the main neurochemical impairment in PD. Of the motor symptoms of PD, akinesia is most strongly related to dopamine depletion and intellectual impairment. It was proposed that cognitive impairment, therefore, results from the same subcortical lesion that causes the motor symptoms (ie, lesion of the nigrostriatal dopaminergic system).[57] A more detailed analysis of the relation between cognitive impairment and motor symptoms, however, revealed that cognitive dysfunction correlated strongly with motor symptoms that respond little, if at all, to levodopa, such as impairment of gait and posture and dysarthria. These findings suggest that non-dopaminergic systems are involved.[58,59] Additional evidence for dopaminergic involvement was provided by investigations of young people exposed to the toxin MPTP (1-methyl-4-phenyl-1,2,3.6-tetrahydropyridine), which induces lesions that are confined to dopaminergic systems. Impairment in executive and visuospatial functions and verbal fluency has been decribed in symptomatic and non-symptomatic patients.[60,61] In addition, learning and retrieval were found to correlate with plasma concentrations of dopamine in "on–off" stages, although absolute concentrations of dopamine did not seem to matter.[62] In a recent study, however, levodopa had no effect on working memory.[63] In a study of neuronal loss in the substantia nigra of demented and non-demented patients with PD, dementia was found to correlate with dopaminergic cell loss in the medial part of substantia nigra, which projects to caudate nucleus.[64] Another study, however, showed neither a difference between demented and non-demented patients nor a relation between neuronal loss and dementia.[65] Striatal dopamine concentrations decrease to the same extent in demented and non-demented patients.[66] In neocortical areas, however, the decrease in dopamine concentrations was greater in demented than in non-demented patients with PD,[67] which suggests a role for the degeneration of mesocortical dopaminergic system in the development of dementia. Although some cognitive deficits seem to benefit from treatment with levodopa in experimental studies,[32] the daily clinical experience that dementia does not improve with levodopa treatment suggests that dopaminergic deficit is not the main neurochemical impairment responsible for dementia in PD.

Monoaminergic deficits

The involvement of other ascending monoaminergic systems, namely noradrenergic and serotoninergic pathways, has also been suggested as the cause of cognitive impairment. The locus coeruleus is severely damaged in patients with PD;

both neuronal loss and norepinephrine depletion were more severe in demented patients with PD.[68,69] Concentrations of norepinephrine were low in the cerebral neocortex and hippocampus in another study, but there was no difference between demented and non-demented patients.[67] Scores in several attentional tasks in non-demented patients with PD seemed to correlate with CSF concentration of MHPG (4-hydroxy-3-methoxyphenylglycol), a norepinephrine metabolite.[70] In two small clinical trials, attention or spatial memory seemed to improve in response to adrenergic α_1 or α_2 agonists in non-demented PD patients.[71,72] Some neuronal loss in raphe nuclei and reduced serotonin concentrations in the striatopallidal complex and in various cortical areas, notably in hippocampus and frontal cortex, was also decribed; however, there was no difference between demented and non-demented patients.[67]

Cholinergic deficits

There is substantial evidence that cholinergic deficits due to degeneration of the ascending cholinergic pathways may significantly contribute to cognitive impairment and dementia in patients with PD. A decrease in cholinergic innervation of the cerebral cortex and severe cellular loss in the basal nucleus of Meynert was described in patients with PD;[73–75] this deficit and cellular loss correlated with the level of cognitive impairment and presence of dementia.[76–80] Cognitive impairment was most closely associated with cholinergic, but not monoaminergic, deficits in temporal and archicortical areas.[81] Dubois and colleagues[82] found that low dose hyoscine, an anticholinergic, caused memory impairment in non-demented patients with PD but not in healthy control individuals, which suggests that there is a subthreshold cholinergic deficit in non-demented patients.

In summary, loss of cholinergic, dopaminergic, and noradrenergic innervation might be the neurochemical deficits that underlie cognitive impairment and dementia in PD. It was proposed that, as dopaminergic deficits may partly be responsible for dysexecutive syndrome, cholinergic deficits may cause impairments in memory, attention, and frontal function, whereas noradrenergic deficits may contribute to impaired attention and serotoninergic deficit may cause depressive symptoms.[32,83]

Correlates in neuroimaging

Structural and functional imaging studies with different methods and tracers have been conducted in demented patients with PD. Whereas Huber and co-workers[84] reported that dementia in patients with PD was not associated with any specific pattern of structural MRI abnormalities, hippocampal atrophy on MRI that was even more severe than in patients with AD was described in demented patients with PD.[85] Hanyu and colleagues[86] reported atrophy of substantia innominata in patients with non-AD dementia, including patients with PD, which was similar to that observed in patients with AD. In single-photon-emission CT studies, perfusion deficits were found in bilateral temporal and parietal cortices,[87] as well as in all cortical—especially temporoparietal—areas, in demented patients with PD, whereas in non-demented patients deficits were restricted to the frontal-lobe.[88] In another study, frontal and (less so) parietal hypoperfusion, as assessed by regional cerebral blood flow single-photon-emission CT, was found in demented patients with PD, whereas non-demented patients did not differ from controls.[89] In contrast, Kawabata and co-workers[89] found low cerebral blood flow in frontal and temporal cortices, basal ganglia, and thalamus in non-demented patients; patients with dementia had significant hypoperfusion in the temporal and parietal cortices—a similar pattern to that seen in patients with AD. In a study with hexamethylpropylenamine oxime as a tracer, regional cerebral perfusion was reduced in parietal, temporal, and occipital cortices in demented patients with PD, in all areas in patients with AD, and was normal in non-demented patients with PD.[91] In a review of single-photon-emission CT studies, Bissessur and colleagues[92] concluded that in demented patients with PD, regional cerebral bood flow assessments commonly show frontal hypoperfusion or bilateral temporoparietal deficits. PET studies have shown widespread glucose hypometabolism in non-demented patients with PD. In patients with dementia, PET had also shown a global decrease in glucose metabolism, with more severe abnormalities observed in the temporoparietal regions.[93] A global decrease in cortical glucose metabolism, predominantly in lateral parietal, temporal, and frontal association cortices and posterior cingulate cortex was reported in demented patients with PD and patients with AD; in demented patients with PD, however, hypometabolism was substantial in the visual cortex but less pronounced in the medial temporal cortex.[94] Finally, presynaptic cholinergic terminal density—as measured by single-photon-emission CT with IBVM ([+/-]-trans-2-hydroxy-3-[4-{3-iodophenyl}piperidyl] -1,2,3,4-tetrahydronaphthalene) an in vivo marker of the vesicular acetylcholine transporter—was low only in the parietal and occipital cortices in non-demented patients with PD whereas an extensive decrease in cortical binding, similar to that observed in patients with AD, was found in demented patients with PD.[95]

Clinicopathological associations

The underlying pathology of cognitive deficits and dementia associated with PD has been a matter of controversy, both in terms of site and type of pathology. This debate may be partly due to methodological differences including referral bias in autopsy studies, retrospective nature of clinical diagnosis, different diagnostic criteria (particularly differentiation from dementia with Lewy bodies), and differences in pathological protocols, including staining methods. Studies of clinicopathological associations in demented patients with PD can be broadly classified into three groups by the suggested causes of dementia: subcortical pathology, limbic or cortical Lewy-body-type degeneration, and those suggesting coincident AD-type pathology. An extensive listing of these studies can be found elsewhere.[96]

Subcortical pathology

Because loss of nigral dopaminergic neurons is the main pathology in PD, the obvious assumption was that this could

also cause cognitive impairment, although many—especially young—patients do not show any obvious cognitive impairment despite severe motor symptoms. Evidence for this hypothesis was provided by Rinne and co-workers[64] who found that cellular loss in the medial substantia nigra was associated with dementia, even after accounting for amyloid burden. Furthermore, Jellinger and Paulus[97] found that demented patients with PD had more cell loss in the medial substantia nigra, but also more severe AD-type lesions in isocortex and hippocampus than non-demented patients. Involvement of other subcortical structures such as locus coeruleus and nucleus basalis of Meynert might also underlie dementia.[65] Components of the thalamus assigned to the limbic loop were recently found to bear the brunt of PD-related pathology (Lewy bodies and Lewy neurites), as opposed to a mild pathology in other thalamic nuclei, and it was suggested that damage to the thalamic components of the limbic loop contribute to cognitive, emotional, and autonomic symptoms in patients with PD.[98]

AD-type pathology

Coincident AD-type pathology might cause dementia in PD. Boller and co-workers[26] found AD-type pathology in the cerebral cortices of all severely demented patients, but in only a small proportion of non-demented patients, with PD. In another study amyloid deposition was found in up to 100% of demented patients and 50% of non-demented patients.[99] In a study of 100 patients with histologically confirmed PD, of the 31 patients with well-documented dementia nine had pathological criteria for AD, three had numerous cortical Lewy bodies, two had a possible vascular cause, and 17 had no definite pathological cause; cortical Lewy bodies were found in all patients, demented or not.[100] Several subsequent studies also found that cortical Lewy bodies were present in all patients independent of dementia status. [101] Similarly Braak and colleagues [102] concluded that concurrent incipient AD with fully developed PD is likely to be the cause of impaired cognition, and stage III or higher AD pathology is the most common cause of intellectual decline in PD. In a large study of 610 consecutive patients with parkinsonism, 30% of those with "PD of the Lewy-body type" were demented and dementia was mostly associated with additional pathology (mainly AD-type) while only 3·5% of patients with "pure" PD without additional brain pathologies had dementia.[103] In a more recent small study, regional neurofibrillary tangle severity ratings were found to best account for dementia.[104] Finally, in 200 consecutive autopsy examinations of patients with PD, 33% had moderate to severe dementia during life and the presence of dementia correlated signicantly with AD pathology: only 3% of patients with neuropathological changes representative of PD alone were demented. In contrast 94% of those patients with dementia had cortical neuropathological changes of AD; the relation to Lewy body pathology was not examined in this study.[105]

Lewy-body-type pathology

A third group of studies suggest cortical or limbic Lewy body type degeneration as the main cause of dementia in PD. Kosaka and colleagues[106] found diffuse cortical Lewy bodies (figure 1) in all of 11 demented patients with PD, Lewy bodies were present only in the brainstem of 12 non-demented patients, and senile plaques were widely distributed in all. In another study Lewy-body densities in the cortex (especially in temporal neocortex) correlated significantly with cognitive impairment in patients with PD, independent of or in addition to AD-type pathology.[107] In three recent studies in which α-synuclein antibodies—a more sensitive marker of Lewy bodies—were used, a similar conclusion was reached: α-synuclein positive cortical (especially frontal) Lewy bodies were associated with cognitive impairment, independent of AD-type pathology, in 45 patients with PD.[108] Cortical Lewy bodies were found to be a more sensitive and specific correlate of dementia than AD-type pathology in 22 demented as compared with 20 non-demented patients with PD; AD-type pathology was found in only a few patients[109] Diffuse or transitional Lewy-body disease was found to be the primary pathological substrate in 12 of 13 patients with PD who later developed dementia. AD-type pathology was modest; only one patient had sufficient pathology to qualify for the pathological diagnosis of AD. There were significant correlations between neocortical Lewy-body counts and senile plaques as well as neurofibrillary tangles, which suggests common origins for these pathologies or that one triggers another. In nine non-demented patients there was minimal pathology beyond the brainstem.[96] In two recent studies, cortical densities of Lewy bodies did not distinguish dementia with Lewy-bodies from dementia in PD;[110] however, Lewy-body densities in the temporal cortex were higher in patients with dementia with Lewy bodies.[110] There was a striking association between the distribution of Lewy bodies in the temporal lobe and well-formed visual hallucinations in all patients (figure 2).[111]

In conclusion, many clinicopathological studies suggest that three types of pathology might cause dementia in PD: Lewy-body-type degeneration in cortical and limbic structures, coincident AD-type pathology in cortical and limbic structures, and pathology in subcortical structures (eg, degeneration of the medial susbtantia nigra and nuclei of other ascending pathways). All these pathologies could cause cognitive impairment in PD. On the basis of recent studies with antibodies against α-synuclein that assessed

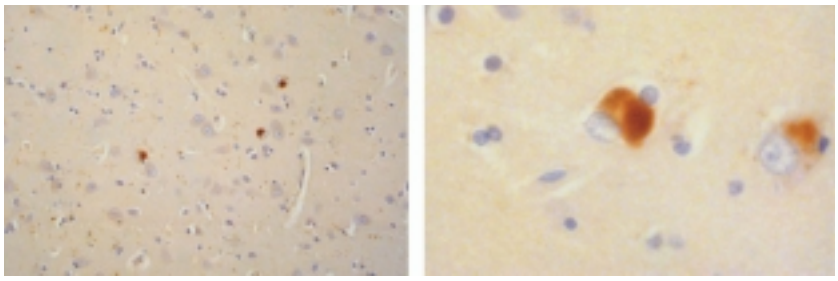

Figure 1. α-synuclein positive Lewy bodies in the cerebral neocortex of a patient with PD who later developed dementia. Original magnifications x10 (left) x40 (right). Courtesy of Dr Tamas Revesz.

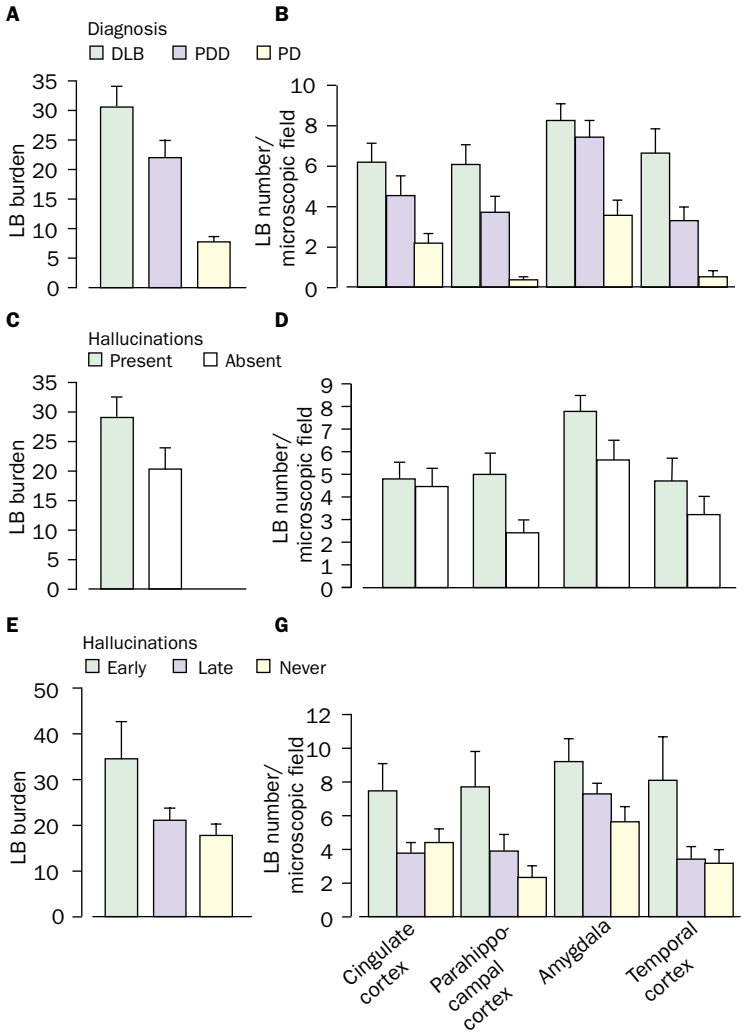

Figure 2. The effects of Lewy bodies on dementia. Total Lewy-body (LB) burden (A) and the individual regions with high LB densities (B) for the three clinicopathological groups, dementia with Lewy bodies (DLB), Parkinson's disease with later-onset dementia (PDD), and Parkinson's disease cases without dementia (PD). The LB burden is calculated by adding the maximum LB density per microscopic field for each of the anterior cingulate cortex, frontal association cortex, parahippocampal cortex, inferior temporal cortex, and amygdala. LB densities were greatest in the amygdala. Both the DLB and PDD groups have greater LB densities than the PD group, although the PDD group was only significantly greater than the PD group in the parahippocampus and amygdala. The DLB group differed from the PDD group in the total sum of LB and in the LB density in the inferior temporal cortex. Bar graph comparing the LB burden (C) and the individual regions with high LB densities (D) for cases who had hallucinations compared with those without them. Cases with hallucinations had greater LB densities in the parahippocampal cortex and amygdala, but no significant differences were found for the overall LB burden, or for the other regions examined. Bar graphs of the total LB burden (E) and the individual regions with high LB densities (F) for the patients who experienced hallucinations early, late, or never in the disease process. Only patients with early hallucinations had a greater LB burden compared with non-hallucinators (E). These patients had higher LB densities in the parahippocampal and inferior temporal cortices (F). Reproduced with permission from Oxford University Press.[110] Courtesy of Heidi Cartwright.

Diagnosis

The diagnostic process in patients with PD and suspected dementia involves two steps: the diagnosis of dementia and differential diagnosis of the cause (ie, if dementia is due to the neurodegenerative process associated with PD or due to another cause).

Diagnosis of dementia in patients with PD may be difficult for several reasons. First, apparent impairment in certain cognitive domains may be difficult to differentiate from motor dysfunction. Second, it may be difficult to decide if impairment in activities of daily living, an essential criterion for the diagnosis of dementia, is due to cognitive or motor dysfunction. Drug effects can further hamper the diagnostic process. Along with a detailed history—which elucidates the onset, course, profile, and chronology of cognitive and behavioural symptoms—neuropsychological testing that is sensitive to executive dysfunction and can differentiate between the type of deficits in certain cognitive domains (eg, storage *vs* retrieval deficit in memory performance) must be done.

The differential diagnosis of dementia in patients with PD includes domain-specific cognitive impairments neither extensive nor severe enough to qualify for dementia, depression, confusional states due to systemic or metabolic disorders, and adverse effects of drugs. Once a dementia syndrome is diagnosed, the differential diagnosis for the cause includes other primary degenerative dementing disorders associated with extrapyramidal features and symptomatic forms of dementia either due to intracranial pathologies, such as normal pressure hydrocephalus, cerebrovascular disease, and tumours or extracranial systemic disorders (including reversible dementias due to adverse effects of drugs such as anticholinergics). Dementia due to PD is included in DSM IV as an entity;[1] the operational criteria are, however, described under "other dementias" which encompasses many other forms of dementia and are, thus, not necessarily specific for this disorder.

When fully established, dementia in PD and dementia with Lewy bodies have substantial overlap, patients may be indistinguishable, both clinically and pathologically, when their history is unknown. On the basis of the current diagnostic criteria for dementia with Lewy bodies,[112] the main difference between these two disorders is that in dementia with Lewy bodies, motor symptoms must not appear more than 1 year before the onset of cognitive symptoms. This time-window is, however, not based on any objective data and is rather arbitrary. Whether these two disorders are motor-onset and cognitive-onset variations of the same disease is a matter of controversy.

several possible pathologies simultaneously, the main change underlying dementia in PD seems to be Lewy-body-type degeneration in the cerebral cortex and limbic structures with associated neuronal and synaptic loss and frequent association of AD-type pathology.

Treatment

Despite optimistic reports in the early years of levodopa therapy, it became apparent in subsequent studies that levodopa has a limited effect on cognitive impairment in PD. The positive effects are probably due to non-specific actions on alertness, mood, and arousal although some more specific effects on dopaminergic transmission may exist for some components of information processing, working memory, or internal control of attention.[32] These beneficial effects, however, may be complicated by serious side-effects such as confusion and pscyhoses, mainly in demented patients.[113,114] There is strong evidence for the involvement of cholinergic deficits in dementia in PD, which prompted the use of cholinergic treatment strategies in this disorder. The first evidence for a favourable effect of cholinesterase inhibitors was reported by Hutchinson and co-workers[115] in six patients with PD and dementia. Tacrine improved cognitive and behavioural symptoms, notably apathy and hallucinations, without detrimental effects on motor functions, which seemed to improve rather unexpectedly. Subsequent small studies tested the effects of donepezil in patients with dementia with Lewy-bodies. Donepezil had favourable effects on confusion, psychosis, and cognition without any deterioration in motor symptoms except for slight worsening of tremor.[116–119] A large, double-blind, placebo-controlled trial in patients with dementia with Lewy-bodies revealed that rivastigmine was superior to placebo especially with regard to hallucinations, anxiety, apathy, and delusions; mental speed also seemed to improve.[120] Recent studies suggest that cholinesterase inhibitors can improve cognitive and behavioural symptoms in dementia in PD. Rivastigmine improved cognitive and general functions,[121] as well as hallucinations, sleep disturbance, and caregiver distress[122] in two open studies. In one small, double blind and two open studies, donepezil reduced cognitive and behavioural deficits in demented patients with PD without worsening parkinsonism.[123–125] In a small open study galantamine was also reported to improve cognitive functions, hallucinations, and parkinsonism in about half of the patients, although parkinsonism worsened in two.[126] In summary there is evidence, mostly from small open studies, that cholinesterase inhibitors might be beneficial in the treatment of dementia in PD. The confirmation of this hypothesis, however, awaits the results of on-going, large, double-blind, placebo controlled trials.

Psychotic symptoms such as hallucinations and delusions are frequently seen in demented patients with PD. In a recent review the use of atypical antipsychotics in the treatment of psychosis associated with PD was assessed. Low-dose clozapine (<50 mg/day) was concluded to be effective and to have an acceptable safety risk. Quetiapine was thought of as investigational only, the data suggested efficacious and good tolerability but were from open studies. Evidence for the efficacy of olanzapine was concluded to be insufficient.[127]

In addition to symptomatic treatment attempts, there have been few studies on the prophylaxis of dementia in PD. Whereas selegiline and tocopherol had no significant beneficial effects in a placebo controlled prospective trial,[128] postmenopausal use of oestrogen replacement therapy was associated with a reduced risk of dementia in PD in a cross-sectional epidemiological study[129]

Search strategy and selection criteria

This review was based on articles identified by a PubMed search with the terms "Parkinson's disease" and "dementia" as the main keywords. Articles were also identified from the reference lists of relevant articles, review papers, and book chapters. Articles for citation were chosen for their historical value, importance, representativeness, ease of access, timeliness, or for the further reading opportunities they provide; larger reviews were preferred where available.

Acknowledgments

I thank Dr Basar Bilgiç for his substantial help with the literature search and in the preparation of the review.

Conflict of interest

I have been consultant in clinical trial protocols on Parkinson's and Alzheimer disease for Novartis, Pfizer, and Eisai.

Role of the funding source

No funding sources were involved in the preparation of this review or the decision to submit it for publication.

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