Folate Metabolism Genetic Polymorphisms and the Susceptibility to Parkinson Disease

Folat Metabolizması Genetik Polimorfizmleri ve Parkinson Hastalığına Duyarlılık

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ABSTRACT

As life expectancy increases over time, the incidence of neurological diseases has increased and it is important to conduct clinical and scientific studies on these issues, as they impair quality of life and cause an additional burden on the health expenditures of countries. Parkinson's disease (PD) is the second most common neurological disorder. Multiple studies have been carried out to elucidate its pathogenesis. It is thought that environmental and genetic factors, enzymes and amino acids in folate metabolism, and enzymatic transformations between vitamins contribute to the development of PD in varying degrees. The levels of homocysteine (Hcy) and vit B 12 levels, and key enzymes on folate metabolism (Methionine synthase reductase MTRR, Methionine synthase; MTR, 5,10-methyleneTHF reductase; MTHFR) may have impact on the development of PD, especially, changes on enzyme activities due to genetic polymorphism. The results obtained from studies on this subject are controversial. In the present review, the impacts of polymorphic enzymes in folate metabolism, and Hcy and B12 vit on the development of PD was evaluated by reviewing recent studies.

Keywords; *Methionine synthase, 5,10-methyleneTHF reductase, Methylenetetrahydrofolate reductase*, Parkinson disease, homocysteine

Received: 04.22.2022 **Accepted:** 06.28.2022

ÖZET

Zamanla yaşam beklentisi arttıkça nörolojik hastalıkların görülme sıklığı da artmış olup, yaşam kalitesini bozduğu ve ülkelerin sağlık harcamalarına ek yük getirdiği için bu konularda klinik ve bilimsel çalışmaların yapılması önem arz etmektedir. Parkinson hastalığı (PD), ikinci en yaygın nörolojik bozukluktur. Patogenezini aydınlatmak için birçok çalışma yapılmıştır. Çevresel ve genetik faktörlerin, folat metabolizmasındaki enzimler ve amino asitlerin ve vitaminler arasındaki enzimatik dönüşümlerin PD gelişimine değişen derecelerde katkıda bulunduğu düşünülmektedir. Folat metabolizması üzerindeki homosistein (Hcy) ve vit B 12 seviyeleri ve anahtar enzimler (Metionin sentaz redüktaz MTRR, Metionin sentaz; MTR, 5,10-metilenTHF redüktaz; MTHFR) PH gelişimi üzerinde etkili olabilir, özellikle, Genetik polimorfizm nedeniyle enzim aktivitelerinde meydana gelen değişiklikler. Bu konuda yapılan çalışmalardan elde edilen sonuçlar tartışmalıdır. Bu derlemede, folat metabolizmasındaki polimorfik enzimlerin ve Hcy ve B12 vit'in PH gelişimi üzerindeki etkileri, son çalışmalar gözden geçirilerek değerlendirilmiştir.

Anahtar Sözcükler: *Metionin sentaz, 5,10-metilenTHF redüktaz, Metilentetrahidrofolat redüktaz,* Parkinson hastalığı, homosistein

Geliş Tarihi: 22.04.2022 **Kabul Tarihi:** 28.06.2022

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doi:http://dx.doi.org/10.12996/gmj.2022.103

INTRODUCTION

Many diseases that develop due to different causes, in which almost the same symptoms of PD are observed, are called "Parkinsonism". The expression of Parkinsonism is the expression of tremor of hands, arms and legs, slowness of body movements, stiffness of muscles, forward-leaning posture, walking with small steps and shuffling, fast and monotonous speech, etc. (1). It refers to many diseases that occur together with typical PD symptoms such as However, in the pictures of parkinsonism, besides the symptoms of PD, there are many additional symptoms, often due to the involvement of other parts of the brain. PD is a disease known to societies since ancient times. PD, known as "Kampavata" in the old Indian health system, was first described by British physician James Parkinson in 1817 as "shaking palsy". (2). The full title of the published article is “An Article on Trembling Paralysis.” With this article, PD has been accepted as a defined medical condition. Article, Dr. It is based on a review of six cases of Parkinson's and is intended to encourage further research on this disease. Only 60 years after the article was published, the French neurologist Jean Martin Charcot gave the necessary importance to PD. After extensive research on it, Dr. Named after James Parkinson (3).

PD is movement disorder and degenerative disease of the central nervous system. PD affects 1-2 per 1000 of the population and the prevalence of PD increases with age. The incidence and prevalence of PD are 1.5–2 times higher in men than in women (4). Risk factors of PD are age, heredity, gender and exposure to some toxins. PD is not encountered at young ages, if there are close relatives with individuals with PD in the family, that is, there is a genetic predisposition to PD, its incidence is higher in males than in females, and occupational exposure to environmental chemicals such as pesticides may cause disease development, although not as much as other factors (5). For gender differences in PD, after progression of the disease, women had better Unified Parkinson's Disease Rating Scale (UPDRS) motor scores than men. However, the prevalence of dyskinesia’s has higher in woman in more than 5 years’ disease. On the other hand, men who have 9 years’ disease show more frequently parkinsonian symptoms than women Symptoms or differences in the development of PD can be occurred due to gender differences, which can be related to different levels of estrogen. There are few findings showing that estrogens play role in the development of PD. Estrogens can be neuroprotective in animals when they are given before and together with toxic insults. Other finding is that the dopaminergic neurons in the substantia nigra (SN) and the striatal dopamine content were more vulnerable due to low level of estrogens compared to its high levels. Unfortunately, the beneficial effects of estrogens have not been proven in humans (6).

The main cause of PD is a loss of nerve cells in SN, which is the part of brain. A lack of dopamine take place in PD in these nerve cells since nerve cells are responsible for producing dopamine. Dopamine provide good connection between brain parts and nervous system and thus control and regulate the required function for movement (7).

Folate metabolism has a critical importance in the risk of PD. There have been many published studies previously showing relationship between genetic polymorphisms in folate metabolism and the susceptibility to PD. These studies demonstrate the controversial results. Meta-analysis can help to arrive at a correct judgment on association with folate metabolism and PD risk.

Studies have showed that homocysteine (Hcy) is important contributor neurodegenerative diseases since it increases apoptosis and mitochondrial dysfunction and oxidative stress. Hcy is formed during the metabolism of methionine (Met) to cysteine (Cys). Hcy amino acid is derived from the demethylation of methionine in methionine and the folate cycles (8). Both folate metabolism and folate Hcy conversion has important role in the development of PD. In an animal study, the injection of Hcy into the substantia nigra or striatum in rats showed that depletion of dopaminergic neuronal cells and leaded to the loss of motor function. Folate levels affect the levels of Hcy and can change the levels of Hcy. Folate levels also depend on the folate-dependent *MTHFR* enzyme, which is effective in folate metabolism (9).

Briefly folate metabolism was presented in Figure 1. 5, 10 -methyl THF converted to 5-methly THF via *MTHFR* and donate a methyl group. This methyl group transfer to Hcy via *MTR* catalyst and creates methionine and THF. *MTRR* is served as a catalyst for the reductive methylation of *MTR* (10). Deficiencies of folate metabolism have important role on PD onset and progression. There have been studies on human that gene polymorphism on folate metabolism increased risk for PD development risk On the other and the role of diet such as dietary B vitamin intake, on PD risk still is not clear (11).

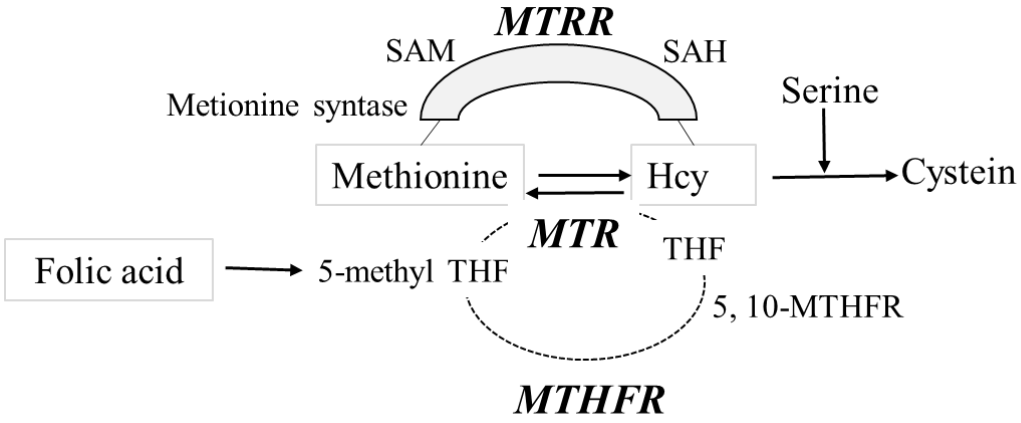

Figure 1. One-carbon pathway

One-carbon metabolism is driven by the methionine cycles and folate which regulate methylation reactgions and DNA synthesis. In the metabolism, SAM is converted to S-adenosyl homocysteine (SAH) and further hydrolyzed to adenosine and Hcy *methyl tetrahydrofolate (MTHF*) as methyl donor. *MTRR, MTR* and *MTHFR* are key enzymes in this metabolic pathway (Figure 1).

The deficiencies in Folate and B12 can have serious biological consequences. The deficient in micronutrients cause defects in the production of SAM and nucleotide synthesis. Genetic alterations, DNA hypomethylation and cell proliferation take places. For example, chronic alcoholism, malnutrition and a vegetarian or vegan diet can cause B12 deficiency (12).Increases or decreases in folate levels may be associated with enhanced and impaired cognitive function. Increased and decreased folate status can be linked to respectively augmented and impaired cognitive functioning. Not only prenatally but also postnatal, folate levels have been shown to alter neurological function.This may be evidence of a role for folates in brain development and postnatal brain functioning and plasticity (13).

The study was conducted to determine the one-carbon metabolic factors associated with the birth outcomes of nulliparous women who have never given birth. To prove this relationship, FA, Vit B and Hcy levels and dietary data were used before and after FA supplementation during pregnancy. Moreover, *MTHFR*, *TCN2* and *MTHFD1* gene polymorphisms were analyzed. Study results showed that maternal *MTHFR A1298C* genotype caused increased risk in preeclampsia, while *TCN2* caused decreased risk for spontaneous preterm birth. In addition, the paternal *MTHFR A1298C (CC)* and *MTHFD1 G1958A (AA)* genotypes have a reduced risk for spontaneous preterm birth, whereas the *MTHFR C677T (CT)* genotype has an increased risk for gestational hypertension (14).

Genetic and environmental factors are not only topic of (PD) studies but numerous investigations. Evaluations and analysis of 2 factors have provided insight into potential pathological mechanisms, such as elevated Hcy levels. In these days, dietary factors such as vit B and folate, naturally found in leafy green vegetables, were thought to be effective in the development of PD and such studies were conducted. Since these dietary factors are folate metabolism and the enzymes (*MTRR, MTR* and *MTHFR*) prominent in this metabolism are polymorphic, they will affect vit B12, folate and amino acid levels and will either contribute or have a positive effect on the development of PD. In other words, individual differences in the development of PD are expected to be caused by these 3 enzymes, *MTRR, MTR* and *MTHFR* (11).

It is well known today that elevated Hcy levels is an independent risk factor for cardiovascular diseases such as heart disease, stroke (15). In last decades, researchers started to research the impact of Hcy levels in neurological and movement disorders and some psychiatric diseases, such as Alzheimer disease, PD, bipolar (16-18).

The findings on association with Hcy levels and these studies are controversial. Zoccollela et al. overviewed 30 studies to evaluate the impact of Hcy levels on PD and they concluded that it was not clear the effect of Hcy on PD pathogenesis and its contribution to the risk of PD uncertain. On the other hand, Dong and Wu conducted comprehensive a meta-analysis and selected eligible studies from January 2000 to November 2018 (approximately 18 years), 26 case-control studies and 1 cross-sectional study. They found that PD patients had higher Hcy levels than controls and furthermore, they divided samples according to the subgroups and levodopa therapy and observed that plasma folate and vitamin B12 levels were lower, Hcy levels higher in PD patients compared to controls (19). Hcy levels are increased in some diseases. The cause of the increase in Hcy may be due to gene polymorphisms on *MTR*, *MTRR* and *MTHFR* which are related to Hcy metabolism. Furthermore, the deficiencies of some vitamin cofactors are also change the levels of Hcy.The most common gene polymorphisms which affect the levels of Hcy are *MTHFR C677T, A1298C*, and *A2756G*. Polymorphic gene may have the low activity and can lead to the lower function than wild genotypes and cause the disruption of Hcy metabolism thus increasing PD risk As I mentioned above, not only genetic polymorphism affect the levels of Hcy but also many factors such as taking excess amount of met, some drug therapies and disease, pregnancy status including lactation period have impact to change the levels of Hcy (20).

The *MTHFR* which has non-coding and 11 coding exons gene is located on chromosome 1p36.3 and catalyzes the conversion of 5,10-methylenetetrahydrofolate which is a carbon donor in nucleotide biosynthesis to 5-methyltetrahydrofolate. This conversion provides a methyl to Hcy for it methylation. Wu et al. conducted meta-analysis including eligible 15 studies according to the search criteria to evaluate whether the *MTHFR* polymorphisms affect the susceptibility to PD. They found significant association *MTHFR* C677T polymorphism and PD risk (T vs. C: OR = 1.24, 95% CI = 1.11–1.38; for *TT + CT* vs. *CC*: OR = 1.27, 95% CI = 1.10–1.46; for *TT* vs. *CC*: OR = 1.56, 95% CI = 1.22–1.98; for *TT* vs. *CT + CC*: OR = 1.43, 95% CI = 1.14–1.79). They detected no association between *MTHFR* A1298 polymorphism and PD. Furthermore, no association was found between the A1298C polymorphism and PD in Caucasian population, as well as Asian population in subgroup analysis by ethnicity (21). Another meta-analysis contained 21 case-control studies (n=3,944 PD patients and n= 4,412 controls) was conducted Diao et al to investigate association between the folate metabolism genetic polymorphisms and the susceptibility to PD. *C677T, A1298C*, and *A2756G* folate metabolism genetic polymorphisms were genotyped and the results showed that there was no link one of 2 gene polymorphisms (*C677T* and *A1298C*) and PD risk however A2756G gene polymorphism had an association with an augmented threat of PD (8). In a hospital base case-control study (211 patients and 218 controls), *MTHFR C677T*, methyl tetrahydrofolate-Hcy methyl transferase *MTR A2756G,* and 5-methyltetrahydrofolate- Hcy methyl transferase reductase (*MTRR A1049G and C1783T*) and the risk of PD relationship were evaluated in Chinese in Taiwan. Only the *MTRR 1049GG* gene polymorphism was associated with the susceptibility of PD. Comparisons were also made to investigate the joint effect of these 4 polymorphisms. It has been observed that it creates a synergistic effect. Although the other 3 gene polymorphisms do not play a role in PD risk individually, their coexistence with the effective *MTRR1049GG* causes a synergistic effect on PD risk (22).

There has been only one study performed with seven functional polymorphisms of one-carbon metabolic pathway in PD patients, furthermore they measured Hcy levels by HPLC and They investigated the effect of these gene polymorphisms (glutamate carboxypeptidase II (*GCPII) 1561 C>T*, reduced folate carrier 1 (*RFC1) 80 G>A*, cytosolic serine hydroxymethyl transferase (*cSHMT) 1420 C>T, MTHFR 677 C*>T, methionine synthase (*MTR) 2756 A>G* and methionine synthase reductase (*MTRR) 66 A>G* polymorphisms) on Hcy levels. They found that Hcy levels were higher in PD patients compared to healthy controls and positive correlation was observed the levels of Hcy with male gender. Only one gene polymorphism, *cSHMT 1420 C>T* gene polymorphism showed protective effect against PD. Joint gene polymorphisms effects were evaluated and they showed synergistic effect the development of PD (23).

Catechol-O-methyltransferase (COMT), which degrade catecholamines catecholestrogens, and various drugs and substances, gene polymorphism also investigated on PD patients to investigated for efficacy of levodopa. Bialecka et al found that COMT gene polymorphism had profound effect on 248 PD patients and they used 254 control subjects. On the other hand, they did not find any association with *MTHFR 677C>T, 1298A>C*, and *SLC19A1 80G>A* alleles/ genotypes and PD risk (24). In contrary to Monika et al. Michalowska et al no associations between gene polymorphisms (*COMT Val158Met* and *T941G MAO-A*) either individually or combined and furthermore, no observed the levodopa-induced dyskinesias (25).

CONCLUSION

Many studies, both clinical and basic science including animal and human, have performed. In many published paper, it has been emphasized that genetic factors have important roles in the PD development. When taking into together all studies and evaluate together, both contribution of folate metabolism genetic polymorphisms and Hcy levels to the development of PD still not clear yet. Of course all vitamin, amino acid and co-factors are involved in various stages of PD development, however not provide certain and accurate data. Not only experimental studies but also studies on autopsy samples such as SN should be conducted and some models should be developed and all findings together should be evaluated to reach robust judgement.

Conflict of interest

No conflict of interest was declared by the authors.

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