Associations between homocysteine, folate, and vitamin B12 and cognitive domains in a convalescent post stroke population

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Introduction

Elevated levels of plasma homocysteine, or decreased levels of folate and vitamin B-12 have been associated with increased risk of Alzheimer's Disease, cerebrovascular and cardiovascular diseases. As homocysteine links the methionine cycle with the folate cycle, homocysteine levels are strongly associated with folate and vitamin B-12 levels. However, there is no clear consensus on the effect of homocysteine, folate or vitamin B-12 on cognition.

Aims

To determine the associations between homocysteine, folate, and vitamin B12 and cognitive sub domains in a cohort of convalescent stroke patients.

		Quartiles of homocysteine level				
		1(lowest)	2	3	4(highest)	p-value
		n=177	n=178	n=176	n=177	
Gender	N females (%)	78(44)	56(31)	47(27)	52(29)	0.003
Age	Mean (SD)	57.1(10.6)	59.0(11.3)	61.1(11.4)	67.4(10.0)	>0.0001
Education	Mean (SD)	6.67(4.05)	6.02(4.40)	5.81(4.61)	4.39(4.13)	>0.0001
Folate	Mean (SD)	19.8(8.48)	16.4(6.92)	16.5(8.70)	14.4(6.96)	>0.0001
Vitamin B12	Mean (SD)	390(235)	335(149)	314(152)	268(168)	>0.0001
Hypertension	Mean (SD)	112(63)	126(71)	134(76)	140(79)	0.005
Diabetes	N yes (%)	80(45)	74(42)	72(41)	68(38)	0.634
Smoking	N yes (%)	56(31)	63(35)	61(35)	58(33)	0.872
Lipid	N yes (%)	85(48)	87(49)	100(57)	91(51)	0.344
Cadiac Risk Factors	N yes (%)	23(13)	21(12)	40(23)	35(20)	0.014
Stroke	TACI/PACI(%)	16(9)	11(6)	24(14)	20(11)	0.113
Race	Chinese (%)	140(79)	145(81)	144(82)	142(80)	0.961
	Malay (%)	20(11)	18(10)	15(8)	20(11)	
	Indian (%)	17(10)	15(8)	17(10)	15(8)	

Table 1: Demographic characteristics at baseline by homocysteine quartiles.

Methods

Patient population

The participants in this study were part of the Singaporean cohort of the Vitamins to Prevent Stroke (VITATOPS) study, a randomised double blind, placebo controlled trial of homocysteine lowering with a folate based therapeutic regime. Briefly, consecutive patients admitted to the Singapore General Hospital, with ischemic stroke or transient ischemic attacks (TIAs) were recruited up to 7 months post-stroke and underwent a full neuropsychological test battery that was administered in the patient's native language. They also had plasma homocysteine and serum folate and serum vitamin B12 levels measured at the same setting.

Statistical Analyses

The relationship between cognitive test scores and homocysteine, folate, or vitamin B-12 was modelled individually in base models that controlled for age, gender and the number of years of education (model 1). The next model (model 2) included as covariates, in addition to age, gender and years of education, risk factors for stroke (smoker, hypertension, diabetes mellitus, previous vascular events) and type of stroke (large stroke (TACI/PACI) versus small stroke (LACI/POCI). In the final model, homocysteine, folate, and vitamin B-12 were included into the regression model along with all the covariates specified in model 2. To facilitate meaningful comparisons of results across different cognitive tests with varying metrics, standardized beta coefficient estimates are presented. All analyses were done with Stata v10.

	Homocysteine			Folate			Vitamin B-12		
Items	Standardized β	p value	Items	Standardized β	p value	Items	Standardized β	p value
Model 3[1]			**Model 3[1]**			**Model 3[1]**		
MMSE	-0.006	0.03	Auditory Detection	-0.017	0.01	Maze Task	-0.001	0.03
Visual Span Forward	-0.014	0.02	Category Fluency (Food)	0.008	0.03	WMS-R Visual Reproduction – Delayed	-0.005	0.01
Auditory Detection	-0.011	0.01	Story Recall - Delayed	0.012	0.09	Picture Recall - Delayed	0.023	0.04
Category Fluency (Food)	-0.004	0.09	WMS-R Visual Reproduction – Delayed Recognition	0.034	0.01			
Story Recall - Delayed	-0.004	0.42	WMS-R Visual Reproduction - Copy	0.004	0.02			
Word List Recall - Immediate	-0.004	0.14	Digit Symbol Task	0.004	<0.01			
Picture Recall - Delayed	-0.009	0.16						

Table 2: Standardized changes in cognitive test scores as related to homocysteine, folate and vitamin B-12 in model 2.

	Homocysteine			Folate			Vitamin B-12		
Items	Standardized β	p value	Items	Standardized β	p value	Items	Standardized β	p value
Model 2[1]			**Model 2[1]**			**Model 2[1]**		
MMSE	-0.008	0.01	Auditory Detection	-0.014	0.04	Maze Task	<-0.001	0.02
Visual Span Forward	-0.015	0.01	Category Fluency (Food)	0.009	0.02	WMS-R Visual Reproduction – Delayed	-0.004	0.04
Visual Span Backward	-0.011	0.05	Story Recall - Delayed	0.016	0.03	Picture Recall - Delayed	0.035	<0.01
Auditory Detection	-0.012	0.01	WMS-R Visual Reproduction – Delayed Recognition	0.035	0.01			
Category Fluency (Food)	-0.005	0.05	WMS-R Visual Reproduction - Copy	0.004	0.01			
Story Recall - Delayed	-0.009	0.09	Digit Symbol Task	0.004	0.01			
Word List Recall - Immediate	-0.005	0.04						
Picture Recall - Delayed	-0.019	0.01						

Table 3: Standardized changes in cognitive test scores as related to homocysteine, folate and vitamin B-12 in model 3.

Result

The demographic and laboratory characteristics of the study population are described in **Table 1** by quartiles of homocysteine levels. Patients in the higher quartiles of homocysteine measurement were significantly more likely to be male, older, less educated, have hypertension, have previous history of vascular events, and have lower levels of vitamin B-12 and folate. homocysteine was significantly inversely correlated with folate (r= -0.246, p<0.001), and with vitamin B-12 (r=-0.248, p<0.001). Vitamin B-12 was significantly correlated with folate levels (r=0.138, p<0.001).

The results of regression analyses based on models 2 and 3 are summarized in **Table 2 and 3** respectively. While items associated with folate and vitamin B-12 were consistent regardless of model, the number of items associated with homocysteine was reduced from eight in model 1 to six in model 2 and to three in model 3. In the final model, homocysteine was associated with the MMSE and attention, folate with visuospatial abilities and executive functioning and vitamin B-12 with visuospatial abilities and short-term memory.

Conclusions

1. Homocysteine was inversely associated with attention and the MMSE
2. Folate was associated with visuospatial ability and executive functioning
   - This appeared to be the most robust association, as this did not weaken, even with addition of homocysteine and Vitamin B12 in the models.
3. Vitamin B-12 was associated with visuospatial ability and short-term memory