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Be vigilant for dementia in Parkinson's disease

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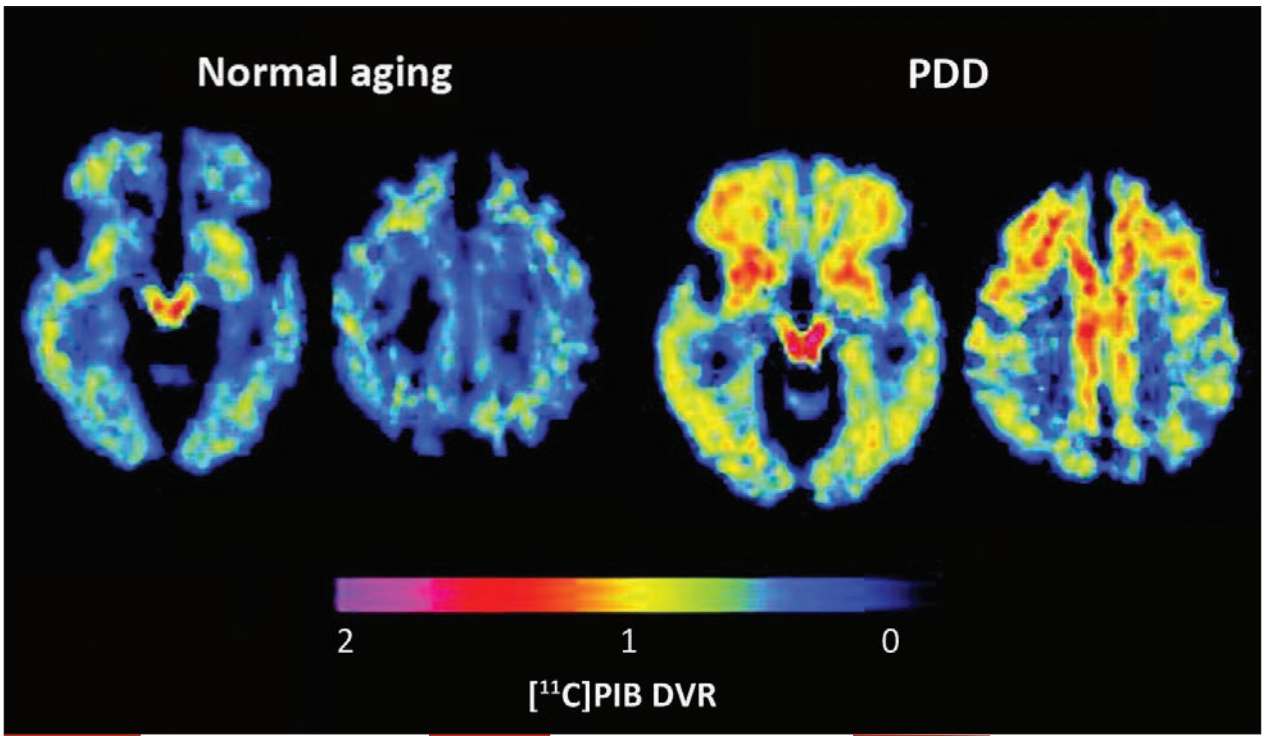

FIGURE 1
Axial summed [11C] PiB PET images in normal aging and in Parkinson's disease dementia (PDD). The PDD patient showed higher amyloid deposition compared with the healthy individual

Which cognitive domains are commonly affected?

PARKINSON'S DISEASE IS A CHRONIC, PROGRESSIVE NEURODEGENERATIVE DISORDER CHARACTERISED by the cardinal motor symptoms of tremor, rigidity and bradykinesia.

Non-motor features including psychiatric symptoms[1] and cognitive decline are also important debilitating aspects of the disease, as they significantly affect quality of life and increase the burden on the carer.[2] It is estimated that up to 80% of patients with Parkinson's disease will eventually develop cognitive impairment over the course of their illness.[3] Cognitive impairment may affect 20-25% of patients at the time of diagnosis and prior to initiation of dopaminergic therapy.[4,5] Cognitive deficits in Parkinson's disease range from subtle visuospatial deficits to Parkinson's disease-related mild cognitive impairment (MCI) and dementia. The distinction between Parkinson's disease MCI and dementia relies on whether cognitive impairment is severe enough to affect activities of daily living.[6]

What are the risk factors for dementia?

CLINICAL CHARACTERISTICS AND RISK FACTORS

Commonly affected cognitive domains in Parkinson's disease include executive function, visuospatial ability and attention control.[7] Visuospatial memory and executive function are essential cognitive skills to carry out daily living tasks and maintain a higher level of adaptive living skills and quality of life. In addition to these cognitive domains, patients with Parkinson's disease dementia may present with deficits in language function and verbal memory.[8-10]

Psychosis may occur in approximately 40% of patients with Parkinson's disease and is associated with an increased risk of developing cognitive impairment.[11] In the early stages of Parkinson's disease, psychosis is most commonly characterised by visual hallucinations, such as 'presence' hallucinations (a feeling that someone is present) and 'passage' hallucinations (where a person, animal or object is seen briefly passing in the peripheral visual field). As the disease progresses formed visual hallucinations of animals or people can also occur.[12-14]

Delusions, auditory and other types of hallucinations most commonly seen in primary psychotic disorders are seen much less frequently in Parkinson's disease.[15] Psychotic symptoms in patients with Parkinson's disease are associated with higher mortality and morbidity rates, longer nursing home stays and increased strain and burnout in carers.[16-18]

Which patients should be referred?

Studies have shown that patients »

Table 1

Risk factors for Parkinson's disease dementia

- Older age of onset
- Visual hallucinations
- Severe motor symptoms with akinetic-rigid subtype
- Olfactory dysfunction
- Working memory and visuospatial dysfunction
- Impaired semantic fluency

with a previous history of visual hallucinations had an increased risk of developing dementia four to eight years following diagnosis of Parkinson's disease.[3,19,20] Other clinical risk factors associated with cognitive decline in Parkinson's disease include older age of onset, severe motor symptom burden and in particular akinetic-rigid subtype and olfactory dysfunction, see table 1, above.[21-23]

In the CamPalGN study, 36% of untreated Parkinson's disease patients had cognitive impairment and 11% had isolated frontostriatal cognitive deficits.[24] At 3-5 years' follow-up, 10% of patients had developed dementia, while 57% showed evidence of cognitive impairment, with frontostriatal deficits being more common in the non-demented group.[25] By ten years, the prevalence of dementia was 46% and the most important neuropsychological predictors of cognitive decline were semantic fluency and the ability to copy an intersecting pentagons figure.[26]

The Parkinson Associated Risk Syndrome (PARS) study has shown impaired working memory in individuals at risk of developing Parkinson's disease suggesting that this cognitive subdomain may be affected even before the onset of motor symptoms.[27]

NEUROBIOLOGICAL MECHANISMS

The mechanisms underlying cognitive impairment in Parkinson's disease have not been fully elucidated. Postmortem studies have shown limbic and cortical α-synuclein pathology in the brain of patients with Parkinson's disease dementia.[28] Neuroimaging studies have shown that one third of Parkinson's disease dementia patients display β-amyloid plaque pathology. Greater β-amyloid deposition is a risk factor for cognitive impairment in patients with Parkinson's disease and accelerates cognitive decline once established, see figure 1, p11.[29,30]

The co-existence of α-synuclein, β-amyloid plaque and tau aggregates has been shown to worsen cognitive impairment in Parkinson's disease.[31] Mesolimbic and mesocortical dopaminergic deficits are associated with cognitive dysfunction in Parkinson's disease.[32,33] However, cognitive deficits do not respond well to dopaminergic treatment,[34] suggesting that other non-dopaminergic systems may contribute to cognitive impairment in Parkinson's disease. Cortical and subcortical cholinergic dysfunction can occur in patients with Parkinson's disease dementia and is usually greater in patients with dementia occurring later in the disease course.[35,36]

Noradrenergic and serotonergic systems may also be involved in the development of cognitive deficits in Parkinson's disease since both atomoxetine and citalopram have been shown to improve executive deficits in Parkinson's disease.[37] Postmortem studies have demonstrated that mitochondrial complex 1 activity and mitochondrial DNA levels are decreased in the brain of Parkinson's disease dementia patients.[38]

Neuroinflammation and in particular increased microglial activation contributes to neuronal loss in Parkinson's disease dementia.[39]

In conclusion, alongside α-synuclein, tau and amyloid pathologies, several other mechanisms, including different neurotransmitter systems, neuroinflammation, and mitochondrial dysfunction, are likely to contribute to cognitive decline in Parkinson's disease.

REFERRAL

Patients with Parkinson's disease who present with symptoms of cognitive decline, behavioural changes or psychotic symptoms should be referred for further investigation.

Identifying these symptoms may require targeted questions during the interview, information from the care givers, or the use of neuropsychiatric and cognitive assessment tools such as the Neuropsychiatric Inventory (NPI) and the Montreal Cognitive Assessment (MoCA) test. The self-reported Non-Motor Symptoms Questionnaire (NMSQ) is a valuable tool to screen for subjective cognitive impairment and has been recommended by NICE and Parkinson's UK.

In a primary care setting, basic investigations should include routine haematology, biochemistry tests (electrolytes, calcium, glucose, renal and liver function), thyroid function tests, serum vitamin B12 and folate levels. A midstream urine test should be included in cases where delirium is suspected, while the need for a chest X-ray or ECG are determined by clinical presentation.

Parkinson's disease patients with suspected cognitive impairment should then be referred to specialist movement disorders clinics. The differential diagnosis in such cases is broad and includes Parkinson's disease MCI, Parkinson's disease dementia, Lewy body dementia, delirium, other dementias, other psychiatric and medical conditions, substance misuse and side effects of medication, see tables 2 and 3, opposite.

The work-up of these patients should include detailed neuropsychological assessment, targeted physical examination, blood tests and neuroimaging studies and referral to a movement disorders clinic.

Once a diagnosis has been established, underlying causes should be addressed and the patient needs to be monitored closely over time.

Diagnosing Parkinson's disease MCI or Parkinson's disease dementia remains a challenge for clinicians from all specialties. Fluctuation in motor symptoms that interfere with daily activities, non-motor symptoms that affect cognitive function and neuropsychological assessments as well as medication already used need to be taken into consideration during the diagnostic process and before implementing targeted management strategies.[40,41]

MANAGEMENT

Parkinson's disease dementia is a progressive disease that could eventually lead to palliative care; thus evidence-based practice is critical in helping patients receive high quality care.

After ruling out other causes of cognitive impairment, GPs should refer the patient to secondary care. A thorough medication review should be carried out with a view to discontinuing any non-parkinsonian medications acting on the central nervous system (e.g. tricyclics), anticholinergic drugs (e.g. trihexyphenidyl), amantadine, and optimising dopaminergic treatment.

As yet, there are no pharmacological disease modifying therapies able to prevent or delay deterioration of cognitive impairment in Parkinson's disease although some medications may ameliorate cognitive and behavioural symptoms. To date, randomised placebo-controlled trials

and a Cochrane review support the use of cholinesterase inhibitors in the treatment of cognitive decline and psychosis in Parkinson's disease.[42,43] However, the response to cholinesterase inhibitor therapy is variable and the distressing side effects such as worsening of tremor, nausea and vomiting may impair compliance. Further research is needed to identify those patients who will benefit from this treatment.

A multidisciplinary team approach is essential. Patients with speech and swallowing difficulties will need speech and language assessment, whereas motor symptoms often require input from a physiotherapist and occupational therapist.

In the context of complex multidrug regimens for motor symptoms with multiple adverse effects, non-pharmacological treatment approaches are highly relevant. NICE recommends the use of psychological interventions for patients with Parkinson's disease dementia.[44] These include cognitive behaviour therapy (CBT), animal-assisted therapy, reminiscence therapy, multisensory stimulation and exercise. CBT can also alleviate impulse control disorders in Parkinson's disease.[45]

Cognitive training (CT) is a promising prevention tool for cognitive impairment in Parkinson's disease. CT may ameliorate or delay cognitive decline by slowing the progression of neurobiological changes contributing to dementia and by promoting processes such as neuroplasticity and/or cognitive reserve.[46] CT programmes have been shown to improve working memory and produce significant transfer improvements to working memory tasks that were not part of the training programme, episodic memory, fluid intelligence and reasoning.[47]

One of the most important aspects in helping patients and their carers with dementia is to plan management at the very beginning, before the point of diagnosis when a patient presents to their GP with symptoms of dementia.

A considered approach to treatment and care planning of the various stages of Parkinson's disease dementia requires that at the early stage the palliative care

Table 2

Diagnostic criteria for Alzheimer's disease, Parkinson's disease dementia and dementia with Lewy bodies

Alzheimer's disease	Parkinsons's disease dementia	Dementia with Lewy bodies
Movement disorder or focal neurological findings absent until late in the course of illness	Movement disorder precedes cognitive decline	Cognitive impairment occurs before or concurrently with parkinsonism but cognitive impairment is more prominent than movement disorder
Insidious onset of impairment in learning and recall plus one or more of the following: ● Aphasia ● Apraxia ● Agnosia ● Executive dysfunction	Insidious onset of: ● Impaired attention ● Executive dysfunction ● Language impairment ● Apathy ● Personality changes ● Psychosis and visual hallucinations	● Pronounced fluctuation in memory function ● Visual hallucinations ● Parkinsonism symptoms ● REM sleep behaviour disorder ● Severe autonomic dysfunction

Table 3

Clinical features of Parkinson's disease dementia compared with delirium and Parkinson's disease psychosis

	Parkinson's disease dementia	Delirium	Parkinson's disease psychosis
Onset	Insidious	Acute or subacute	Varies
Course	Steadily progressive, gradual decline in cognition	Develops over a short period of time, tends to fluctuate	Progressive with exacerbations and remissions
Conscious level	Clear	Often impaired, fluctuating over time	Clear
Cognitive deficits	Complex attention, executive function, learning and memory, language, perceptual-motor, social cognition	Significant changes in baseline cognition with memory deficits, reduced attention and disorientation	No significant change in baseline cognition
Hallucinations	Not common	Common	Characteristic
Key symptoms	● Clear evidence of decline in memory and learning	● Reduced ability to direct, focus, sustain and shift attention ● Reduced orientation to the environment	● Mild visual distortions, visual hallucinations, especially presence or passage, auditory hallucinations, delusions

»

key points

SELECTED BY

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It is estimated that up to 80% of patients with Parkinson's disease will eventually develop cognitive impairment over the course of their illness. Even at the time of diagnosis, cognitive impairment has been reported in 20-25% of patients. Commonly affected cognitive domains are executive function, visuospatial ability and attention control. In addition, patients with Parkinson's disease dementia may present with deficits in language function and verbal memory.

Psychosis may occur in approximately 40% of patients with Parkinson's disease, and is associated with an increased risk of developing cognitive impairment. In the early stages of Parkinson's disease, psychosis is most commonly characterised by visual hallucinations, such as 'presence' hallucinations (a feeling that someone is present) and 'passage' hallucinations (where a person, animal, or object is seen briefly passing in the peripheral visual field). As the disease progresses formed visual hallucinations of animals or people can also occur.

Studies have shown that patients with Parkinson's disease with a history of visual hallucinations had an increased risk of developing dementia, four to eight years following diagnosis of the disease. Other clinical risk factors associated with cognitive decline in patients with Parkinson's disease include older age of onset, severe motor symptom burden and in particular akinetic-rigid subtype and olfactory dysfunction.

Patients with Parkinson's disease who present with symptoms of cognitive decline, behavioural changes or psychotic symptoms should be referred for further investigation. Parkinson's disease patients with suspected cognitive impairment should be referred to specialist movement disorders clinics. The differential diagnosis in such cases is broad and includes Parkinson's disease mild cognitive impairment, Parkinson's disease dementia, Lewy body dementia, delirium, other dementias, other psychiatric and medical conditions, substance misuse and side effects of medication.

There are no pharmacological disease modifying therapies able to prevent or delay deterioration of cognitive impairment in Parkinson's disease, although some medications may ameliorate cognitive and behavioural symptoms. To date, randomised placebo-controlled trials support the use of cholinesterase inhibitors in the treatment of cognitive decline and psychosis in patients with Parkinson's disease. However, the response to treatment is variable and side effects such as worsening of tremor, nausea and vomiting may impair patient compliance. NICE recommends the use of psychological interventions for patients with Parkinson's disease dementia. These include cognitive behaviour therapy (CBT), animal-assisted therapy, reminiscence therapy, multisensory stimulation and exercise. CBT can also alleviate impulse control disorders in Parkinson's disease.

focuses on educating the patient and family about symptoms, treatment options, prognosis and identifying support resources with advance care planning discussions.

In the middle stages as the disease progresses, the patient gradually loses various modalities of function, requiring varying levels of assistance. At this stage palliative care providers may begin to work more closely with care givers, to develop coping strategies for the shifting roles that may occur in the family unit.

In the late stages of the disease, dementia, debility, dysphagia, and difficulties with communication become more prominent. Furthermore, at this stage the psychosocial aspects of the disease can be severe. A multidisciplinary approach may be required to facilitate home care services including home safety evaluations to improve independence.

Evidence has shown that patients who are more prepared for a diagnosis of dementia seem to be better adjusted to receiving one.[48] The GP should arrange a referral to specialist services and discuss what will happen to the patient during the assessment process and how long this might take. The GP can also provide support with managing any other conditions the patient may have (e.g. diabetes, hypertension, depression and anxiety).

Managing depression in patients with Parkinson's disease should involve exclusion of other medical problems that can cause depressive symptoms, such as hypothyroidism. SSRIs and CBT are considered first-line treatments, while tricyclic antidepressant drugs are poorly tolerated because of their anticholinergic effect.

Moreover, GPs can offer general advice on ways of preventing illness and promoting fitness including nutritional advice and counselling.

GPs can also make the patient and their carer aware of planning for the future and lifestyle changes that will have to be made, including possible driving restrictions, see Useful information box, p15.

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Useful information

Parkinson's UK
www.parkinsons.org.uk

The Cure Parkinson's Trust
www.cureparkinsons.org.uk

Driving and Vehicle Licensing Agency
Assessing fitness to drive: a guide for medical professionals
www.gov.uk/government/publications/assessing-fitness-to-drive-a-guide-for-medical-professionals

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