

Correlation of Cerebral Atrophy and White Matter Hyperintensity Burden in MRI with Clinical Cognitive Decline

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ABSTRACT

Objective: Dementia is a disease of gradual memory and cognitive loss that affects an individual's day-to-day activities and is caused by permanent brain damage. Majority of patients are from the elderly population and only 2 to 10 % of affected population is less than 65 years.

Materials and Methods: We obtained a correlation of severity of white matter hyperintensity (WMH) burden in MRI with severity of clinically assessed cognitive decline. And also analysed the severity of cerebral atrophy in MRI with severity of clinically assessed cognitive decline.

Results: In our study Fazekas scoring for WMHs showed a sensitivity of 87.5% and specificity of 83.3% on correlation with clinical cognitive decline assessed by ADAS-Cog. Also, MTA scale for cerebral atrophy showed a sensitivity of 72% and specificity of 88% on correlation with clinical cognitive decline assessed by ADAS-Cog. Significant P-value have been obtained for both the above visual rating scales of MRI (Fazekas and MTA) by linear regression, on correlation with clinically assessed cognitive decline.

Conclusion: White matter disease assessed by Fazekas scale and cerebral atrophy by MTA scale on MRI brain correlated well with cognitive decline clinically assessed by neuropsychological tests.

Keywords: Cerebral atrophy; hyperintensity; MRI; clinical cognitive decline (Siriraj Med J 2022; 74: 323-329)

INTRODUCTION

Dementia is a syndrome of progressive cognitive and memory decline affecting an individual in his daily activities, due to irreversible neuronal damage. Dementia is predominantly a disease of the elderly population and only 2 to 10 % of affected population is less than 65 years.¹ According to an estimate, number of people affected by dementia will be reaching over 81 million by the year 2040 globally, doubling in every 20 years. There will be approximately 150 million elderly individuals (those aged over 60 years) constituting about 12.30% of total population by 2025 in India.²⁻⁴

The structure and function of the brain change as people become older. Memory, attention, executive cognitive function, language, and visuospatial ability are just a few of the cognitive functions that degrade as people become older.⁵ There is grey matter and white matter volume loss.⁶ Areas more prone to grey matter volume reduction are the prefrontal cortex and medial temporal lobe containing the hippocampus.^{7,8} The frontal lobe's corpus callosum and white matter experienced the most dramatic volume reductions.^{8,9} The white matter tract's integrity deteriorates with age, as seen by MRI diffusion tensor imaging.¹⁰ As individuals age, the number

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and length of dendrites decreases, as does the loss of dendritic spines and axons, as well as there is significant loss of synapses.¹¹ The loss of synapses is an important structural sign of ageing.^{12,13}

Cognitive decline is most commonly diagnosed clinically. Clinical tests such as the Mini Mental State Examination (MMSE), the Alzheimer Disease Assessment Scale (ADAS cog), and the Verbal Fluency Test, Cognitive Abilities Screening Instrument, Clock drawing test etc. are often used. Risk factors of Dementia on Magnetic resonance imaging (MRI) include brain atrophy, cerebral microhaemorrhages, and cerebral small vessel disease. Alzheimer disease (AD) is characterized by atrophy in specific brain regions, which includes the hippocampus, Para hippocampal cortex, entorhinal cortex, inferior parietal lobule, precuneus, and cuneus.^{14,15}

Microhaemorrhages, depending on their locations, play roles in both AD-related and vascular-specific pathology in dementia development.¹⁶ Haemorrhages, particularly in deep gray and white matter, are more likely to be associated with hypertensive arteriolar disease and are therefore considered vascular sign.¹⁷ White matter hyperintensities (WMHs) and lacunar infarcts are signs of small vessel disease.¹⁸⁻²² They contribute to vascular dementia but may also be associated with the pathogenesis of AD.^{23,24} WMHs are regions of increased intensity on T2-weighted and FLAIR MRI sequences that are usually assessed using rating systems based on ocular evaluation of the lesion nature and size.

The purpose of this research is to detect the continuing process of neurodegeneration as early as possible, when intervention options are most viable, as our understanding of the risk factors and treatment of dementia has improved.²⁵ Our aim here is to obtain a correlation of severity of WMH burden in MRI with severity of clinically assessed cognitive decline and to study severity of cerebral atrophy in MRI with severity of clinically assessed cognitive decline.

MATERIALS AND METHODS

The proposed study was a Hospital Based Retrospective Cross-Sectional Study and carried out in the department of Radiodiagnosis in collaboration with the Department of Psychiatry, IMS & SUM Hospital, Bhubaneswar, India.

The present study was done on 40 patients of age more than 45 years with an incidental finding of T2/FLAIR Hyperintensity & cerebral atrophy on MRI. They all underwent neuropsychiatric screening by MMSE (Mini Mental State Examination) test.²⁶ All patients having score less than 23 were included in the study. They were further evaluated by various visual rating scales like

Fazekas scale, Medial Temporal Atrophy scale (MTA Scale) & Global Cerebral Atrophy scale (GCA scale) for grading the cortical atrophy and WMH. After assessing the atrophy and WMH in MRI, the patients were subjected to a battery of neuropsychiatric tests like Verbal fluency test, ADAS-Cog, Montreal Cognitive Assessment test.²⁷ Lastly after obtaining all the scores, a correlation between the MRI grading of atrophy & WMH with the severity of cognition decline assessed by neuropsychiatric tests was established with the help of statistical analysis. Exclusion Criteria was Post stroke patients; space occupying lesions in brain; history of depression, psychosis and substance use disorder excluding nicotine use; seizure disorder; and any contraindications to MRI.

RESULTS

The maximum number of patients in our study belonged to the age group of 65-69 years, making a total of 20 cases out of 40 (i.e., 50% of the total). Second largest number of patients (9 in number) belonged to the age group 60-64 years (i.e., 22.5% of the total), followed by 4 cases in 70-74 years age group (i.e., 10% of the total) and 3 cases in 50-59 age group. Also 10% of the cases (4 in number) were seen in ≥ 75 years of age. The youngest patient of the study sample was 56 years old and the oldest patient of the study sample was 78 years old. Our study sample had 23 females (i.e., 55% of the total) and 17 males (i.e., 45% of the total). Among them 21 were diabetic (i.e., 52.5% of the total) & 19 were non-diabetic (i.e., 47.5% of the total) and 25 were hypertensive i.e., 62.5% of the total & 15 were non-hypertensive (i.e., 37.5% of the total). Out of the 40 patients, 14 were both hypertensive and diabetic (i.e., 35% of the total) and 26 were either hypertensive or diabetic (i.e., 65% of the total).

Patients assessed for cognitive decline by MMSE (as the screening tool) showed about 22 of them (i.e., 55% of the total) had mild cognitive impairment; followed by 14 subjects who had moderate cognitive impairment (i.e., 35% of the total). Severe cognitive impairment was seen in only 4 study samples (10% of the total). On Fazekas visual rating scale, about 22 of them had mild WMH (grade 1) i.e., 55% of the total and about 14 of them had moderate WMH (grade 2) i.e., 35% of the total. Severe WMH (grade 3) was seen in 4 patients i.e., 10% of the total (Fig 1). Assessment on MTA scale showed no atrophy (Score 0) in 2 patients, i.e., 5% of the total. Score 1 atrophy was seen in 16 patients (i.e., 40% of the total). Score 2 atrophy was seen in 12 patients (i.e., 30% of the total). Score 3 atrophy was seen in 8 (i.e., 20% of the total) and Score 4 atrophy was seen in 2 (i.e., 5%

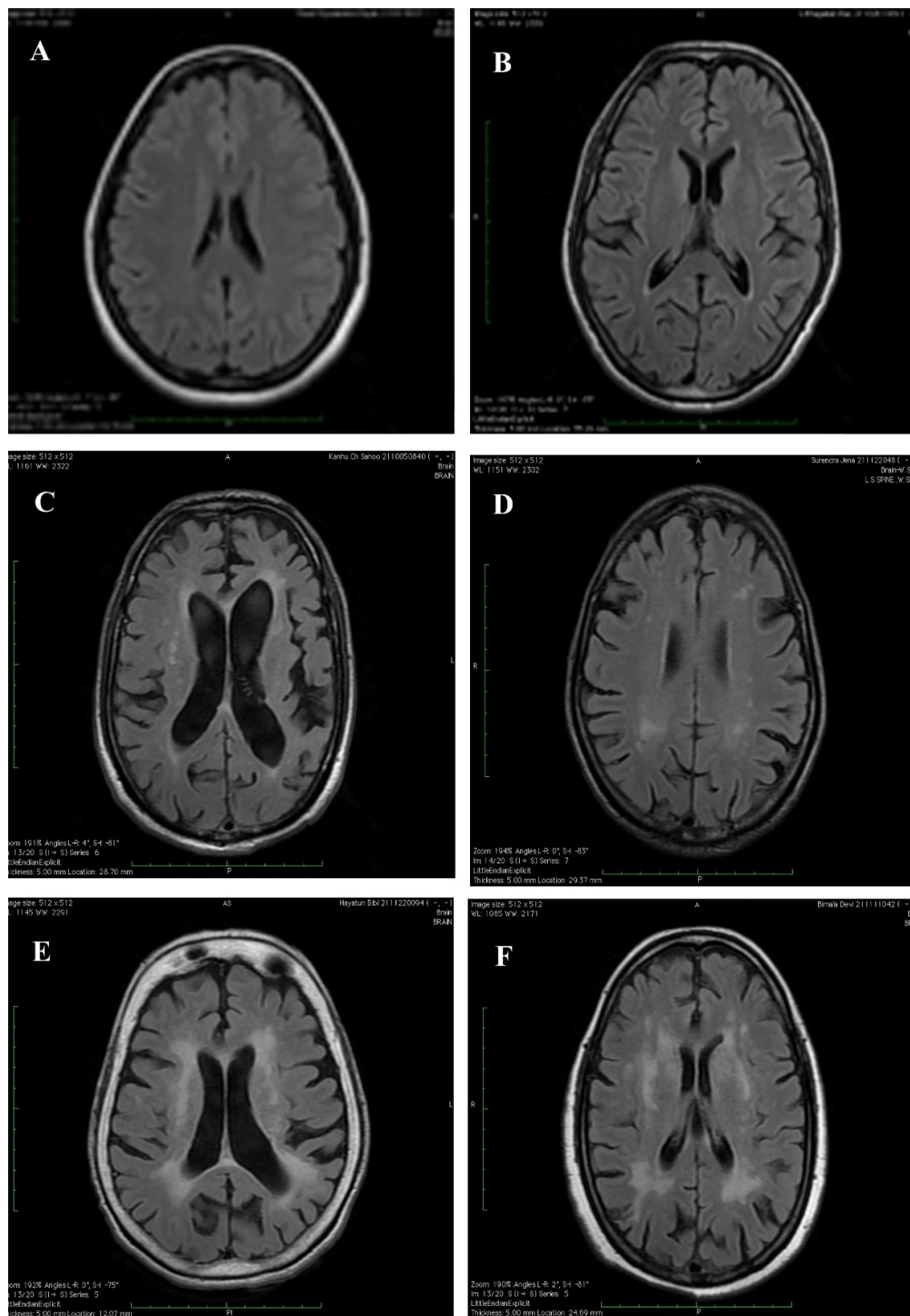


Fig 1. Grade of FAZEKAS scale; A,B) grade-1; C,D) grade-2; E,F) grade-3

of the total). Score ≥ 2 was considered abnormal in less than 75 years of age and Score ≥ 3 was considered abnormal in more than 75 years of age.

Out of 40 patients, Grade 0 (no atrophy) is seen in 22 patients in GCA scale, i.e., 55% of the total. Grade 1 atrophy is seen in 14 patients (i.e., 40% of the total). Grade 2 atrophy is seen in 4 patients (i.e., 10% of the total). However, no cases show severe atrophy. Since

GCA scoring showed inconclusive result in terms of assessment of severity of cognitive decline we use only MTA scoring for further assessment of sensitivity and specificity. Further assessment for cognitive decline by neuropsychiatric test ADAS-Cog showed about 22 of them (i.e., 55% of the total) had mild cognitive impairment, followed by 18 subjects who had moderate to severe cognitive impairment (i.e., 45% of the total).

The Sensitivity of Fazekas scoring in the assessment of severity of cognitive decline was 87.5%. The Specificity of Fazekas scoring in the assessment of severity of cognitive decline was 83.3%. P-value for fazeka scale correlation with clinical cognitive decline is 0.000013, which is significant. The Sensitivity of MTA scoring in the assessment of severity of cognitive decline was 72%. The Specificity of MTA scoring in the assessment of severity of cognitive decline was 88%. P-value of medial temporal lobe atrophy correlation with clinical cognitive decline by linear regression is 0.0006, which is significant. The Sensitivity of Combined Medial temporal atrophy (MTA) and Fazekas scoring in the assessment of severity of cognitive decline is 66.6%. The Specificity of Combined Medial temporal atrophy and Fazekas scoring in the assessment of severity of cognitive decline is 87.5% (Tables 1&2).

DISCUSSION

Dementia is a disease of elderly seen generally in age of more than 65 years. In the present study, the mean age of the participants was 66.15 years and 70% of the participants were more than 65 years of age. Aging is a very important risk factor for dementia as with advancing age the incidence of dementia increases exponentially between ages 65 to 90 and doubles approximately every 5 years.²⁸ With aging there is loss of grey as well as white matter volume manifesting as cerebral atrophy. In neurons, structural abnormalities include a decrease in the number, length and amount of dendrites, as well as an increase in segmental demyelination axons and a significant loss of synapses. Progressive dementia is also observed in patients having low serum vit B12 level, patients with carcinomatous meningitis, patients undergoing neurosurgical procedures; and among the caregivers of dementia patients.²⁹⁻³⁵

TABLE 1. Result of FAZEKAS, MTA scale and combined FAZEKAS+MTA scale in assessment of severity of cognitive decline.

| Clinical (ADAS-COG) / FAZEKAS | Moderate to severe cognitive decline (≥ 2) | Percentage | Mild cognitive decline (< 2) | Percentage |
|---------------------------------------|---|------------|----------------------------------|------------|
| Moderate to severe cognitive decline | 14 | | 4 | |
| Mild cognitive decline | 2 | | 20 | |
| Clinical(ADAS-COG)/MTA | | | | |
| Moderate to severe cognitive decline | 16 | | 2 | |
| Mild cognitive decline | 6 | | 16 | |
| Clinical(ADAS-COG)/MTA+FAZEKAS | | | | |
| Moderate to severe cognitive decline | 16 | 2 | | |
| Mild cognitive decline | 8 | 14 | | |

TABLE 2. Sensitivity and specificity of FAZEKAS, MTA scale and combined FAZEKAS+MTA scale in assessment of severity of cognitive decline.

| | FAZEKAS | MTA scale | Combined FAZEKAS+MTA |
|-------------|---------|-----------|----------------------|
| Sensitivity | 87.5% | 72% | 66.6% |
| Specificity | 83.3% | 88% | 87.5% |

The research group had a modest female majority with 57.5 percent of the participants being female. It has been proposed that due to loss of estrogen or other hormonal changes in association with other factors, there is increased risk in postmenopausal women, and estrogen replacement therapy has been shown to reduce the risk of AD in them.³⁶

Diabetes and hypertension are important risk factors for dementia. In the study, 52.5% (21 out of 40 study subjects) were diabetic and 62.5% (25 out of 40) were hypertensive. Insulin receptors are abundant in cognition-related brain areas, as well as in the blood-brain barrier.³⁷ Insulin resistance reduces the quantity of glucose that enters the brain in diabetic individuals, resulting in neuronal damage.³⁸ It's also been suggested that a hyperglycemic state in the brain leads to the development of glycated end products, which may lead to neuroinflammation.³⁸ High SBP has been linked to decreased regional and overall brain sizes;³⁹⁻⁴³ as well as brain volume declines over time.⁴⁴ When compared to normotensive people, hypertension people's brains have more amyloid plaques, atrophy, and neurofibrillary tangles.^{45,46} Sustained rises in blood pressure may cause cerebral vascular remodeling and, as a consequence, cognitive impairment. Hypertension causes endothelial dysfunction, which disrupts the microvasculature's coordinated connection of neurons, glia, and cerebral blood flow.⁴⁷

The majority of research individuals exhibited mild cognitive impairment (22 out of 40) and 45 percent had moderate to severe cognitive impairment, according to the MMSE and ADAS-COG assessments. It could be because our study group had the mean age of 66.1 years and majority of them were under the age group 60-70 years. According to the study conducted by Sengupta et al, 2014, Cognitive impairment among elderly people in India out of 268 total patients, 60% had mild cognitive impairment as the maximum number of the patients in the study were less than 70 years of age. The patients with increasing age had moderate to severe cognitive decline and lesser MMSE scores.⁴⁸

In our study on assessment by Fazekas Scale for WMHs, 55% of the study subjects were rated as grade 1, suggesting that these subjects had mild cognitive decline. About 45% of the subjects were rated as grade 2 or grade 3 suggesting that these subjects had moderate to severe cognitive decline. WMH is associated with cognitive decline, especially in the domains of attention, executive function, and processing speed.^{49,50} Hypoxic injury caused by atherosclerosis-induced hypoperfusion has been suggested as a possible etiological factor.⁵¹ On

correlation of data obtained by neuropsychological test ADAS-Cog and Fazekas scoring, we found sensitivity of 87.5% and specificity of 83.3%. Linear regression analysis between Fazekas and ADAS-Cog showed a P-value of < 0.001, which is highly significant. In the Landmark LADIS study, it was shown that the baseline severe white matter changes had an association with worse scores on MMSE and ADAS-Cog.⁵² WMH has also been connected to poor performance on global cognitive evaluations, executive abilities, speed and motor control, attention, naming, and vasoconstriction praxis, and is an independent predictor of dementia and cognitive decline.⁵³

MTA Scale is also used in the present study for assessment of severity of cognitive decline by MRI. Out of 40 patients, 55 % of the total study subjects had moderate to severe atrophy (Score ≥ 2) and 45% had mild atrophy (Score <2). The MTA scale shows a good correlation with manual hippocampal assessments when utilised in combination with cognitive function, as well as increased clinical importance. Automated volume measurement and volume of cortical thickness estimates have the same sensitivity and specificity.^{54,55} On correlation of data obtained by neuropsychological test ADAS-COG and MTA scoring, we found sensitivity 72 % and specificity of 88%. Linear regression analysis between MTA and ADAS-COG showed a P-value of <0.001 which is highly significant. In a study done by Jules j Claus et al on 1165 patients of Alzheimer disease and subjective cognitive impairment, it was seen that optimal MTA cut-off values for the age ranges <65, 65–74, 75–84 and ≥ 85 years were ≥ 1.0 , ≥ 1.5 , ≥ 2.0 and ≥ 2.0 and Corresponding sensitivity & specificity values were 83.3%, 86.4%; 73.7%, 84.6% and 73.7%, 76.2%, 84.0%, 62.5% respectively.⁵⁶

Limitations of the study: The data in this study came from a cross-sectional survey and, there was no follow up. Confounding factors like diabetes and hypertension may have affected the results interpretation in our study as scale of dementia will vary according to duration of both illnesses.

CONCLUSION

Cognitive impairment, which is a typical sign of ageing, is often considered as a precursor to more serious disorders like Alzheimer's disease, dementia and depression. The role of white matter disorders and brain shrinkage in cognitive decline and dementia is becoming more generally recognised. White matter disease assessed by Fazekas scale and cerebral atrophy by MTA scale on MRI brain correlated well with cognitive decline clinically assessed by neuropsychological tests. In our

study Fazekas scoring for WMHs showed a sensitivity of 87.5% and specificity of 83.3% on correlation with clinical cognitive decline assessed by ADAS-Cog. Also, MTA scale for cerebral atrophy showed a sensitivity of 72% and specificity of 88% on correlation with clinical cognitive decline assessed by ADAS-Cog. Significant P-value have been obtained for both the above visual rating scales of MRI (Fazekas and MTA) by linear regression, on correlation with clinically assessed cognitive decline.

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