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Homocysteine and cognitive function in very elderly nondemented subjects

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Abstract

Objectives—To examine the association of homocysteine with cognitive functioning in very elderly (80+ years of age) community dwelling individuals.

Method—228 non-demented community dwelling individuals were assessed with a broad neuropsychological battery. Bloods were drawn to measure homocysteine levels, serum vitamin B12 and folate, and for APOE genotype.

Results—Higher homocysteine levels were associated with poorer executive function/language scores (r=−.311). The association persisted when serum B12 and folate were controlled for (r=−.308). Homocysteine levels were not associated with memory score (r=.120).

Conclusions—In very elderly nondemented community dwellers, high homocysteine levels are associated with poorer executive/language function but not with memory. This possible differential affect of homocysteine on cognitive functions suggests it may affect only specific brain regions or mechanisms underlying healthy executive functioning.

Keywords

dementia; cognitive performance; homocysteine

OBJECTIVES

Elevated plasma homocysteine levels have been linked to poorer performance in numerous cognitive domains,1 including attention, executive function,2 recall memory, poor psychomotor speed,3 and overall cognitive functioning.2 Elevated homocysteine levels are often found in patients with Alzheimer's disease and vascular dementia,2 when compared with cognitively normal individuals. High homocysteine is a risk factor for cardiovascular disease, 2 which is a risk factor for dementia.4 The connection between homocysteine and cognition appears well supported, but most studies have focused on younger or cognitively impaired elderly participants, and the connection may vary by age. 2,5

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Numerous confounding factors have made these relationships unclear. Age, sex, physical health, tobacco use, genetics, and nutrition are associated with homocysteine levels and are also related to dementia or cognitive decline. 2 The role of B-vitamins and of folate, which can lower homocysteine levels,2 is controversial. Some studies have found low levels of B-vitamins in patients with AD 3 or cognitive impairment, 5 and have found low B-vitamin levels to predict cognitive decline.3 However, some serum levels of B-vitamins, like B-12 or folic acid (vitamin B9) may not influence the relationship between homocysteine and cognition.5 Additionally, although B-vitamins may lower homocysteine levels, there is little proof that B-vitamins can prevent, slow the onset of, or reverse cognitive decline.2 Homozygosity for the apolipoprotein e4 (APOE4) allele may also increase the influence of homocysteine on cognitive decline.1

In this study, we examined the relationship between homocysteine and cognition in a very elderly sample of non-demented subjects, taking into account many of the factors that are associated with both cognition and homocysteine.

METHODS

We assessed cognitive function and homocysteine levels in 228 individuals between the ages of 80 and 101. These participants were recruited from the New York City area primarily through talks and ads and from the James J. Peters Veteran Affairs Hospital at the Bronx. All participants were nondemented, based on a Clinical Dementia Rating score of zero (no dementia) and Mini-Mental State Examination appropriate for age and education norms.6,7 Subjects were discussed in a clinical consensus conference where their intact cognitive status was confirmed.

Sociodemographic characteristics (including age, sex, and years of education) were recorded, as well as medical conditions and medication use. Participants also provided a blood sample (after fasting for 4 hours) for analyses of homocysteine, vitamin B12, folate, and APOE genotyping using standard methods. All protocols were reviewed and approved by the Institutional Review Boards of Mount Sinai and the Bronx VAMC. To reduce the number of correlations between homocysteine levels and the 11 neuropsychological measures, factor analysis summarized them into two orthogonal factors: memory (immediate recall, delayed recall, recognition, and savings), and executive/language function (Trails A and Trails B, diamond cancellation, letter cancellation, animal fluency, Shipley vocabulary, and Boston naming test) factors. Partial correlations controlling for age, sex, years of education, smoking status, and APOE4 carrier status (having at least one E4 allele) were performed to examine the association between homocysteine and the cognitive factors. We further analyzed these associations including vitamin B12 and folate as covariates. Additional analyses were run to determine associations between vitamin levels and cognitive factors, and interactions between homocysteine, cognitive factors, and APOE4. Finally, descriptive analyses were run to examine differences in those with high and low homocysteine. Subjects with complete data were included in the analyses. Homocysteine levels, vitamin B12, and folate were normalized using a square root transformation.

RESULTS

The sample consisted of 199 participants (59.8%, male) above the age of 80 (mean age 86.8 ± 4.0, mean years of education 14.6 ± 3.6). 20.6% participants had one or two APOE4 alleles. The majority of participants had homocysteine, serum B12, and serum folate levels in the normal range. 16.1% of participants had a homocysteine level above 15 mcmol /liter 1 a value considered the upper normal limit. 2.5% of participants had a serum B12 level

considered low,8 below 200 pg/mL, and no participants had a deficient level (below 3 ng/mL) 8 of serum folate. Participant characteristics can be found in Table 1.

Controlling for age, sex, and years of education, homocysteine was negatively associated with executive/language functions (r= −.311, df= 193, p< .001), but was not associated with memory (r= .120, df= 193, p=.095). These correlations were significantly different from one another (z = −2.91, p=.002), 9 and results remained unchanged when serum B12 and folate levels were included as covariates. Further, homocysteine was not correlated with B12 (r=.116, df=193, p=.107) or folate (r=−.091, df= 193, p=.208), when controlling for years of education, sex, age, and APOE4 status.

Additional analyses to examine the relationships between cognition variables and vitamin levels were run. Executive/language functioning was not correlated with vitamin B12 (r=.011, df=176, p=.888) or folate (r=.016, df= 176, p=.836), and memory functioning was not correlated with vitamin B12 (r=.031, df= 176, p=.681), or folate (r=.078, df= 176, p=.301), when controlling for years of education, sex, age, APOE4, and smoking status.

To examine the importance of APOE4 to the relationships between homocysteine and cognition, partial correlations with an interaction variable were run. When controlling for age, sex, years of education, and vitamins B12 and folate, no interaction was found between homocysteine, APOE4, and executive-language (r=.090, df= 190, p=.215), or between homocysteine, APOE4, and memory (r=.060, df= 190, p=.405).

The data were analyzed for descriptive purposes, stratifying homocysteine at its median, to examine demographic, cognitive, or vitamin level differences between those with high and low homocysteine. No difference between those above median homocysteine level and below median homocysteine level existed for age, (t(197)= .252, p=.801), years of education, (t(197)=.129, p=.897), vitamin B12 level (t(197)= .804, p=.422), or folate level, (t(197)= .705, p=.482).

CONCLUSIONS

In this very elderly non-demented sample, higher levels of homocysteine were associated with lower executive-language functioning, after controlling for sociodemographic variables and APOE genotype. This relationship remained unchanged after including B12 and folate levels in the statistical model. This is consistent with studies of younger samples examining relationships of homocysteine and cognitive functioning in healthy elderly and elderly with dementia, in which correlations between homocysteine and non-memory functions have been found.1‚2‚3 However, high homocysteine was not associated with memory, and the correlation between executive-language functioning and homocysteine was significantly different from that found between memory and homocysteine. Executive-language functioning and memory functioning were not correlated with serum vitamins B12 or folate, suggesting that the relationships were not moderated by these vitamins.

Several mechanisms for the relationship between executive-language functioning and homocysteine have been identified. High homocysteine levels may increase the risk of cardiovascular disease, a risk factor for dementia,4 by promoting silent brain infarcts and atherosclerosis, causing cognitive impairment.2‚3 Additionally, high homocysteine levels may produce neuronal cell damage by activating *N*-methyl-D-aspartate receptors.2‚3 High levels of homocysteine may cause increased white matter lesions 2 and hippocampal atrophy,3 each associated with dementia. Hypomethylation affects catecholamine neurotransmitters, myelin, and protein synthesis, leading to cell damage and an increase in amyloid β deposits, possibly resulting in cognitive impairment.3 The cellular damage related to elevated levels of homocysteine may result in cognitive impairment or dementia.

The majority of studies investigating homocysteine and cognition have utilized young elderly or individuals with dementia, while studies that included older, healthy elderly have demonstrated less consistent results. 5 Importantly, participants in this study exhibiting higher homocysteine and lower executive-language functioning scores did not demonstrate clinical symptoms of dementia. However, the neurodegeneration resulting in dementia begins years before clinical-level cognitive symptoms are identified. These individuals who scored lower on cognitive tasks may be demonstrating the earliest signs of cognitive decline, and homocysteine is an early marker for dementia.

More difficult to clarify is the unusual finding regarding memory. Although much of the literature suggests that high homocysteine has a detrimental effect on memory,1,3 some studies examining this relationship in the very elderly have found the effects to be weak or nonexistent.5 Our study supports the research suggesting that the relationships between homocysteine and memory may be age-dependent, and appear diminished or nonexistent in very old age.5

Studies of oldest-old and old-old individuals are finding that risk factors for dementia and cognitive decline in younger elderly, including cardiovascular, genetic, and familial factors, may not apply to these persons.10 This study suggests that homocysteine may not directly impact all cognitive functioning, or impact functioning in similar ways, but may correlate with specific cognitive domains. Such findings are similar to those observed with c-reactive protein (CRP) where high levels of CRP were associated with worse executive-language functions, but *better* memory functions.10 A possible interpretation is that, in very old age, cardiovascular risk factors may be negatively correlated with cognitive functions, such as executive functioning, in which deficits may be considered a natural effect of aging. They may be uncorrelated or positively correlated with cognitive functions like memory, the loss of which may be indicative of incipient dementia, rather than a natural degenerative process. 11 As in the CRP study, homocysteine might be related to the natural decline of executive and language functioning. However, these participants are defined by their strong memory functioning, having reached a very old age without dementia, so homocysteine may not impact their memory in the same way it may impact younger individuals. Further, individuals who survive to age 80 are likely robust, 5 and may be less susceptible to negative effects of homocysteine, perhaps explaining its lack of a relationship with memory, and possibly also the lack of a relationship with B12, folate, or age.

The unusual finding could be also explained by antagonistic pleiotropy, which suggests that successful aging is an outcome of complicated adaptations and restructuring of metabolism. 12 Protective variables may become detrimental later in life, or detrimental factors may become protective later in life. High homocysteine levels associated with high memory functioning could represent an adjustment of metabolism in robust individuals, able to adapt to the problems of aging.

This study has limitations. Although longitudinal data is being collected, the data analyzed here were cross-sectional, not permitting causal investigations. This is not an epidemiologic sample, which is very difficult to collect on a sample of the very elderly. Participants were not analyzed for the gene methylenetetrahydrofolate reductase (MTHFR), mutations of which are related to increased levels of homocysteine, and increased mortality risk for some. 8 These participants are nondemented very-elderly, who likely possess factors supporting strong mental health, including good nutrition and physical health, physical activity, social interaction, and genetic fortune.

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Table 1

Participant characteristics

	Participant characteristics	**Association to homocysteine**
N	199	
Age	86.8 (4.0)	*p*=.815
Years of education	14.6 (3.6)	*p*=.831
Sex	119 Male	
Homocysteine	11.81 mcm/liter (4.3 SD) Range: 2.1–38.5 mcm/liter	
Serum B12	679.9 pg/mL (408.9 SD) Range: 122.1–2226.0 pg/mL	*p*=.107
Serum Folate	21.7 ng/mL (5.8 SD) Range: 5.2–40.0 ng/mL	*p*=.208