Chapter

Homocysteine and Dementia in Parkinson Disease

Jin Jun Luo, Lin Zhang and Nae J. Dun

Abstract

Parkinson disease (PD) and dementia are neurodegenerative disorders that can be frequently seen in the elderly. Homocysteine (Hcy) is an intermediary metabolite from methylation, which is highly relevant to body physiologic activities including DNA metabolism. Elevated plasma level of homocysteine (eHcy) is seen in normal aging individuals and patients with neurologic disorders such as PD or dementia. Although clinical observations confirm the finding that eHcy is prevalent in PD patients, the former is not a recognized etiology causing PD but rather, an adverse outcome related to the therapy of dopaminergic supplementation. Notably, eHcy may exacerbate various medical and neurologic conditions such as cardiovascular diseases, stroke, mild cognitive impairment, all of which are potential risks for dementia. This chapter discusses the concerns of eHcy relative to dementia in PD.

Keywords: dementia, homocysteine, neurodegeneration, Parkinson disease

1. Introduction

Parkinson disease (PD) is a progressive, neurodegenerative disorder caused by multifactorial including genetic and environmental influences [1, 2]. PD is the second most common neurodegenerative disorder after Alzheimer disease (AD), affecting approximately 1.5–2% of individuals over 65 years and 4% over 80 years of age. Incidence of PD is estimated ranging from 5 to >35 per 100,000 populations [3]. In an early population-based study with pathologically confirmed clinical diagnoses in Minnesota, USA, the incidence of PD was 21 cases per 100,000 person-years [4]. Onset of PD before 50 years of age is not common, but the incidence escalates 5–10-fold from the sixth to the ninth decade of life [2–6]. Noticeably, PD is twice as common in men than in women in most populations [5, 7], suggesting gender and/or age may play a role in the development of PD [8]. The exact cause for PD is not fully understood and much research has been directed the past 200 years toward the underlying etiology responsible for the development of PD.

2. Clinical features of PD

Clinical manifestations of PD include motor and non-motor symptoms. The classic motor features of PD are tremor, rigidity, akinesia/bradykinesia, and postural instability (mnemonic "TRAP") [9] although recent revision of the diagnostic criteria excludes postural instability as a fourth hallmark (**Figure 1**). PD has a wide variety of non-motor symptoms such as cognitive impairment, sleep disturbances,

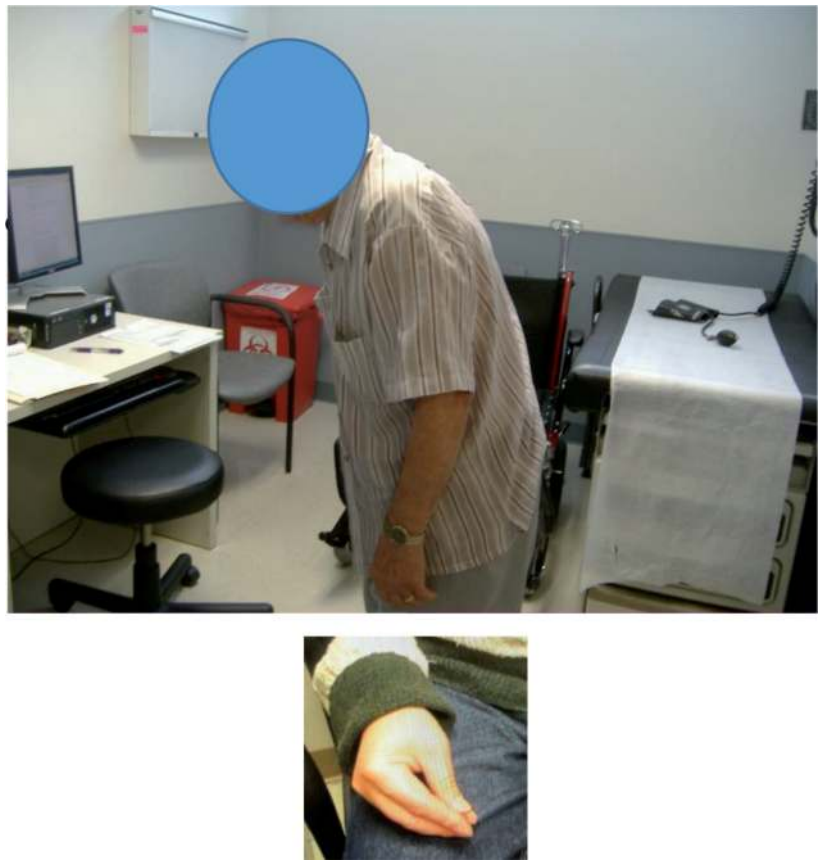

Figure 1.
Features of Parkinson disease.

depression, and hallucinations [10, 11]. The neuropathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra resulting in striatal dopamine deficiency and intracellular inclusions of Lewy body containing aggregates of α-synuclein. Loss of dopaminergic neurons in the substantia nigra is responsible for the inability to synthesize an adequate amount of the neurotransmitter dopamine in the brain. Treatment of PD usually includes pharmacological replacement of striatal dopamine, in addition to non-dopaminergic agents to treat both motor and non-motor symptoms, and surgical interventions such as deep brain stimulation for refractory motor symptoms.

3. Why dementia in PD?

Dementia is an acquired, irreversible neurodegenerative disorder manifesting progressive impairment in cognitive function and affecting the awareness of surroundings. It is caused by structural and/or functional disturbances in the cerebral cortex, its subcortical connections, or both. It may result from genetic and environmental influences. Dementia and cognitive impairment are the leading chronic disease contributors to disability and particularly, dependence among older people worldwide [12]. Many diseases including neurologic such as stroke, severe brain traumatic injury, and depression; and non-neurologic such as cardiovascular, toxic, malnutrition, systemic infection/inflammation can now be added to the list, particularly of health consequences of aging, causing initially cognitive decline, or mild cognitive impairment (MCI), and subsequently advancing to dementia.

Dementia has been estimated to affect 5–20% of populations older than 65 years [13, 14] and its incidence increases with age. A recent epidemiologic study [15] based on the database of System for the Development of Research in Primary Care (SIDIAP) in Spain enrolled with 1,035,046 subjects, mainly women (56.2%), from urban areas (80.9%) and 75.7 (7.9) years old on average disclosed that the estimated incidence of dementia was at 9.5/1000 person-years (95% CI 9.3–9.7), adjusted for gender at 9.3/1000 person-years (95% CI 9.0–9.6), age at 8.8/1000 person-years (95% CI 8.4–9.2), and combining age-and-gender at 8.6/1000 person-years (95% CI 8.0–9.3). Interestingly, women have a higher incidence than men, and the incidence increased with age: namely 25 times higher in the individuals of 90 years and older than in the 65–69 years [15]. Indeed, the incidence of dementia increases exponentially worldwide with increasing age; [16] particularly, early hallucinations and akinetic-dominant PD were associated with an increased risk of dementia [17]. Based on the available estimates for the global incidence of dementia dating from 2010, the incidence of dementia doubled with every 5.9-year increase in age, from 3.1/1000 person-years at age 60–64 to 175.0/1000 person-years at age 95+ [16]. The number of people living with dementia worldwide in 2015 was estimated to be at 47.47 million, reaching 75.63 million in 2030 and 135.46 million in 2050 [12, 18].

Dementia in PD (PDD) is a clinical syndrome with impaired attention, executive dysfunctions, and secondarily impaired memory. The most significant deficits are loss of cholinergic activities and the degrees of Lewy bodies in certain limbic and cortical areas in neuropathology, both of which correlate well with the clinical severity of dementia in PDD [19]. Clinical trials have shown cholinesterase inhibitors, which may be beneficial in PDD [19].

Notably, dementia in PD was not initially included in the article "*An Essay on the Shaking Palsy*" published in 1817 by James Parkinson [20–22], who first described the symptoms and signs of 6 patients, the differential diagnosis, etiology, and contemporary treatment in his monograph comprising 5 chapters and 66 pages. This eponymous disease was named after him. Importantly, many atypical clinical features of PD have been subsequently detailed over the past several decades. Among those non-motor symptoms of PD, dementia was not recognized until 3 decades ago and now is increasingly being recognized [23]. Robust clinical studies have been conducted on the epidemiology, clinical features, pathological correlations, and treatment of dementia in PD. The International PD and Movement Disorders Society published new clinical criteria for PD diagnosis in 2015 that manifestation of concomitant dementia is no longer as an exclusion criterion [21, 22]. The new diagnostic criteria accept the diagnosis of PD independent of when dementia arises (before or within the first year as well as after that) as long as the clinical criteria for PD are fulfilled. These diagnostic criteria have been validated subsequently by demonstrating high sensitivity and specificity compared with the gold standard, expert diagnosis with higher sensitivity and specificity [24]. It is now known that PDD represents one of the most significant non-motor symptoms, especially in more advanced PD [25, 26]. The prevalence of PDD has been reported ranging from 20 to more than 70% of PD patients depending on the diagnostic criteria employed and the nature of the study population conducted [19, 27]. An earlier study has reported the point prevalence of PDD to be approximately 30% [28], indicating that dementia is common in PD. Importantly, PDD is associated with increased mortality, impairments in well-being, caregiver strain with increased health care, and institutionalization costs [29–31]. Risks of developing dementia in PD have drawn intense interest and they are often an important topic for health workers, patients, and their families given its significant impact [32]. Searching for the risks, predictors, and measures of prevention for dementia in PD patients continues.

4. What is mild cognitive impairment?

Mild cognitive impairment (MCI) is a medical condition, encountered with normal aging, that clinically borders between early dementia and cognitive impairments. Individuals who experience MCI are still able to perform daily activities, but with evidence of a gradual decline in memory or other cognitive functions. MCI is divided into two subtypes: amnestic and nonamnestic, but neither type meets the diagnostic criteria for dementia. MCI is considered a prodrome to dementia as the rates of conversion from MCI to dementia are greater than that of normal cognition associated with aging [33]. Cognitive decline includes deficit in executive, visuospatial function, attention, and memory. Behavioral symptoms are frequent including apathy, visual hallucinations, and delusions. Notably, the most prominent pathology in PDD is the expression of Lewy body type of inclusions. Insofar as the biochemical deficit is concerned, a cholinergic hypoactivity has been documented. Placebo-controlled randomized trials with cholinesterase inhibitors have shown modest but significant benefits in cognition, behavioral symptoms, and global functions [27]. Clinical observations and laboratory animal studies have shown that homocysteine plays a role in MCI and dementia.

5. What is homocysteine?

Homocysteine (Hcy) is an intermediary metabolite during the transmethylation of the essential sulfur-containing amino acid methionine. Hcy can be either remethylated to methionine or converted to cysteine through the transsulfuration pathway (**Figure 2**). In remethylation, there are two different pathways. One is the 5-methyltetrahydrofolate (5-MTHF) pathway. 5-MTHF is an active form of folate serving the methyl donor in the methionine synthase reaction, which requires vitamin B12 as a cofactor. 5-MTHF is produced by a reaction catalyzed by

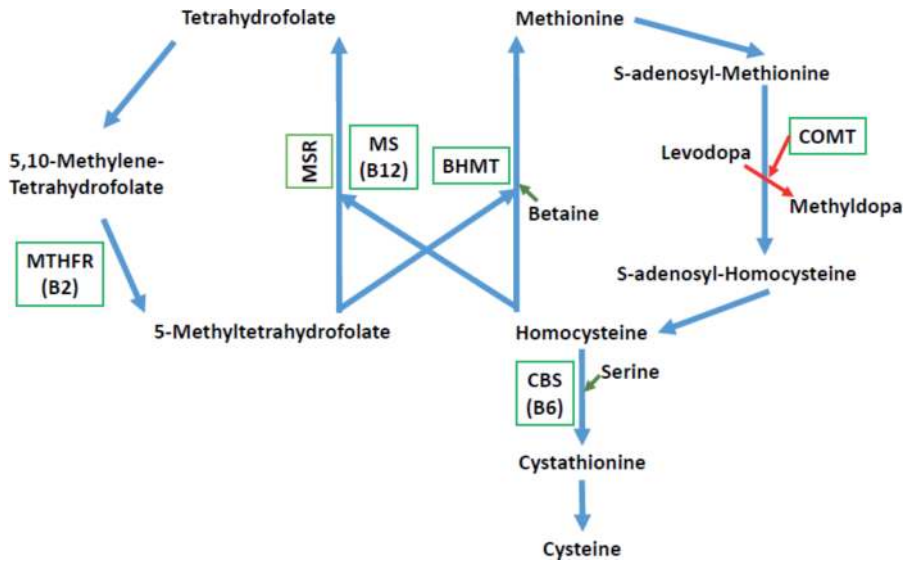

Figure 2.
Homocysteine metabolism. BHMT: *betaine-homocysteine methyltransferase;* CBS: *cystathionine beta-synthase; COMT: catechol-O-methyltransferase;* MTHFR: *5,10-methylene tetrahydrofolate reductase;* MS: *methionine synthase; MSR: methionine synthase reductase.* BHMT *is active in liver; CBS requires peridoxal phosphate (vitamin B6); MTHFR requires riboflavin (*B2*); MS requires methylcobalamin (*B12*);* MSR *is required for the reductive activation of MS. Methylation of levodopa and dopamine by COMT, that uses* S*-adenosylmethionine as a methyl donor to generate* S*-adenosylhomocysteine.*

5,10-methylenetetrahydrofolate reductase (MTHFR), which is a common, thermolabile enzyme. The methyl donor 5-MTHF is generated from 5,10-MTHF through the enzyme MTHFR. 5-MTHF is mainly synthesized in the liver and then distributed to various tissues and cells in the body where it acts as a methyl donor for transferring to Hcy *via* methionine synthase, which regenerates methionine. Mutations or polymorphisms of MTHFR may result in a decreased enzymatic activity, such as cytosine to thymidine substitution at the position 677 (C677T) or adenine to cytosine at 1298 (A1298C) of the MTHFR gene. Approximately 5% of the general population and 17% of patients with coronary artery disease are C677T homozygous. Polymorphism of A1298C is also linked with reduced enzymatic activity. Heterozygosity for both of these polymorphisms (C677T and A1298C) in pregnant women is associated with a greater risk of neural tube defects in newborns [33–40].

The second pathway whereby Hcy is methylated to methionine is by the enzyme betaine-homocysteine methyltransferase (BHMT). BHMT is also rich in the liver, whereas methionine synthase (MS, a B12-dependent enzyme) is present in all tissues and requires 5-methylene tetrahydrofolate as a methyl donor. The MS gene has several mutations and polymorphisms. Substitution of adenine to guanine at 2756 (A2756G) of MS has an allele frequency ranging from 8 to 32% in different populations; for example, mutation and polymorphisms occur in 8% of the population in West Bengal in India, 11% in East Asia, 17% in European, 18% in American, 28% in African, and 32% in South Asian populations [41]. The A2756G allele is associated with a moderate effect on Hcy levels [37]. Initially, this variant was thought to be associated with lower enzyme activity, causing elevated plasma level of homocysteine (eHcy) and DNA hypomethylation [42]. However, subsequent investigations suggested a modest inverse association between 2756GG polymorphism and Hcy levels, indicating increased enzymatic activity of the variant genotype with an effect to reduce Hcy levels [43].

Methionine synthase reductase (MSR) is critical for the reductive activation of MS. Mutation in the gene for MSR results in an autosomal recessive disorder of folate/cobalamin metabolism, leading to hyperhomocysteinemia, hypomethioninemia, and megaloblastic anemia. At least 11 mutations with defective MSR genes have been reported [44].

In the transsulfuration pathway, cystathionine beta-synthase (CBS), which requires vitamin B6 as a cofactor, converts Hcy to serine with the formation of cystathionine, which is subsequently cleaved to form cysteine by cystathionase. More than 150 mutations with a change in single amino acid have been reported in the CBS gene that causes eHcy and homocystinuria. The most common mutation substitutes the amino acid isoleucine with the amino acid threonine at position 278 in the enzyme. Another common mutation, which is the most frequent cause of homocystinuria in the Irish population, replaces the amino acid glycine with the amino acid serine at position 307, causing eHcy and homocystinuria [33, 34, 38, 40].

6. Why is Hcy a concern in PDD?

eHcy has been considered as a risk factor for various pathophysiologic conditions including normal aging, static lifestyle with lack of physical exercise, cigarette smoking, cardiovascular disorders, chronic kidney disease, hypertension, hyperlipidemia, etc. Earlier clinical observations revealed the presence of eHcy in PD patients, which was initially considered to be relevant to PD neurodegeneration [45]. However, subsequent studies showed a lack of convincing evidence that eHcy and PD were causally related; [46] rather, eHcy could be generated by the administration of dopaminergic agents, which was confirmed in patients in clinical [47–51] and animals in laboratory studies [52, 53].

eHcy may exert its neurotoxic effects *via* a direct and/or indirect intracellular action by stimulating free radical production, provoking oxidative stress response, increasing cytosolic calcium level, rendering hypersensitivity to excitotoxicity, interfering with mitochondrial function, depleting ATP reserve, impairing transmethylation of DNA, resulting in DNA breakage, and leading to neural cell death and apoptosis [33, 38, 54, 55].

The most common cause of eHcy is the deficiency of folate or vitamin B12, enzymatic derangements due to genetic mutation or polymorphisms, and/or environmental stress alone or in combination. However, the occurrence of eHcy in patients with PD has been proven not to be causally related to vitamin deficiency but an adverse effect of dopamine supplementation from methylation of levodopa and dopamine by catechol-O-methyltransferase (COMT), an enzyme that uses *S*-adenosylmethionine as a methyl donor to generate *S*-adenosylhomocysteine, which is rapidly converted to Hcy [51, 56].

eHcy is also a risk factor for vascular disease and potentially for dementia. eHcy is observed to be associated with the transition from being cognitively healthy to develop dementia [57–59]. Observations from a longitudinal clinical study over 6 years revealed that eHcy is an independent risk factor for the decline of cognitive performance in normal elderly subjects [60] and patients with AD; therefore, a negative role of eHcy in cognitive functions was proposed [13]. To support this claim, a study on the relationship between eHcy and hippocampal function or generalization performance was performed. The result demonstrated the role of eHcy in declining cognitive function in both healthy controls and patients with MCI [58]. Additionally, a double-blind, randomized controlled clinical study showed an association of the degrees of eHcy with the rates of brain atrophy in elderly with MCI [59]. Indeed, dopamine supplementation therapy with levodopa may render patients with PD at an increased risk for vascular disease by promoting eHcy and therefore, susceptible to becoming PDD [51] *via* the mechanism of COMT in levodopa therapy [51, 56]. However, controversy exists regarding the evidence for associations between MCI and eHcy [61–63] and dementia in long-term PD patients. A recent retrospective study [32] has investigated the frequency of PDD in a pooled 2327 PD patients across the UK and Australia. Of the PD participants, 36 with disease durations of 20 years or longer were identified. Among these 36 patients with long durations of PD, only 7 (19%) were recognized as probable PDD, and 34 (94%) manifested a non-tremor dominant phenotype. The authors concluded that the prevalence of dementia in long-term PD patients may be lower than anticipated and the trajectory of cognitive decline in PD patients can be different [32].

7. How should we deal with Hcy in PD?

As aforementioned, eHcy in patients with PD may result from the adverse effect of therapeutic dopamine supplementation with levodopa, rather than a vitamin deficiency [51, 64–66]. This observation has been confirmed in several independent studies showing that pharmacologic treatment of PD patients with levodopa therapy is associated with eHcy, which may irreversibly promote the occurrence of atherosclerotic vascular disease and stroke, both are risk factors for MCI and dementia [48, 67].

It is a standard practice to administer a peripheral-acting dopa decarboxylase inhibitor (DDCI; carbidopa) simultaneously with levodopa to treat PD patients, in which DDCI prevents levodopa from being metabolized into dopamine peripherally. However, co-administering a DDCI with levodopa results in increased metabolism of levodopa to 3-O-methyldopa via the enzyme COMT in peripheral

tissues [68]. Apparently, COMT activity requires S-adenosyl-L-methionine (SAM) as the methyl donor, leading to the formation of the by-product, S-adenosyl-L-homocysteine (SAH), which can be further hydrolyzed to homocysteine leading to eHcy [53]. Indeed, eHcy has been detected in PD patients treated with levodopa, compared to age- and sex-matched controls, and to non-levodopa treated PD patients, and also has been replicated in laboratory animals [52, 53]. The increase in the blood level of Hcy after administering a single dose of levodopa can be reduced with co-administering a COMT inhibitor, such as entacapone [53, 69], suggesting that a COMT inhibitor can prevent levodopa-induced eHcy via the COMT mechanism and bears potential therapeutic benefits in reducing the risk of eHcy-related vascular diseases [69].

It is noteworthy levodopa, the most effective drug known in the treatment of PD, has been shown to be able to induce eHcy in PD patients [47, 49–52, 56, 66, 70–72]. This increase is even more pronounced in patients with polymorphisms of the enzyme MTHFR, such as C677T [49, 72].

Clinical observations revealed that eHcy may be involved with various neurologic conditions, including MCI, dementia, epilepsy, stroke, and neurodevelopmental disorders [33]. In addition, eHcy-induced neurotoxicity has been demonstrated, causing hippocampal neuronal death [55], which may be associated with cognitive decline leading to dementia. Hcy can be marked in humans by radiological evidence of white matter lesions as well as silent brain infarcts and atrophy of the cerebral cortex and hippocampus [73], even in healthy, middle-aged adults [74].

Epidemiologic studies have shown that eHcy is an independent risk factor for cardiovascular diseases and responsible for about 10% of total risk [75], even in the youths [76]. eHcy may cause vascular endothelial cell dysfunction leading to hypercoagulation, atherosclerosis, and stroke [77], which may, in turn, play a role in the pathogenesis of neurodegeneration, causing MCI and dementia [38]. The estimated hierarchy of eHcy relevant to the risk of cardiovascular diseases and stroke was proposed as 7 μM, low; 8–11 μM, moderate; 12–16 μM, high; >16 μM, very high [78]. Laboratory studies showed that eHcy potentiates Aβ neurotoxicity in cultured neurons [79], which is relevant to the development of AD and dementia. In organotypic cultures, both Hcy and its metabolites exhibit excitotoxic potency by interaction with various glutamate receptor subtypes [79, 80].

Evidence from clinical and preclinical studies has shown that eHcy is a risk factor for stroke, coronary artery and cardiovascular disease, and dementia [39, 40, 73, 81–85]. Levodopa therapy, rather than the course of PD, was proposed to cause eHcy in PD patients. The deficiency of folate or vitamin B12 does not fully explain eHcy in these patients [51]. Collectively, findings of levodopa associated with eHcy [47, 49–52, 56, 66, 70–72] suggested a disconcerting possibility that levodopa therapy may cause eHcy and subsequently increase the risk of dementia and other medical conditions such as atherosclerotic cardiovascular disease, stroke, and MCI [33, 67, 86]. Notably, the mean plasma Hcy levels in patients with PD were 31% higher in levodopa-treated patients, which was as a consequence of levodopa methylation by COMT [51], and eHcy in PD patients treated with levodopa is observed to be associated with a nearly twofold increased prevalence of coronary artery diseases [51]. A treatment aiming to decrease the formation of eHcy in PD patients may bear the potential beneficial and remote effects for patients with PD. [33, 67, 86]

Additionally, eHcy was considered as a strong and independent risk factor for osteoporotic fracture of the hip in the elderly [87, 88], particularly for elderly women [88]. Patients with homocystinuria are frequently associated with skeletal deformities, including osteoporosis. Importantly, eHcy also has been documented as an independent risk for peripheral neuropathy [89–93]. Collectively, eHcy may play a role in promoting adversely effects on daily living in PD patients.

Currently, no effective therapy to cure neurodegeneration is clinically available. The best approach in clinical practice is primarily prevention through the modification of acquired risk factors [33, 67, 86]. As aforementioned, eHcy may play a role in promoting the early onset of various medical and neurologic conditions even during normal aging [60], potentially accelerates neurodegeneration, and exacerbates symptoms of those ailments, and prophylactic treatment of eHcy may be beneficial. In fact, generation of eHcy from levodopa administration is associated with a greater reduction in Hcy from co-administration of a COMT inhibitor and entacapone [56, 94]. Clinically, administration of vitamin B-complex with folate to reduce eHcy is inexpensive, potentially effective, and devoid of significant adverse effects, therefore, having an exceptionally favorable therapeutic index [75, 95, 96]. Well-designed prospective randomized placebo-controlled clinical trials may be warranted to evaluate the efficacy of co-administering vitamin B-complex with folate to patients with eHcy in order to delay the onset or mitigate the severity of neurologic disorders [67, 86]. Of course, elimination of the occurrence of atherosclerotic cardiovascular disease or MCI and dementia should not be expected even when folate status is kept sufficiently high and in B-complex regimen. Similarly, improvements in folate status may not eliminate cognitive decline in patients with PDD. Administration of B-complex with folate is inexpensive and with an exceptionally favorable benefit/risk ratio. However, direct evidence of eHcy as a therapeutic target in order to prevent dementia is currently not available. The therapeutic efficacy of lowering eHcy to prevent PDD remains to be firmly established [78].

8. Summary

PD is a progressive, neurodegenerative disorder. The high prevalence of PDD is the most common manifestation of non-motor symptoms of PD. eHcy can be seen in many pathologic and physiologic conditions such as normal aging, deficiency of vitamin B12 or folic acid, enzymatic deviation due to genetic polymorphisms, concomitant chronic diseases, or dopamine supplementary therapy. eHcy has been considered as an independent risk factor for many medical and neurological conditions including atherosclerotic cardiovascular diseases, stroke, and MCI, all of which are potential risks for the development of dementia in PD. Additionally, eHcy may cause osteoporosis, hip fracture, and peripheral neuropathy, which may worsen daily living and compromise the quality of life in patients with PDD. Treatment with COMT inhibitor and B-complex together with folate to prevent or reduce eHcy in PD patients may prove to be a potentially valuable and cost-effective approach to exerting therapeutic efficacy of reducing eHcy.

Conflict of interest

All authors reported no conflict of interest.

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