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Characterization of Mild Cognitive Impairment in Parkinson's Disease

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Abstract

Parkinson's Disease (PD) is characterized as an "α-synucleinopathy," denoting the accumulation of highly phosphorylated and abnormally aggregated α-synuclein. This condition significantly impacts individuals by presenting a spectrum of motor and non-motor symptoms. The neuronal loss in the substantia nigra, located in the midbrain, underlies PD, leading to dopaminergic deficiency and the disruption of the nigra-striatal pathway. This, in turn, may contribute to brain atrophy, white matter alterations, and other related changes. Beyond the well-known motor symptoms like bradykinesia, rigidity, rest tremor, and freezing of gait, PD manifests a range of non-motor symptoms. Among these, Mild Cognitive Impairment (MCI) stands out, reflecting deficits in cognition, behavior, and mood. The degeneration spans several brain areas, including the pre-frontal cortex, limbic region, and midbrain. Consequently, individuals with MCI experience challenges in planning, judgment, memory, emotions, and the reward system. Mild Cognitive Impairment serves as an early indicator of cognitive changes from a healthy state, often affecting one of the five cognitive domains: attention, executive function, language, memory, and visuospatial ability. This thesis reviews existing literature on Mild Cognitive Impairment in Parkinson’s Disease, with a specific focus on associated biomarkers and clinical characterization.

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Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's Disease. The disease presents motor and non-motor symptoms, which may last years that interrupt daily life and these affect the individuals', families and caregivers' lives. While PD was originally a motor disease, it later became a more complex "brain disease" by research and definition. The motor symptoms are rigidness in movements and muscles, bradykinesia, inflexibility, rest tremor, alien limb (involuntary movement of hands and arms "without the control of the brain"), slowness, especially in the initiation of the movement, and freezing of gate. Motor symptoms can manifest themselves in two types: tremor-dominant and akinetic-rigid. Non-motor symptoms represent the ones that are cognitive impairments. There may be impairments in one or more than one of five cognitive domains: attention, executive function, language, memory, and visuospatial ability. It may be only in one cognitive domain or may be in multiple. Also there are circuitries affected and which are involved in mood, cognition, and behaviour. Symptoms related to planning, and judgement, which are related to pre-frontal and frontal cortices; reward system involving nucleus accumbens, medial forebrain bundle, ventral tegmental area; and emotions with the amygdala and its connections, limbic system.

Parkinson's Disease is an "α-synucleinopathy", in this case, which highly phosphorylated and abnormally aggregated α-synuclein refers to the accumulation of phosphorylated "α-synuclein". It is due to neuronal loss in the substantia nigra, which is located in the midbrain. Thus, this causes striatal dopaminergic deficiency, and also affects the nigra-striatal pathway (pathways to striatum). The disease is under the "umbrella term" of Lewy-body dementia (LBD) which corresponds to the definition of disorders that are caused by Lewy-body pathology. It can be said that α -synucleins are the "building blocks" of Lewy

bodies. The accumulation of Lewy bodies in the brain stem and then spreading to the cortex causes disruptions in neurons.

When considering the initial discovery and history of the disease, James Parkinson is the one who gave the disease a medical description (1817) and many scientists contributed to the scientific knowledge afterward. He wrote an essay called “Essay on the Shaking Palsy”. But earlier on, symptoms resembling parkinsonism – which represents Parkinson-like symptoms that will be mentioned below- were also described.

> *“As examples, Sylvius de la Boë wrote of rest tremor, and Sauvages described festination (Sylvius de la Boë 1680; Sauvages 1768; Tyler 1992). Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provide descriptions that suggest Parkinson's disease (Manyam 1990; Zhang et al. 2006). In succinct and pithy English, Parkinson captured the clinical picture:*
>
> *‘Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.’”*
>
> (Goetz, 2011).

In the process of helping to define Parkinson's Disease, Jean-Martin Charcot helped distinguish it from other neurological conditions that shared some of the similar symptoms. Charcot also distinguishes bradykinesia definitionally: based on the patients he observed, he states that the patients do not actually show symptoms due to weakness in their muscles, but only due to slowness of movements (Goetz, 2011). Charcot, together with his students, reveals that Parkinson's Disease is a spectrum disorder with different symptoms and divides it into two different types: "rigid/akinetic" and "tremorous". The first of these is manifested by more "rigid", slow movements, while the other is characterized more by tremors. They used

the name “Parkinson's Disease” instead of “shaking palsy” because the disease is not always characterized by tremors, and it may manifest differently with rigidity and slowness and no tremor (Goetz, 2011).

Clinical manifestations include a number of other symptoms which are not related to mobility. Depression may be seen before the onset, generally, occurs early in the disease and may sometimes precedes Parkinson’s Disease (PD) symptoms. In patients, there are less expressed feelings of sadness, and fearfulness, and there is more anhedonia and apathy. There is slowing in the movements, fatigue, poor insight and a mask-like face concealing emotions. Also apathy with lack of motivation and interest (related to dopaminergic deficiency), and emotions may seen. Individuals show symptoms that they are no longer enjoying the activities which generally they like involving, and no goals for future. Anhedonia, apatia and depression are closely connected with each other. Anxiety is also often comorbid with depression and may precede PD. In addition, there may be panic attacks, phobias, general anxiety disorder, and excessive rumination about upcoming events, and these may trigger tremors. Visual hallucinations may be due to medications that are used to end or relieve the symptoms, and it is the most prevalent psychotic symptom in PD. This may be due to the advanced disease degeneration of visual and perceptual areas in the cortex.

There is no precise treatment to cure the disease or prevent it before the onset. Although there is not yet a medication that completely relieves all symptoms and can be considered as the definitive solution to the disease, there are pharmacological and non-pharmacological treatment methods. At the same time, these treatment methods can limit disability and have a positive impact on progress on of disability.

Mild Cognitive Impairment (MCI) is cognitive alterations defined for the first time, in the context of Alzheimer’s Disease (AD) (Weil et al., 2018). The term MCI was first used in

1988, and the first clinical criteria were established by the Mayo Clinic in 1999 (Anderson, 2019). These criterias were as following:

> *"(1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment for age and education; (3) largely normal general cognitive function; (4) essentially normal activities of daily living; and (5) not demented."*
>
> (Anderson, 2019).

Previously, the initial description of MCI was more related to memory problems, closer to the current "amnestic MCI". In fact, MCI includes not only the memory domain but all five cognitive domains. At first, it was only associated with memory complaints, but later, as the number of studies increased, it was revealed that MCI also had an effect on other cognitive domains, and the definition of MCI was shaped accordingly. MCI can be seen in multiple disorders and related to cognitive impairment in five cognitive domains: attention, executive function, language, learning and memory and visuospatial ability. According to the clinical explanations and classification, if cognitive impairment is only in one cognitive domain, it is considered as "single domain MCI", and if it is more than one cognitive domain, it is considered as "multi-domain MCI". In the classification of the subtypes of MCI, Peterson and Morris did the explanation and clarification (2005) of subtypes as: amnestic MCI/ non-amnestic MCI and multiple domain MCI/ single domain MCI (Yu et al., 2023). Detailed classification of MCI is according to these: amnestic MCI, indicating isolated memory impairment; dysexecutive MCI, mild in memory and visuo-spatial domains, and significant impairment in domains of attention and executive function; and dysnomic MCI, which is mild to moderate impairment in memory and language, and not necessarily and not always observed in attention and executive function domains (Yu et al., 2023).

Similar to AD, in PD MCI may evolve into dementia. The factors contributing to the development of dementia are various, associated with the lifestyle, biological and genetic history, and the progression of the disease. With MCI, there are some alterations in terms of atrophy, in the brain regions such as medial temporal lobe; hippocampus and entorhinal regions, and posterior cingulate cortex, assessed by magnetic resonance imaging (MRI) (Anderson, 2019). Also, hypometabolism in the posterior cingulate cortex and temporoparietal cortex is associated with cognitive decline, and these are assessed by fluor-odeoxyglucose positron emission tomography (FDG-PET); and in parietal cortices and hippocampus, there is hypoperfusion and these alterations are measured by single-photon emission computed tomography (SPECT) (Anderson, 2019). In the formation of MCI, the formation of neurofibrillary tangles and amyloid plaques may be observed, as in AD. In this case, PET (position emission tomography) is used as the imaging system. Nevertheless, β-amyloid accumulation is not a biomarker that is seen in MCI in every case. MCI can be seen due to many diseases; it can be seen due to PD, AD, Lewy Body dementia, Multiple Sclerosis (MS), traumatic brain injury, and ALS and so on, which in all the cases the etiology is different, the biomarkers are different, and prevention and treatment techniques are different, accordingly. In fact, if β-amyloid plaques have been observed in studies, it may be an indicator that MCI developed as a consequence of overlapping AD pathology. Thus, if β-amyloid accumulation is observed with MCI, it may be comorbid with AD. MCI in PD is similar to amnestic MCI in Alzheimer's Disease.

We can characterise MCI as the transition between healthy cognition and dementia, affecting 10 to 15% of the population over the age of 65 (Anderson, 2019). In the older population, the frequency of MCI is thought to be between 3 and 19%; depending on the context, conversion rates to dementia might range from 13% to 33% during a 2-year period, and notably, after a year, 44% of MCI patients returned to normal in a community setting

(Weil et al., 2018). MCI prevalence is increasing especially in low-income and developing countries. The amounts spent for the disease are quite high and according to economic calculations, an intervention that is implemented in 2025 and delays the onset of dementia by five years will result in a 40% decrease in dementia prevalence and related healthcare expenses over the next 25 years (Anderson, 2019). Individuals' lives with MCI quality of life (QoL) decreases significantly, but they can manage their daily routine tasks, and housework, that is, the activities of daily living (ADL) remains intact. In instrumental activities of daily living scale (IADL) the abilities and skills may also remain intact and also can be altered. The important difference here is that the skills we use in daily life change to some extent, affecting our daily work and quality of life, but not deprived of basic skills.

> *"Another important conceptualization is the Clinical Dementia Rating (CDR) of 0.5, termed "questionable dementia." (Hughes, Berg, Danzinger, Coben and Martin) [8] A CDR of 0.5 includes the following features, as judged by a clinician: (1) mild consistent forgetfulness; partial recollection of events; (2) fully oriented; (3) only doubtful or mild impairment, if any, in independent functioning; (4) no major influence on home life, hobbies, or intellectual interests; and (5) fully capable of basic activities of daily living. Researchers at Washington University in St. Louis, Missouri, in particular have advocated the use of the CDR, arguing that what others call MCI is in fact early-AD, and therefore there is no need to view MCI (or a CDR of 0.5) as a separate entity from AD. (Morris, Storandt and Miller) [9]"*
>
> (Anderson, 2019).

MCI patients may also experience anxiety, depression, low mood, and occasionally irritability and agitation due to the disorder. Forgetfulness and not being capable to remember what has been done before (daily, routine including instrumental activities) can make someone distressed and these also can affect the progression of the disease. Having good social support, for all; the patients, caregivers and family members, is crucial. Being active, involving in sports that are aerobic, mediterranean style diet, social support, social engagement and seeing new places, communicating with new people without making so much effort and pressure, could help the progression of the disease slow down. These are also crucial for the patients not to progress any comorbid disease, and may help them overcome the disease's side effects, which are also psychological and emotional. On the contrary, no longer being engaged in activities that were enjoyed before, seeing friends, new places, and interested in hobbies, etc. would have an opposite effect: untreated depression, anhedonia, anxiety and these are not helping with the disease's progression.

There is no form of treatment yet that can completely stop MCI progression and its effects and restore these cognitive alterations to a healthy state. However, there are methods to relieve symptoms; pharmacological and non-pharmacological. Another crucial concern is delaying MCI before it progresses to dementia, enhancing quality of life (QoL), ADL, and providing social support by combined pharmacological and non-pharmacological approaches together for the treatment. Some of these non-pharmacological treatments are aerobic exercise, cognitive training, rTMS, tDCS, and non-invasive brain stimulation (Aarsland et al., 2021). Cognitive Behavioral Therapy (CBT) is also a helping way to relieve stress, anxiety, and depression which have undermining effects for PD-MCI.

1. PARKINSON'S DISEASE

PD is the second most common neurodegenerative disease. Symptoms in PD occur as a result of disruption of dopamine neurotransmitters, and dopaminergic pathways. The substantia nigra, located in the midbrain (close to medial inferior temporal lobe), secretes the neurotransmitter dopamine. From here, a path called "nigrostriatal pathway" is formed to the striatum. In this way, many basic functions such as initiation of the movements, control of the movements and muscles, regulation of the movements, reward system, motivation and memory related activities take place. As the dopamine neurotransmitters here eliminate due to various and unknown reasons, this pathway also begins to eliminate, and PD symptoms may start to show itself. PD symptoms include motor, non-motor, behavioural, affective, and sensorial ones. PD manifests itself primarily by the loss or reduction of the sense of smell. This follows a progressive path starting from the olfactory bulb and brainstem, reaching cortical structures in the advanced stages of the disease. In the early stages, patients are presymptomatic. As the disease progresses, the substantia nigra, midbrain regions and the basal forebrain are affected, and pathological changes are observed in the neocortical and premotor areas (Yaliman & Şen, 2011). The diagnostic criteria for PD is published by Movement Disorders Society (MDS) as the Table 1 shows. (Table 1) (Postuma et al., 2015).

Table 1 MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form (Postuma et al., 2015)

The first essential criterion is parkinsonism defined as: bradykinesia, in combination with at least 1 of rest tremor or rigidity.

Diagnosis of **Clinically Established PD**:

1. Absence of absolute exclusion criteria

2. At least two supportive criteria, and

3. No red flag

Diagnosis of **Clinically Probable PD**:

1. Absence of absolute exclusion criteria

2. Presence of red flags counterbalanced by supportive criteria

If 1 red flag is present, there must also be at least 1 supportive criterion

If 2 red flags, at least 2 supportive criteria are needed

No more than 2 red flags are allowed for this category

Supportive criteria:

1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:

a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).

b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

2. Presence of levodopa-induced dyskinesia

3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria:

1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus within the first 5 years of disease

4. Parkinsonian features restricted to the lower limbs for more than 3 y

5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

8. Normal functional neuroimaging of the presynaptic dopaminergic system

9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flag

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset

2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment

3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y

4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

5. Severe autonomic failure in the first 5 y of disease. This can include:

a) Orthostatic hypotension —orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or

b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset

7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y

8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)

9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)

10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

REM, rapid eye movement; MIBG, metaiodobenzylguanidine; UPDRS, Unified Parkinson Disease Rating Scale.

(Postuma et al., 2015)

1.1. Clinical Features

1.1.1. Motor and Non-Motor Symptoms

Neurological examination is important in diagnosing PD. The symptoms generally are characterized by an asymmetric appearance, and includes tremors, rigidity (the condition of a certain part of the body or a certain extremity being stiff and rigid, patients may feel pain and fatigue due to the contraction immobility of the muscles caused by rigidity), bradykinesia (slowness of movement and speed), akinesia (the inability to voluntary movement of limbs and muscles) and postural abnormalities. There are some factors that are clinically effective in distinguishing PD from other parkinsonism symptoms. These are the prominent rest tremor in PD, little or no balance problems in the early stages of the disease, asymmetry of parkinsonian signs, and the presence of a clinically significant response to levodopa treatment. Motor findings may manifest themselves in the early stages of the disease (prodromal stage), with symptoms such as fatigue, feeling of weakness, moderate incoordination, difficulty in writing, slowness of movements, and pain. In most patients, the symptoms are in one half of the body, and approximately 50% of them begin as tremors (Cakmur, 2011).

Secondary motor symptoms; hypomimia, dysarthria, dysphagia, sialorrhea, micrographia, shuffling, festination, freezing, slowing down of daily living activities, blepharospasm and dystonia. These symptoms may not manifest themselves in the same way in everyone, and they do not all have to be present together. Since PD has an insidious progression, mild symptoms such as decreased or lost sense of smell and shoulder pain may not be noticed at first. Symptoms such as slowing of movements in one extremity, rest tremor, and clumsiness in fine motor movements may spread throughout the body over time and present a more general and noticeable appearance. These conspicuous symptoms include alien limb, leaning of the body to one side, shuffling, slowing down of all movements and walking, postural changes, rigidity, and bradykinesia becoming evident, slowing down, or stopping of

arm movements during walking, dulling and disappearance of spontaneous facial expression, and finally over time, due to dopaminergic deficiency, the patient has difficulty in performing voluntary motor movements and the movements slow down. PD is the neurodegenerative disease for which pharmacological treatment is most successful (Cakmur, 2011) and to diagnose PD, it is important that the patient is responsive to motor symptoms due to the administration of levodopa treatment (Balestrino & Schapira, 2020). Other motor disturbances different from the cardinal ones (tremor, bradykinesia/ akinesia/ hypokinesia, postural instability, and rigidity) are gait disturbances. These are such as freezing of gait, start/ target/ obstacle hesitation, and festination (Balestrino & Schapira, 2020).

Among many symptoms such as sensory symptoms, hyposmia, psychiatric symptoms (depression, anxiety, apathy, hallucinations, psychosis), gastrointestinal symptoms (constipation), genitourinary symptoms (sexual dysfunction, urgency, reduced libido, urinary frequency), dysphagia, dysarthria, hypophonia, sialorrhea, cardiovascular symptoms, dysrhythmias, disturbances of sleep and wakefulness (Balestrino & Schapira, 2020) cognitive impairment (MCI, dementia) plays a vital role in patient's quality of life. Cognitive deficits can be seen in the early stages of untreated disease. Since the disease's progression is insidious, early diagnosis is of vital importance especially in terms of detecting cognitive impairment to improve quality of life, and disease not to develop into dementia.

2. MILD COGNITIVE IMPAIRMENT

2.1. Diagnostic Criteria and Symptoms

Mild cognitive impairment (MCI) is a state between healthy cognition and dementia. It was also counted as a prodromal stage of Alzheimer's Disease (AD) (Goldman & Litvan, 2011). With this "in-between stage" status, Peterson et al. identified some criteria for MCI (Goldman & Litvan, 2011). These were as following:

> "*1) a memory complaint, preferably corroborated by an informant, 2) impairment in memory as documented according to appropriate reference values, 3) essentially normal performance in non-memory cognitive domains, 4) generally preserved activities of daily living, and 5) not demented*."
>
> (Goldman & Litvan, 2011).

Later, the characteristics and symptoms of MCI are clinically defined by Winblad et al. according to the information that MCI is not an impairment only due to AD, or it does not necessarily develop to AD. The revised change in the criteria indicating that the cognitive impairment is "not normal for the age", a categorisation as indicating the symptoms as amnestic and non-amnestic, due to the impairment in memory domain present or not, and including the number of cognitive domains that are impaired (single or multiple) (Goldman & Litvan, 2011). These led to a more explained, global and detailed classification and helped to identify and understand the impairment better. Also, National Institute on Aging and Alzheimer's Association workgroup revised the criteria as following:

> "*1) concern regarding a change in cognition as reported by the patient, reliable informant, or clinician observation, 2) impairment in one or more cognitive domains with evidence by impaired cognitive performance greater than the patient's age and educational background (often considered as scores 1 to 1.5 standard deviations [SD]*

below appropriate normative data, though specific cutoff scores are not stipulated) or a decline in performance over serial evaluations, 3) preservation of independence in functional abilities, and 4) insufficient evidence of dementia."

(Goldman & Litvan, 2011).

According to MDS (Movement Disorder Society) standardized diagnostic criteria is as the following:

"*Based on UK PD Brain Bank Criteria—reflecting a gradual decline as reported by either the patient or informant, not sufficient to significantly interfere with patients' functional independence. Second, cognitive deficits are reported on a formal neuropsychological examination as performances approximately 1–2 standard deviations below appropriate norms. MDS diagnostic criteria encompassed two operationalization levels for neuropsychological examination. Level I criteria are based on impairment in a global cognitive test validated for use in PD or in a brief neuropsychological assessment (i.e., less than two tests for each of cognitive domains assessed, i.e., attention/working memory, executive function, memory, visuospatial skills, and language). Level II criteria, based on a comprehensive neuropsychological evaluation, require an impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains. The Level II criteria allow MCI subtyping (i.e., single domain or multiple domain)*."

(Cammisuli et al., 2019).

The DSM-5 (DSM-5; APA, 2013), has broadened the concept of cognitive impairment and included it into an umbrella definition of Neurocognitive Disorder (NCD): NCD can be minor like in the case of MCI if it fulfils specific criteria (Yu et al., 2023). These criteria are:

> *" (1) a mild decline in cognitive function reported by the patient, an informant, or clinician, (2) a modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing, (3) independence in everyday activities, (4) not delirium, (5) not explained by another mental disorder."*
>
> (Yu et al., 2023).

Eventually, MCI and NCD are different in some aspects. One of these factors is age. A young individual may also be diagnosed with mild NCD due to mental distress or substance abuse, while MCI is generally considered to be in association with neurodegenerative disorders and frequently in elderly people. Even though both of them are not due to any other conditions and delirium, they show changes in this aspect. The etiology of NCD could be due to many diseases and conditions including traumatic brain injury, HIV infection and so on (Yu et al., 2023). In addition, domain of social cognition is counted as well to be impaired in mild NCD, but not in MCI (Yu et al., 2023).

2.2. Diagnosing and Assessment

Neuropsychological testing plays a critical role in detecting MCI in addition to physiological measurement and imaging techniques. Test scores in neuropsychological testing are of great importance apart from being only biomarkers. These are vital tasks such as determining at what level the disease is progressing, determining which cognitive domain there is regression, taking the necessary precautions to prevent the course of the disease and its transformation into dementia, and creating a treatment plan for the patient.

2.2.1. Neuropsychological Testing

A typical and comprehensive neuropsychological testing and assessment lasts for 90 minutes to three hours (Yu et al., 2023). Many tests and scales are used for the patients, including MoCA (Montreal Cognitive Assessment) and MMSE (Mini Mental State Examination).

2.2.2. Assessment of Memory

The memory domain is of absolute importance for the progression and course of the disease. Although there are many reasons for this, one reason is that MCI is seen as a biomarker of whether it will later develop into normal cognition or dementia**.** According to the assessments together with other biomarkers, prevention techniques for MCI not to develop dementia may be established. Since the timing is also important, this would provide better timing to know the progression beforehand. In the transformation of MCI into AD, there is a regression especially in the episodic memory in the memory domain (Yu et al., 2023). In the assessment of episodic memory, immediate recall and delayed recall are measured. Immediate recall is assessed generally in the tests as group of basic words are read aloud to the patient, and then the patient is then asked to repeat the words she /he heard aloud (usually in no particular order). While in delayed recall, first, the consultant reads aloud the words, as in the immediate recall, then, after at the end of the assessment or after other domains are measured depending on which assessment instrument is used, the patient is asked to "remember" the words read and say them out loud. Making these assessments is directly linked to learning and our ability to do our daily tasks easily. These tests that measure learning are tests such as word list learning tests and reading short stories. Some of these tests include the Rey Auditory Verbal Learning Test (RAVLT), the California Verbal Learning Test, and the Wechsler Memory Scale (Yu et al., 2023).

2.2.3. Assessment of Non-Memory Cognitive Domains

Assessment of memory and non-memory cognitive domains can be done by several types of neuropsychological testing, and a neuropsychological assessment can include all the domains, or different batteries and tests can be used for each of them.

A key component of both the "subcortical dementia" syndrome in Parkinson's disease and non-demented PD is executive function (Goldman & Litvan, 2011). Executive function is one of the non-memory cognitive domains and it includes the capacity to organize, plan, initiate, and regulate goal-directed behavior. It is dependent on the frontal-striatal circuitry, which includes prefrontal regions like the dorsolateral prefrontal cortex and its connections to the basal ganglia.

2.3. Symptoms in MCI

2.3.1. Neuropsychiatric Symptoms

Neuropsychiatric symptoms can be challenging and restrictive in the patient's life. It would be better for the patient to have a psychologist or psychiatrist in addition to the caregivers and the clinician while taking care of the patient and continuing the treatment. When there is a cognitive decline, comorbid conditions should be reviewed, precautions should be taken, and treatments should be applied. These situations may cause discomfort to the patient and may also slow down and complicate the treatment process of PD and MCI. The symptoms may occur as depression, anxiety, irritability, and sleep disturbances. One in three patients with MCI have at least one neuropsychiatric disorder whose symptoms are indicated in the preceding month (Yu et al., 2023). Depression is the most reported symptom, and after there comes irritability and sleep disturbances (Yu et al., 2023). Additionally, there is mounting evidence that loneliness and MCI are related (Yu et al., 2023). In addition to the physical support of the caregiver, social support is also very important for the difficulties that

may be experienced in daily life (activities of daily living and instrumental activities of daily living) during the course of MCI. In the relationship between depression and MCI, not only MCI affects depression but depression can trigger cognitive impairment and in addition, when comparing MCI with depression and MCI alone, turning into dementia, the likelihood of the individual with depression turning into dementia is higher.

2.4. Neuroimaging Findings, Neurobiology and Biomarkers of PD-MCI

Since the underlying reasons and patients vary across the disease, biomarkers for predicting the cognitive impairment and progression are still not completely able to represent a profile which is cheap, reliable, non-invasive and comfortable to apply for the patient. Generally, in studies the researchers are looking through the MCI-NC (normal cognition) versus others. This means that in some studies, researchers compare the patients who has MCI with normal cognition and other subtypes. There are significant findings between the differences in PD-MCI and PD with normal cognition, in one study the following were observed in PD with MCI patients: decreased network in alpha activity over the occipital lobe, increased network involving beta activity over the frontal lobe associated with a reduction over the parietal lobe, a reduction of networks in theta and delta activity in the parietal lobe and an increased network in theta and delta activity over the frontal lobe (Cammisuli et al., 2019). Also, over the occipital regions, electroencephalography (EEG) analysis showed a significant decrease of alpha power spectral density (PSD), and in the left temporal region it has shown an increase of delta PSD, in PD-MCI patients, compared to PD patients with normal cognition (Cammisuli et al., 2019).

Another widely confirmed relationship between PD and other disorders is documented by the correlation between PD-MCI and Rapid Eye Movement Sleep Behavior Disorder (REM Sleep Behavior Disorder) and olfactory dysfunction (Cammisuli et al., 2019). These findings may help early disease detection and intervention. In addition, there are some

deficiencies in the studies, these are including that studies have small sample sizes, lack of uniform PD-MCI definitions, longitudinal follow up, and detailed neuropsychological examination (Goldman & Litvan, 2011).

Among the biomarkers of PD-MCI, different aspects should be considered. Apart from some different findings, there are biomarkers that researchers agree on and can be seen as a sign. CSF markers that are seen for AD with MCI are also valid for PD-MCI. Among these, there are biomarkers such as low beta-amyloid 1-42 peptide and elevated total tau or phosphorylated tau levels (Goldman & Litvan, 2011). It was revealed that CSF-beta amyloid 1-42 levels were significantly correlated with memory impairment but did not have a significant effect on domains such as attention/executive or visuospatial dysfunction (Goldman & Litvan, 2011). A couple of studies have been done, but these are again limiting since they are not only studies for PD-MCI, but are still important for cognitive impairment and PD. In these studies, for instance, the gene called functional polymorphism in the catechol-O-methyl transferase gene (COMT Val158Met) changes the activity of dopamine-regulating enzymes in the prefrontal cortex, so these gene variants may also affect executive function (Goldman & Litvan, 2011). In addition, the microtubule-associated protein tau gene (MAPT) H1/H1 genotype has been implicated as a risk factor for PDD and has been suggested to cause greater posterior cortical cognitive impairments (Goldman & Litvan, 2011). When we look at the structural and metabolic findings, Beyer et al. (2007) conducted a study using voxel-based morphometry (VBM), and compared PD-MCI patients to PD without MCI, and found that PD-MCI patients had reduced gray matter in the left frontal and bilateral temporal lobe regions, but the results were not significant.

One of the blood-based biomarkers is “plasma neurofilament light chain (NFL)”. NFL is a blood-based biomarker for AD and Parkinsonian pathologies (Lin et al., 2018). It is one of the three subunits of neurofilaments. These neurofilaments are specific cytoskeletal proteins

of neurons and are especially abundant in largely myelinated axons (Lin et al., 2018). When axons are damaged somehow, these NFLs diffuse in CSF and thus, later in blood. Thus, it is believed that higher levels of NFL means that there is severe cerebral axonal degeneration (Lin et al., 2018). Considering this, various studies are being conducted to examine if NFL is correlated with various neurodegenerative disorders and can be considered a biomarker. Studies have shown that NFL may show degeneration in many neurodegenerative disorders. These neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, atypical parkinsonian disorders (APD), multiple sclerosis (MS), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), and it is a strong indicator especially in AD and PDD. In neuropsychological evaluation, a higher MCI score is also associated with a high degree of NFL and causes cognitive impairment by affecting non-motor symptoms rather than motor symptoms. It is also an indicator to distinguish PD from APD, and its levels are higher in MS, progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) than in PD and healthy controls (Lin et al., 2018). Lin et al. (2018) conducted a study involving 119 AD, 56 MCI, 26 PDND, 23 PDD, and 59 healthy controls (HC) by clinical evaluation and after measurement of plasma NFL levels. The results showed that plasma NFL levels are similar in MCI and PD patients, and MCI and PDND. Lower MMSE scores correlated with higher plasma NFL levels and MMSE scores. Moreover, NFL levels were correlated significantly in all AD patients, especially stronger in significance in the MCI group (Lin et al., 2018). Compared to PDND, there were higher plasma NFL in PDD patients. This indicates that plasma NFL levels may express the extension of cognitive dysfunction in PD (Lin et al., 2018), however, all this alone did not show that MCI patients in the study had higher plasma NFL compared to HC. We can conclude that plasma NFL levels are a more sensitive and stronger biomarker for AD, and later for PD than other neurodegenerative diseases. In addition, it can be counted as a feasible and non-invasive

method for diagnosing, and NFL is seen more as a biomarker in correlation with prognosis and disease progression, but it is limited as a diagnostic marker. Researchers have also conducted studies on whether plasma p-tau181 is a reliable biomarker. Accordingly, Batzu et al. (2022) conducted a study to investigate whether plasma p-tau181 is a reliable biomarker to understand cognitive performance in PD-MCI. Although some studies suggest that plasma p-tau181 concentration increases in PD, cross-sectional or longitudinal associations with cognitive performance have not been observed. This means that p-tau181 does not affect cognitive performance in longitudinal aspect.

In addition, epsilon 4 allele is a high risk predictor of AD and MCI (Anderson, 2019).

2.4.1. Structural Findings of MCI

By neuroimaging techniques, there is a consensus on widespread atrophy in PD with cognitive impairment (Biundo et al., 2016). There are mixed-MCI studies which researchers found significant grey matter atrophy in the following regions in the brain: MTL (medial temporal lobe), limbic regions (amygdala, hippocampus and para-hippocampus), uncus, caudate, precuneus, thalamus, and cingulate cortex (Yu et al., 2023). Even though these findings are from mixed-MCI studies, they also found similar findings when they compared amnestic MCI (aMCI) patients and healthy controls (HC), in other words, similar structural atrophies are found in the same places in amnestic MCI, according to meta-analyses (Yu et al., 2023). There are accelerated cortical thinness in PD-non demented patients compared to similar controls' which are at baseline (Biundo et al., 2016). In addition, in PD-MCI, there is cortical thinness in both anterior and posterior regions, proving that high-level cognitive function spreads and works together.

There are cortical atrophies in right anterior temporal regions, left prefrontal and insular regions, and right parietal and occipital regions (Cammisuli et al., 2019). Also a study

(Xiuqin et al., 2018) shows that early drug-naive PD-MCI patients show atrophy in the right entorhinal cortex (ENT) compared to patients with PD-normal cognition (Cammisuli et al., 2019). In another study (Schrag et al., 2017) researchers found that dopamine uptake reduction on caudate nucleus may be a better predictor of cognitive decline in PD with consideration of patients' age and CSF biomarkers, by using the single-photon emission computed tomography imaging of dopamine transporters (DAT-SPECT) (Cammisuli et al., 2019).

2.4.2. Diffusion Tensor Imaging (DTI) / White Matter Hyperinsensities (WMH)

Diffusion Tensor Imaging (DTI) measures the microstructural integrity of white matter (WM) fibres. This is measured indirectly via fractional anisotrophy (FA) and mean diffusivity (MD). While FA describing the directionality of the diffusion process, MD describes “the mean of diffusion coefficients across the X, Y and Z axes” (Yu et al., 2023). If FA is high, it means that the directionality of the diffusion is high. Studies found that in age-related WM degeneration, fractional anisotrophy is low, and mean diffusivity is high (Yu et al., 2023). Accordingly, in MCI patients, there is reduced FA in the posterior cingulate gyrus, para-hippocampal gyrus, thalamus and caudate in the left hemisphere, and bilateral precuneus (Yu et al., 2023). Many studies conducted to find biomarkers or prevention and treatment techniques to understand the mechanisms laying under the cognitive impairment and MCI. One of the studies (Zhao et al., 2017) show that there is a decrease in local and global network efficiency.

In another study (Rashidi-Ranjbar et al., 2020), they examined the structural network differences between MCI and HC and found the following: there are fewer hubs (highly connected regions in the frontal executive network compared to HC in both aMCI and non-amnestic MCI (naMCI) patients (Yu et al., 2023). In light of these and a couple of similar studies, it can be said that there are disrupted structural connections especially in the limbic

region (Yu et al., 2023). In the continuous injury of WM, FA is low and MD is high and in its extreme cases there is white matter hyperintensities (Yu et al., 2023). While white matter hyperintensities' lesions are more and more and in larger volume, cognitive functions worsen in time, and especially in attention, executive function, and in processing speed. Diffusion abnormalities are correlated with memory deficits in the posterior cingulate and hippocampus in non-demented PD patients, even though in the absence of the volume loss (Biundo et al., 2016). Agosta et. al. found that there are no GM atrophy, and structural WM alterations in frontal regions in PD-MCI patients, compared to healthy controls (Biundo et al., 2016). In the light of the findings, the researchers suggested that, with the consistency of the WM findings, PD may mainly arise from synaptic dysfunction, which leads to cellular death, and that PD can be detected by DTI even before cortical atrophy occurs.

2.4.3. Resting State fMRI

Resting state fMRI (rs-fMRI) uses BOLD signals (blood-oxygen level dependent) to measure spontaneous low-frequency fluctuations to understand the functional architecture of the brain (Lee et al., 2012). Basically, this investigates the synchronous activations of spatially distinct areas, in the resting state. Resting state means that this measurement is under rest; thus, not task related, and at the absence of a stimulus. According to this, many studies and meta-analysis have been done, and in a meta-analysis study (Lau et al., 2016) researchers examined the difference between healthy controls and aMCI patients, in the resting-state activation. According to this, in aMCI patients, following are observed: reduced activation in DMN (default mode network) (right/medial posterior cingulate, right angular gyrus, right para-hippocampal gyrus), right middle temporal gyrus, right fusiform gyrus, and increased activation in the left middle temporal gyrus and left supramarginal gyrus (Yu et al., 2023).

Another study (Li et al., 2015) compared mixed MCI patients and healthy controls. Accordingly, they found a decreased activation in the left middle temporal gyrus, left middle

frontal gyrus, medial frontal gyrus and right precuneus. In superior temporal gyrus, middle temporal gyrus, supramarginal gyrus and in left hemisphere the inferior parietal lobule have increased activation (Yu et al., 2023). Gu and Zhang (2019) found reduced activation in the default mode network (DMN), which the estimated region of right posterior cingulate gyrus/ precuneus and uncus, and superior temporal gyrus, and increased activation in left inferior parietal lobule and superior parietal lobule. Pan et al. (2017) made a meta-analysis that only examines resting state amplitude of low-frequency fluctuations (ALFF) (Yu et al., 2023). In DMN, salience network (bilateral fronto-insular cortices), and visual network (occipitotemporal cortex) reduced activation is observed and in visual network (right lingual gyrus, left middle occipital gyrus, and left inferior temporal gyrus), and left hippocampus increased activation is observed. In addition, there are worse MMSE scores among aMCI associated with larger ALFFs decreases in the precuneus/cuneus cortices. These areas are known as important for memory and cognitive processing (Yu et al., 2023). The reason some of these in-region and inter-region activations are high that is the compensation for limitations in other areas.

2.4.4. Task Based fMRI

Task based fMRI is that the activation in the brain depends on the stimulus and task when measured by fMRI. The brain is not at rest but involving in a stimulus. Terry et al. (2015) did a meta-analysis and pooled memory-related task-based fMRI studies' results, and reported that there is an increased activation in: left cerebellum and left lingual gyrus. Again, when we look at the results which Nellessen et al. (2015) did a meta-analysis in division of memory into encoding and retrieval (which the former one is related more to learning, and second one is remembering), and then again, they divided into visual and verbal memories. They looked at memory encoding (both verbal and visual) in mixed-MCI patients. There was an increased activation in the right hippocampus. While they looked at retrieval tasks in

mixed-MCI patients and there was a reduced activation for verbal tasks in right anterior insula/ inferior frontal gyrus and lastly reduced activation for visual tasks in left fusiform gyrus, and left hippocampus (Yu et al., 2023). To summarize, these findings and others jointly reveal that there is an abnormality and atypical patterns of memory-related activation in the DMN, limbic region and fronto-parietal network.

2.5. Prevalence

The inclusion of normal control groups or the use of normative data for neuropsychological tests, the amount and type of neuropsychological tests or domains assessed, the exclusion of PD dementia (and criteria used), variations in populations studied (e.g., clinic or community based; incident or prevalent PD), and other factors all contribute to the variation in frequency estimates of PD-MCI (Goldman & Litvan, 2011). At the same time, when doing, analysing and interpreting the assessments, it is important to exclude (or include accordingly) other factors such as comorbid diseases, sleep disturbances, behavioural problems, mood disorders and so on. These can provide a more precise picture in terms of understanding the etiology of the disease, distinguishing it from other diseases and factors, and determining appropriate prevention and treatment methods.

The Mini-Mental State Examination (MMSE) score was used to define cognitive impairment. 24 and subpar performance on a modified Tower of London task that suggested frontal lobe function, or a pattern recognition memory task reflecting temporal lobe function; the modified Tower of London task cut-off score was <8/14 based on age- and IQ-matched normative data, and pattern recognition memory task scores were more than one standard deviation (SD) below normative mean scores. Within this group, 13/159 (8%) had dementia (Goldman & Litvan, 2011). Muslimovic et al. (2005) conducted a study in the Netherlands with 115 newly diagnosed PD patients and 70 cognitively normal, healthy controls. This study classifies 24% of PD patients and compares them with 4% of the control group. These

are people who have cognitive impairment but do not have dementia. They conducted a couple of assessments and the results provide evidence that cognitive dysfunction develops early in Parkinson's disease and even before dopaminergic medication is started for the disease's motor symptoms (Goldman & Litvan, 2011).

%25.8 of PD patients also have MCI. PD with MCI may convert to PD-NC (Parkinson’s Disease with normal cognition) but this percentage is %25. Converting from PD-MCI to PDD is %60 during five years of follow up (Aarsland et al., 2021).

2.6. MCI in PD and MCI in Other Conditions

30%- 40% of PD patients have cognitive impairment (Cammisuli et al., 2019). Cognitive impairment in PD can be seen even in the early stages of PD. Later, according to the process, this cognitive impairment may convert to MCI, and even dementia. The contributing factors that PD converts into MCI are that male gender, increasing age, lower level of education, its development due to non-motor features, depression, and anxiety. Other associated conditions with PD with cognitive deterioration are motor disease severity, metabolic syndrome, and akinetic-rigid phenotype PD (Cammisuli et al., 2019). Apart from these, applications that may prevent cognitive deterioration include doing aerobic exercises and making it a lifestyle, sustainability of having a life as physically non-stable, especially continuing them at later ages, and having a high QoL.

Typical cognitive complaints in non-demented PD include impaired word finding, slower processing, trouble planning or multitasking, and a decline in attention and concentration (Goldman & Litvan, 2011). MCI in PD is similar to amnestic MCI in AD and MCI is also between the normal cognition and dementia (Weil et al., 2018). Generally, PD-MCI patients show non-amnestic features, that is, there are greater difficulties and regressions in other cognitive domains; such as visuospatial function, attention and executive function.

However, it shows that some of the PD-MCI patients in fact have amnestic features and show more cognitive deficits than in memory but other cognitive domains. Non-demented PD patients may also show impairment in the following: cognitive sequencing, planning, set maintenance or shifting to a novel stimuli, visuospatial, visuo-perceptual, visuo-constructive abilities, spontaneous speech problems and verbal fluency, and comprehension of complex sentences (Goldman & Litvan, 2011).

2.7. Pharmacological and Non-Pharmacological Interventions

2.7.1. Pharmacological Interventions

A study (Hinson et al., 2017) showed that treatment with atomoxetine would improve cognition in executive functioning, including executive control, set-shifting, and working memory (Cammisuli et al., 2019). Since cholinergic degeneration may contribute to gait impairments, psychosis, cognitive impairment and REM-sleep disorder, cholinesterase inhibitors like rivastigmine may be another useful medication in order to help PD patients (Cammisuli et al., 2019).

2.7.2. Non-Pharmacological Interventions

2.7.2.1. Cognitive Training Interventions

There are computerised training tests for the intervention, and they are used according to the benefit/ treatment that is wanted. N-back test is an example of this, and it is thought to improve working memory.

2.7.2.2. Mindfulness Based Cognitive Training

Mindfulness is a therapy technique used in clinical settings, for many diseases including mood and anxiety disorders. Mindfulness is being “here” and being here “now”, at its fundamental principle. Meditations, “mind and body exercises”, and yoga are some of them which the body and the mind are involved together. Mindfulness-based exercises are

considered to be more useful for improving attention. The gains are focused attention (directing and sustaining attention), and open monitoring (being here and now, in a non-judgemental manner and moving away from distractions by training the mind to follow moment-by-moment) (Yu et al., 2023). These exercises and trainings are helping to an increase in GM volume, and functional reorganization. What this means is that networks that have not been used as the others before are also used, thus serving a compensatory function.

2.7.2.3. Physical Activity Interventions

As in mindfulness-based therapies, physical activity is also suggested for many diseases, mental and physical. Physical activity helps the circulation of oxygen and blood, and detoxification. By this, it is good for brain, mental health and body, if it is done under necessary conditions, and when it is personalized. The other benefits include gliogenesis, neurogenesis, synaptogenesis, and angiogenesis. Physical exercise is increasingly important, and even dancing provides cognitive benefits. Studies have shown that cognitive exercise, along with motor training, is very useful for global cognitive function, processing speed, sustained attention, and mental flexibility. Such activities are also beneficial for cardiac health and are known to play an important role in sympathetic modulation, reduce dopaminergic neuron damage, oxidative stress and cellular inflammation (Cammisuli et al., 2019). Physical activity is seen not only as a means of improving well-being and delaying the onset of any disease, but also as a preventive role for many diseases. It also has a stress-reducing effect on cortisol levels. Physical exercise helps to structure basal ganglia functions related to motor commands by reducing the change of dopaminergic neurons in the substantia nigra and also ensures the concentration of brain-derived neurotrophic factor (Cammisuli et al., 2019). In many studies conducted with animals, we see the importance of physical exercise for the brain and nervous system. As an example, we can determine that when PD rats are given an aerobic exercise lasting between 20 and 60 minutes, 5 days a week for 4 weeks, this causes the

expression of the glial fibrillary acidic proteins in the dorsal striatum to be restored (Cammisuli et al., 2019). Moreover, such activities also have neuroprotective effects in the cerebellum in mice (Cammisuli et al., 2019). Therefore, it is also very effective in movement and balance control.

Physical activities including walking, aerobic exercises (which is best for oxygen and blood circulation), resistant training, and balance training. As with medications and other interventions, there are various guidelines for these physical activities. Just as there are personalized physical training and exercise techniques for HC, a personalized program can be created for MCI patients, taking into account the person's health conditions and physical condition. This will both make the patient more motivated, provide more suitable progress for the course and progression of the disease, and give better results. According to a consensus guideline for MCI patients (Lautenschlager et al., 2019), programs can be listed as follows: (1) 150 minutes of moderate or 90 minutes of vigorous aerobic exercise per week, (2) resistance training at least twice a week, (3) balance training exercises: these can be considered as a very effective exercise in maintaining the patients' balance and against falls, (4) as mentioned above, these exercises are shaped according to the physical and environmental conditions and health status of the patient (Yu et al., 2023). According to meta-analysis, there is a gain in global cognition in mixed-MCI patients (Yu et al., 2023). In addition to global cognition, there is also a significant gain in domains including memory, executive function, language, and visuo-spatial.

2.7.2.4. Nutritional Supplements

Since nutritional supplements require less effort for the patients, it seems more feasible compared to cognitive behaviour approach and physical exercise, and it generally seems easier to patients.

In Omega 3 capsules there are n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs), and these capsules contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and they help protecting the neurons and it also prevents neuronal loss and damage. DHA also helps reducing beta-amyloid plaques aggregations (Yu et al., 2023). It also provides a protection against dementia, cardio-vascular diseases and diabetes. An other nutritional supplement is ginkgo biloba. Yang et al. conducted a study in 2016 and found that ginkgo biloba improves MMSE scores among mixed-MCI patients. Gingko biloba helps downregulating amyloid-beta induced toxicity, and fibrillogenesis and metal dyshomeostasis as Caspase 3 and 12 (Yu et al., 2023). It also helps preventing the damage to neuronal cells and facilitates cerebral vascularization, and vasodilation. Some of other supplements are also has been tried on patients such as B, C, D, E vitamins, but its exact effect is controversial as consistent results were not obtained in these RCTs. In some researches, some of these vitamins such as E and B are effective (Olivera-Pueyo & Pelegrín-Valero, 2017). These vitamins have antioxidant effects and thus, it has protective effects for neurons, and against neurodegeneration and cognitive impairment. Andrews et al. (2023) did a systematic review and examined dietary pattern, food, and nutritional supplement on MCI and cognitive impairment. The results show that it is one of the preventing factors in the progression of MCI and its transformation into dementia. Mediterranean diet is a balanced and ingredient-rich type of diet that includes regular consumption of fruits, vegetables, whole grains, olive oil, cheese, yogurt, fish and seafood, and low to moderate alcohol consumption, especially wine. Mediterranean diet provides better cognitive performance and is nutritious. In addition, there are studies that show low carbohydrate diet improves memory (Andrews et al., 2023) and although some studies have not proven their effectiveness to be high, the following foods are stated to be beneficial for cognitive impairment, these are: grape juice, cocoa flavanols, phyto-nutrients, probiotics, blueberries (Andrews et al., 2023). These are some of the foods

that have been shown by some studies to be beneficial for cognition domains, but their full effectiveness is still debatable.

2.7.2.5. Non- Invasive Brain Stimulation

Several types of NIB (non-invasive brain stimulation) are used to improve cognition including tDCS (transcranial direct current stimulation) and rTMS (repetitive transcranial magnetic stimulation). In tDCS, a cap is placed on the patient/participant's skull, where electrodes are attached depending on the regions, and a low electrical current is delivered to these regions through them. This current usually varies between 1 and 2 mA. One of the anodes (electrode) is placed in the corresponding brain region according to the domain and cognitive ability to be stimulated. Here, the incoming electric current stimulates and activates the neurons in the resting state. Therefore, a functionality occurs in this region, and if it is stimulated repeatedly, neuronal excitability occurs in this region for more than 24 hours (Monte-Silva et al., 2013). This requires the practitioner to be highly qualified, as it may cause long-term functional changes in the brain. In rTMS, strong electrical signals are sent through a coil to the desired brain areas. It also can be used repetitively. How strong the signal is and its frequency are adjustable, and neuronal firing as well as inhibition in desired areas is possible. As with many medications, NIBS techniques may have some adverse effects. Side effects of rTMS can be described as dizziness, head and scalp pain, and facial twitching, while for tDCS they are reported as itching, tingling and burning (Yu et al., 2023). Although high doses and repeated use may cause some problems, neither of them has any known, proven and irreversible side effects. But this is an information limited to what has been done on humans. It has been observed in some animal experiments that tDCS can cause severe damage, such as lesions in the brain, with excessive use. In general, there are researchers who report that rTMS may be more harmless, at least in terms of its known side effects.

2.8. Treatment Considerations

As with other different diseases, there are many things to consider regarding treatment methods for neurodegenerative diseases and cognitive decline. Correct methods and sustainability of the treatment of scientifically validated techniques for treatment provides great convenience for the patient in terms of time, ADL and progress. However, for example, in cognitive training, even if the activities are repeated frequently, doing these activities one after the other may cause a pause in performance after a while. One of the reasons for this may be that the patient has become accustomed to these activities and continues them in a sort of “memorized” manner.

When it comes to physical activity and exercise, it is easy to do and does not require an equipment generally, but it only has benefits on patients who are motivated and disciplined, and also has limitations on patients who have disabilities and physical difficulties. Non-invasive brain stimulation techniques require the practitioner to be qualified and the patient must be prepared for the side effects of the application, so it is very limited. Nutrition supplements and vitamins are easy to obtain and use, when it is combined with other treatment methods, it shows beneficial effects. The limitation of nutrition supplements and vitamins is that the effects are quite weak compared to other medications and treatments.

DISCUSSION

Parkinson's Disease (PD) stands as the second most prevalent neurodegenerative condition, yet much of its complexity remains to be fully unraveled. It induces degeneration in motor functions, accompanied by a spectrum of non-motor symptoms that significantly impact individuals' lives. PD is classified as an α-synucleinopathy, characterized by the accumulation of phosphorylated and abnormally aggregated α-synuclein. The root cause lies in the loss of neurons in the substantia nigra of the midbrain, disrupting the nigro-striatal pathway and resulting in dopaminergic deficiency in the brain, giving rise to a myriad of symptoms.

The cardinal motor symptoms encompass tremors, rigidity, bradykinesia, akinesia, and postural abnormalities, typically presenting with an asymmetric appearance. Additional manifestations include hypomimia, dysarthria, dysphagia, sialorrhea, micrographia, shuffling, festination, freezing, and a slowing down of daily living activities. Non-motor symptoms extend to sensory issues, especially in the predromal stage with olfaction, psychiatric symptoms, and cognitive impairment, including Mild Cognitive Impairment (MCI) and dementia. Remarkably, over one-third of PD patients concurrently experience MCI, a condition marked by cognitive abnormalities yet preserved independence in daily activities.

Mild Cognitive Impairment (MCI) primarily manifests in the domains of memory, executive function, and visuospatial abilities. The gradual progression of this condition underscores the importance of neuropsychological assessments, such as the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), in detecting MCI. Executive function impairments, critical for organizing, planning, initiating, and regulating goal-directed behavior, become evident during daily activities. Additionally, neuropsychiatric symptoms, including depression, anxiety, REM sleep behavior disorder, and

hallucinations induced by treatment drugs, pose additional challenges, significantly disrupting the daily lives of affected individuals.

Exploring neuroimaging findings that remain under investigation, researchers have observed low beta-amyloid 1-42 peptide levels and elevated total tau or phosphorylated tau levels. Elevated tau levels may disrupt neuronal connections further, and a significant correlation between CSF-beta amyloid 1-42 levels and memory impairment has been identified. Genetic factors, such as the catechol-O-methyl transferase gene (COMT Val158Met), can alter the activity of dopamine-regulating enzymes in the prefrontal cortex, potentially impacting executive function.

Among the blood-based biomarkers, "plasma neurofilament light chain (NFL)" has gained attention. Increased levels of NFL may be associated with AD and Parkinsonian pathologies, with a higher MCI score linked to elevated NFL levels, influencing cognitive impairment, particularly in non-motor symptoms. Notably, studies suggest that plasma NFL levels serve as a more sensitive and robust biomarker for Alzheimer's Disease (AD) and later for Parkinson's Disease (PD) compared to other neurodegenerative diseases.

While some studies indicate a high concentration of p-tau181 in PD, there is insufficient evidence for a significant correlation with cognitive impairment in the longitudinal aspect. Atrophy in the brain, attributed to neuronal loss, is evident in significant grey matter atrophy in regions such as the medial temporal lobe (MTL), limbic regions (amygdala, hippocampus, and para-hippocampus), uncus, caudate, precuneus, thalamus, and cingulate cortex. Examining structural findings with Diffusion Tensor Imaging (DTI), consistent with white matter findings, suggests that PD may primarily arise from synaptic dysfunction, leading to cellular death. Importantly, DTI may detect PD even before cortical atrophy becomes apparent.

As the root cause of the disease remains elusive, the available treatment options and interventions remain limited. One notable approach is Levo-dopa treatment, which has shown efficacy in alleviating cognitive impairment in Parkinson's Disease (PD) patients. Additionally, recommended interventions include engaging in physical activity, incorporating nutritional supplements such as ginkgo biloba, omega-3, and adopting a Mediterranean diet. Non-invasive brain stimulation techniques like repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) (with a preference for rTMS), Cognitive Behavioral Therapy (CBT), cognitive training, and mindfulness practices are also suggested. While some researchers propose that cannabis may alleviate symptoms, its usage comes with associated side effects.

Extensive research efforts are ongoing and have been conducted to explore treatments for PD and Mild Cognitive Impairment (MCI). Given the constant influx of new information, there is optimistic speculation that it might eventually become feasible to prevent not only PD but also other neurodegenerative disorders before their onset.

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