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Short Communication

Cognitive impairment in Parkinson's disease: Multidisciplinary Symposium Clinical Management of Parkinson's disease

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Abstract

People with Parkinson's disease (PD) and their care partners frequently report cognitive decline as one of their greatest concerns. Mild cognitive impairment affects approximately 20–50% of people with PD, and longitudinal studies reveal dementia in up to 80% of PD. Through the Parkinson's Disease Foundation Community Choice Research Award Program, the PD community identified maintaining cognitive function as one of their major unmet needs. In response, a working group of experts across multiple disciplines was organized to evaluate the unmet needs, current challenges, and future opportunities related to cognitive impairment in PD. Specific conference goals included defining the current state in the field and gaps regarding cognitive issues in PD from patient, care partner, and healthcare professional viewpoints; discussing non-pharmacological interventions to help maintain cognitive function; forming recommendations for what people with PD can do at all disease stages to maintain cognitive health; and proposing ideas for how healthcare professionals can approach cognitive changes in PD. This paper summarizes the discussions of the conference, first by addressing what is currently known about cognitive dysfunction in PD and discussing several non-pharmacological interventions that are often suggested to people with PD. Second, based on the conference discussions, we provide considerations for people with PD for maintaining cognitive health and for healthcare professionals and care partners when working with people with PD experiencing cognitive impairment. Furthermore, we highlight key issues and knowledge gaps that need to be addressed in order to advance research in cognition in PD and improve clinical care.

Introduction

Neuropathological studies of patients who died with PDD demonstrate widespread cortical and limbic involvement with neurodegeneration, neuronal loss, and deposition of Lewy bodies and Lewy neurites.Clinical correlations, however, yield conflicting results as to which neuroanatomical areas and neuropathologies are most important in the clinical expression of PD cognitive impairment.Basal ganglia pathology, particularly in its associative (cognitive) areas, may also contribute to cognitive deficits.While PD is an α-synuclein-mediated disease, autopsy studies and cerebrospinal fluid biomarker studies suggest that amyloid pathology contributes to cognitive impairment in PD in some cases.Co-existing synuclein and amyloid pathology may invoke synergistic processes.Cerebrovascular disease contributes to some cases of PD cognitive impairment, with evidence of microvascular ischemia on pathology and white matter hyperintensities on neuroimaging.PD cognitive impairment also reflects dopaminergic, cholinergic, serotonergic, and noradrenergic neurotransmitter deficiencies. Functional neuroimaging and neuropathological studies measuring neurotransmitters support the roles of dopaminergic and cholinergic deficits in PD cognitive impairment.

The prevalence of dementia in PD increases with age, disease duration, motor severity, postural instability/gait disorder phenotype, baseline cognitive impairment, and presence of other non-motor and neuropsychiatric issues.REM sleep behavior disorder is closely related to PD cognitive impairment,and greater daytime sleepiness has been associated with worse cognition in PD.Social isolation, depression, and medical illness may worsen cognition in general and in PD.

Even after accounting for these factors, however, cognitive function varies among individuals. This variable expression implies potential genetic or environmental modifiers. Some genetic causes or risk factors for PD (e.g., LRRK2) are generally not associated with prominent cognitive dysfunction, whereas α-synuclein duplication and triplications, GBA, and MAPT mutations have been linked to cognitive deficits and dementia.The *ApoE4* allele has been associated with memory and semantic fluency in PD and may increase the risk of PDD, though studies are conflicting.Study results have been conflicting regarding the role of polymorphisms in BDNF and COMT genes in PD cognitive impairment.In non-PD populations, co-morbidities such as obesity, diabetes, and hypertension may be associated with cognitive decline. This is also the case for diets high in saturated fat, trans-fat, and refined carbohydrates, or low in berries, green leafy vegetables, nuts, vitamin B12, and folate.[3]At present, data are limited regarding the role of co-morbidities and diet in PD cognitive impairment.Preliminary reports suggest that elevated levels of homocysteine and plasma phospholipids and lower levels of serum uric acid may be associated with worse cognition in PD.Environmental risk factors present compelling opportunities for intervention. However, whether modifying these risk factors would change the progression of PD cognitive impairment is unknown.

Cognitive Change

Many people attribute cognitive changes to "aging," and a major concern expressed by people with PD and their care partners is whether cognitive deficits are related to aging or to PD. Cognitive changes in people with PD need to be benchmarked against normative data and age-related changes.

Cognitive decline without dementia can occur in aging, perhaps because neuropathological processes such as neuronal loss, deposition of amyloid, tau, and α-synuclein, and vascular changes, often found post-mortem, are common as we age.The progression of cognitive decline is a key element in attributing changes to underlying disease-related processes. In general, cognitive changes in "normal" aging should not interfere significantly with everyday activities that require cognitive abilities. If they do, however, this may suggest an abnormal process and signal an increased risk of developing MCI or dementia. Changes in functional abilities and everyday activities due to cognitive decline can be difficult to identify if they are mild. Distinguishing whether problems in everyday activities are due to cognitive or motor problems in PD, or a combination of both, can be challenging, and appropriate measures for determining this are needed.

In "normal" aging, cognitive problems typically involve difficulty with recalling and generating words or names (tip of the tongue phenomenon). Deficits in word or name recall, however, are also common in PD.When objective evidence accompanies subjective cognitive changes without a substantial impact on function, this is defined as MCI, a concept also applied in PD.MCI is a risk factor for dementia in both aging and in PD populations. Community-based studies demonstrate that aging is associated with changes in several cognitive domains, notably speeded measures and recall (aspects of the so-called fluid intelligence), but with relative preservation of others such as vocabulary (crystallized intelligence).Normative ranges for cognitive performance have been defined for older adults and throughout the life span.

Potential Pathologic Processes Underlying Cognitive Domain Impairments

While the attention and frontal-executive functions appear to be the predominant cognitive domains affected in PD, it is clear from the previous sections that the pattern of cognitive domain impairments in PD is complex. In fact, some PD patients exhibit relatively isolated impairments in memory, while others in frontal-executive or visual-spatial function (24, 25). This suggests that the neuropathologic substrates of cognitive impairment in PD may also be variable. Studies on the neuropathologic basis of CI in PD are still somewhat limited.

An important issue in reviewing the literature on the neuropathological substrates of cognitive impairment in PD is variable methodologies used to evaluate the pathologic changes. For example, alpha-synuculein immunohistochemistry to visualize Lewy bodies has only been available for the last 10 years (9, 46). Neuropathologic studies prior to that time may have missed Lewy-related pathology (LRP) in regions such as the limbic system and neocortex. In addition, there have been changes in the criteria used to pathologically diagnose Alzheimer's disease. Neuropathologic confirmation of AD now necessitates the presence of both sufficient neuritic plaque and neurofibrillary tangle pathology (40). In the past some studies, using criteria available at that time, diagnosed coexistent neuropathologic AD based solely on the severity of cortical plaque pathology (26, 37). In recent years, there has also been further refinement of the clinical diagnosis of PDD, versus other similar clinical syndromes such as Dementia with Lewy bodies. Currently, the clinical criteria for PDD require the presence of motor parkinsonism precede dementia by at least a year (the so called "one year rule") (16). In the past some studies selected patients on the basis of the coexistent parkinsonism and cognitive impairment without regard to the timing of the onset of these symptoms. Thus, cases with dementia preceding parkinsonism were included in the analysis of the neuropathologic basis of dementia in PD, when current criteria would classify these cases more accurately as Dementia with Lewy bodies (33). These are important considerations when evaluating studies of the neuropathologic basis of dementia in PD.

Medical Treatment

Medications are the most common therapy for PD.[12,20,23] The goal is to correct the shortage of dopamine; it is this deficiency that causes the symptoms.

Pharmacological treatment is usually started when symptoms become disabling or disrupt daily activities. Treatments may differ according to the patient's symptoms, age, and responses to specific drugs. It often takes time to find the best combination of drugs for each patient.

Levodopa and Levodopa/Carbidopa

Levodopa (l-dopa, l-3,4-dihydroxyphenylalanine), the metabolic precursor of dopamine, is the single most effective agent for treating PD. Levodopa itself is largely inert; both its therapeutic and adverse effects result from decarboxylation of levodopa to dopamine.

When taken orally, levodopa is absorbed rapidly from the small bowel by the transport system for aromatic amino acids. Drug concentrations in the plasma usually peak between 0.5 and 2 hours after an oral dose. The half-life in plasma is short (one to three hours). The rate and extent of absorption of levodopa depend on the rate of gastric emptying, the pH of gastric juice, and the length of time the drug is exposed to the degradative enzymes of the gastric and intestinal mucosa. Competition for absorption sites in the small bowel from dietary amino acids may also affect the absorption of levodopa; taking levodopa with meals delays absorption and reduces peak plasma concentrations.

Entry of the drug into the CNS across the blood–brain barrier is also mediated by a membrane transporter for aromatic amino acids, and competition between dietary protein and levodopa may occur at this level. In the brain, levodopa is converted to dopamine by decarboxylation primarily within the presynaptic terminals of dopaminergic neurons in the striatum. The dopamine produced is responsible for the therapeutic effectiveness of the drug in PD; after release, it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism or is metabolized by the actions of monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT).

In clinical practice, levodopa is almost always given in combination with a peripherally acting inhibitor of aromatic l-amino acid decarboxylase, such as carbidopa or benserazide (not available in the U.S.), which does not penetrate well into the CNS. If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and other peripheral sites, so that relatively little unchanged drug reaches the cerebral circulation and probably less than 1% penetrates the CNS.

Conclusion

PD generally follows a progressive course. The benefits of levodopa often diminish with time, and serious adverse effects may complicate long-term levodopa treatment. Levodopasparing interventions (e.g., dopamine agonist monotherapy or rasagiline in early PD), may be able to delay motor complications, whereas the initiation of levodopa might be withheld until the patient needs additional symptomatic benefit or if side effects limit the use of other agents. The symptomatic treatment of mild PD is probably best avoided until a disability or symptoms begin to affect the patient's lifestyle.

Treatment of early PD with MAO-inhibitors, dopamine agonists, or levodopa/carbidopa improves quality of life. Because there is no compelling evidence favoring any single drug, treatment should be individualized.

For the initial treatment of PD, the American Academy of Neurology recommends levodopa to improve motor disability or a dopamine agonist to lessen motor complications. After decades of clinical observation, levodopa has endured as the most effective primary medicinal agent.

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