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EC NEUROLOGY
Research Article

Association of Cognitive Impairment in Parkinson's Disease

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Received: August 09, 2022; **Published:** September 09, 2022

Abstract

Cognitive impairment (CI) in Parkinson's disease (PD) can be divided into a predementia stage known as mild cognitive impairment (MCI) and an advanced stage of memory loss which is dementia of Parkinson's disease (PDD). We also know that subjective cognitive decline (SCD) can be a risk factor for MCI in PD. Several longitudinal studies in recent past had shown MCI as a harbinger of dementia in PD patients. However, it is a known fact that cognitive dysfunction in PD is variable where reversal or stabilization of cognitive problems at a certain stage is common. Several contributors to CI are known which may include genetics, accumulation of alpha-synuclein, neurotransmitter dysfunction and vascular risk factors to name a few. There is no disease modifying therapeutic treatment available at this moment for CI in PD. However, this review will highlight some other modalities which may be effective in these complicated cases.

Keywords: *Cognitive Impairment (CI); Parkinson's Disease (PD); Mild Cognitive Impairment (MCI); Subjective Cognitive Decline (SCD), Parkinson's Disease Dementia (PDD)*

Introduction

Parkinson's disease (PD) was previously understood as a pure movement (or motor) disorder, however at the present time the perception has changed. PD is now considered to be a multisystem disease affecting many regions of the nervous system [1]. PD symptoms are divided into motor and non-motor for simplicity and better understanding. Several neuro-transmitter and their systems within the brain are involved which includes acetylcholine, noradrenaline, serotonin and dopamine [2,3]. Several NMSs are known to be associated with advanced stage of PD however cognitive impairment (CI) is the most common among all [4]. CI is found in approximately 30 - 40% of PD patients [5]. The presence of CI in PD and of the contribution of the basal ganglia to cognitive function in general remains debatable [6].

CI associated with PD comprises of subjective cognitive decline (PD-SCD), mild cognitive impairment (PD-MCI) and dementia (PDD). However, in recent times PD-SCD had been extensively studied and has gained a lot of attention. Several longitudinal studies had shown that 50% of patient diagnosed with PD for 10 years developed dementia over time [7-9]. Among those with PD, point prevalence of dementia ranges between 30% and 40% [10].

Within the general population, PDD accounts for 3% - 4% of dementia of all types compared to Alzheimer's disease (AD) which is around 50% - 70% and vascular dementia (15% - 25%) [11]. CI in PD reduces the quality of life, increases mortality and intensifies caregiver burden and health-related expenditure [12-15].

Methods

Literature search

We systematically searched the PubMed, Web of Science, PsycInfo and Google Scholar databases for articles published since inception up to December 2020 regarding CI in PD. Keywords related to desired objectives in accordance with PICO criteria were used to explore the articles. The included articles were searched for publications that met the study criteria. Initial search did not have any language restriction. The keywords selected were: ("Parkinson" OR "Parkinson's" OR "Parkinson disease" OR "Parkinson's disease" OR "PD" OR "paralysis agitans" OR "akinetic rigid syndrome") AND ("cognition" OR "cognitive decline" OR "cognitive dysfunction" OR "cognitive impairment" OR "MCI" OR "dementia").

Inclusion criteria

Eligible literature was included if they simultaneously fulfilled the predefined criteria: 1) clearly stated diagnostic criteria for PD and PD-CI carried out by experienced clinicians which comprised with patients meeting the United Kingdom Brain Bank criteria (UK BBC) for PD, use of mini-mental status examination (MMSE), Montreal Cognitive Assessment (MoCA), movement disorder society (MDS) 2007, criteria for PDD, MDS 2012 criteria for PD-MCI or neuropsychological testing for cognitive assessment.

Exclusion criteria

Studies were excluded if they were commentaries, letters, reports, conference abstracts, editorials and reported a disease other than PD-CI.

Results

The electronic search yielded 12132 articles in total which were then reviewed by titles and abstracts. The full text of 3439 articles was reviewed of which 238 articles met the predefined inclusion criteria. The whole selection process is shown in the flow diagram (Figure 1).

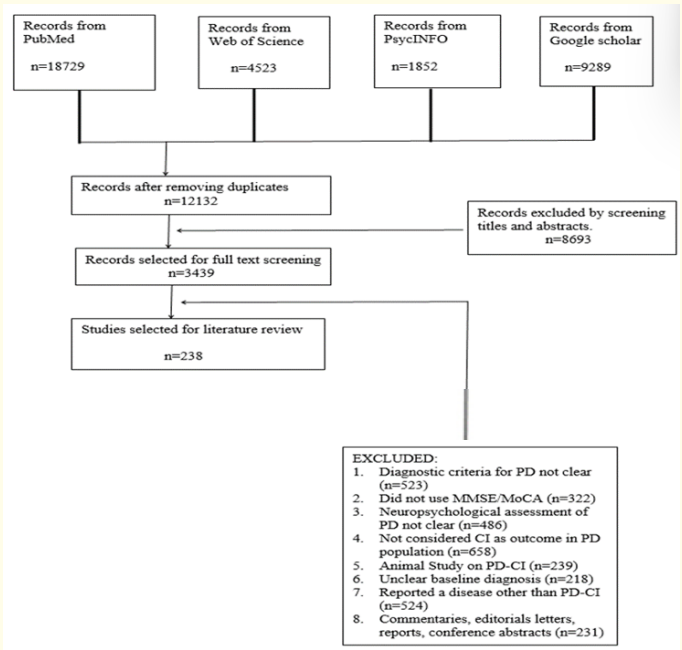

Figure 1: *Flowchart describing the approach used to identify all eligible studies.*

Cognitive subtypes in PD

Subjective cognitive decline (SCD)

In the general population, SCD is considered to be an important risk factor for amnestic MCI and AD [16-18]. However, patients with PD-SCD have an increased risk of developing PD-MCI compared to those who does not have SCD [19,20]. In one long term follow up study of 7.5 years, it reported that PD-SCD is a risk factor for progression to dementia [21]. Recent research has shown that SCD in patients with PD reflects disease-related cortical thinning and cognitive dysfunction more closely than SCD without PD [22].

Mild cognitive impairment (MCI)

MCI is thought to be an intermediate state between normal cognition and dementia, especially of Alzheimer type [23]. The National Institute on Aging-Alzheimer's Association workgroup looked at MCI in patients with AD based on the biomarker findings beyond CI [24]. In 2012, Movement disorder society (MDS) published the PD-MCI diagnostic criteria to improve the understanding of PD-MCI [25,26]. MDS published level I and level II criteria, out of which level II criteria allows subtyping of MCI in single or multiple domains.

PD-MCI does not cause significant cognitive deficits to impair activities of daily living compared to PDD. However, MDS criteria does not precisely define the impairment in cognitive tests and a large-scale validation is ongoing [27].

MDS study group after taking several factors like age, sex, education, severity of motor signs and depression concluded that Level I PD-MCI criteria can be an independent contribution to the risk of developing of PDD [28]. Multiple domain cognitive impairment was found to be more frequent than single-domain impairment with MDS Level II criteria which included visuospatial deficits, memory and executive functioning [25.29]. PD-MCI patients can be differentiated from PD patients with normal cognition by PD–Cognitive Rating Scale and Mattis Dementia Rating Scale-2 [30].

MCI is recognized from the earliest stages of PD, evident in 15% - 20% of de novo, untreated patients [31], with estimates of between 20% and 60% of patients showing MCI after diagnosis [32-34]. Recently, two cross-sectional studies found the prevalence of PD-MCI at 33% and 64%, respectively [35,36]. A recent study also found out the incidence rate of PD-MCI to be 184.0/1000 Pyar [37].

A multicenter cross-sectional study from southern Italy looked into the most frequent MCI subtype. They found amnestic MCI multidomain phenotype was the most frequent (39.1% of the overall sample and 43.9% in newly diagnosed PD) in their data. A positive significant association between age, motor scores and MCI was found, while a negative association was observed between MCI and educational level [38].

Increasing age, male gender and lower education level was associated with PD-MCI. However, several non-motor symptoms like anxiety, depression, autonomic dysfunction, day time sleepiness and sleep behavior disorders are known to influence the development of PD-MCI [39]. A significant association between PD-MCI and rapid eye movement sleep behavior disorder (RBD) [40] and olfactory dysfunction exists [41].

A prospective study with 4 years' follow-up looked at the rate of progression from MCI to dementia in PD patients. They found a strong association of PDD development from PD-MCI compared to PD patients with normal cognition after controlling several factors like age, stage of the disease, education and gender [42]. A recent longitudinal study also found out 19% - 62% of patients progress from PD-MCI to PDD when followed from 2 to 5 years after diagnosis [43]. A 5-year population-based study found out 39.1% with PD-MCI progressed to dementia within this follow up period and the conversion rate to dementia with persistent PD-MCI at 1 year was 59.1% [44].

A prospective longitudinal cohort study from Norway reported MCI at PD diagnosis predicted a highly increased risk for early dementia. However, the authors also found out in their study that some PD patients with persistent MCI at baseline reverted to normal cognition. PD-MCI converters performed worst on tests of executive function at baseline and were older compared to the PD-MCI reverters [45]. Two longitudinal studies also found out that 11% to 27.8% of PD-MCI patients reverted to near normal cognition when followed up for 5 years [46,47].

A very common understanding has evolved in recent times which is known as "dual syndrome hypothesis". It is reported that PD-MCI patients who had executive dysfunction secondary to changes in the dopaminergic pathways less likely converts to PDD. However, deficits in acetylcholine (ACh) pathways in PD-MCI patients with deficits in visuospatial function and memory, are prone to develop rapid deterioration of cognition and conversion to PDD [48]. Lastly, there is increasing evidence of the role of small vessel disease (SVD) in the causation of motor symptoms, functional and cognitive decline in PD [49].

Disturbances of sleep-wake cycle, autonomic dysfunction, cognitive deficits and behavioral changes are seen in PDD. PDD can be considered as a dysexecutive syndrome with multitude of problems mainly attention deficit, visuospatial dysfunction and executive impairment. Moderate memory impairment, apathy and psychosis are also seen in PDD patients. Memory deficit may include implicit, episodic and working memory [50]. Episodic memory impairment in PDD was found to be less severe than that in AD [51]. However, a subpopulation of PDD has a limbic type of memory deficit similar to that seen in AD [52].

In the early stages of PDD, core language functions are usually preserved. The authors found word finding difficulties as the primary reason behind pauses in spontaneous speech. However, difficulties in comprehension of complex sentences were found which was most likely to be caused by attentional deficits [51,53].

Several behavioral symptoms like depression, hallucinations, insomnia, anxiety and apathy were also seen in patients with PDD. PDD patients was found to have several autonomic symptoms including urinary incontinence, constipation, syncope and falls secondary to postprandial or orthostatic hypotension, sexual dysfunction and reduced heart rate variability [50].

A comparative study assessed cardiovascular autonomic function to determine the prevalence of orthostatic hypotension in patients with AD, dementia with Lewy body (DLB), vascular dementia and PDD by using power spectral analysis of heart rate variability and Ewing's battery of autonomic function tests. They found autonomic dysfunction was more prominent in PDD as compared to others [54]. Few studies looked at the commonest sleep and sleep-wake cycle disturbances in PDD. RBD, sleep disruption, excessive daytime sleepiness and insomnia were the most common [55,56].

Approximately 10% of patients manifest dementia within 3 years of PD diagnosis, this is increased to 46% by 10 years after diagnosis and 83% by 20 years [57-59]. In the general population aged 65 years and over, the prevalence of PDD was 0.3 to 0.5%. It was also reported in the general population that 3 to 4% of patients with dementia were estimated to be due to PDD [10]. The likelihood of developing dementia increases with disease progression, with a cumulative incidence of 75%–90% of patients developing dementia during the disease course [60,61].

A cross-sectional retrospective study over a period of 18 years reported age and duration of PD as risk factors for dementia. However, in patients over 85 years, duration of disease was less important factor in cognitive decline. Higher rates of dementia in PD patients were seen in males compared to females [62]. A community-based study looked at the age of onset on PD and the risk of developing dementia. They found out age of patient and not age of onset is linked to developing dementia over time [63].

The Sydney Multicentre Study of PD looked at de novo patients with idiopathic PD over a 20-year period. They found out PD patients developed dementia at around 70 years independent of disease onset. It was also found that those patients with early onset PD had no defect in linguistic ability prior to the onset of dementia [64].

The postural instability gait disorder (PIGD) phenotype is a risk factor for incident dementia in PD. It is found to be associated with a more rapid cognitive dysfunction as compared to tremor-dominant phenotype [65,66]. Few studies argued that cognitive impairment especially attention problem and PIGD can be linked to ACh deficit. This is mainly due to degeneration of nucleus basalis of Meynert (nbM) and the pedunculopontine nucleus (PPN) [67,68].

Recent data have suggested that the immune response may contribute to CI. A recent study looked at the plasma cytokine profile like tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), interleukin-10 (IL-10) levels in synucleinopathies with dementia and PD without dementia. They found out less pronounced immune response in PD without dementia compared to synucleinopathies associated with dementia like DLB and PDD. Elevated TNF-alpha and IL-6 was found in DLB and PDD compared to controls, whereas IL-10 was increased in PDD compared to controls [69].

In another multicenter validation study, which looked at the eight predictors of dementia (age, male sex, baseline RBD, orthostatic hypotension, MCI, bilateral onset, hallucinations and falls/freezing) in PD, the strongest determinant for dementia development was the co-existence of RBD, MCI and orthostatic hypotension at baseline [70]. Another study found out severe motor disability most potent risk factor for the development of PDD [71].

Mechanisms of CI

Neuropathological studies

The presence of α-synuclein in brain tissue is positively correlated to severity of PD as shown in several autopsy studies [72-74]. It was reported that in PD, cognitive impairment was associated with alpha-synuclein-positive cortical lewy bodies independent of AD type pathology. Cognitive dysfunction has been linked to loss of nerve fibers in subcortical nuclei projecting into the striatum, midbrain and limbic system [75]. PDD can be diagnosed with α-synuclein with high sensitivity and specificity [76].

The Braak pathological stage [77] is the propagation of lewy pathology from medulla oblongata to the neocortex in a six-stage caudo-rostral way that has been linked to cognitive dysfunction [78-79]. However, association of CI with evidence of Lewy pathology within the neocortex in not true for all brains. Another study found out Lewy body relative to α-syn does not cause neural death but may be a marker for neural protection [80]. Alternately it is also possible that those with neocortical Lewy pathology may have expired before developing cognitive dysfunction [81].

AD-related pathology like tau neurofibrillary tangles (NFTs) and amyloid beta plaques (Aβ) also display a crucial role in the CI of PD patients [82-84]. It is also found that 40% - 50% of pathologically proven PDD cases also fulfill pathological diagnostic criteria for AD [81]. Recently it was reported that Aβ deposition in patients with PD is associated with impairment of attention [85], however, it was also reported that there is no relationship between Aβ deposition and CI [86]. The contradiction of conclusion among these two studies may be due to different research methodology which needs detailed exploration in future studies.

A study looked at the presence of combined NFT, Aβ and Lewy pathology in PD patients who has developed dementia. They found out high cortical amyloid-β score and older age at onset were associated with dementia in a shorter time period. It was also reported that a combination of Alzheimer- and Lewy- type pathologies was a better correlate to PDD [87]. The above-mentioned trio was also found to be

synergistic in an animal model and animal models suggest that the trio may be synergistic [88]. A multicenter, prospective, longitudinal study of older people in the UK found out elderly brains had coexisting AD and PDD pathology because of the association between presence of NFT and Aβ and increasing age [89]. However, pathological and histological studies of PD-MCI subjects are lacking.

Genetics

Genetic polymorphisms correlative with tau proteins and dopamine regulation contribute to the occurrence and development of CI in PD. Catechol-O-methyltransferase (COMT) polymorphism is considered not to be a risk factor for dementia development but through frontostriatal dopaminergic pathways influences performance on executive function [90]. However, greater posterior cortical cognitive deficits had been associated with microtubule-associated protein tau (MAPT) gene polymorphisms.

It has been reported in few studies that PDD shows stronger association MAPT H1/H1 genotype [90], but few other studies have not found the same association [91,92]. A recent study demonstrated the association of neurocognitive deficits in recently diagnosed PD patients. It is also found that regional brain activations are influenced by genotype. A direct causal relationship was found between decreased activity of the posterior visual network during visuospatial tasks and MAPT H1 homozygotes [93]. The association between H1/H1 genotype and PDD decreases over time [59]. The influence of MAPT H1 on cognition might be greatest at disease onset [94], which is further supported by fMRI findings [93].

Glucocerebrosidase (GBA) associated PD has a younger onset and a higher risk of dementia development. The point prevalence of dementia in GBA-associated PD is around 50%, twice that of sporadic PD [95]. The progression of dementia in GBA-associated PD is faster than sporadic PD [96], but the reason is not clearly understood. Pathologically, findings of sporadic PD are similar to that of GBA-associated PD, although GBA is present in the majority of Lewy bodies [97]. GBA gene mutation causes α-syn accumulation and aggregation by changing key important functions of organelles like lysosomes, mitochondria and endoplasmic reticulum [98].

One meta-analysis looked at the influence of apolipoprotein E (APOE) gene in PD-CI. The study found that patients with at least one E4 allele had risk of development of dementia. However, the authors think publication bias and heterogeneity might have existed in this study [99]. APOE-E4 carriers had more rapid cognitive decline in subjects with average disease duration of 7 years at onset of trial [92].

Two longitudinal studies also reported that APOE in newly diagnosed PD had no association with dementia development over 5 years [90] and 9.7 years [100]. A recent study also reported about the influence of APOE on dementia progression in PD which might be greater with advancement of age [94].

Neurotransmitter dysfunction

Dopamine

Severity and motor symptoms had been associated with dopaminergic stimulation of frontostriatal cortical loops which in turn can cause executive functional deficit in PD [101]. An improvement of spatial working memory, planning [102] and also attention flexibility [103], occurred when PD patients were tested on the "ON" phase compared to the "OFF". Executive function tests such as motor sequencing learning [104] and reversal learning [105] were shown to deteriorate in the "ON" state. Considering the above-mentioned findings, the relationship between cognitive performance and dopamine is non-linear.

In order to explain these findings a hypothesis known as "dopamine overdose hypothesis" was proposed. It is primarily based on the sequential degeneration of dopaminergic neurons and pathways within the substantia nigra pars compacta (SNpc). A study found out that

in patients with PD-MCI having executive dysfunction correlated with the denervation of striatal dopamine and D2 receptor deficiency in the insula lobe region [106]. Dopaminergic neuron deficiency in the ventral tegmental area (VTA) tend to convert to dementia in PD patients at autopsies [107].

A cross-sectional multicenter cohort found out age related dopaminergic nigrostriatal neuronal deficit was responsible for executive impairment in PD patients [108]. A causal relation between CI in PD, dopaminergic deficiency and withdrawal of dopaminergic therapies exists [109].

Acetylcholine

Acetylcholine (Ach) regulates attention in humans via projections from the basal forebrain nuclei to the Dorsolateral Prefrontal Cortex (DLPFC) [110]. A study reported that certain tasks which require attention causes transient increase of ACh levels in the prefrontal cortex [111]. A cohort study found out that more rapid CI was associated with baseline deficits of attention in PD patients [112]. Reduction in acetylcholinesterase (AChE) and vesicular acetylcholine transporter (VAChT) in cholinergic neurons is seen in patients with PD and PDD [113].

Neuroimaging findings has shown the disruption of ascending cholinergic pathway is primarily important in development of dementia in PD [114]. A very substantial decrease in uptake of VAChT in the cerebral cortex in PDD as compared to PD patients without dementia where decreased uptake is seen only in occipital and parietal lobe only [115].

One study also reported a severe cholinergic deficit in various cortical regions in PDD patients as compared to non-demented PD patients [116]. Another study reported that insufficiency of Ach receptors in thalamus, hippocampus, midbrain, cerebellum and temporal cortex is related to cognitive dysfunction in PD-MCI [117]. It was also shown previously that anticholinergic drugs used in PD patients to control motor symptoms like tremor were significantly associated with a decrease in the MMSE score [118].

Serotonin and noradrenaline

There is growing evidence of the influence of serotonin and noradrenaline on cognition in PD [119,120]. Loss of noradrenergic neurons from the locus coeruleus and serotonergic neurons from the dorsal and median raphe nuclei is seen in PD [119]. It was shown previously that cognition in PD is associated with the downregulation of serotonin receptors but its role in executive function was not found [121].

GABA

Nigrostriatal GABAergic neurons express adenosine A2A receptors which has been used as drug target to improve motor functioning in PD. These receptors are also found in the neocortex and thalamus. Increased receptor activity has been linked to the worsening of cognition. Molecules with adenosine A2A receptor antagonism may increase dopamine in the prefrontal cortex, which in turn can improve cognition in PD [122,123].

Other risk factors

It is a widely accepted fact that dementia is common in older PD patients with longer disease duration [124]. However, a recently published multicenter retrospective study found that in the long-term PD patients the prevalence of dementia might be lower than anticipated. The authors think there is a need to investigate other factors that might affect the outcome of CI in long-term PD patients [125].

Lifestyle factors like smoking can act synergistically with cardiovascular and cerebrovascular disease leading to CI in early PD [126]. A predementia syndrome known as motoric cognitive risk syndrome (MCRS) is characterized by slowness of gait and cognitive deficit can be caused by cerebrovascular disease and PD [127].

In the non-PD population, vascular risk factors (VRFs), such as diabetes, hypertension and obesity have been associated with CI [128]. Modifiable VRFs have been linked to CI in PD [129]. A large prospective longitudinal study found out that patients with recent onset PD with multiple VRFs are prone to develop CI over time [130]. These VRFs act especially on attention and executive functions in PD [131]. Combining all these metabolic risk factors, a vascular risk score (VRS) is formed, which is similar to the modified Framingham risk score (mFRS) excluding smoking history [132]. This VRS thus accounts for the two main VRFs, diabetes and hypertension, that have been associated with cognitive dysfunction in early PD cross-sectionally [133,134]. A recent study also reported the association of orthostatic hypotension and PD-MCI [135].

It was found that poor response to dopamine agonist therapy in PD patients led to development of PDD [61,136]. Side effects of dopamine and other agents such as visual hallucinations and delirium are correlated with the occurrence of PDD [137]. Another study also found depression in PD patients was more inclined to have dementia in the future [138].

Biomarkers

Several review papers have discussed in detail the biomarkers which can identify the early stages of PD and those who are at risk of developing PDD. Biomarkers which had been studied in detail either as a single entity or combined are cerebrospinal fluid (CSF) analysis, imaging modalities and electrophysiologic techniques [139-141].

Cerebrospinal fluid

The most common CSF proteins studied in PD have been the AD markers Aβ42, total tau (t-tau) and phosphorylated tau (p-tau), neurofilament light chain (NFL) and the PD marker α-synuclein [140]. Low CSF Aβ42 has been linked to cognitive decline in PD patients [142,143]. CI in PD-MCI and its relation to the presence of tau proteins in not clear. High levels of t-tau and p-tau has been associated with PD-CI [144].

Impaired memory and naming in PDD are associated with high CSF tau and p-tau [145]. Reduced memory and executive function among patients who had just started levodopa therapy has been linked to higher CSF p-tau and p-tau/Aβ42 [146]. Association of CSF levels of total α-synuclein to cognitive decline in PD seems inconsistent with low [147] and high [148,149] values have been reported.

A study also found that levels of CSF t-tau, p-tau, total α-synuclein, neurofilament light chain and YKL-40 levels increased significantly over a period of 2 years in PD. It was associated with cognitive decline and the increase of abovementioned CSF biomarkers correlated with longer disease duration [150]. These findings are keeping with studies which reported about the increase of α-synuclein levels with more severe degeneration of brain. However, a recent longitudinal single-center cohort study with recently diagnosed PD was followed up for a 24-month period. No change in α-synuclein or other CSF markers was found [151].

Plasma

One study found that high levels of plasma Aβ42 and t-tau are associated with later cognitive decline in amnestic MCI [152]. One research also reported that plasma α-syn level correlated with cognitive decline but not motor severity in patients with PD [153]. A recently concluded meta-analysis found hyperhomocysteinemia was related to PD-CI [154].

A study looked at the deterioration of white matter microstructure across cognitive stages in PD using diffusion tensor imaging (DTI). The authors found loss of white matter tract integrity in PD and these changes increase with cognitive decline. The commonest findings include functional impairment in executive function, attention and learning and memory. The pattern of white matter loss in PD-MCI is characterized by cortical atrophy which proceeds into subcortical areas during the course of disease pathology [155].

Structural magnetic resonance imaging (MRI) studies found a loss of volume within the frontal, parietal, posterior cortices and hippocampus which correlated memory with decline in PD-MCI [156-158]. A longitudinal study also reported that patients with PD-MCI has faster rate of cortical thinning which correlates with cognitive deficit [159].

There is significant thinning of the frontal, parietal, temporal and occipital regions, plus further atrophy of the parahippocampus, hippocampus, insular and cingulate once the patient is diagnosed with PDD [160-163]. Supratentorial white matter hyperintensities were also suggested to be associated with CI in PDD patients [164]. PD-CI is associated with functional connectivity damage of posterior cingulate right medial temporal lobe and microstructural damage of left hippocampus [165]. A recent study used voxel-based morphometry (VBM) to monitor grey matter volume changes. They found right entorhinal cortex atrophy in early drug-naïve PD-MCI which in turn may serve as a biomarker for diagnosis [166].

A study with resting-state functional MRI (fMRI) has demonstrated progressively impaired connectivity of posterior brain regions in PD. This finding correlated with a reduction in cognitive performance [167]. Another study on resting-state fMRI documented hyperactivity in the opercular part of right inferior frontal gyrus and hypoactivity associated with cognitive decline in the occipital areas in early PD-MCI [168]. Disruption of cortico-striatal and frontal cortex functional connectivity is being linked to cognitive decline in PDD [169,170].

A multi-delay multiparametric arterial spin labeling (ASL) perfusion MRI found out that arterial transit time (ATT) may be a more sensitive marker than cerebral blood flow (CBF), in detecting PD-MCI in the early stage [171]. ASL perfusion imaging has found patterns of hypoperfusion in patients with PDD compared with PD patients with normal cognition [172].

Dopamine decarboxylase and vesicular monoamine transporter-2 positron emission tomography (PET) imaging have demonstrated a decrease in regional mesolimbic and meso-cortical monoaminergic capacity in patients with PDD [173,174]. Early in the course of PD, cholinergic PET molecular imaging has shown loss of cholinergic activity occurring throughout the cortex but is much more severe in the forebrain in PDD [175]. Reduced levels of acetylcholinesterase were correlated with worse performance on tests of memory, executive functioning and attention in PD subjects without CI [175,176].

Studies that looked at glucose metabolism using PET have shown metabolic decreases in the parietal, temporal, cingulate and frontal cortices in PD-MCI and PDD [177,178]. Aβ PET imaging indicates that cortical and striatal Aβ pathology is relatively infrequent (incidence 15 - 20%) in patients with PDD [179-181]. The combined presence of striatal and cortical Aβ plaques was associated with worse CI in PD as compared to cortical β-amyloidopathy alone [182]. One research showed that Aβ retention in patients with PD-MCI predicted an increased risk of future cognitive decline [183]. Recent research reported that PDD patients had tau cortical aggregates and that tau PET data could be a marker of CI [184].

Electrophysiology

One study has reported that PD with executive dysfunction showed a decrease in fast wave activities and increase in slow wave activity in the frontal lobe [185]. Another study assessed the relationship between CI and quantitative EEG (QEEG) in PD. They concluded that slowing of EEG was more prominent in patients with PD-CI [186]. A study found out that increase in low-frequency delta and theta wave EEG spectral power distinguishes PDD from PD and AD [187].

A QEEG study showed that individuals with low background rhythm frequency are prone to develop dementia than those with high background rhythm frequency. This can be considered as a potential predictive biomarker for incidence of dementia in PD [188]. Furthermore, a significant decrease in alpha power spectral density (PSD) over the occipital lobe and an increase of delta PSD over the left temporal region in PD-MCI patients with QEEG analysis was seen [189].

Slowing of peak frequency magnetoencephalogram (MEG) is also predictive of dementia in PD [167]. Evoked potential studies in PD had suggested that a delayed P3b component in an oddball task is considered as a trait-like marker of PD-CI and PDD [190].

Combination of biomarkers

Low Aβ42, high t-tau and p-tau were associated with reduced grey matter volume in patients with PDD, but not in PD and non-PD controls [191,192]. A reduced striatal uptake was associated with low CSF levels of t-tau and p-tau [193], but not α-synuclein. The relationship between disruption of MRI-measured resting-state functional connectivity (rs-fcMRI) brain networks and CSF levels of potentially pathogenic proteins that reflect brain pathology in PD was looked at. They found abnormal α-synuclein accumulation led to disruption of motor-related brain functional connectivity in PD subjects [194].

Management

Pharmacological

There is enough evidence that the disturbed cholinergic system may be an important cause of CI in patients with PD. A research clinical trial reported cholinesterase inhibitors (ChEIs) can benefit PD patients with CI by significantly slowing the loss of the Mini-Mental State Examination score [195]. Another recent study showed rivastigmine as an useful therapeutic agent for improving cognitive function in PD patients [196]. A 24-week, randomized, double-blind, placebo-controlled, crossover, single-site study of the rivastigmine transdermal patch has shown some benefit in PD-MCI patients. The benefits seen were improvements on global cognition rating, health status, severity of anxiety and performance-based measure on cognitive abilities [197]. Rasagiline, a selective monoamine oxidase B inhibitor was not found to improve cognitive status in patients with PD-MCI [198].

In one study atomoxetine, a selective noradrenaline reuptake inhibitor (SNRI) was responsible for significant improvement of cognition in PD patients as compared to placebo [199]. A double blind, randomized, placebo-controlled study showed, 40 mg atomoxetine improved decision making, problem solving and attention in PD [200]. Atomoxetine has been shown to improve executive functioning in PD-MCI patients. However, improvements seen were subjective [201].

Apomorphine most likely via an antioxidant property has been shown to reduce Aβ accumulation and toxicity [202]. Apomorphine infusion was associated with the improvement of several non-motor symptoms [203]. Apomorphine use in PD patients without dementia reduced Aβ deposition in brain as compared to untreated patients [204].

A recent meta-analysis reported memantine, a blocker of N-Methyl-D-aspartate (NMDA) receptors have a positive effect on global cognitive and motor function, executive functions, processing speed, attention span and enhances memory ang language abilities [205]. One research group believes dopaminergic agents help in improving task planning, cognitive function and working memory in PD patients [206], whereas others think dopamine has no significant therapeutic effect on cognitive slowing in PD [207,208]. Creatine and CoQ10 has been shown to delay PD-MCI progression by decreasing oxidative stress and improving mitochondrial energy metabolism [209].

Rivastigmine was shown to improve cognition and activities of daily living in PDD patients and benefit was seen in 15% cases. It was also found out that the use of ChEIs had a good outcome on global assessment, cognitive function and behavioral symptoms in PDD patients [210,211]. A recent meta-analysis showed cholinesterase inhibitors (ChEIs) as the only proven therapeutic agent which can increase cognitive function in PDD [195].

In a placebo-controlled study, rivastigmine was shown to have moderate improvements in PDD but with increased incidence of nausea, vomiting and tremor [212]. An improvement in attention by rivastigmine in a post-hoc analytic study on PDD was reported [213]. PDD patients had greater therapeutic benefit with rivastigmine who had visual hallucination at baseline [214].

A randomized, double-blinded study reported donepezil as an effective agent in improving cognition and executive function in PDD [215]. A multicenter trial showed PDD patients might benefit from treatment with memantine [216]. However, a study did not find favorable benefit of memantine on CI and behavioral symptoms in PDD patients [217]. A recent study reported that nicergoline administration for 12 months in PDD patients may slow the progression of CI in affected brain regions [218].

Prime importance should be given to eliminate aggravating factors such as inappropriate sensory stimuli and undue environmental factors in PDD patients [219]. Whether these therapies can slow the progression from PD-MCI to PDD is not known and should be addressed in future research.

Nonpharmacological

Cognitive training

A recent study which looked at the effectiveness of cognitive training in PD reported minimal but statistically significant improvements in working memory, processing speed and executive functioning in patients with mild to moderate PD [220].

Physical exercise

Proper physical exercise is known to improve motor symptoms and cognitive dysfunction especially the executive function of PD patients [221-223]. Dancing, resistance training and aerobic exercise can induce neurogenesis which may be used in PD-CI as a rehabilitation process [224,225]. A randomized clinical trial reported improvement of working memory and attention span in mild-to-moderate PD patients with no dementia after 24 months of Progressive Resistance Exercise Training (PRET) or modified Fitness Counts (mFC) [226].

Exergames

In recent years, a combined technology of physical exercise and cognitive training has been developed, which has been used in PD patients' recovery. It is reported that the intensity of exercise is linked with an increase in gray matter volume in the anterior cingulate cortex and prefrontal cortex and improvement in speech, memory and is in connection with an increase in the dorsolateral prefrontal cortex [227]. Several RCTs have shown improvement of cognitive function in PD by applying exergaming technology [228,229].

A 6-week home-based training period of exergaming was done in PD subjects. There was improvement in cognitive function, attention and motor dual- tasking [230]. Dancing and cognitive exercise is effective in improving processing speed and mental flexibility in mild to moderate stage PD patients having clinical diagnosis of at least 6 years. A bigger improvement of cognition was seen when treadmill training was performed three times a week for about 60 minutes in a total of 24-week time period [231].

Nutrition

Lower risk of CI is associated with intake of fish and polyunsaturated fatty acids. Marine-derived dietary docosahexaenoic acid intake was associated with lower risks of dementia [232]. One recent study also showed low vitamin D is associated with reduced hippocampal volume and connection deficits in elderly people with MCI [233]. Recent literature published reported higher plasma levels of thiamine and phosphate is associated with a lower risk of MCI in male PD patients [234]. Another study reported low plasma and urine uric acid levels associated with worse cognitive performance in PD [235].

Neurostimulation

A randomized controlled trial found improvement of cognitive and affective functions by cognitive training [236]. Reduction of depressive symptoms and improvement of motor and cognitive function was noted on PD-MCI patients with repeated sessions of transcranial direct current stimulation (tDCS) with stable effects at 3-months follow-up [237]. Improvement of social cognition of PD-MCI patients was seen when tDCS was applied over the medial prefrontal cortex [238].

The effect of repetitive transcranial magnetic stimulation (rTMS) on cognitive dysfunction in PDD in a pilot study. They found out improvement of motor function and improvement of cognition if rTMS was applied over M1 [239]. One recent study also reported active intermittent "theta burst" stimulation (iTBS) might improve overall cognitive performance in patients with PD-MCI and that this effect can last up to one month [240].

Discussion

The current work involved comprehensively analyzed the subtypes of PD-CI which includes SCD, MCI and PDD. SCD is considered to be a risk factor in AD and amnestic MCI in general population.

PD-CI is common and has a negative impact on patients' and care providers. CI is a nonmotor symptom, which has been linked to nondopaminergic and dopaminergic systems. PD-CI in the prodromal state might occur very early in the course of the disease, without any evidence of motor symptoms. Recent research has established high frequencies of conversion of PD-SCD and PD-MCI to PDD. MCI is a common feature in PD, even at the time of diagnosis which may improve in the short term or remain stable. However, the risk of conversion to PDD exists over a variable period of time.

Cumulative influence of age, genetic susceptibility, neurotransmitter changes and imbalances, smoking, VRFs like hypertension, DM, obesity and neurodegeneration caused by α-syn and AD-related pathology is different in each PD patient. Imaging, electrophysiology, plasma and CSF biomarkers have been studied in great detail in PD-CI. Published literature consistently shows the association between rapid cognitive decline and reduced CSF Aβ42 concentrations.

Even after enormous research advances, apart from the efficacy of ChEIs for the treatment of PDD, no additional treatment or preventive options has evolved for PD-MCI and PDD. A deeper understanding of PD-CI is required via knowing the pathophysiology, identification of biomarkers and VRFs to identify accurately those most at risk.

Conclusion

All in all, clinicians and neurologists need to move towards individualized, targeted therapy for better outcome. It is imperative for the research community to correlate various mechanisms triggering CI in PD and replicate these findings in high-quality prospective studies with larger sample size and randomized controlled trials in different geographic locations.

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