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Original Article

Functionality of patients with post-stroke hemiplegia: Does serum folate level matter?

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ABSTRACT

Objectives: This study aims to investigate the possible effects of folate on the functional outcomes of patients with post-stroke hemiplegia.

Patients and methods: Between January 2012 and March 2015, a total of 80 patients with hemiplegia (51 males, 29 females; mean age 60.3±13.2 years; range, 19 to 95 years) at least three months post-stroke were included in this study. Serum folate levels (ng/mL), Brunnstrom recovery stages of the lower limb, and Functional Ambulation Category (FAC) scores were recorded. All patients were divided into two groups according to the Brunnstrom stages (Category I; Stage 1-3 and Category II; Stage 4-6) and FAC scores (non-functional ambulatory; score 0-2, functional ambulatory; score 3-5).

Results: The mean serum folate level of the patient group was 6.8±2.8 ng/mL. Serum folate levels differed significantly between the Brunnstrom categories with lower levels in patients with poorer motor recovery (Category I) (p=0.047). Folate levels were also lower in non-functional ambulatory patients than those in patients with functional ambulation (p=0.046).

Conclusion: Lower serum folate levels are associated with poorer ambulation potential and impaired lower limb motor recovery in patients with post-stroke hemiplegia.

Keywords: Folate, folic acid, hemiplegia, post-stroke hemiplegia, stroke.

Folate, which is a unique substance and water-soluble vitamin B, is definitely a must for proper function of the surviving human body. The reason of its necessity throughout life lies within the crucial role of folate in one-carbon metabolism. It is required for both the utilization and the transfer of one-carbon units inside the pathways related to the metabolism of methionine and amino acids, as well as the biosynthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[1,2]

Folate plays a number of roles in various stages of the life cycle including fetal period, childhood, adulthood, and elderly.[2] The emerging evidence also supports its role in reducing the risk of stroke.[3,4] Up to date, several studies have been carried out regarding the preventative function of folate from stroke[3,4] and it is now well-established that low plasma folate concentration serves as a risk factor for stroke.[5] In addition, folate supplementation is beneficial in terms of stroke prevention, particularly in regions without folate fortification.[3,4]

Despite the extensive research on this area, data regarding the potential relationship between folate levels and the functionality of stroke survivors still remains scarce. Therefore, in the current study, we aimed to investigate the possible effects of folate on the functional outcomes of post-stroke hemiplegic patients.

PATIENTS AND METHODS

Between January 2012 and March 2015, a total of 80 patients with hemiplegia (51 males, 29 females; mean age 60.3±13.2 years; range, 19 to 95 years) at least three months post-stroke who were admitted to the department of physical medicine and rehabilitation were included in this study. *Inclusion criteria were as follows:* aged ≥18 years and a history of at least

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three-month post-stroke hemiplegia. *Exclusion criteria were as follows:* aged <18 years; coexistence of major organ failure (i.e., cardiac, renal or hepatic); presence of any malignancy; receiving folate supplementation; history of intestinal resection). The study protocol was approved by the local Ethics Committee of Çukurova University Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The demographic variables including age (years), sex and disease duration (months) of the patients were recorded. Serum folate levels (ng/mL) was measured using the immunoassay method (Beckman Coulter Unicel DXI 800) (Beckman Coulter Inc., Brea, CA, USA) in blood samples obtained following a-12-h fasting. The functional status of the patients at the time of blood sampling was evaluated both with the Brunnstrom recovery stage[6] of the lower limb and the Functional Ambulation Category (FAC) score[7] The Brunnstrom recovery stage scores indicate clinical severity of hemiplegia in six stages (from 1 to 6), where scores of 1 and 6 represent paralysis and normal strength, respectively.[6] The FAC evaluates ambulation in six categories ranging from 0 to 5, where 0 refers to the inability of walking or requirement of at least two assistants for walking and 5 represents independent walking anywhere.[7] All patients were divided into two groups according to the Brunnstrom recovery stage. Patients with Brunnstrom score of 1-3 (no deviations from synergy) were assigned as Category I, whilst those with Brunnstrom score of 4-6 (deviations from synergy) were assigned as Category II. The patients were also classified as non-functional ambulatory (FAC score of 0-2) and functional ambulatory (FAC score of 3-5) according to their FAC scores. Serum folate levels were compared between the Brunnstrom categories and between the ambulation categories.

Statistical analysis

Statistical analysis was performed using the PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in mean ± standard deviation (SD) or number and frequency. Normality of the data was checked using the Kolmogorov-Smirnov test. As the data were not normally distributed ($p<0.05$), non-parametric tests were performed. The Mann-Whitney U test was used for between group comparisons of the continuous variables. A *p* value of <0.05 was considered statistically significant. With an effect size of 0.44, Type I error rate of 0.05, and sigma of 1.98, the achieved post-hoc power of this study is 0.67.

RESULTS

In all patients included in the study, the mean disease duration was 26.2±38.9 (range, 3 to 192) months. The distribution of patients across the Brunnstrom scales and ambulation categories are shown in Table 1. Accordingly, 50% of the patients were in the Brunnstrom Category I, while the other half was in Category II. Of the patients, 47.5% were non-functionally ambulatory, whereas 52.5% were functionally ambulatory. The distribution of sex did not differ between the FAC groups ($p>0.05$). In the non-ambulatory group (FAC score 0-2), the mean age was higher and the disease duration was shorter than those in the ambulatory group ($p=0.019$ and $p=0.022$, respectively). Regarding the Brunnstrom categories, none of these variables differed between two categories ($p>0.05$ for all).

The mean and median folate levels were 6.8±2.8 ng/mL and 6.0 ng/mL, respectively. There was a significant difference in the folate levels between the groups with lower levels in Category I ($p=0.047$). Additionally, a comparative analysis was performed

Table 1. The distribution of patients across Brunnstrom scales and ambulation categories

Brunnstrom scale	n	%	FAC score	n	%
1	10	12.5	0	17	21.25
2	10	12.5	1	17	21.25
3	20	25.0	2	4	5.0
4	22	27.5	3	9	11.25
5	16	20.0	4	26	32.5
6	2	2.5	5	7	8.75

FAC: Functional ambulation category.

Table 2. Serum folate levels according to Brunnstrom and ambulation categories

			Serum folate level (ng/mL)			
	n	%	Mean±SD	Median	Min-Max	*p*
Brunnstrom						
Category I (Brunnstrom 1-3)	40	50	6.2±2.5	5.9	2.7-13.8	0.047
Category II (Brunnstrom 4-6)	40	50	7.4±2.9	7.1	1.6-15.7	
Functional ambulation category						
Non-functional (FAC 0-2)	38	47.5	6.3±2.7	5.6	1.6-13.8	0.046
Functional (FAC 3-5)	42	52.5	7.3±2.8	6.9	2.9-15.2	

SD: Standard deviation; Min: Minimum; Max: Maximum.

between the FAC groups. Functional ambulatory patients revealed significantly higher levels of folate than the non-functional ambulatory group (p=0.046) (Table 2).

DISCUSSION

The results of the current study showed that *(i)* post-stroke hemiplegia patients with increased clinical severity (Brunnstrom score 1-3) had lower serum levels of folate than those in Category II (Brunnstrom score 4-6) and *(ii)* serum folate levels were lower in non-functional ambulatory patients (FAC score 0-2) than those in patients with functional ambulation (FAC score 3-5). Overall, in the light of these findings, we suggest that low folate level is associated with lower limb recovery and ambulation capacity in post-stroke hemiplegia.

Up to date, the relationship between serum folate level and the functional status in stroke survivors has been remained as an unknown issue. However, there are several clinical trials investigating the link between the functional outcomes of post-stroke hemiplegia patients and serum levels of homocysteine, which is metabolized by the contribution of folate.[8,9] Demethylation of 5-methy tetrahydrofolate (5-MTHF) is required for the metabolization of homocysteine to methionine. In other words, folate, which acts as the methly donor inside the remethylation cycle, is an essential substance for homocysteine metabolism.[1,10] Disrupted transmethylation of homocysteine to methionine contributes to hyperhomocysteinemia.[11] Thus, a close negative relation exists between folate and plasma homocysteine levels[11] and, therefore, the deficiency of folate serves as an independent factor for hyperhomocysteinemia.[12]

In previous studies, hyperhomocysteinemia has been shown to interfere with the proper muscle function and functionality.[13-17] Kado et al.[13] found that elevated homocysteine levels were associated with an increased risk for decreased physical function among highly functioning men and women aged 70 to 79 years. Additionally, higher levels of homocysteine were found to be related to decreased quadriceps strength and gait speed, and thus, to late-life, self-reported disability in community-dwelling elderly.[14] Another study showed that increased homocysteine levels were associated with the calf muscle density in patients with lower extremity peripheral arterial disease.[15] Also, nearly statistically significant association was reported between high homocysteine levels and poorer isometric plantar flexion strength.[15] Swart et al.[16] and van Schoor et al.[17] also reported that high plasma homocysteine increased the risk of reduced physical performance in elderly. The studies conducted among post-stroke hemiplegic patients are much more conflicting.[8,9,18] Contradicting the theory regarding hyperhomocysteinemia, a clinical trial conducted by Song et al.[9] revealed that there was no link between plasma homocysteine levels and functional outcome during the first 12 months in post-stroke survivors. Similarly, Unal et al.[8] found no correlation between homocysteine levels and functional status during the first three months of stroke. However, in these two studies, no blood samples were obtained during follow-up visits; rather, the blood samples were collected once, within the first 24 hours after the onset of stroke symptoms.[8,9] Repeated measurements of homocysteine simultaneously with the functional assessments at each follow-up might have yielded different results in these studies.

Furthermore, the results of the present study indicate that folate level definitely matters and decreased folate levels are associated with poorer outcomes in patients with hemiplegia. Low serum folate may have a negative impact on the muscle function and physical performance through its action on hyperhomocysteinemia.[19] In other words, the homocysteine-lowering effect of folate may contribute to increased functional outcomes in patients with higher folate levels.[11,20] Additionally, folate may interfere with neurogenesis following stroke. Although the existing evidence are derived from *in vitro* studies, folate has been shown to increase neural stem cell proliferation following acute ischemic stroke and to enhance early functional recovery in head injury.[21,22]

Nonetheless, there are several limitations to this study. First, since there are no available data regarding the homocysteine levels of the patients, we were unable to clarify whether the association of folate with functionality was related to hyperhomocysteinemia. Second, the retrospective design precluded to obtain the longitudinal impact of folate levels on functional improvement following stroke. On the other hand, there are some strengths of the present study. First, the ratio of the patients in each category for the Brunnstrom scale and FAC is almost identical, which provides a reliable comparative analysis. Second, serum folate levels and functional status were able to be assessed in hemiplegic patients at least three months post-stroke. Since most recovery occurs within the first three months following stroke,[23] this methodology also enhances the reliability of the results derived from this study.

In conclusion, lower serum folate levels are associated with poor lower limb recovery and impaired ambulation in hemiplegic patients at least three months post-stroke. However, further prospective studies are needed to elucidate the exact underlying mechanism and to evaluate the impact of folate supplementation on functional outcomes among stroke survivors.

Declaration of conflicting interests

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