Homocysteine in Alzheimer`s Disease and Related Disorders

By

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Worldwide, most people with AD and other dementias are cared for at home, usually by a spouse or a daughter.

In low-income and middle-income countries, the estimated proportion of people with dementia living at home is around 94%, compared with around 66% in high-income countries.

Several follow-up studies have consistently shown that the extent to which dementia shortens life expectancy depends on age at onset, gender, and dementia subtype.

Life Expectancy

In people aged 75 years or older, the effect of dementia on lifespan is similar to that of CVD, but lower than that of cancer. Years of life lost is an estimate of the average additional years a person would have lived if he or she had not died prematurely. It is an alternative to death or mortality rates, but gives more weight to deaths that occur among young people. Years of life lost can be estimated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs. CVD=cardiovascular disease.

Age-specific prevalence of dementia

As shown by world region and in major countries, Patterns of age-specific prevalence of dementia are similar across worldwide regions, but vary substantially among the oldest old (age ≥90 years).

Pathways to Alzheimer's disease
Epidemiological and genetic studies of people with non-genetically determined (ie, sporadic) AD have identified mechanisms that might underlie brain Aβ accumulation, neuronal tau hyperphosphorylation, and synaptic deficits, ultimately leading to cognitive impairment and dementia


In familial AD, the disease begins with Aβ pathology. It seems likely that different causative pathways result in distinct disease subtypes, which should be treated differently.

The identification of subtypes of patients, with homogeneous pathogenesis and prognosis, will facilitate research and result in more accurate and personalised treatments for sporadic and familial AD.

Pathological changes associated with CSF biomarkers for Alzheimer's disease

Schematic representation of a neuron, showing the pathological changes associated with the three core CSF biomarkers of Alzheimer's disease
- Increased CSF concentration of T-tau is a marker of axonal degeneration

- Increased CSF concentration of P-tau suggests the presence of neurofibrillar tangles, and

- Decreased CSF concentration of the 42-aminoacid form of Aβ (Aβ42) relates to senile plaque pathology.

- In future, newly discovered CSF, blood, or brain imaging (eg, MRI, PET) biomarkers could allow early diagnosis, including the subtyping of Alzheimer's disease, and personalised-medical approaches to treatment and prevention.

Homocysteine Metabolism
• Homocysteine (Hcy) is a sulfur-containing amino acid synthesized in one-carbon metabolic cycle. It is metabolized either by transsulfuration to cysteine or by remethylation to methionine.

• Several factors are known to increase Hcy level including male gender, older age, higher body weight, lower folic acid and vitamin B dietary intake, cigarette smoking, alcohol abuse, chronic renal disease, as well as certain medications such as diuretics and fibrates.
• Interindividual differences in Hcy levels might be also attributed to certain genetic risk factors that influence the activity of one-carbon metabolism.

• Primarily, high Hcy levels have been exclusively regarded as a risk factor for cardiovascular diseases. Indeed, it has been found that Hcy may lead to endothelial injury triggering a cascade of processes resulting in atherosclerosis.
• Elevated mean levels of total Hcy were also found in a recent study of 24 patients with dystonia, as compared with controls (19.3 vs. 13.9 μmol/l), with a significant trend toward an association between the severity of dystonia and total Hcy.

• Previous experimental studies found that changes in Hcy levels are directly related to neurological disorders, such as MCI, AD, stroke, and movement disorders.


Mechanisms of Homocysteine Action
• Several mechanisms may underlie causative links between neurological disorders and higher Hcy levels.

• There are studies showing that high levels of Hcy may lead to dysfunction in glutaminergic & dopaminergic neurotransmission systems, which are altered in several brain disorders.

• It has been reported that Hcy in high concentrations may serve as an agonist at the glutamate binding site and a partial antagonist at the glycine coagonist site within the NMDA receptors

• Further, Christie et al. have found chronic exposure to Hcy in rats impairs synaptic transmission. In addition, high Hcy levels may be toxic to dopaminergic neurons, which can perhaps explain the links between Hcy and dopamine-related neurological disorders, such as PD or dystonia, as we discuss in the following

Mechanisms of homocysteine action as relevant to neurological disorders:

- Homocysteine may interact with NMDA receptors altering glutamatergic transmission

- Initiate endothelial damage, exert toxic effects on dopaminergic neurons


• Initiate neuronal apoptosis, induce oxidative stress
• Lead to mitochondrial dysfunction, and
• Influence DNA Methylation altering gene expression


• The link with cardiovascular disorders exists also in AD, since the brain vascular pathology with neuropathological hallmarks of AD and has been found to precede the onset of dementia.

• At the neural level, most existing studies found that variations in Hcy level affect the hippocampus.


• Along the same lines, studies in rats found that hyperhomocysteinemia is associated with impaired performance in the Morris water maze task, which tests spatial learning and memory, and was found to rely on the hippocampus.

• Further, some studies also found that Hcy acts on the cortex & hyperhomocysteinemia leads to atrophy in the prefrontal cortex.


• The exact neural and behavioral mechanism of Hcy is not known. Neural studies have shown that Hcy acts on various brain regions, including the hippocampus, the cortex, and the basal ganglia.

• Higher Hcy levels lead to atrophy in the frontal, parietal, and temporal areas.

• Importantly, recent clinical trials are investigating the therapeutic efficacy of Hcy-lowering drugs in AD patients (see www.clinicaltrials.gov). These studies and clinical trials stress the importance of understanding the relationship between Hcy and cognition.

• In the following, we review studies investigating the relationship between Hcy levels and symptom clusters in patients with neurological disorders.
Homocysteine and MCI
• MCI is a state of cognitive decline greater than that expected for an individual’s age and education level, but falling short of dementia.

• Clinical Dementia Rating (CDR) and Global Dementia Scale (GDS) are two commonly used clinical measures of memory impairment in MCI. Some studies define MCI based on a CDR score of 0.5, while others define it based on GDS score of 3.

• Studies suggest that MCI may reflect gradual accumulation of dementia pathology, though at a level not yet sufficient to cause a catastrophic decline in cognitive function. This is particularly true of the MCI subgroup with memory loss as a predominant syndrome, a condition termed amnestic MCI.

• Individuals with amnestic MCI are at increased risk to develop AD within the next several years. Specifically, studies suggest that individuals with amnestic MCI tend to progress to AD at a rate of 10–15% per year, and many researchers consider it to be an early or prodromal form of AD.

• Along the same lines, many studies have shown that low levels of Hcy in individuals with MCI are protective against conversion to dementia.

• There are few studies that have tested the relationship between cognitive function and Hcy levels in MCI. Most prior studies that have shown Hcy levels to be correlated with cognitive performance have used questionnaires rather than using DSM-IV criteria.
Recently, however, we found that total Hcy levels are higher in subjects with MCI than in healthy controls. In the same study, we found no difference between MCI individuals and healthy controls in a cognitive task that measures learning and generalization processes.

However, we found that individuals with MCD make more generalization errors than healthy controls and individuals with vMCD (GDS = 2 & MCD, GDS = 3).
• Our results are in agreement with prior results showing a link between hippocampal function, generalization performance, and total Hcy levels.

• Importantly, our study is perhaps among the first to test the relationship between learning (and generalization) of rules and Hcy levels in healthy controls and individuals with MCI.

Homocysteine and Alzheimer`s Disease
• Blood total Hcy was examined in a British study of 30 patients aged 65 years and above, who were recruited from a psychogeriatric assessment center, all had a diagnosis compatible with the criteria for AD. The total Hcy level in the patients was highly significantly elevated in comparison to age matched controls [61].

Another British case–control trial involved 164 patients with dementia found that the total Hcy was higher and both serum folate and vitamin B12 lower both in patients with AD and patients with histopathologically confirmed AD compared to controls.

The association with total Hcy levels was independent of age, gender, social class, smoking habits, and the apoE4 genotype.

• Association with white matter hypoattenuation was calculated on the basis of 137 probable and definite AD (104 confirmed postmortem) patients, 38 cases of other types of dementia, and 279 controls, from whom a CT scan and total Hcy were obtained.

• White matter hypoattenuation was associated with age, dementia severity, cerebral infarcts, and systolic hypertension.

• Total Hcy was strongly associated with the severity of white matter hypoattenuation, and degree of atrophy.

Further, many studies have reported that lowering Hcy levels enhances memory and cognition in individuals with MCI and AD.

Importantly, it was also shown that baseline measures of Hcy levels in AD patients and healthy subjects predict behavioral dysfunction in the future, as measured by the Cambridge Cognitive Testing Battery (CAMCOG), Mini-Mental State Examination (MMSE), and the cognitive subscale of the Alzheimer’s Disease Assessment Tool (ADAS-Cog).

Homocysteine and Vascular Dementia
• Vascular dementia is considered the second most common type of dementia in the elderly after AD, and it is estimated to account for about 15% of dementia cases.

• Subcortical vascular encephalopathy is characterized by stepwise progressive memory deficits and cognitive decline, typical gait disorders, and incontinence. Sclerosis of small cerebral arteries and arterioles with diffuse periventricular white matter abnormalities and central lacunar lesions are observed in these patients.
• In a recent study, patients with vascular dementia exhibited surprisingly high concentrations of total Hcy compared to controls and even to patients with cerebral macroangiopathy. This indicates that Hcy may cause injury to small cerebral arteries and arterioles rather than larger arteries.

• In this study, reduced levels of vitamin B12 and B6 were commonly present, and the levels of total Hcy correlated with the folate and vitamin B6 levels.

• Vascular diseases may contribute to the pathogenesis of AD by lowering the threshold for overt cognitive impairment and dementia caused by pathophysiological mechanisms specific to AD.

• In one study, 101 patients who complained about cognitive disturbances were tested using the MMSE, laboratory investigation, brain imaging, and electroencephalography; 33% of the patients with subjective memory complaints, 45% of patients with AD, and 62% of the patients with vascular dementia had hyperhomocysteinemia (≥15 μmol/l).
The expected assumption that hyperhomocysteinemia should be more prominent in vascular dementia and age, tau protein levels, and prominent apoE4 alleles in AD was not confirmed, as hyperhomocysteinemia was common in both patient groups; vascular dementia and AD did overlap considerably.

• A recent study found that elevated plasma total Hcy levels in patients with vascular dementia could only partly be attributed to cobalamin/folate deficiency or renal impairment.

• Several studies also found links between Hcy and stroke. The prevalence of hyperhomocysteineemia (>15 μmol/l) is less than 5% in a general population, but as high as 50% in patients with stroke. Stroke in these patients is accompanied by a higher rate of cerebral microangiopathy and multiple infarctions than in other stroke patients.

• In a recent study, plasma Hcy levels were positively associated with the presence of ischemic stroke, but not coronary heart disease, in Chinese hypertensive patients.

• There was also a strong positive correlation between total Hcy and lipid peroxide and a strong negative correlation with the plasma concentration of ascorbic acid, which points to a Hcy-related oxidative pathogenetic mechanism.


Homocysteine and Multiple Sclerosis
• A negative correlation between serum vitamin B12 and the progression of MS is reported in the literature. More recently, total Hcy and vitamin B12 levels were measured, along with neurotransmitters and other variables in CSF of patients with MS.

• Total Hcy levels were highly significantly increased and vitamin B12 levels decreased in the CSF of MS patients compared to controls. Increased CSF levels of total Hcy in MS were also confirmed in a subsequent study.

• Serum levels of vitamin B12 and folate decreased in patients with relapsing remitting MS, but Hcy levels increased significantly. In addition, there were significant correlations between mean higher serum Hcy levels and duration of disease and treatment with β-interferon.

• One study recommends to conduct prospective trials to determine whether the treatment with supplements and correct biomarker levels in the early stage of the disease can change the course of the disease and to perform regular checking of the serum level of Hcy in patients who use disease-modifying drugs.

Homocysteine and Parkinson`s Disease
• Significantly elevated plasma levels of total Hcy have been reported in patients with PD [80–83]. In one study, the levels of Hcy were elevated by 60% in levodopa-treated patients with a marked elevation occurring in patients with the MTHFR 677TT genotype.

• Another group has recently confirmed that plasma total Hcy levels are significantly higher in patients treated with levodopa (mean±SD; 16.1±6.2 μmol/l) compared to patients not on levodopa (12.2 ± 4.2 μmol/l, p < 0.0001).

• Furthermore, this study showed that patients, whose plasma total Hcy levels were in the highest quartile (>17.7 μmol/l), had an increased prevalence of coronary artery disease.

• These findings have implications for the treatment of PD in patients at risk of vascular diseases and potentially for those at risk of dementia and depression as well.

The effect of high Hcy levels on ventricular dilatation (percentage of intracranial volume (%ICV)) and total tissue volume at baseline and longitudinally after 36 months was studied where age, sex, education, and l-dopa duration in PD patients were included as covariates. The study found that elevated Hcy levels correlated positively with ventricular dilatation (%ICV) ($p = 0.008$). At baseline, patients with a high Hcy level ($>14 \mu\text{mol/l}$) had higher ventricular volume (%ICV) than patients with a low Hcy level ($\leq 14 \mu\text{mol/l}$) ($p = 0.03$), which persisted over 36 months ($p = 0.03$).

Conclusion
There has been growing evidence in the last years, linking elevated Hcy levels with several neurological disorders. Moreover, Hcy, a nonprotein neurotoxic amino acid, has been proposed as a risk factor for cognitive decline in neurodegenerative disorders such as AD or PD but also in disorders with less established origins such as schizophrenia and bipolar disorder.

Further research is warranted to unravel the molecular mechanisms underlying Hcy influence on nervous system damage and to clarify the role of Hcy in the etiology and prognosis of neurological symptomatology.
• It is also important to establish which mental disorders are linked with changes of Hcy levels in the blood plasma and whether the changes in Hcy concentrations depend on a clinical state of mental disorder (e.g., whether the disorder is in the early, middle, or late stage of progression or in remission).

• It is of great importance since there is some evidence showing that nutritional fortification with folic acid and vitamin B12, parallel to reduction of Hcy levels, may have influence on the course of the disorder and result in symptom reduction.
From genetic and genomic discoveries to precision medicine Starting with genetic and genomic discoveries, future research studies need to integrate data from all research areas to construct testable hypotheses and draw meaningful conclusions about the functional consequences of the known Alzheimer's disease genes and loci.

GWAS=genome-wide association study. WES=whole-exome sequencing. WGS=whole-genome sequencing.
These integrated analyses could push the research frontier forward, allow personal risk profiles to be generated, and ultimately help to shape individualised strategies for intervention.

Defeating Alzheimer's disease and other dementias: a priority for European science and society
THANK YOU