Depression, Parkinson disease, Alzheimer disease. *The homocysteine hypothesis*

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The elevated plasma levels of homocysteine (Hcy) have traditionally been looked upon as a risk factor for systemic vascular diseases, particularly stroke and vascular dementia. However, in recent years, increasing Hcy levels have been detected in neurodegenerative diseases including Alzheimer disease (AD), depression, and idiopathic Parkinson's disease (PD). Simultaneously, increasing evidence suggests that depression, PD, and AD may co-occur. Although some of the included studies presented methodological issues, the reviewed literature suggests a potential comorbidity, which deserves further investigation. Therefore, according to recent literature, this study was to hypothesize that depression, AD, and PD may be part of a spectrum. This hypothesis, if confirmed, would help us progress in the understanding of pathophysiological links between depression, PD, and AD, and may lead to the formulation of new pathogenesis and new therapeutic approaches to these 3 diseases.

Several studies reported that depression is common in patients with neurologic disorders such as AD and PD, and it is related to cognitive decrement and can even represent the first signs of a neurodegenerative process. Depression is one of the most frequent comorbid psychiatric disorders in AD. In AD, the presence of depression comorbidity corresponds to increases in AD-related neuropathologic changes beyond age, gender, level of education, and cognitive status, suggesting an interaction between depression and the neuropathologic processes in AD. Research further pointed out that the increase in the degree of anxiety and depression is directly proportional to the severity of AD. As for PD, generally at later stages of disease progression, although it is primarily considered a movement disorder, the high prevalence of psychiatric complications suggests that it is more accurately conceptualized as a neuropsychiatric disease. Depression, cognitive impairment, and other psychosis are particularly common in PD. With regard to AD, there is a great probability of developing concurrent PD in AD and vice-versa than would be predicted by independent prevalence of each disease. Studies suggest that up to 75% of patients with PD may eventually develop dementia, and approximately half of subjects with PD dementia have enough AD pathology to attain a neuropathologic diagnosis of AD. Further, Caballol et al,[1] supposed that dementia in PD probably develops as a result of progressive involvement of subcortical and cortical structures by Lewy-type pathology and associated Alzheimer-like histological changes. Besides the increasing evidence mentioned above that depression, PD, and AD may co-occur, in recent years, simultaneously, increasing studies indicated that Hcy is involved in depression, PD, and AD. Homocysteine is a marker for B-vitamin deficiency (folate, B12, B6). Hyperhomocysteinemia (HHcy) causes hypomethylation, which is an important mechanism that links Hcy to dementia. Hyperhomocysteinemia is also very common in patients with PD. Epidemiological studies have shown a dose-dependent relationship between concentrations of Hcy and the risk for neurodegenerative diseases such as PD. Moreover, HHcy and vitamin B deficiency are reported to have a causal role in depression. The higher the levels of serum Hcy are; the severer the depressive disorder is. Accordingly, in the present paper, we hypothesize that depression, AD, and PD may be part of a spectrum, and that Hcy contributes to the pathophysiology underlying this spectrum.

A recent study[2] found that moderately disabled multiple sclerosis patients with elevated Hcy levels are particularly prone to develop depressive symptomatology, and there is significant correlation between Hcy levels and Beck Depression Inventory scores. Further study showed that higher Hcy levels at baseline were associated with a higher risk of incident depression at follow-up. Clearly, the cross-sectional nature of this study could not establish causality, but prompted the interest for Hcy level in depression. Recent evidence suggests that changes in the metabolic fate of Hcy, leading to HHcy, may also play a role in the pathophysiology of neurodegenerative disorders, particularly PD. Studies found that the level of mean plasma Hcy was significantly higher in PD patients than in controls, and the plasma (t)Hcy levels were increased by around 30% in patients with PD compared with controls. These studies suggested that Hcy might be implicated in the pathophysiology of PD. Evidence on Hcy in AD is now well documented by Liu et al.[3] In their studies, 31 AD patients, and 23 normal controls (NC group) underwent examination of plasma concentrations of Hcy, mini mental state examination, activity of daily living scale, Hachinski ischemic score, and Hamilton's depression scale. The severity of AD was evaluated according to the global deterioration scale. The results show that the plasma Hcy levels of the AD patients were (14.0 ±3.0 micromol/L) significantly higher than that of the NC group (9.8 ±2.5 micromol/L, $p<0.01$), and its alteration in level may be associated with the severity of AD. Their findings lend strong support for Hcy involvement in AD. There is limited research considering these 3 disorders as being part of the same spectrum and Hcy has seldom been considered a factor involved in the comorbidity between AD, PD, and depression.

The exact mechanisms explaining how Hcy contributes to the pathophysiology of these 3 disorders need further investigation. However, it is possible that Hcy leads to depression, PD, and AD via its impact on diverse mechanisms, such as apotosis, oxidative stress, and changes of monoamine or dopamine neurotransmitters, and so forth. Homocysteine, a sulphur-containing amino acid formed by demethylation of methionine, is involved in numerous processes of methyl group transfer, all playing pivotal roles in the biochemistry of the human body. Increased Hcy plasma levels (HHcy), which may result from a deficiency of folate, vitamin B6 or B12, or mutations in enzymes regulating the catabolism of Hcy, may have important implications in patients affected by causing basal ganglia disturbances, by exerting neurotoxic effects, contributing to neurotransmitter imbalance in motor circuits, and increasing the risk for vascular insults and cognitive dysfunctions. Due to the destructive effect of Hcy on the brain, an involvement of Hyc in depression, PD, and AD would seem plausible.

The prevalence of depression in later life increases with plasma tHcy. High tHcy accounts for approximately 15% of prevalent cases. In the Health in Men Study, Almeida et al,[4] found that the odds ratio (OR) of prevalent depression increased 4% (OR, 1.04; 95% confidence interval [CI], 1.02-1.05) with every unit increase of tHcy (micromoles per liter). And the meta-analysis further showed that older adults with high tHcy had increased risk of depression (OR, 1.70; 95% CI, 1.38-2.08). The association between tHcy and depression implies that higher concentrations of tHcy increase the risk of depression and that lowering tHcy by 0.19 mg/L could reduce the odds of depression by around 20%. Though the metabolic mechanism by which Hcy contributes to the pathogenesis of depression is as yet unknown, evidence showed that Hcy might cause depression by alteration of neurotransmitters. The potential mechanism for the Hcy effect on transmitters is by inhibition of the enzyme necessary to catalyze the methylation reactions between the catecholamines and S-adenosylmethionine.

Recently, elevated Hcy concentrations were observed in patients with PD. Evidence suggests that Hcy is potentially a risk factor for neurologic deterioration. Researchers recently observed that serum concentrations of tHcy were increased in PD patients and that methylation status might link Hcy metabolism to neurodegenerative proteins in patients with PD. Total serum levels of Hcy in levodopa-treated and -untreated parkinsonian patients, as well as in control healthy subjects matched by age and gender, were also investigated and the result showed that tHcy concentrations were significantly higher in both levodopa-treated and -untreated PD patients than in control subjects. Though the mechanism by which Hcy contributes to the pathogenesis of PD is as yet unknown, there is evidence that increased Hcy levels might accelerate dopaminergic cell death in PD, through neurotoxic effects.[5]

A recent study[6] investigated both baseline concentrations of Hcy and changes in these concentrations as predictors/correlates of incident dementia. In 625 elderly patients without dementia at baseline, 518 (83%) were followed over a 2.4-year period and were clinically assessed for incident dementia and AD. Serum concentrations of Hcy were measured at the baseline and follow-up assessments. The results showed that the onset of dementia was significantly associated with an exaggerated increase in Hcy concentrations over the follow-up period. Similarly, another investigation[7] tested whether baseline concentrations of Hcy relate to the subsequent rate of cognitive decline in patients with established AD. As a result, baseline Hcy levels showed a concentration-response relationship with the subsequent rate of decline in the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly scores: the higher the Hcy, the faster the decline. The relationship was significant in patients aged <75 years who had not suffered from a prior stroke. Though the mechanism by which Hcy contributes to the pathogenesis of AD is as yet unknown, Popp et al,[8] supposed that disturbed homocysteine metabolism is a risk factor for AD and may contribute to the disease pathophysiology by increasing both amyloid-beta production and phosphorylated tau accumulation. In their studies, Popp et al,[8] concluded that alteration of the Hcy metabolism is related to increased accumulation of phosphorylated tau and may contribute to the neurofibrillary pathology in normal aging and in AD. However, we should note that these results of metabolic disorder of Hcy and the association of Hcy in depression, PD, and AD patients have to be carefully interpreted. Both findings do not necessarily imply causality. The present findings and interpretations are preliminary and should be confirmed and validated in future longitudinal studies. However, increasing studies clearly support previous findings of involvement of Hcy in depression, PD, and AD.

The hypothesis of Hcy as a common factor contributing to the pathophysiology of depression, PD, and AD, if confirmed, might have relevant implications for the treatment of patients presenting with these conditions, suggesting that decreasing Hcy levels in serum might be effective for these 3 disorders. Therefore, the same treatment could address the 3 different diseases, simplifying the management of these 3 disorders when they are comorbid, which is, nowadays, quite challenging.

Though previous studies have been limited by small numbers, short treatment duration, sometimes-inconsistent data, or a lack of studies on pathogenesis, which discloses the role of Hcy in depression, PD, and AD. These many studies provide strong support for a contribution of Hcy in the pathophysiology of depression, PD, and AD. Since research into the putative Hcy role in depression, PD, and AD, has been strikingly scarce, a detailed metabolic mechanism of Hcy and related studies are needed to provide answers to these questions. Moreover, as most of our suggestions are still speculative, longitudinal studies, clinical trials, and animal model studies should be conducted to confirm the hypothesis underlying the pathophysiology of the spectrum including depression, PD, and AD. Confirmatory data from sufficiently powered randomized trials of Hcy-lowering therapy are now required to test if the relationship between tHcy and the 3 diseases is truly causal. In addition, we suggest that this hypothesis be evaluated by researching the relationship between Hcy and other possible pathogens of depression, PD, and AD such as metabolism, apotosis, neurotransmitters, and so forth, to further confirm whether Hcy plays a common contribution to depression, PD, and AD.

In conclusion, depression, AD, and PD may be part of a spectrum, and Hcy contributes to the pathophysiology underlying this spectrum. Further studies are required to confirm this hypothesis.

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References

1. Caballol N, Martí MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. ***Mov Disord*** 2007; 22: 358-366.
2. Triantafyllou N, Evangelopoulos ME, Kimiskidis VK, Kararizou E, Boufidou F, Fountoulakis KN. Increased plasma homocysteine levels in patients with multiple sclerosis and depression. ***Ann Gen Psychiatry*** 2008; 7: 17.
3. Liu XQ, Liu XQ, Jiang P, Huang H, Yan Y. [Plasma levels of endogenous hydrogen sulfide and homocysteine in patients with Alzheimer's disease and vascular dementia and the significance thereof]. ***Zhonghua Yi Xue Za Zhi*** 2008; 88: 2246-2249. Chinese
4. Almeida OP, McCaul K, Hankey GJ, Norman P, Jamrozik K, Flicker L. Homocysteine and depression in later life. ***Arch Gen Psychiatry*** 2008; 65: 1286-1294.
5. Qureshi GA, Qureshi AA, Devrajani BR, Chippa MA, Syed SA. Is the deficiency of vitamin B12 related to oxidative stress and neurotoxicity in Parkinson's patients? ***CNS Neurol Disord Drug Targets*** 2008; 7: 20-27.
6. Kim JM, Stewart R, Kim SW, Shin IS, Yang SJ, Shin HY, et al. Changes in folate, vitamin B12 and homocysteine associated with incident dementia. ***J Neurol Neurosurg Psychiatry*** 2008; 79: 864-868.
7. Oulhaj A, Refsum H, Beaumont H, Williams J, King E, Jacoby R, et al. Homocysteine as a predictor of cognitive decline in Alzheimer's disease. ***Int J Geriatr Psychiatry*** 2010; 25: 82-90.
8. Popp J, Lewczuk P, Linnebank M, Cvetanovska G, Smulders Y, Kölsch H, et al. Homocysteine metabolism and cerebrospinal fluid markers for Alzheimer's disease. ***J Alzheimers Dis*** 2009; 18: 819-828.