

Homocysteine and Peripheral Neuropathy

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Abstract

Introduction: Elevated plasma level of homocysteine (eHcy) has been observed to be related to various neurological conditions including peripheral neuropathy (PN). However, studies on eHcy as an independent risk factor for the development of PN are sparse. To explore the association of eHcy with PN, we conducted a clinical observational study.

Methods: Retrospective chart review was performed over 5 years on patients with peripheral neuropathy or with primary headaches as controls. Patients with simultaneously measured homocysteine, methylmalonic acid, Vitamin B12 and folate were recorded. Patients without homocysteine measurement or with any identifiable etiologies, other than eHcy, for neuropathy were excluded. Demographic, clinical and laboratory data were analyzed.

Results: A total of 202 subjects who met the inclusion and exclusion criteria were collected, including 161 with PN and 41 with headaches. Higher levels of homocysteine were observed in PN patients ($15.5 \pm 12.2 \mu\text{mol/L}$, 95% CI: 0.6369-8.2631, $p = 0.02$) than in the headache controls ($10.6 \pm 3.4 \mu\text{mol/L}$). Additionally, the frequency of eHcy was also significantly higher in PN (51.6%, OR: 4.39, 95% CI: 1.91-10.09, $p = 0.0002$) than in headache controls (19.5%).

Discussion: The current study confirmed the previous observation that increased prevalence of eHcy is seen in patients with PN and validated the hypothesis that eHcy may potentially be an independent risk factor contributing to the etiology of PN.

Keywords

Homocysteine, Hyperhomocysteinemia, Peripheral neuropathy, Risk factor

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid that can be toxic at high levels to neuronal cells. Elevated Hcy (eHcy) has been reported to be associated with various neurological conditions, such as stroke, mild cognitive impairment and dementia, Parkinson's disease, multiple sclerosis, epilepsy and peripheral neuropathy (PN) [1]. Clinical studies have found that eHcy exacerbates diabetic neuropathy [2]. Our group previously reported that eHcy is a risk factor for the development of PN based on clinical multifactorial risk analyses [3]. However, few studies, particularly on isolated eHcy and PN, are seen

in literature. To explore the association of the isolated eHcy and PN in patients without any other concurrently identifiable risk factors for PN, we performed this observational study.

Methods

Charts of patients with PN or primary headaches (HA, as control) seen in the Temple University Hospital Neuromuscular Clinic from January 1, 2014 to December 31, 2018 were retrospectively studied. Charts were retrieved using the diagnostic codes for PN (355.9/ICD9 and G62.9/ICD10) and HA (784.0/ICD9 and R51/ICD10). The diagnosis of neuropathy was made based on clinical information and neurologic examination, as outlined previously [3, 4]. Demographic, clinical and laboratory data were recorded. Subjects who were excluded were those without plasma Hcy measurement, or those with an established diagnosis of PN such as acute or chronic inflammatory demyelination polyneuropathy; PN with identifiable etiologies, other than eHcy, such as diabetes mellitus, liver or renal diseases, infections, trauma, or recipients of organ transplant, chemo or radiation therapies; secondary HA such as brain structural changes, infections, or recipients of cranial surgical procedures; and abnormal or absence of simultaneous laboratory studies of B12, folate or methylmalonic acid (MMA) with Hcy. Statistical analyses including odds ratio (OR) and 95% confidence interval (CI) for two independent samples, when appropriate, were performed using two-tailed unpaired *Student t-test* and Chi-square analysis. A p value less than 0.05 was considered significant. This study was approved by the Institutional Review Board of Temple University Hospital.

Results

A total of 16,086 charts were initially screened. Two hundred and two subjects who met the inclusion and exclusion criteria were studied, including 161 patients with PN (age = 60.9 ± 14.4 years, mean \pm SD; male/female = 66/95) and 41 with HA (age = 48.3 ± 17.2 , M/F = 6/35). Significantly higher levels of Hcy were observed in the PN cohort (15.1 ± 12.2 $\mu\text{mol/L}$, Ref: < 12.0 , 95% CI: 0.6369 - 8.2631, $p = 0.02$) than in HA (10.6 ± 3.4 $\mu\text{mol/L}$, Table 1). Additionally, significantly increased frequency of eHcy was also observed in subjects with PN (51.6%, OR: 4.39, 95% CI: 1.91-10.09, $p = 0.0002$) compared to HA (19.5%) (Table 2).

Discussion

In this study on patients without any concurrently identifiable risk factors for PN, we confirmed that significantly higher plasma levels of isolated Hcy and higher prevalence of eHcy were observed in patients with PN compared to HA controls (Table 1 and 2). Our study supported the hypothesis that eHcy may potentially be an independent risk factor for PN contributing to the etiology of PN [3].

Clinical manifestations of isolated eHcy-induced PN in adults are mainly sensory symptoms [4], such as numbness,

Table 1: Demographic and laboratory data.

	PN	HA	Reference	P =
n	161	41		
Age	60.9 ± 14.4	48.3 ± 17.2		0.00003
Female	95	35		
Male	66	6		
BMI	30.1 ± 6.9	33.6 ± 10.8	20-25 kg/m ²	0.01
Hcy	15.1 ± 12.2	10.6 ± 3.4	< 12.0 $\mu\text{mol/L}$	0.02
MMA	203.3 ± 190.6	151.8 ± 120.6	87 - 318 nmol/L	0.15
Vit B12	535.1 ± 327.5	531.5 ± 421.3	200 - 1,100 pg/mL	0.96
Folate	15.3 ± 6.6	12.9 ± 4.2	< 3.4 ng/mL	0.04
HbA1C	5.8 ± 1	5.9 ± 0.9	$< 5.7\%$	0.54
Vit D	23.4 ± 10.9	24.9 ± 12.1	30 - 100 ng/mL	0.57
Creatinine	1 ± 0.9	0.8 ± 0.1	0.80 - 1.30 mg/dL	0.13
TSH	2 ± 1.5	2.7 ± 4.4	0.40-4.50 mIU/L	0.19
HDL	52.9 ± 16.7	55.8 ± 18.4	> 39 mg/dL	0.55
LDL	95.4 ± 42.7	92.9 ± 28.2	0 - 99 mg/dL	0.83

*Two-tailed unpaired Student t-test. PN: Peripheral Neuropathy; HA: Headaches (control); BMI: Body Mass Index; MMA: Methylmalonic Acid; Vit: Vitamin; HbA1C: Glycated Hemoglobin; TSH: Thyroid Stimulating Hormone; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoproteins.

Table 2: The frequency of eHcy in PN and HA.

	PN	HA
n	161	41
eHcy	83	8
Normal Hcy	78	33
eHcy Rate (%)	51.6	19.5
	P = 0.0002	

*Two-tailed Chi-square t-test.

tingling and pain in a glove-and-stocking pattern distribution. In patients with Parkinson's disease, eHcy could be caused by levodopa monotherapy and was found to be associated with peripheral nerve degeneration, marked by decreased sensory nerve action potentials and perception of vibration [5]. Neurophysiologic studies of patients with eHcy-induced PN showed evidence of mildly mixed demyelination and distal axonal degeneration, suggestive of a mild large-fiber sensorimotor neuropathy [6]. Interestingly, central somatosensory large fibers may also be involved [7].

eHcy exerts neurotoxic effects causing neuronal injury by overstimulating NMDA receptors, inducing calcium influx [8] which provokes excitotoxic and oxidative stress, damages DNA and leads to neuronal death or apoptosis, which has been demonstrated in laboratory *in vitro* cell culture and *in vivo* animal studies [9]. However, eHcy-induced

neurotoxicity may be nonspecific. In addition to PN, eHcy can be seen in various neurologic conditions, such as stroke, mild cognitive impairment, dementias, multiple sclerosis, epilepsy, neurodevelopmental disorders and Parkinson disease with levodopa monotherapy [1, 5]. eHcy-induced neurotoxicity can be demonstrated in laboratory showing hippocampal neuronal death [9]. Clinical studies have shown that eHcy is associated with cognitive decline leading to dementia, which can be marked by radiological evidence of white-matter lesions as well as silent brain infarcts and atrophy of the cerebral cortex and hippocampus [11]. It has been estimated that an increase of 4.0 $\mu\text{mol/l}$ in plasma homocysteine significantly increased occurrence of diabetic neuropathy [11]. However, clinical trials on the effect of lowering eHcy levels in preventing and treating eHcy-related neurologic disorders produced mixed results [1, 12]. Notably, studies on treating isolated eHcy-induced PN are absent.

Plasma Hcy level in human is regulated by two metabolic pathways: remethylation and transsulfuration (Figure 1). In the remethylation pathway, Hcy can reversibly be converted into methionine either *via* betaine-Hcy methyltransferase or methionine synthase with vitamin B12 and folate as cofactors or *via* methylenetetrahydrofolate reductase (MTHFR) with folate as a cofactor. In transsulfuration pathway, Hcy is irreversibly catalyzed into cystathionine by cystathionine β -synthase (CBS) with vitamin B6 as a cofactor [1]. Generation of Hcy status is less actively associated with dysfunction of transsulfuration in human. Notably, B12 deficiency causes both eHcy and increased MMA whereas folic acid deficiency causes only eHcy (Figure 1B). Deficiencies in vitamin B12,

vitamin B6 and folate, or dysfunction of MTHFR or CBS, alone or in combination, can lead to eHcy [1].

Incidentally, higher plasma levels of folate were detected in our patients with PN compared with HA controls (Table 1), which may be due to therapeutic supplementation for eHcy. Folic acid is generally nontoxic but may mask undiagnosed pernicious anemia. An anecdotal report showed that folate at elevated levels of 65–180 ng/mL may be neurotoxic [13]. However, a subsequent double-blind study aiming to verify the claim showed no differences in emotional and neurocognitive functions in healthy volunteers with folate levels ranging 32.5 to 95 ng/mL [14]. In our PN group, folate levels ranged 15.3 \pm 6.6 ng/mL, which appears to be a nontoxic level.

There were several limitations in our study. First, this was a retrospective observational study without intervention. Second, no electrodiagnostic or pathologic studies were performed. Third, genetic studies such as sequencing MTHFR and CBS genes were not performed. Lastly, the influences of obesity and aging in patients with PN were not addressed. Obesity may be a risk factor for PN [15] but more so for primary HA, as seen in our study. Clearly, aging [1] is associated with eHcy and increased prevalence of PN particularly in individuals older than 65 years. The prevalence of PN has been reported to be approximately 7% in the elderly, 40% of whom are labelled “idiopathic” [16]. A recent study showed that eHcy was associated with worse sensory and motor peripheral nerve function in the elderly, implicating increased disability in the elderly population possibly through a mechanism of eHcy-induced neurotoxicity [17].

Conclusion

Our study confirmed the previous observations that significantly higher plasma levels of isolated eHcy and increased prevalence of eHcy were seen in patients with PN and supported the hypothesis that eHcy may potentially be an independent risk contributing to the etiology of PN. Findings of our study are important because eHcy-induced PN may be potentially treatable and preventable. Although studies on treating *isolated* eHcy related PN remain absent currently in the literature, randomized double blind placebo control clinical trials are warranted.

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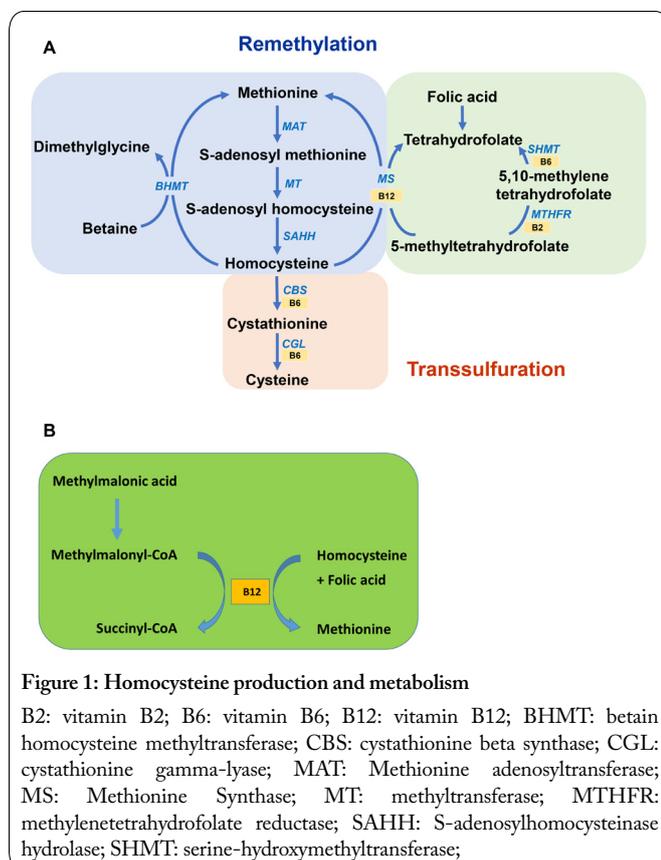


Figure 1: Homocysteine production and metabolism

B2: vitamin B2; B6: vitamin B6; B12: vitamin B12; BHMT: betain homocysteine methyltransferase; CBS: cystathionine beta synthase; CGL: cystathionine gamma-lyase; MAT: Methionine adenosyltransferase; MS: Methionine Synthase; MT: methyltransferase; MTHFR: methylenetetrahydrofolate reductase; SAHH: S-adenosylhomocysteinase hydrolase; SHMT: serine-hydroxymethyltransferase;

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