Hyperhomocysteinemia in L-Dopa Treated Patients with Parkinson's Disease: Potential Implications in Cognitive Dysfunction and Dementia?

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Abstract: *Background*: Hyperhomocysteinemia has been associated with cognitive dysfunction and dementia. The incidence of dementia in Parkinson's Disease (PD) patients is higher than in the general population and plasma Homocysteine concentrations are increased in L-dopa treated PD patients.

Objective: We evaluated the possible correlations between L-Dopa related hyperhomocysteinemia and cognitive dysfunction in PD.

Methods: A Medline literature search was performed to identify all published studies on Homocysteine and cognitive dysfunction and dementia during the course of PD from 1966 to 31/03/2010.

Results: Sixteen studies were found for review; ten studies focused on homocysteine and cognitive dysfunction in PD patients, five on homocysteine and PD dementia and two on homocysteine and markers of neurodegeneration in PD. The design of the study was retrospective in 14 studies, while 2 had a prospective design, with a variable follow-up period (from 24-weeks to 2 years). In most of the studies plasma homocysteine levels significantly correlated with cognitive functions, dementia and markers of neurodegeneration in PD patients. However, some studies did not confirm these findings. Several factors may concur to explain these partially conflicting results, including the retrospective design of the studies, their small sample size, their high percentage of excluded patients, and the use of a wide range of neuropsychological tasks in assessment of cognitive dysfunctions across the available studies.

Conclusions: Available data seem to indicate a potential role of L-dopa related hyperhomocysteinemia on cognitive impairment and dementia during the course of PD.

Keywords: Parkinson's disease, Dementia, homocysteine, L-dopa, cognitive dysfunctions.

INTRODUCTION

Homocysteine (Hcy) is a sulfur-containing metabolite of the essential amino acid methionine [1]. In humans, plasma Hcy concentrations are regulated by its remethylation to methionine, catalyzed by methylenetetrahydrofolate reductase (MTHFR), and by transulfuration to cysteine, by cystathionine-β-synthase (CβS) [1]. Overall, plasma Hcy concentrations vary widely in the general population, but levels do not exceed 12 micromol/L in about 90% of the subjects [2].

Hcy trespasses blood-brain barrier through a specific carrier; therefore cerebrospinalfluid (CSF) and plasma concentrations are correlated [3]. The brain may be particularly vulnerable to high Hcy levels (starting from 10 micromol/L), because it lacks the two aforementioned major metabolic pathways for its elimination [4]. Confirming these observations, elevated plasma Hcy levels have been associated with mild cognitive impairment (MCI) [5], vascular dementia [5] and Alzheimer's Disease (AD) [6,7]. In addition, both *in vitro* and *in vivo* studies evidenced that Hcy directly exerts on neurons multiple specific detrimental actions, that can be involved in the development of cognitive dysfunction and dementia [2, 8-11]. These neurotoxic mechanisms include excitotoxic aminoacids-mediated damage, mitochondrial dysfunction, free radicals and cytosolic calcium accumulation, apoptotic pathways activation and amyloidal plaques deposition [1,2, 8-11].

Parkinson disease (PD) is an idiopathic neurodegenerative disorder mainly characterized by dopaminergic cell death and dopamine depletion in neurons projecting into the striatum from the substantia nigra of mesencephalus [12].

Cognitive dysfunction and dementia are common non-motor symptoms of PD [13]. The incidence of dementia in PD (PD-dementia) is two to six times higher than in the general population and increases with disease duration [14], reaching 83% after 20 years [15]. The exact causes of dementia onset in PD and the underlying neurobiological mechanisms are still unknown. Several studies have recently observed that plasma Hcy levels raise in PD patients treated with L-dopa, the most effective drug in the symptomatic management of PD, when compared to age and sex matched controls and to patients with other neurodegenerative disorders, as AD and MCI [16-19]. The hyperhomocysteinemia in PD patients has been related to the O-methylation of L-dopa by the enzyme catechol-O-methyltransferase. During this methylation process, S-adenosylmethionine (SAM) is utilized as a methyl donor with the production of S-adenosylhomcysteine (SAH), which is then readily hydrolyzed to Hcy [16-18].

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It has been suggested that Hcy may contribute to hasten the disease progression and to the development of cognitive impairment and dementia in PD; however, to date, the clinical relevance of the L-dopa associated with hyperhomocysteinemia and its effects on the disease course are still undetermined [16-18].

The aim of our study review was to examine the current literature concerning a possible association between elevated plasma Hcy levels and the presence of cognitive dysfunction and dementia in PD.

METHODS

A Medline literature search was performed to identify all published studies on Hcy and cognitive dysfunction and dementia during the course of PD up to 30/03/2010, using the MeSH terms "homocysteine", "folate", "B-vitamins", "Parkinson's Disease, "dementia", "cognitive dysfunction", "pathogenesis", "Lewy Body", "Amyloid". Published abstracts were included, and additional references were taken from article citations.

BODY OF THE REVIEW

Following data extraction, 16 studies (10 studies on Hcy and cognitive dysfunction in PD patients [20-29], 5 on Hcy and PD dementia [29-33] and 2 on Hcy and neurodegeneration markers in PD [19,34]) were found for review. fourteen studies were retrospective [19-21,23-32,34], while 2 studies were prospective [22,33], with a variable follow-up period (from 24-weeks to 2 years). Eleven studies were available as full papers and 5 only in abstract form.

Ten studies assessed the possible correlations between plasma Hcy levels and cognitive functions in PD patients [20-29]. The studies were conducted in Europe, US and Asia. All but one studies had a retrospective, cross-sectional design; the only available prospective study was conducted in a US cohort of 72 consecutive patients, over a 2-year of follow-up period [22] (Table **1**). In most of the studies plasma Hcy levels significantly correlated with cognitive functions in non-demented PD patients and elevated plasma Hcy was associated with an increased risk for cognitive impairment (Table **1**). However, some studies did not confirm these findings; three studies found no correlation [24,25,28,29] and in the only prospective study there was no difference in individual tasks between subject with high and low Hcy [22]. Several factors may concur to explain these partially conflicting results; first, the high exclusion rate in some of these studies [22,24], that could have skewed their results by excluding cases with the worse clinical feature [22]. Second, the use of a wide range of neuropsychological tests in assessment of cognitive dysfunction across the available studies. The neuropsychological evaluation for PD-dementia still remains debated [35]; several scales have been proposed, but validation data on their use in PD-dementia are still lacking [35]. Finally, the small sample size of the studies may have influenced the statistical power of their results; indeed in none of the studies more than 100 PD patients were enrolled.

Hcy and PD-dementia

Five studies evaluated the correlation between plasma Hcy and dementia during the course of PD [29-32]. The study design was retrospective and the number of patients included in the studies was relatively small in most of the studies. Plasma Hcy levels were significantly higher in patients with PD dementia, compared to non demented patients in all but one studies (Table **1**). A linear correlation with scores on neuropsychological tools was also observed. In one study patients with Hcy levels (>18.9μmol/L) had a 4-fold higher risk for dementia, compared to patients with low Hcy levels (<12.4μmol/L), after correction for possible confounding factors [30]. Finally, a double blind placebo-controlled clinical trial on rivastigmine in PD dementia conducted on 342 patients revealed that patients with Hcy levels higher than 14micromol/L (which has been associated with a doubling in the risk for AD) [36] presented a greater beneficial effect on cognition and activities of daily living from treatment [33].

Hcy and Markers of Neurodegenerations in PD

Two studies focused on the possible associations in PD patients between plasma Hcy levels and circulating markers of neurodegeneration, as circulating amyloid-beta into as amyloid-beta [19,34]. In both studies Hcy levels positively correlated with plasma amyloid-beta, even levels after adjustments for age and creatinine ($p < 0.0001$) [19,34], In a recent study from Germany plasma Hcy also correlated with platelet alpha-synuclein [34]. Significant negative correlations were also found between plasma SAH and amyloid-beta ($p=0.007$), and between SAM and alpha-synuclein ($p=0.033$) [34]. In the study from US, plasma Hcy levels also correlated with worse cognition [19]. Although these data need further confirmation, the results given can be interpreted as indirect proofs of a positive relationship between plasma Hcy and neurodegeneration process during the course of PD.

DISCUSSION

In the present study, the evaluation of literature data indicates that L-dopa related plasma hcy levels may influence the development of cognitive impairment and dementia during the course of PD. However, data from the available studies are still controversial and present several limitations. First, results have been provided in most of the cases by retrospective studies; second, the study sample is overall small, with only two studies including more than 100 PD patients [30,33]. Finally, no population based study on this issue has been published to date.

Despite all these considerations, there are several evidences that show that Hcy levels are increased in PD patients treated with L-dopa and that elevated plasma Hcy levels are associated with AD and vascular dementia [1,36]. Although the exact pathogenetic mechanisms of PD dementia still remain debated, it is therefore reasonable to hypothesize that Hcy may play a role in the pathogenesis of PD-dementia [37]. The pathologic substrate of PD-dementia includes neuronal loss, Lewy body pathology, Alzheimer's-type pathology, basal forebrain cholinergic degeneration and vascular

Table1. Characteristics and Results of Studies on Homocysteine and Cognitive dysfunction and PD Dementia in Patients with PD

Authors	Year	Country	Study design	Number of subjects	Neuropsychological tests	Significance of association	Results
Homocysteine and cognitive dysfunctions in PD							
-O'Suilleabhain *et al*. [20]	2004	US	Cross-sectional study	-79 consecutive PD patients	-MMSE -Controlled oral word association test -Stroop color-word task	Yes	-Patients with elelvated plasma Hcy levels (>14micromol/L) had overall worse cognition (Odds Ration: NA; p<0.1) and performed worse on any of the cognitive measures
-Zoccolella *et al*. [21]	2005	Italy	Cross-sectional case-control study	-35 PD patients: 14 with cognitive dysfunctions, 21 without cognitive impairment	-MMSE -FAB	Yes	-Mean Hcy levels were significantly higher in the group with cognitive dysfunctions (21.2+/-7.4 vs. 15.8+/-4.4 micromol/L; p=0.0001) -Logistic regression analysis showed that the risk of cognitive dysfunction progressively increased according to Hcy levels after correction for age, sex and B-vitamin status (odds ratio: 19.1; 95% CI: 1.5-241.4; p=0.02).
-Ozer *et al*. [23]	2006	Turkey	Cross-sectional, case-control study	- 39 PD patients, 28 healthy controls)	-Short test of mental status -Clock drawing test	Yes	-A trend for lower scores in overall cognitive functions ad frontal functions (Clock drawing test: Odds Ratio: NA; p=0.08) -Significant correlation between plasma Hcy levels and scores on visuo-spatial (Odds Ratio: NA; p<0.05) and executive tasks (Odds Ratio: NA; p=0.001).
-Hassin-Baer *et al*. [25]	2006	Israel	Cross-sectional study	- 72 consecutive PD patients	-Frontal Assessment Battery (FAB) -Mini Mental State Examination (MMSE) -Trail making test (TMT)	No	-Hcy levels stratified into tertile did not significantly correlate with any of the neuropsychological tasks (Odds Ratios: NA)
-O'Suilleabhain *et al*. [22]	2006	US	2-years prospective study	-97 consecutive PD patients	-MMSE -Controlled oral word association test -Stroop color-word task	No	-Elevated plasma Hcy levels (>14micromol/L) was associated with overall worse cognition (p<0.01) both at baseline ad at the end of follow-up (p=0.0025) -Tests assessing attention, visual memory tended to have a greater deterioration in the group with elevated plasma Hcy -However the overall decline in cognitive functions was not statistically significant in multivariate analysis (Odds Ratios: NA; p=0.2) -Results were similar for any individual outcome, due to the small sample size and the high percentage of study drop-out. -Almost 20% of the original cohort was not evaluated at the end of the study.
-Nakaso *et al*. [27]	2006	Japan	Retrospective study	- 95 consecutive PD patients	-not available	Yes	-Elevated Hcy levels were associated with faster disease progression and particularly psychosis during the course of PD (p=NA).
-Shin *et al*. [28]	2006	South Korea	Cross sectional case-control study	- 18 PD patients, 27 AD patients, 41 healthy controls	-Korean version of CERAD	No	-No difference in Hcy levels among PD patients with or without cognitive dysfunction (Odds Ratio: NA; p: NA)
-Stathis *et al*. [26]	2006	Greece	Cross sectional case-control study	- 31 PD patients, 11 healthy controls	-Clock test	Yes	-Significant correlation was observed between Hcy levels and cognitive dysfunction (Pearson's correlation coefficient r=-0.54; p<0.002)

(Table 1). Contd…..

Authors	Year	Country	Study design	Number of subjects	Neuropsychological tests	Significance of association	Results
-Camicioli *et al*. [24]	2009	Canada	Retrospective, case-control study	- 51 prevalent PD cases and 50 age\sex-matched controls	-MMSE -FAB- -Cumulative Illness Rating Scale -Geriatric Depression scale	No	-Hcy did not correlate with global measures of cognitivon, but patients with PD had higher GDS score (p=NA) -High percentage of excluded patients 226/270 from the original cohort of PD patients -The study did not correlate plasma Hcy with cognitive functions among PD patients
Homocysteine and PD dementia							
-Litvinenko *et al*. [31]	-2005	Russia	Cross sectional case-control study	50 consecutive PD patients: 30 demented, 20 non-demented patients)	MMSE -FAB -Mattis dementia rating scale (MDRS) -Not available criteria for the diagnosis of dementia	- Yes	-Plasma Hcy levels significantly correlated with MDRS, MMSE, FAB scores (r= 0.6; p<0.01) -Among demented patients plasma Hcy levels were significantly associated with white matter brain lesions (p<0.001)
-Menendez *et al*., [32]	-2007	Spain	Retrospective study	88 PD patients	-MMSE -TMT -Tower of Hanoi test -No mention on adopted criteria for the diagnosis of PD dementia	Yes	-Dementia was more common among patients with elevated plasma Hcy levels (>15micromol/L; 30%) compared to patients with normal Hcy levels (<12micromol/L; 15%; ODDS ratio: NA; p=NA)
-Barone *et al*. [33]	-2008	Italy, Uk, the Netherlands, Austria, US)	24-week double-blind, placebo-controlled clinical trial on rivastigmine	342 PD patients	-AD assessment scale (ADAS-Cog) -Clinician Global impression of change -Activity of daily lving (ADL)-Diagnosis of dementia: MMSE score: 10-24	Yes	-Patients with high Hcy levels (>14micromol /L) at baseline had lower ADL score (p=0.025) -During the study period, patients with high Hcy levels had greater effect of rivastigmine on cognitive functions and activity of daily living functions -Significant changes in ADAS-Cog (4.0; p<0.01), MMSE and ADL score was observed in of patients with high Hcy levels -44% of patients with high Hcy levels referred marked, moderate or minimal improvement after treatment with rivastigmine, compared to 26% of patients treated with placebo. This result was confirmed even after controlling for confounding factors.
-Zoccolella *et al*. [30]	-2009	Italy	Retrospective, case control study	142 patients: 88 with dementia, non demented PD patients	-MMSE -FAB Dementia was diagnosed according to Diagnostic and Statistic Manual for Mental Disorders revised fourth edition (DSM-IVR)	Yes	-Hcy levels were higher (20.7µmol/L versus 15.8; p=0.002) in PD patients with dementia compared to non-demented. Multivariate logistic regression revealed that Hcy levels [Odds ratio comparing the top (>18.9µmol/L) with the bottom tertile (<12.4µmol/L): 3.68; 95%CI:1.14-11.83; p=0.003], age and motor impairment were associated with dementia.

(Table 1). Contd…..

Authors	Year	Country	Study design	Number of subjects	Neuropsychological tests	Significance of association	Results
-Rodriguez-Oroz *et al*. [29]	2009	Spain	Cross sectional case-control study	89 L-dopa treated PD patients aged >60 years and with disease duration>10 years (37 cognitively normal, 22 having mild cognitive impairment, 30 demented) and 30 age and sex-matched controls)	-MMSE -Blessed dementia rating scale -Yesavage depression rating scale -Dementia diagnosis according to DSM IV -Mild cognitive impairment diagnosis according to Petersen's criteria	No	-Plasma Hcy levels were significantly higher in PD patients compared to controls (8.55micromol/L; p<0.0001) -There was no difference between demented PD patients (15.4 micromol/L) PD patients with cognitive dysfunctions (15.1) and non demented PD patients (14.9) -Hcy levels did not predict the cognitive status (Odds Ratio: NA; p=0.403) in a multivariate model including age, B-vitamin status. -Results were similar when pooling together PD patients with any degree of cognitive impairment (Odds Ratio: NA; p=NA) -There was no association between MTHFR, cystathionine-beta-synthase, methionine-synthase polymorphisms and cognitive dysfunctions and dementia in PD patients
Homocysteine and neurodegenerative markers							
-Irizarry *et al*. [19]	2005	US	Cross sectional case-control study	- 93 PD patients, 145 patients with Alzheimer's Disease, 47 with Mild Cognitive Impairment, 67 with cerebral amyloid angiopathy, 25 with hypertensive intracerebral hemorrhage and 88 nondemented controls	Not available	Yes	-Hcy levels were significantly increased in PD patients, compared to the other groups (p<0.01) -In PD patients plasma Hcy levels were significantly correlated with worse cognition -Hcy levels positively correlated with plasma Abeta levels even after adjustments for age and creatinine (p < 0.0001)
-Obeid *et al*. [39]	2009	Germain	Cross sectional study	45 nondemented PD patients	Not available	Yes	- Significant negative correlations were found between plasma SAH and amyloid-beta (p=0.007) and between SAM and alpha-synuclein (p=0.033) -Plasma Hcy levels were significantly correlated with platelet levels of alpha-synuclein and amyloid-beta (p=0.007)

pathology [37]. Hcy may be involved in all these pathogenetic mechanisms of cognitive dysfunction and PD-dementia, through several potential mechanisms of action (Fig. **1**).

1. Lewy Body Pathology

The most consistent pathological hallmark of PD-dementia is the accumulation of Lewy Bodies (LB) in limbic and cerebral cortical areas [37,38]. The main constituent of LB inclusions is alpha-synuclein, a 140-amino acid peptide that is expressed in the presynaptic terminals of neuronal cells and regulates dopamine biosynthesis and homeostasis [37,38]. This protein abnormally misfolds and accumulates in PD, but its exact role in the pathogenesis of PD-dementia is still unclear [37,38].

Recent studies found a strict correlation between plasma Hcy levels and platelet alpha-synuclein, supporting the hypothesis that the L-dopa related elevation in plasma Hcy may contribute to increase the concentrations of alpha-synuclein [34].

The most likely underlying mechanism is the hypomethylation, consequent to the depletion of SAM which is used as methyl-donor in the catabolism of L-dopa [34]. The limited availability of SAM might enhance the expression of alpha-synuclein gene [34]. This pathogenetic hypothesis is supported by animal studies that found that lower SAM is associated with an enhanced retention of isoaspartyl-rich alpha-synuclein [39], and by the observation of an increase in alpha-synuclein concentrations in other conditions characterized by hypomethylation, such as chronic alcoholism [40].

Another possible mechanism may be the up-regulation of the Hcy induced reticulum protein. HERP protein has been recently observed and up-regulated in the core of Lewy bodies [41].

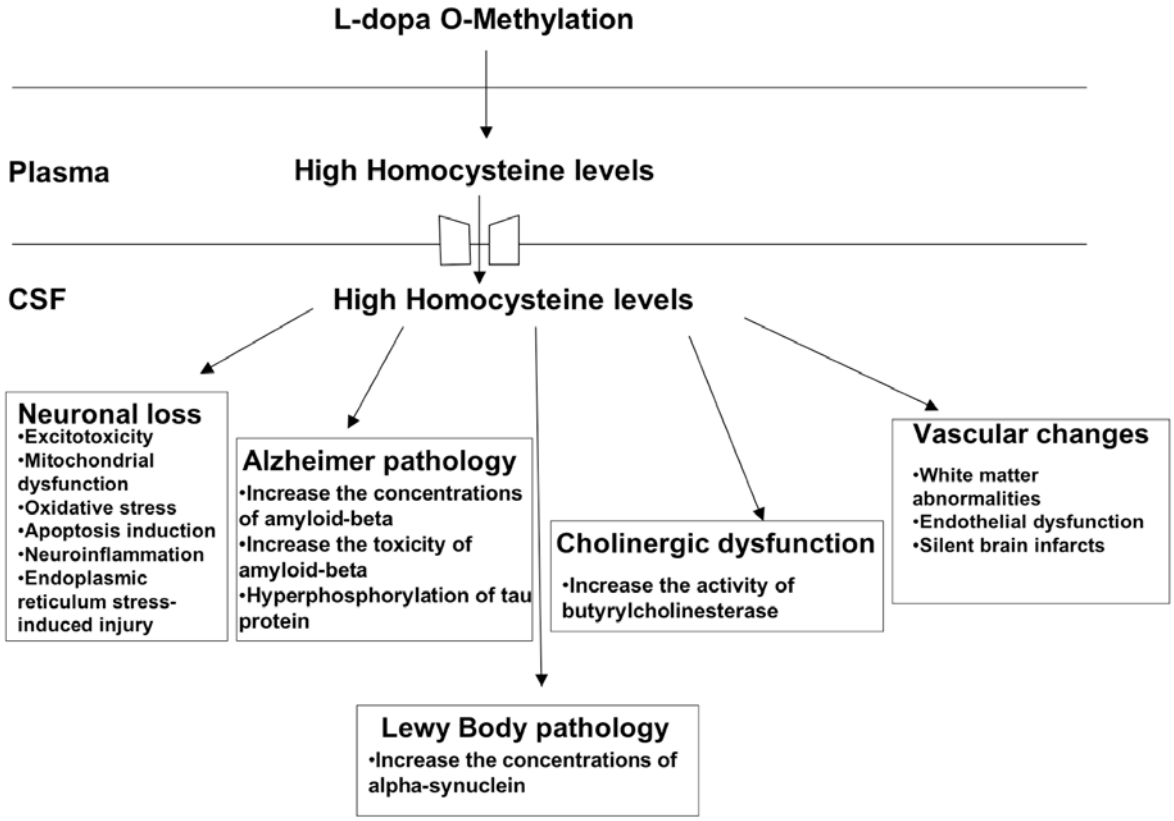

Fig. (1). Hypothetical neuropathological mechanisms of action of Homocysteine in the pathogenesis of Parkinson's Disease Dementia.

2. Hcy and Neuronal Loss

The rate and extent of cortical and subcortical atrophy are increased in PD patients with cognitive dysfunction and dementia, compared to healthy controls and cognitively intact PD patients [35,37]. Key areas appear the caudate, hippocampus and amygdale. There are several *in vitro* evidences that Hcy induces subcortical atrophy and causes neuronal hippocampal loss [1,8,42]. In healthy elderly people, the hippocampal width decreased significantly with the increase of Hcy plasma concentrations, regardless of age and body mass index [43]. Finally, plasma concentrations of Hcy correlate negatively to hippocampal and cortical volumes determined by MRI [43].

Hcy can cause neuronal loss by two main pathogenetic mechanisms: direct damage and astrocytes-mediated damage on neurons.

a. Direct Damage to Neurons

Several *in vitro* studies observed that Hcy is toxic to neuronal cells, even at low physiological levels of 10 micromol/L [1,8,11,44]. Different potential detrimental effects on neurons have been characterized *in vitro* and in cell cultures. (Fig. **1**) Hcy could damage neurons by inducing oxidative stress, through enhancing the production of radical oxygen species and nitric oxide, and by sensitizing neurons to amyloid-beta toxicity [1,44-46]. Another potential pathogenetic pathway is induction of excitotoxicity to motor neurons by its catabolites Homocysteic-acid and Hcy thiolactone, which can directly stimulate both *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate excitotoxic receptors, possibly leading to intracellular calcium accumulation and motor neuron degeneration [1,44]. The Hcy-thiolactone may also induce cell death and apoptosis, even at physiological level [47]. Hcy thiolactone can also be incorporated into intra or extracellular proteins leading to the alteration of their structure and function [47]. Finally, Hcy may induce mitochondrial dysfunction [9], endoplasmic reticulum stress-induced injury [41], activate apoptotic cascades and neuronal death mechanisms [11].

b. Neuronal Damage Mediated by Reactive Astrocytes and Inflammation

Hcy can increase PARP and p53 expression and activity in astrocytes [1,10]. These proteins might regulate cell fate as essential modulators of death and survival transcriptional programs and may increase the vulnerability of neurons [10].

On the other hand, elevated plasma concentrations of Hcy can compromise the integrity of the blood-brain barrier (BBB) in mice [48], increasing the permeability and consequently the entrance of potentially neurotoxic factors and peripheral immune blood cells, which may exacerbate the inflammatory response [48].

3. Alzheimer's Type Pathology

The hallmark of AD pathology is the accumulation of neurofibrillary tangles, neuritic plaques and of the insoluble amyloid-beta [1,36,44]. The main component of AD pathology is amyloid-beta, which is produced from amyloid-beta

precursor protein (APP) and accumulates in the intracellular and the extracellular space, leading to amyloid plaques [1,36,44]. Pathological studies revealed that Alzheimer-like pathology, especially amyloid-plaques, frequently coexists to LB pathology in PD [38], and that PD patients have more Alzheimer's-like pathology compared to age-matched controls [35]. There is however a difference in severity and distribution of AD pathology between patients with PD dementia and AD [49]. Although some clinico-pathological studies found a correlation between MMSE scores and Alzheimer's-like pathology [35], the influence of amyloid-plaques on the clinical expression of the disease still remains undetermined [37].

Several *in vitro* studies found that Hcy may interfere with the production and the accumulation of all the pathological hallmarks of AD [34,36,44]. A positive association between plasma concentrations of Hcy and that of amyloid-beta has been recently observed in normal aging and in neurodegenerative disorders, including PD [19,34]. In addition, the Hcy-responsive endoplasmic reticulum protein enhances the accumulation of amyloid-beta in the brain [50]. On the other hand, Hcy potentiates the amylod-beta toxicity both in cultured neurons and in APP transgenic mice, probably by enhancing oxidative stress [34,44]. Another mechanism of action is the hyperphosphorylation of tau-protein, an intracellular microtubule-associated protein that participates in forming the neurofibrillary tangles [1,44]. A positive correlation between levels of Hcy and phosphorylated tau protein has been recently observed in elderly subjects both in plasma and cerebrospinal fluid [34,51].

Confirming these observations recent studies conducted in PD patients, found that elevated Hcy levels increase the expression of APP or its hydrolysis to amyloid-beta [34]. Consistently, blood concentrations of Hcy and amyloid-beta appear strictly correlated [19,34]. The most likely pathogenetic mechanism is the hypomethylation, as a trend for negative correlation was found between plasma SAM and platelet amyloid-beta [34].

4. Forebrain Cholinergic Dysfunction

The involvement of the ascending cholinergic pathway with diffuse cortical projection has been suggested as a cause of cognitive dysfunction and dementia in PD [34]. Deficit in ascending cholinergic pathway is common in PD and may contribute particularly to impaired memory, attention and executive functions that are frequently observed during the course of the disease [38]. Consistently, pathological studies evidenced that there is a prominent neuronal loss in forebrain regions, as nucleus basalis of Meynert, in PD-dementia [38,52]; this cellular loss is associated with reduced cholinacetyltransferase and acetylcholinesterase activity both in nucleus basalis of Meynert and in the cerebral cortex [38]. The degree of cholinergic deficits in PD significantly correlated with the severity of dementia [53], and resulted more extensive compared to AD, both in pathological and *in vivo* study with PET [54,55].

Hcy thiolactone, the cyclic metabolite of Hcy, is capable of altering the activity of human cholinesterases, enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine [56]. The most pronounced effect is the increases in the activity of butyrylcholinesterase [56]. Consistently, a recent clinical trial on rivastigmine in PD dementia, patients with high Hcy levels had greater effect of the drug on cognitive functions and activity of daily living functions. Forty-four percent of patients with high Hcy levels referred marked, moderate or minimal improvement after treatment with rivastigmine, compared to 26% of patients treated with placebo [33]. These findings suggest that Hcy could contribute to worsen the cholinergic deficiency observed in PD.

5. Vascular Changes

The elevation of Hcy plasma levels has been associated with increased risk for cardiovascular diseases, cerebrovascular diseases (including stroke, vascular dementia, silent brain infarcts), peripheral vascular diseases and venous thrombosis [2]. Starting from a plasma concentration threshold of 10 micromol/L, the vascular risk progressively increases following a linear dose-response relationship [2]. Basic research has shown that elevated Hcy may have various adverse vascular effects, including altered function of low density lipoprotein receptors, enhanced rate of atheromatous plaque formation in large arteries, increased proliferation of vascular smooth muscle cells, direct damage to endothelial activity, and increased platelet activity and procoagulant effects [2,16].

Many studies looked at links between PD and atherosclerosis with conflicting results and the relationship between the risk of atherosclerosis and PD remains uncertain [17].

L-dopa related hyperhomocysteinemia could cause detrimental vascular effects in the brain even in PD patients [16,46]. In agreement with this hypothesis, a significant correlation between plasma Hcy levels and markers of endothelial dysfunctions has been observed in PD patients [57]. Moreover, in two recent cross-sectional studies, Nakaso *et al.* [58] found an increased intima-media thickness of the carotid artery in L-dopa treated PD patients with plasma Hcy levels > 10micromol/L; Rogers and coworkers [59] observed that L-dopa treated PD patients in the highest Hcy quartile ($\geq$ 17 micromol/L) had a significant 1.7–fold relative risk for coronary heart disease, whereas no increased risk was detected in patients with L-dopa-associated Hcy elevation ranging from 14.1 to 17 micromol/L, levels that are associated with coronary artery disease in other populations. These results strongly support the possibility that the vascular effect of Hcy has clinical implications in L-dopa treated PD patients.

However, one should consider the confounding role of other factors, such as smoke. Cigarette smoking is protective against PD [12], but is considered a risk factor for vascular disease [60] and dementia [61].

COMMENTS

Based on the results of available studies, it is reasonable to hypothesize that L-dopa related Hcy participates to the pathogenesis of cognitive impairment (particularly on executive and visuo spatial functions) and dementia during the course of PD. Hcy can interfere with all the pathogenetic

substrates of PD-dementia, by increasing the concentration of alpha-synuclein and amyloid-beta, causing neuronal loss, by the induction of cholinergic dysfunctions, and brain microvascular changes. As Hcy status could also reflect B-vitamin metabolic function, we believe that the management of L-dopa related hyperhomocysteinemia with supplementation of the diet with B-vitamins should be encouraged to reduce such a detrimental contribute. This treatment is relatively safe, avoid of side effects and effective in reducing plasma Hcy levels [62]. Although there is still a lack of clinical trial investigating supplements of B-vitamins and folate in the process of cognitive decline in patients with PD and dementia, several studies conducted in different cohorts provided recently significant insights. Supplementation of the diet with vitamin Bs and folate had significant effects on cognitive decline [63], cognitive change after stroke [64], and on the serum levels of amyloid [65].

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