Neuropsychiatric Disease and Treatment Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Association of Vitamin B12 and Polymorphism of *TCN2* with Early-Onset Post-Stroke Depression

Jingyuan Zhang[1,2], Qiao Liao[1,2], Hengshu Chen[1,2], Fan Liu[1,2], Dongren Sun[1,2], Shihang Luo[1,2], Yeqing Xiao[3], Weiye Xu[4], Fafa Tian[1,2], Mingyu Song[1,2]

[1]Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, 410005, People's Republic of China; [2]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, 410005, People's Republic of China; [3]Department of Neurology, Hengyang Central Hospital, Hengyang, Hunan, 421001, People's Republic of China; [4]Department of Human Anatomy and Neurobiology, School of Basic Medicine, Central South University, Changsha, Hunan, 410005, People's Republic of China

Correspondence: Mingyu Song, Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, 410005, People's Republic of China, Tel +86 13548782904, Fax +86 73184327332, Email songmingyu1986@126.com

Background: Post-stroke depression (PSD) is a common neuropsychiatric complication after a stroke with complex mechanisms. However, few studies have identified the role of vitamin B12 and folate in the occurrence and pathophysiology of PSD. The aim of our study is to investigate the relationship among vitamin B12, folate, their transporter genes, and early-onset PSD.

Method and Material: A total of 173 ischemic stroke patients were recruited in Xiangya Hospital of Central South University. We collected peripheral blood samples, clinical data, and demographics at admission. The 17-item Hamilton Depression Scale was used for screening for the existence of depression at 2 weeks after stroke onset. Serum vitamin B12 and folate level were measured based on double-antibody sandwich enzyme-linked immune-sorbent assay. Four single nucleotide polymorphisms (SNP) of *transcobalamin 2* (*TCN2*) and solute carrier family 19 member 1 were genotyped using SNPscan^{TM} multiplex SNP typing Kit.

Results: Eighty-four patients were diagnosed with PSD at 2 weeks after stroke onset, and the incidence rate was 48.6%. Serum vitamin B12 level in PSD group was significantly lower than those in the non-PSD group (p=0.018). Binary logistic regression revealed that *TCN2* rs1801198 GG genotype and G allele were associated with an increased risk of PSD after adjustment for confounding factors (for GG genotype, OR = 4.253, 95% CI = 1.711~10.572, p = 0.002; for G allele, OR = 2.134, 95% CI = 1.362~3.343, p = 0.001). Moreover, individuals with the rs1801198 G allele in the PSD group exhibited lower vitamin B12 level than those with the rs1801198 G allele in the non-PSD group (p=0.045).

Conclusion: *TCN2* rs1801198 and vitamin B12 are associated with the risk of early-onset PSD, and they may be involved in the development of PSD. Our study presents a novel standpoint for the treatment of PSD and gains insights into the mechanistic underpinnings of PSD.

Keywords: post-stroke depression, vitamin B12, folate, single nucleotide polymorphisms, *TCN2*, *SLC19A1*

Introduction

Stroke was estimated to be the second-leading cause of death and the third-leading cause of disability and death globally.[1] In China, stroke is also the primary cause of death and disability, and the burden of stroke is increasing due to an aging population and the rising prevalence of inadequately managed risk factors, such as diabetes and hypertension.[2,3] Post-stroke depression (PSD) is one of the most common neuropsychiatric sequelae after stroke and occurs in approximately one-third of stroke survivors at any one time.[4] PSD is determined to be associated with high mortality and poor functional prognosis, including worse functional and motor recovery, poorer cognitive impairment, lower quality of life, and declined social function, compared with stroke survivors without PSD.[5–9] Early identification and timely treatment are crucial to PSD, which can improve the prognosis of patients. Therefore, it is of substantial clinical significance to investigate the mechanism of PSD and search for the susceptibility factor of PSD.

Received: 22 July 2024
Accepted: 16 November 2024
Published: 26 November 2024

Vitamin B12 and folate are water-soluble vitamins and play a critical role as coenzymes for enzymatic in different biological systems, which are essential for maintaining the health of the nervous system.[10,11] Previous researches demonstrated that low serum concentration of vitamin B12 and folate may be the risk factor of first ischemic stroke in hypertensive population.[12] Higher serum vitamin B12 level and supplementation of vitamin B12 were associated with better functional outcome of ischemic stroke patients.[13,14] A meta-analysis proved that low vitamin B12 and folate level was related with depression in the aged, and only vitamin B12 but not folate was inversely correlated with depression in children and adolescents.[15,16] Intaking diet rich in vitamin B12 and folate may decrease the risk and improve the treatment of depression.[17–19] Vitamins B6, B12, and folic acid could enhance the antidepressant efficacy of citalopram for over 1 year.[20] Therefore, vitamin B12 and folate are implicated in both stroke and depression, spanning from risk factors to influencing prognosis. However, research on the role of vitamin B12 in PSD is still limited. A study involving a limited number of participants indicated the relationship between vitamin B12 deficiency and increased levels of fatigue and depression in lacunar stroke patients.[21] Almeida et al found that the combined use of vitamins B6, B12, and folic acid could reduce the hazard of major depressive episodes after stroke or transient ischemic attack.[22]

Vitamin B12 has a highly complexed structure with complicated mechanisms of its assimilation and transportation within the human body.[23] From the gastrointestinal tract to the bloodstream, vitamin B12 is transported with the help of haptocorrin and intrinsic factor.[24] About two-thirds of circulating vitamin B12 is bound to haptocorrin, and the rest vitamin B12 is coupled to transcobalamin (TC) and forms holotranscobalamin. Holotranscobalamin is responsible for delivering vitamin B12 to cytoplasm through the transcobalamin receptor, and it is considered as the biologically active vitamin B12.[25,26] Furthermore, folate is mainly transported from the extracellular space into the cell via reduced folate carrier (RFC).[27] Notably, TC and RFC are encoded by *transcobalamin 2* (*TCN2*) and *solute carrier family 19 member 1* (*SLC19A1*), respectively, and their genetic mutation would significantly influence the bioavailability of vitamin B12 and folate.[28,29] However, at present, there is no research investigating the relationship between genes related to cellular uptake of vitamin B12 and folate, such as *TCN2* and *SLC19A1*, and the occurrence of PSD.

Our research is aimed to examine the association of serum vitamin B12 and folate level with patients with PSD at 2 weeks after stroke (early-onset PSD). We focused on the genes related to cellular uptake of vitamin B12 and folate and explored the potential genetic mechanisms of PSD.

Methods and Material

Study Population

Patients were consecutively recruited in Xiangya Hospital of Central South University, Changsha from August 2019 to August 2021. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved and reviewed by the Ethics Committee of Xiangya Hospital of Central South University (ethical approval No. 201910842). Written informed consent was obtained from the patients or their nearest relatives. The inclusion criteria were as follows: (1) ischemic stroke confirmed by magnetic resonance imaging and cerebral computed tomographic scan; (2) age between 18 and 75 years old; (3) hospital admission within 2 weeks after stroke onset; and (4) ability to coordinate the evaluation and complete the questionnaire. The exclusive criteria were as follows: (1) comorbid with other neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, and epilepsy; (2) brain dysfunction caused by other non-vascular causes, for instance, encephalitis, brain trauma, brain tumor, and so on; and (3) history of depression, schizophrenia, and other mental disorders.

Data Collection and Clinical Assessment

Demographics, medical history, and clinical characteristics of patients were collected. The neurological deficits were assessed with the National Institutes of Health Stroke Scale (NIHSS) within 24 hours after hospital admission by neurologists. Barthel Index (BI) scores and modified Rankin Scale (mRS) scores were also collected. Mini-mental State Examination (MMSE) was used to quantify the cognitive status. The depressive and anxious symptoms were evaluated with the Hamilton depression scale 17 item (HAMD) and Hamilton anxiety scale (HAMA), respectively. The diagnosis

of PSD was defined as the total score of HAMD > 7 at 2 weeks after stroke.[30–32] All researchers involved in conducting cognitive and depression assessments were blinded to genetic and clinical data after uniform training.

Blood Sample Collection, Storage, and Measurements of Vitamin B12 and Folate

Fasting peripheral blood samples were collected in the morning of the second day of admission using vacutainer tubes with the anticoagulant ethylenediaminetetraacetic acid. The samples were centrifuged within 30 minutes of collection, and the serum was stored at −80°C until analysis. Vitamin B12 and folate concentrations were measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit (Mlbio), provided by Shanghai Genesky Biotechnology Co., Ltd., China, in accordance to the manufacturer's instructions. Each sample was tested in triplicate, and the average value was used. The minimum detectable dose was less than 0.1 pmol/mL for vitamin B12 and 0.1 ng/mL for folate. The inter- and intra-assay coefficients of variation were less than 10% and 15%, respectively.

Single Nucleotide Polymorphism (SNP) Selection and Genotyping

We selected four SNPs of *TCN2* (rs1801198, rs9606756, and rs9621049) and *SLC19A1* (rs1051266) previously reported and their minor allele frequencies were more than 0.05 based on the information in the National Center for Biotechnology Information SNP database.[33–35] We used SNPscan™ multiplex SNP typing Kit (Cat#: G0104K, Genesky Biotechnologies Inc., Shanghai, China) to genotype SNPs. The procedure of this technique has been reported in the previous study.[36] To ensure quality control, the same process was applied to analyze 5% of the duplicated DNA samples.

Statistical Analysis

We conducted statistical analysis by SPSS version 23.0 for windows (SPSS Inc., Chicago, IL, USA). Mann–Whitney test, Wilcoxon signed-rank test, and Student's *t*-test were conducted to assess the presence of differences in median values. Differences between proportions were assessed with the χ^2-test or Fisher's exact test. Equal variance was evaluated using the *F*-test, and normality was evaluated through the Shapiro–Wilk normality test. Binary logistic regression analysis was used to examine the association between genotypes and PSD. Hardy-Weinberg equilibrium test was performed by the SHEsis, an online program.[37,38] The statistical significance threshold was defined as two-sided p-value <0.05. Categorical variables were presented in percentages, while continuous variables were depicted as either the median with interquartile range or the mean ± standard deviation, depending on the distribution of the data (normal or non-normal).

Result

Demographics and Clinical Characteristics of the Study Population

A total of 173 patients diagnosed with ischemic stroke were ultimately included in this study (Figure 1). Eighty-four patients were diagnosed with PSD at 2 weeks after stroke onset, accounting for 46.8% of the study population. Clinical characteristic and demographics of PSD and non-PSD group were presented in Table 1. Compared with the non-PSD group, the PSD group was more likely to have a lower BI score (p=0.017), and higher HAMA score (p<0.001). The NIHSS score and gender composition between PSD and non-PSD group reached marginal significance (p=0.051 and p=0.059 respectively). No significant differences were identified in age, marital status, body mass index (BMI), educational level, vascular risk factors (smoking, drinking, diabetes mellitus, and hypertension), lesion location, mRS score, and MMSE score.

Association Between Genotype of TCN2 and SLC19A1 and Early-Onset PSD

The genotype frequencies of the analyzed polymorphism of *TCN2* and *SLC19A1* were in agreement with the Hardy–Weinberg equilibrium in the PSD and non-PSD group (p>0.05). We adopted binary logistic regression to examine the relationship between *TCN2, SLC19A1*, and PSD. We found that *TCN2* rs1801198 GG genotype (OR = 3.612, 95% CI = 1.542~8.457, p = 0.003) and G allele (OR = 1.996, 95% CI = 1.299~3.067, p = 0.002) were associated with elevated risk of PSD. After adjustment for confounding factors (age, gender, BMI, NIHSS score, and MMSE score), the association between rs1801198 and PSD remained statistical significance (for GG genotype, OR = 4.253, 95% CI = 1.711~10.572,

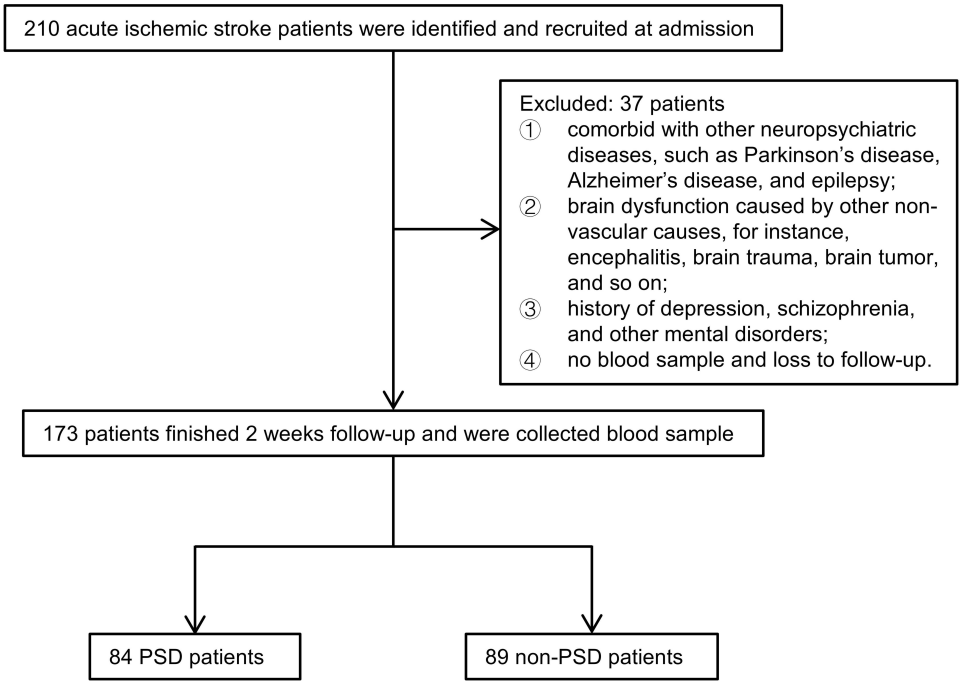

Figure 1 Study recruitment profile.
Abbreviations: PSD, post-stroke depression.

p = 0.002; for G allele, OR = 2.134, 95% CI = 1.362~3.343, p = 0.001) (Table 2). No significant differences were found in genotypes and allele frequencies of other SNPs between PSD and non-PSD group (Table 2).

Association of Serum Vitamin B12 Concentration with PSD

The serum vitamin B12 concentration in the PSD group was significantly lower than that in the non-PSD group (p=0.024), while there was no significant difference between patients with and without PSD in folate level (Table 1). Binary logistic

Table 1 Clinical and Demographic Characteristics of PSD and Non-PSD Patients

Characteristics	PSD (n=84)	Non-PSD (n=89)	*p*-value
Age (years), mean±SD	56.56±11.47	57.42±10.07	0.602
Male, n (%)	51 (60.7%)	66 (74.2%)	0.059
Married, n (%)	76 (90.5%)	83 (93.3%)	0.502
Educational level			
Junior middle school and below, n (%)	47 (56.0%)	50 (56.2%)	0.633
Senior high/polytechnic school, n (%)	23 (27.4%)	20 (22.5%)	
University and above, n (%)	14 (16.7%)	19 (21.3%)	
BMI (kg/m^2), mean±SD	23.64±2.83	23.73±2.67	0.813
History of smoking, n (%)	43 (51.2%)	55 (61.8%)	0.159
History of drinking, n (%)	42 (50.0%)	48 (53.9%)	0.605
History of hypertension, n (%)	55 (65.5%)	63 (70.8%)	0.453
History of diabetes, n (%)	27 (32.1%)	22 (24.7%)	0.279

(*Continued*)

Table 1 (Continued).

Characteristics	PSD (n=84)	Non-PSD (n=89)	*p*-value
Lesion location			
Anterior circulation, n (%)	53 (63.1%)	52 (58.4%)	0.819
Posterior circulation, n (%)	27 (32.1%)	32 (36.0%)	
Both, n (%)	4 (4.8%)	5 (5.6%)	
NIHSS score, median (IQR)	2.5 (1, 7)	2 (1, 4)	0.051
BI score, median (IQR)	85 (35, 100)	100 (70, 100)	0.017
mRS score, median (IQR)	2 (1, 4)	2 (1, 3)	0.168
MMSE score, median (IQR)	25 (23, 28)	26 (23, 29)	0.291
HAMA score, median (IQR)	12 (9, 18)	5 (3, 7.5)	<0.001
Vitamin B12 (pmol/mL), mean±SD	379.36±106.13	415.83±103.88	0.024
Folate (ng/mL), mean±SD	25.11±3.40	25.95±3.82	0.128

Notes: Values are shown as number (percentage) or as medians (IQR) and mean (SD). Statistical significance was accepted at $p < 0.05$.

Abbreviations: PSD, post-stroke depression; SD, standard deviation; IQR, interquartile range; BMI, body mass index; NIHSS, National Institutes of Health and Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale; MMSE, Mini-Mental State Examination; HAMA, Hamilton anxiety scale.

Table 2 Association of Genotypes of TCN2 and SLC19A1 and PSD

Genotypes and Alleles	PSD	Non-PSD	OR [$CI_{95\%}$]	*p*-value	Adjusted OR [$CI_{95\%}$]	*P*-value
rs1801198 (*TCN2*)						
C/C	13	29	Ref	-	Ref	-
G/C	37	39	2.116 [0.957~4.681]	0.064	2.243 [0.979~5.141]	0.056
G/G	34	21	3.612 [1.542~8.457]	0.003	4.253 [1.711~10.572]	0.002
G	105	81	1.996 [1.299~3.067]	0.002	2.134 [1.362~3.343]	0.001
C	63	97				
rs9606756 (*TCN2*)						
A/A	80	88	0.277 [0.025~2.076]	0.189	0.205 [0.022~1.907]	0.164
A/G	4	1				
A	164	177	0.232 [0.026~2.094]	0.193	0.210 [0.023~1.932]	0.168
G	4	1				
rs9621049 (*TCN2*)						
C/C	83	89	0.943 [0.058~15.325]	0.967	0.812 [0.048~13.656]	0.885
C/T	1	1				
C	167	178	0.944 [0.059~15.206]	0.967	0.814 [0.049~13.451]	0.886
T	1	1				
rs1051266 (*SLC19A1*)						
T/T	19	20	Ref	-	Ref	-
T/C	40	50	0.842 [0.397~1.788]	0.655	0.822 [0.380~1.781]	0.620
C/C	25	19	1.385 [0.583~3.293]	0.461	1.278 [0.519~3.151]	0.594
T	78	90	1.207 [0.791~1.841]	0.383	1.146 [0.741~1.771]	0.540
C	90	88				

Notes: Adjusted model: The adjusted OR was adjusted for age, gender, body mass index, NIHSS score, and MMSE score.

Abbreviations: PSD, post stroke depression; OR, odds ratio; CI, confidence interval; *TCN2, transcobalamin 2; SLC19A1*, solute carrier family 19 member 1.

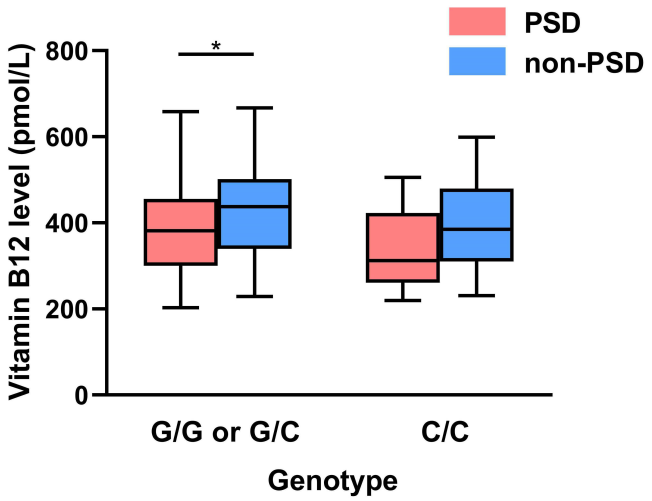

Figure 2 Comparison of serum vitamin B12 concentrations was conducted based on the presence or absence of the *TCN2* rs1801198 G allele in both PSD and non-PSD patients. The central line shown in each box plot indicates the median of data. Whiskers extend to cover the whole range of values. Statistical significance was accepted at $p < 0.05$. *$p < 0.05$.

regression was conducted to assess the relationship between vitamin B12 level and PSD. Lower vitamin B12 level was the risk factor of PSD (OR = 0.997, 95% CI = 0.994~0.999, $p = 0.025$). Even after adjusting for confounding factors (age, gender, BMI, NIHSS score, and MMSE score), it remains statistical significance (OR = 0.997, 95% CI = 0.994~1.000, $p = 0.046$). Furthermore, serum vitamin B12 level was examined with regard to the distribution of the *TCN2* rs1801198 genotype and PSD. We found that among patients with the G allele in the PSD and non-PSD groups, the serum vitamin B12 level in the PSD group was notably reduced compared to the non-PSD group (p=0.045, Figure 2).

Discussion

To the best of our knowledge, this is the first study to explore the potential association among vitamin B12, folate, polymorphism of their transportation gene, and early-onset PSD. We found that *TCN2* rs1801198 GG genotype and G allele were the independent risk factors of early-onset PSD, and PSD group had relatively lower vitamin B12 than non-PSD group did.

In our study, the incidence of PSD at 2 weeks after stroke onset was 46.8%, which is consistent with previous studies.[39,40] However, our incidence is a little higher than approximate one thirds previously reported.[41] This discrepancy may be attributed to the heterogeneity among different depression screening tools. The BI score of PSD group was significantly lower than non-PSD group, indicating more impaired activity of daily living in PSD group, which was consistent with previous researches.[42,43] PSD group had higher HAMA scores than the non-PSD group, and this could be explained by the coexistence of anxiety in patients with depression.[44]

TC, encoded by *TCN2*, is an essential protein involved in the transportation and cellular uptake of vitamin B12.[45] *TCN2* rs1801198 is a missense C>G polymorphism in exon 6 that results in an amino acid substitution of proline to arginine at codon position 259, which plays a negative role in regulating the binding affinity of TC with cobalamin.[34] This substitution significantly reduced serum holotranscobalamin level to exert an adverse effect on vitamin B12 cellular delivery and one carbon metabolism, and a meta-analysis shows individuals with rs1801198 GG genotype tend to have lower serum holotranscobalamin level and higher serum homocysteine level.[28,46] Our study demonstrated that *TCN2* rs1801198 GG genotype and G allele and lower serum vitamin B12 level are associated with increasing risk of early-onset PSD. Besides, we found that PSD patients with *TCN2* rs1801198 GG genotype have lower vitamin B12 level than non-PSD patients, which indicate that vitamin B12 may affect the occurrence of early-onset PSD, depending on the transportation function of TC. We speculated that stroke patients with lower vitamin B12 level and rs1801198 G allele are more susceptible to PSD. In consistent with our study, Huijts et al found that first-ever lacunar stroke patients with a deficiency of vitamin B12 are more likely to suffer from PSD and post-stroke fatigue.[21]

Vitamin B12 may influence PSD via following potential pathophysiological pathways. Firstly, cobalamin constitutes a crucial component for the synthesis of monoamine neurotransmitters in the brain, and dysregulation of monoamines system is deeply involved in the pathophysiology of PSD.[47,48] Secondly, vitamin B12 possesses antioxidant properties. A recent research reported that depression and anxiety induced by nicotine withdrawal could be ameliorated by vitamin B12 via alteration of oxidative stress and inflammation.[49,50] Thirdly, vitamin B12 plays a crucial role in myelin formation and remyelination, substantially contributing to nerve regeneration following ischemic stroke.[10,51] Myelin damage is also recognized as an important factor in the etiology of depression.[52] We speculate that vitamin B12 may influence PSD via the synthesis of myelin. Fourthly, vitamin B12 plays a vital role in one carbon metabolism. Vitamin B12 acts as the coenzyme in the remethylation pathway of homocysteine, and deficiency of vitamin B12 is constantly associated with higher homocysteine level.[53] An animal research demonstrated that homocysteine can aggravate depressive like behaviors N-methyl-d-aspartate receptors-mediated synaptic plasticity in post-stroke rats.[54] Clinical researches found that homocysteine at admission was related to PSD at 2 weeks and 3 months after stroke onset.[55,56]

A previous case-control study reported that PSD patients tend to have lower serum folate level.[57] However, the folate level did not show significant difference in our research, possibly due to the difference of experimental design and study population. Despite the lack of direct evidence proving the association between folate and PSD, folate may potentially influence PSD. Numerous studies reported that folate deficiency is linked to an elevated risk of developing depression, as well as more severe depressive symptoms, longer episodes of depression, and an increased likelihood of depressive symptom relapse.[58–62] In animal study, Yabe et al found that deficiency of folate could impede neuronal immaturity in the dentate gyrus, thus inducing depression-like state, while S-adenosylmethionine supplantation could prevent it.[63,64]

Several limitations in our study should also be acknowledged. Firstly, our study is a hospital-based cross-sectional study, and all patients were recruited within the hospital setting. Berkson's bias could not be entirely avoided. Additionally, selection bias exists in our study. We excluded patients with severe strokes, as well as those with significant dysarthria and aphasia who were unable to complete the interviews and questionnaires. Secondly, our study has a limited sample size. The included patients were primarily from the Chinese Han population and predominantly from south central China. As a result, the conclusion could not be over-interpreted. Thirdly, the dietary patterns of the participants were not recorded in our study, although they can influence the serum levels of vitamin B12 and folate. Including this information would contribute to a better understanding of the etiology of PSD. Fourthly, we only detected serum vitamin B12 and folate level at admission and examined the association with them and PSD at 2 weeks after stroke onset. In the future, researchers should conduct a longitudinal study and explore how vitamin B12 and folate changes during the course of PSD.

Conclusion

Overall, our findings demonstrated that lower vitamin B12 at admission and *TCN2* rs1801198 GG genotype and G allele were associated with elevated risk of early-onset PSD. Our study provided the theoretical basis of vitamin B12 supplementation in the prevention and treatment of PSD. Further studies need to confirm these findings in a larger sample cohort and explore the curative effect of vitamin B12 supplementation in PSD.

Abbreviation

PSD, post-stroke depression; *TCN2, transcobalamin 2; SLC19A1, solute carrier family 19 member 1*; TC, transcobalamin; RFC, reduced folate carrier; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale; MMSE, Mini-mental State Examination; HAMD, Hamilton depression scale; HAMA, Hamilton anxiety scale; SNP, single nucleotide polymorphism, SNP; BMI, body mass index.

Data Sharing Statement

The data used to generate the results can be made available upon request from the corresponding author.

Ethics Approval and Informed Consent

The protocol was reviewed and approved by the Ethics Committee of Xiangya Hospital of Central South University (ethical approval No. 201910842). Written informed consent was obtained from all subjects or their caregivers.

Consent for Publication

All authors read and approved the final manuscript.

Acknowledgment

We express our gratitude to Jun Yang from the Department of Psychiatry at Second Xiangya Hospital for assisting with proofreading. Our appreciation extends to all participants and authors involved in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Key R&D Program of China (2017YFC1310003) for Fafa Tian.

Disclosure

The authors declare no financial or other conflicts of interest.

References

1. Feigin VL, Stark BA, Johnson CO. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795–820. doi:10.1016/s1474-4422(21)00252-0
2. Tu WJ, Wang LD, Yan F. China stroke surveillance report 2021. *Military Med Res*. 2023;10(1):33. doi:10.1186/s40779-023-00463-x
3. Tu WJ, Zhao Z, Yin P, et al. Estimated Burden of Stroke in China in 2020. *JAMA Netw Open*. 2023;6(3):e231455. doi:10.1001/jamanetworkopen.2023.1455
4. Towfighi A, Ovbiagele B, El Husseini N, et al. Poststroke Depression: a Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(2):e30–e43. doi:10.1161/str.0000000000000113
5. Williams OA, Demeyere N. Association of Depression and Anxiety With Cognitive Impairment 6 Months After Stroke. *Neurology*. 2021;96(15):e1966–e1974. doi:10.1212/wnl.0000000000011748
6. Zhang L, Sui M, Yan T, You L, Li K, Gao Y. A study in persons later after stroke of the relationships between social participation, environmental factors and depression. *Clin rehabilitat*. 2017;31(3):394–402. doi:10.1177/0269215516641300
7. Yuliana S, Yu E, Rias YA, Atikah N, Chang HJ, Tsai HT. Associations among disability, depression, anxiety, stress, and quality of life between stroke survivors and their family caregivers: an Actor-Partner Interdependence Model. *J Adv Nurs*. 2023;79(1):135–148. doi:10.1111/jan.15465
8. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102–109. doi:10.1016/j.arr.2019.01.013
9. Wang S, Wang CX, Zhang N, et al. The Association Between Post-stroke Depression, Aphasia, and Physical Independence in Stroke Patients at 3-Month Follow-Up. *Fronti Psychiatry*. 2018;9:374. doi:10.3389/fpsyt.2018.00374
10. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS Neurosci Ther*. 2020;26(1):5–13. doi:10.1111/cns.13207
11. Pourié G, Guéant JL, Quadros EV. Behavioral profile of vitamin B(12) deficiency: a reflection of impaired brain development, neuronal stress and altered neuroplasticity. *Vitamin hormon*. 2022;119:377–404. doi:10.1016/bs.vh.2022.02.002
12. Qin X, Spence JD, Li J, et al. Interaction of serum vitamin B(12) and folate with MTHFR genotypes on risk of ischemic stroke. *Neurology*. 2020;94(11):e1126–e1136. doi:10.1212/wnl.0000000000008932
13. Markišić M, Pavlović AM, Pavlović DM. The Impact of Homocysteine, Vitamin B12, and Vitamin D Levels on Functional Outcome after First-Ever Ischaemic Stroke. *Biomed Res Int*. 2017;2017:5489057. doi:10.1155/2017/5489057
14. Zhou L, Wang J, Li M, et al. Low vitamin B(12) levels may predict the risk of ischemic stroke: a cross-sectional study. *J Clin Neurosci*. 2023;117:125–135. doi:10.1016/j.jocn.2023.09.024
15. Esnafoglu E, Ozturan DD. The relationship of severity of depression with homocysteine, folate, vitamin B12, and vitamin D levels in children and adolescents. *Child Adolescent Mental Health*. 2020;25(4):249–255. doi:10.1111/camh.12387
16. Petridou ET, Kousoulis AA, Michelakos T, et al. Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. *Aging Mental Health*. 2016;20(9):965–973. doi:10.1080/13607863.2015.1049115
17. Berkins S, Schiöth HB, Rukh G. Depression and Vegetarians: association between Dietary Vitamin B6, B12 and Folate Intake and Global and Subcortical Brain Volumes. *Nutrients*. 2021;13(6):1790. doi:10.3390/nu13061790
18. Wu Y, Zhang L, Li S, Zhang D. Associations of dietary vitamin B1, vitamin B2, vitamin B6, and vitamin B12 with the risk of depression: a systematic review and meta-analysis. *Nutr Rev*. 2022;80(3):351–366. doi:10.1093/nutrit/nuab014
19. Khosravi M, Sotoudeh G, Amini M, Raisi F, Mansoori A, Hosseinzadeh M. The relationship between dietary patterns and depression mediated by serum levels of Folate and vitamin B12. *BMC Psychiatry*. 2020;20(1):63. doi:10.1186/s12888-020-2455-2

20. Almeida OP, Ford AH, Hirani V, et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. *Br J Psychiatry*. 2014;205(6):450–457. doi:10.1192/bjp.bp.114.145177
21. Huijts M, Duits A, Staals J, van Oostenbrugge RJ. Association of vitamin B12 deficiency with fatigue and depression after lacunar stroke. *PLoS One*. 2012;7(1):e30519. doi:10.1371/journal.pone.0030519
22. Almeida OP, Marsh K, Alfonso H, Flicker L, Davis TM, Hankey GJ. B-vitamins reduce the long-term risk of depression after stroke: the VITATOPS-DEP trial. *Ann Neurol*. 2010;68(4):503–510. doi:10.1002/ana.22189
23. Guéant JL, Guéant-Rodriguez RM, Alpers DH. Vitamin B12 absorption and malabsorption. *Vitamin hormon*. 2022;119:241–274. doi:10.1016/bs.vh.2022.01.016
24. Mitchell ES, Conus N, Kaput J. B vitamin polymorphisms and behavior: evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline. *Neurosci Biobehav Rev*. 2014;47:307–320. doi:10.1016/j.neubiorev.2014.08.006
25. Keller P, Rufener J, Schild C, Fedosov SN, Nissen PH, Nexo E. False low holotranscobalamin levels in a patient with a novel TCN2 mutation. *Clin Chem Lab Med*. 2016;54(11):1739–1743. doi:10.1515/cclm-2016-0063
26. Gick GG, Arora K, Sequeira JM, Nakayama Y, Lai SC, Quadros EV. Cellular uptake of vitamin B(12): role and fate of TCblR/CD320, the transcobalamin receptor. *Exp Cell Res*. 2020;396(1):112256. doi:10.1016/j.yexcr.2020.112256
27. Alpers DH. Absorption and blood/cellular transport of folate and cobalamin: pharmacokinetic and physiological considerations. *Biochimie*. 2016;126:52–56. doi:10.1016/j.biochi.2015.11.006
28. Oussalah A, Levy J, Filhine-Trésarrieu P, Namour F, Guéant JL. Association of TCN2 rs1801198 c.776G>C polymorphism with markers of one-carbon metabolism and related diseases: a systematic review and meta-analysis of genetic association studies. *Am J Clin Nutr*. 2017;106(4):1142–1156. doi:10.3945/ajcn.117.156349
29. Wang X, Wang Y, Ma X, et al. Gender-specific association of SLC19A1 and MTHFR genetic polymorphism with oxidative stress biomarkers and plasma folate levels in older adults. *Exp Gerontology*. 2023;178:112208. doi:10.1016/j.exger.2023.112208
30. Li Y, Zhang M, Xue M, Liu D, Sun J. Elevated monocyte-to-HDL cholesterol ratio predicts post-stroke depression. *Fronti Psychiatry*. 2022;13:902022. doi:10.3389/fpsyt.2022.902022
31. Liu Y, Liu L, Zhi Z, et al. Higher serum lipocalin 2 is associated with post-stroke depression at discharge. *BMC Neurol*. 2023;23(1):294. doi:10.1186/s12883-023-03319-y
32. Zeng YY, Cheng HR, Cheng L, et al. Comparison of poststroke depression between acute ischemic and hemorrhagic stroke patients. *Int J Geriatric Psychiatry*. 2021;36(4):493–499. doi:10.1002/gps.5444
33. Cho Y, Kim JO, Lee JH, et al. Association of reduced folate carrier-1 (RFC-1) polymorphisms with ischemic stroke and silent brain infarction. *PLoS One*. 2015;10(2):e0115295. doi:10.1371/journal.pone.0115295
34. Kurnat-Thoma EL, Pangilinan F, Matteini AM, et al. Association of Transcobalamin II (TCN2) and Transcobalamin II-Receptor (TCblR) Genetic Variations With Cobalamin Deficiency Parameters in Elderly Women. *Biol Res Nurs*. 2015;17(4):444–454. doi:10.1177/1099800415569506
35. Liu J, Jiang Y, Liu D, et al. Relationship between cobalt transporter II gene rs9606756 site mutant and serum homocysteine level and recurrent cerebral infarction in young and middle-aged people. *Minerva medica*. 2021;112(2):261–268. doi:10.23736/s0026-4806.20.06462-9
36. Cheng J, Li Y, He Q, et al. Essential hypertension in patients exposed to high-arsenic exposed areas in western China: genetic susceptibility and urinary arsenic metabolism characteristics. *J Trace Element Med Biol*. 2021;67:126778. doi:10.1016/j.jtemb.2021.126778
37. Li Z, Zhang Z, He Z, et al. A partition-ligation-combination-subdivision EM algorithm for haplotype inference with multiallelic markers: update of the SHEsis. *Cell Res*. 2009;19(4):519–523. doi:10.1038/cr.2009.33
38. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res*. 2005;15(2):97–98. doi:10.1038/sj.cr.7290272
39. Chau JPC, SHS L, Zhao J, et al. Factors Associated with Post-Stroke Depression in Chinese Stroke Survivors. *J Stroke Cerebrovasc Dis*. 2021;30(11):106076. doi:10.1016/j.jstrokecerebrovasdis.2021.106076
40. Li G, Miao J, Pan C, et al. Higher Serum Lactic Dehydrogenase is Associated with Post-Stroke Depression at Discharge. *Clin Interventions Aging*. 2021;16:2047–2055. doi:10.2147/cia.S341169
41. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9(8):1017–1025. doi:10.1111/ijs.12357
42. Li G, Miao J, Sun W, et al. Lower Serum Uric Acid Is Associated With Post-Stroke Depression at Discharge. *Fronti Psychiatry*. 2020;11:52. doi:10.3389/fpsyt.2020.00052
43. Shen H, Tu X, Luan X, Zeng Y, He J, Tang W. Serum lipid profiles and post-stroke depression in acute ischemic stroke patients. *Neuropsychiatr Dis Treat*. 2019;15:1573–1583. doi:10.2147/ndt.S204791
44. Choi KW, Kim YK, Jeon HJ. Comorbid Anxiety and Depression: clinical and Conceptual Consideration and Transdiagnostic Treatment. *Adv Exp Med Biol*. 2020;1191:219–235. doi:10.1007/978-981-32-9705-0_14
45. Kose E, Besci O, Gudeloglu E, et al. Transcobalamin II deficiency in twins with a novel variant in the TCN2 gene: case report and review of literature. *JPEM*. 2020;33(11):1487–1499. doi:10.1515/jpem-2020-0096
46. Castro R, Barroso M, Rocha M, et al. The TCN2 776CNG polymorphism correlates with vitamin B(12) cellular delivery in healthy adult populations. *Clin Biochem*. 2010;43(7–8):645–649. doi:10.1016/j.clinbiochem.2010.01.015
47. Ekinci GN, Sanlier N. The relationship between nutrition and depression in the life process: a mini-review. *Exp Gerontology*. 2023;172:112072. doi:10.1016/j.exger.2022.112072
48. Frank D, Gruenbaum BF, Zlotnik A, Semyonov M, Frenkel A, Boyko M. Pathophysiology and Current Drug Treatments for Post-Stroke Depression: a Review. *Int J Mol Sci*. 2022;23(23):15114. doi:10.3390/ijms232315114
49. Pahlavani H, Masoudi M, Khoshroo N, et al. Vitamin B(12) reversed anxiety and depression induced by adolescent nicotine withdrawal through alteration the inflammatory, oxidative and serotoninergic profiles in male rats. *Biochem Pharmacol*. 2023;217:115832. doi:10.1016/j.bcp.2023.115832
50. van de Lagemaat EE, de Groot L, van den Heuvel E. Vitamin B(12) in Relation to Oxidative Stress: a Systematic Review. *Nutrients*. 2019;11(2):482. doi:10.3390/nu11020482
51. Yahn GB, Abato JE, Jadavji NM. Role of vitamin B12 deficiency in ischemic stroke risk and outcome. *Neural Regeneration Res*. 2021;16(3):470–474. doi:10.4103/1673-5374.291381

52. Fries GR, Saldana VA, Finnstein J, Rein T. Molecular pathways of major depressive disorder converge on the synapse. *Mol Psychiatry*. 2023;28(1):284–297. doi:10.1038/s41380-022-01806-1
53. Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab*. 2017;14(1):78. doi:10.1186/s12986-017-0233-z
54. Wang M, Liang X, Zhang Q, et al. Homocysteine can aggravate depressive like behaviors in a middle cerebral artery occlusion/reperfusion rat model: a possible role for NMDARs-mediated synaptic alterations. *Nutr Neurosci*. 2023;26(6):483–495. doi:10.1080/1028415x.2022.2060642
55. Li Y, Cao LL, Liu L, Qi QD. Serum levels of homocysteine at admission are associated with post-stroke depression in acute ischemic stroke. *Neurological Sci*. 2017;38(5):811–817. doi:10.1007/s10072-017-2848-2
56. Zhang J, Zeng C, Huang X, et al. Association of homocysteine and polymorphism of methylenetetrahydrofolate reductase with early-onset post stroke depression. *Front Nutr*. 2022;9:1078281. doi:10.3389/fnut.2022.1078281
57. Chatterjee K, Fall S, Barer D. Mood after stroke: a case control study of biochemical, neuro-imaging and socio-economic risk factors for major depression in stroke survivors. *BMC Neurol*. 2010;10(1):125. doi:10.1186/1471-2377-10-125
58. Levitt AJ, Joffe RT. Folate, B12, and life course of depressive illness. *Biol Psychiatry*. 1989;25(7):867–872. doi:10.1016/0006-3223(89)90266-7
59. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. *J Clini Psych*. 2004;65(8):1090–1095. doi:10.4088/jcp.v65n0810
60. Ramos MI, Allen LH, Haan MN, Green R, Miller JW. Plasma folate concentrations are associated with depressive symptoms in elderly Latina women despite folic acid fortification. *Am J Clin Nutr*. 2004;80(4):1024–1028. doi:10.1093/ajcn/80.4.1024
61. Reynolds EH, Preece JM, Bailey J, Coppen A. Folate deficiency in depressive illness. *Br J Psychiatry*. 1970;117(538):287–292. doi:10.1192/S0007125000193250
62. Sachdev PS, Parslow RA, Lux O, et al. Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. *Psychol Med*. 2005;35(4):529–538. doi:10.1017/s0033291704003721
63. Araki R, Nishida S, Oishi Y, Tachioka H, Kita A, Yabe T. Methyl Donor Supplementation Prevents a Folate Deficiency-induced Depression-like State and Neuronal Immaturity of the Dentate Gyrus in Mice. *Neuroscience*. 2022;485:12–22. doi:10.1016/j.neuroscience.2022.01.007
64. Nishida S, Araki R, Baba A, et al. Post-weaning folate deficiency induces a depression-like state via neuronal immaturity of the dentate gyrus in mice. *J Pharmacol Sci*. 2020;143(2):97–105. doi:10.1016/j.jphs.2020.02.007