



## Elevated Homocysteine Level and Brain Atrophy Changes as Markers to Screen the Alzheimer Disease: Case Series

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Alzheimer disease (AD) is the most common cause of dementia worldwide. Its clinical manifestations include a progressive loss of memory and other cognitive domains, as well as brain atrophy. An elevated homocysteine level ( $>15 \mu\text{mol/L}$ ), known as hyperhomocysteinemia, is also an attributing risk factor for AD, vascular pathologies, and brain atrophy. Neuroimaging studies including T2-weighted magnetic resonance imaging scans revealed white matter hyperintensities in the periventricular and deep white matter, enlarged ventricles, widened sulci, and decreased white matter mass, which are features of aging, as well as cerebrovascular changes. This case series investigated changes in biochemical marker levels including serum homocysteine, folate, and vitamin B12, and the degree of atrophic variations in cortical-subcortical white matter in AD. The present study hypothesized that serum homocysteine levels might be used as a surrogate marker to screen for AD at an earlier stage.

**Key Words:** Alzheimer's disease, Brain atrophy, Homocysteine, Vitamin B12

### INTRODUCTION

Alzheimer disease (AD) is an age-related progressive neurodegenerative disorder that presents with several neuropsychological impairments, including gradual loss of memory, cognitive decline, mental confusion, and changes in brain atrophy. An elevated homocysteine level ( $> 15 \mu\text{mol/L}$ ), known as hyperhomocysteinemia,<sup>1)</sup> might initiate oxidative stress or changes in DNA methylation, subsequently leading to cortical and subcortical atrophy. Furthermore, it causes neurotoxicity and interferes with neurotransmission in the brain.

Homocysteine is an integral part of the methionine cycle, which involves its remethylation by the methionine synthase enzyme, a process that requires vitamin B12, folate as a cofactor, and 5-methyl tetrahydrofolate (THF) as a methyl donor. Further, S-adenosyl methionine synthase induces methionine to join with adenosine

triphosphate to form S-adenosyl methionine (SAM), which requires vitamin B6 and pyridoxal-5'-phosphate (PLP), which is a universal methyl group donor. Due to SAM depletion, it is converted to S-adenosyl-homocysteine, which is further hydrolyzed into homocysteine. Disturbances in homocysteine metabolism may arise from deficiencies in vitamin B12, folate, or other related pathological conditions.<sup>2)</sup> Such disruptions have the potential to worsen the condition by contributing to the formation of neuritic plaques, including amyloid plaques and neurofibrillary tangles.<sup>3)</sup>

Imaging studies, including magnetic resonance imaging (MRI)-based studies of cortical atrophy, are surrogate methods used to evaluate neurodegenerative changes in the brain or diagnose AD.<sup>4,5)</sup> Although aging is an important factor related to brain atrophy, the shrinkage of the cerebral cortex is hastened in the progression from mild cognitive impairment to AD. Furthermore, the evaluation of changes in brain atrophy could help in determining

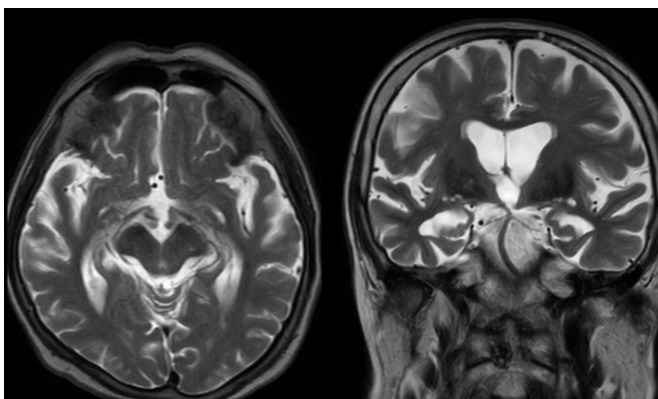
the severity of AD.<sup>6)</sup> White matter hyperintensity (WMH) has been most commonly noted on T2-weighted fluid-attenuated inversion recovery sequences, and are features of aging and cerebrovascular changes.<sup>7)</sup>

The results of the present case series demonstrated that hyperhomocysteinemia occurring due to folate and vitamin B12 deficiency may be associated with brain atrophy or the severity of cognitive impairment—Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA). Moreover, we performed an in-depth evaluation of anatomical changes in the brain after MRI of four older adults with cognitive impairment and observed that serum homocysteine levels may be correlated with changes in brain atrophy.

## CASE REPORT

### Case 1

An 80-year-old woman was brought by her daughter to the geriatric department of JSS Hospital with concerns over her mother's moderate forgetfulness, confusion, and misplacing items at home. Her daughter complained that the patient had acted irritated, anxious, and less interested in communicating with family members and neighbors for the past 6 months. The patient was examined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria followed by a cognitive test. The patient scored 16/30 on the MMSE and 13/30 on the MOCA. Moreover, the patient was moderately affected by psychiatric issues in the Neuropsychiatry Innovatory Questionnaire (NPI) and was able to perform activities of daily living. MRI showed atrophy of the cerebral cortex (prominent sulci), enlarged ventricles, and bilateral temporoparietal atrophy (Fig. 1). Further investigation of the biochemical parameters revealed a significantly



**Fig. 1.** Case 1 represents bilateral temporoparietal and parietotemporal cortices atrophy as well as enlarged ventricle and widened sulci.

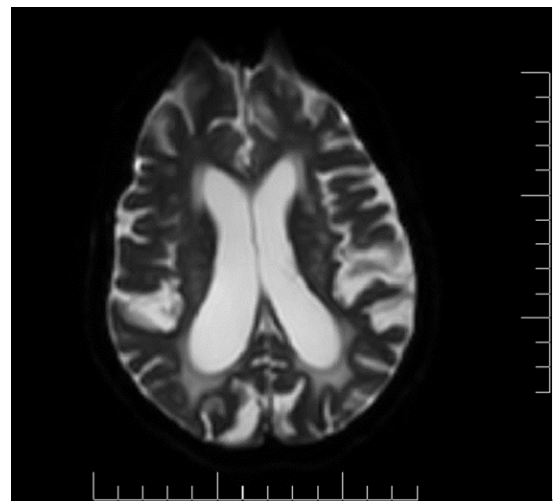
increased serum homocysteine level (21  $\mu\text{mol/L}$ ; reference range 5–15  $\mu\text{mol/L}$ ) and decreased folate level (4.2  $\text{ng/mL}$ ; reference range 4.6–34.8  $\text{ng/mL}$ ). However, the patient's vitamin B12 level remained within the normal range (429  $\text{pg/mL}$ ; reference range 197–771  $\text{pg/mL}$ ). The biochemical investigations were performed using a Cobas6000 clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) following standard operating procedures in the Department of Biochemistry, JSS Hospital, Mysore, India.

### Case 2

A 74-year-old woman was accompanied by her son to the geriatric department at JSS Hospital with concerns about her severe forgetfulness of recent events, language problems, and confusion. Her son complained of her irritation, anxiety, and depression that had lasted for 1 year. The patient scored 10/30 on the MMSE and 9/30 on the MOCA and was severely affected by neuropsychiatric issues and inability to perform activities of daily living on functional assessment (IADL). Additionally, MRI showed cerebral cortex atrophy, enlarged sulci and ventricles, reduced gyri volume, and chronic small-vessel ischemic changes. WMHs were observed bilaterally in the frontoparietal cortex (Fig. 2). Biochemical investigation revealed homocysteine, folate, and vitamin B12 levels of 22.5  $\mu\text{mol/L}$ , 3.2  $\text{ng/mL}$ , and 194  $\text{pg/mL}$ , respectively.

### Case 3

A 76-year-old woman was accompanied by her husband to the geriatric department at JSS Hospital with complaints of her forgetfulness of recent events and mild confusion. Her husband complained that the patient had felt anxious and depressed for 3



**Fig. 2.** Case 2 represents progressive enlarged lateral ventricle, sulci, decreased mass of gyri chronic small vessel ischemic changes, and white matter hyperintensities noted in bilateral frontoparietal cortices.

months. She scored 23/30 on the MMSE and 22/30 on the MOCA, was mildly affected on the NPI domains, and was able to perform activities of daily living on functional assessment (IADL). Radiological examination and MRI showed age-related cerebral atrophy with chronic small-vessel ischemic changes. WMHs were observed bilaterally in the frontoparietal cortex (Fig. 3). However, in the analysis of blood serum, her homocysteine, folate, and vitamin B12 levels were measured at 12  $\mu\text{mol/L}$ , 20  $\text{ng/mL}$ , and 333  $\text{pg/mL}$ , respectively.

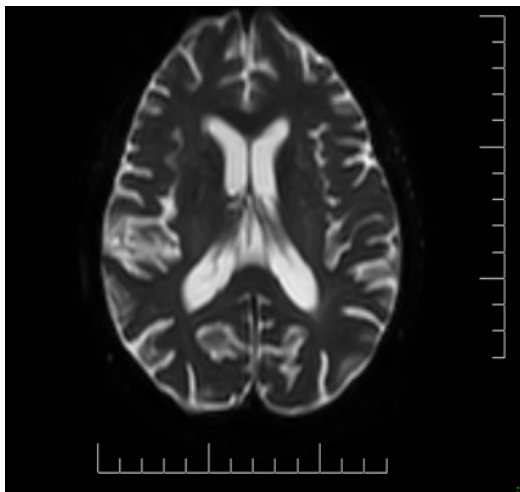
#### Case 4

A 72-year-old man was accompanied by his son to the geriatric department at JSS Hospital complaining of severe forgetfulness in recent events, confusion, and less interest in performing household tasks. On cognitive assessment, he scored 10/30 on the MMSE and 9/30 on the MOCA and had severely affected NPI domains. The functional assessment (IADL) score was 0, indicating dependence on a caretaker to perform activities of daily living. Similarly, MRI showed age-related cerebral atrophy with chronic small-vessel ischemic changes. Multifocal, ill-defined hypodensities were observed in the frontal, parietal, and temporal lobes (Fig. 4). Blood serum investigation showed homocysteine, folate, and vitamin B12 levels of 8  $\mu\text{mol/mL}$ , 17.1  $\text{ng/mL}$ , and 1,985  $\text{pg/mL}$ , with a significant increase in vitamin B12 level.

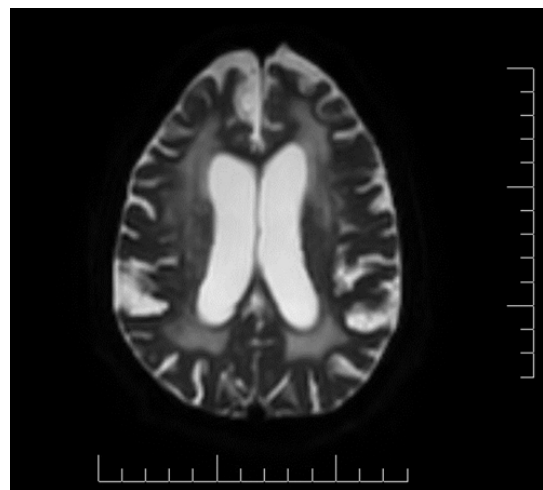
## DISCUSSION

Evaluation of atrophic changes in the cerebral cortex and their correlation with serum homocysteine levels is necessary to unravel

AD severity and etiology. The results of the present study revealed elevated homocysteine levels and decreased folate and vitamin B12 levels in two of the four cases. MRI revealed bilateral temporoparietal cortex atrophy, decreased cerebral cortex mass, prominent sulci, enlarged lateral ventricles, and chronic small-vessel ischemic changes. Similarly, WMHs noted in the bilateral frontoparietal and temporal cortices as well as in the periventricular and deep white matter. A meta-analysis study reported that patients with increased levels of homocysteine and lower folate levels might have increased susceptibility to AD.<sup>8)</sup> Another study confirmed decreased vitamin B12 and folate levels but elevated homocysteine levels in patients with AD compared with healthy control subjects.<sup>9,10)</sup> Elevated homocysteine levels and reduced MMSE scores are significantly associated with AD dementia and cognitive impairment.<sup>11)</sup> Increased homocysteine levels are also associated with AD or vascular-associated dementia progression and also promote the inflammation of blood vessel walls.<sup>12)</sup> Temporoparietal atrophy is a sensitive marker to detect the early stage of AD as neurofibrillary tangles start in the medial temporal lobes and further accumulate in the temporoparietal cortices, leading to episodic memory impairment.<sup>13)</sup> A recent study reported that WMH is a surrogate marker of AD.<sup>14)</sup> Moreover, the severity of cognitive impairment and its progression to AD are in proportion with WMH.<sup>15)</sup> Cerebral small-vessel disease, cerebrovascular changes, and AD are strongly correlated, which could be dominant factors at an early stage of AD.<sup>16,17)</sup> Prominent lateral ventricles and generalized cerebral atrophy are the most significant features of Alzheimer's dementia and are associated with cognitive impairment.<sup>18,19)</sup>



**Fig. 3.** Case 3 represents age-related cerebral atrophy with chronic small vessel disease. White matter hyperintensities were noted in the frontoparietal cortex and periventricular deep white matter.



**Fig. 4.** Case 4 represents progressive enlarged lateral ventricle, sulci, decreased mass of gyri, and chronic small vessel disease. Multifocal ill-defined hypodensities were noted involving bilateral frontal, parietal, and temporal lobes.

### Novelty of the Study

This is the first case series of patients clinically diagnosed with AD based on cognitive (MMSE, MOCA), behavioral (NPI), and functional (IADL) tests and MRI scans revealing reduced white matter mass, enlarged sulci, and ventricles to be reported in Southern India, particularly in the older adult population (age 65–85 years). Our study aimed to uncover specific associations between cognitive and functional behavior tests and changes in brain atrophy.

Additionally, the study aimed to identify potential correlations with elevated levels of homocysteine and decreased levels of vitamin B12 and folate. These measures were explored as a screening tool to detect AD at its earliest stage.

### Conclusion

The present case series provides experimental evidence suggesting that homocysteine is a neurotoxin and a modified risk factor for neurodegenerative diseases, particularly AD and vascular dementia. Progressively enlarged lateral ventricles with cerebral atrophy and WMHs in different lobes of the cerebral cortex could be used as surrogate markers to screen for AD.

Vitamin B12 and folate deficiencies lead to increased homocysteine levels, which may aggravate brain atrophy and cognitive impairment. Evaluation of serum homocysteine levels and brain atrophy will act as a roadmap for geriatricians and neurologists to screen for AD, which may help in the early identification of pathological processes. Hence, the potential benefits of diet and medications could aid in reducing homocysteine levels and hinder cognitive decline, AD, and atrophy of the cerebral cortex in the older adult population.

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### CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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### AUTHOR CONTRIBUTIONS

Conceptualization, RPS, CSV; Data curation, CSV, PP; Investigation, RPS, PP; Methodology, RPS, AKY, SP; Project administration, RPS; Supervision, CSV, SJ, PP; Writing-original draft, RPS, CSV; Writing-review & editing, AKY, SD, SJ.

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