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Hippocampal Volume Loss as A Marker of Cognitive Decline in Dementia and Mild Cognitive Impairment: A Comprehensive Prospective Study

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ABSTRACT

Background: Hippocampal atrophy is a hallmark of cognitive decline observed in dementia and mild cognitive impairment (MCI). This study investigated hippocampal volumes across individuals with dementia, MCI, and healthy controls to explore structural changes and their association with cognitive performance.

Methods: The present study included 62 participants categorized into three groups: dementia (DEM, N=22), MCI (N=15), and healthy controls (N=25). Hippocampal volumes were measured using 1.5 Tesla MRI. Cognitive function was assessed with the Mini-Mental State Examination (MMSE). Pearson correlation and ANOVA with post hoc Tukey's HSD tests were performed to analyze group differences and relationships between hippocampal volume and cognitive parameters.

Results: The mean hippocampal volumes were significantly smaller in the DEM group compared to the MCI and healthy groups ($P < 0.0001$). Right hippocampal volumes were 1.69 ± 0.47 cm³ in the DEM group, 2.12 ± 0.23 cm³ in MCI, and 2.64 ± 0.33 cm³ in healthy participants. A progressive hippocampal volume loss of 34.7% from MCI to DEM was observed. Significant differences in MMSE scores were found between groups ($P < 0.005$). A strong positive correlation between MMSE scores and hippocampal volumes was noted in the DEM group ($r = 0.55$, $P < 0.05$).

Conclusions: The findings confirm that hippocampal atrophy is a key feature of cognitive decline, with substantial volume loss observed in dementia patients compared to MCI and healthy individuals. The strong correlation between hippocampal volume and cognitive performance in dementia underscores the role of hippocampal measurements as potential diagnostic and monitoring biomarkers.

Keywords: Hippocampal atrophy, Dementia, Cognitive impairment, Healthy controls, Hippocampal volume

INTRODUCTION

The hippocampus, a crucial brain region responsible for memory formation and cognitive function, undergoes pathological alterations in neurodegenerative disorders like Alzheimer's disease (AD) and mild cognitive impairment (MCI). Advanced radiological techniques, particularly hippocampal volumetry by MRI, have gained prominence for their capacity to enhance diagnostic sensitivity and accuracy.[1-5] Quantitative volumetric analysis is instrumental in identifying seizure lateralization and evaluating the potential for effective seizure control in mesial

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temporal lobe sclerosis (MTLS).[6] Moreover, volumetric assessments are pivotal in distinguishing between types of dementias and identifying pseudodementia a condition frequently confused with true dementia.[7] Bilateral hippocampal atrophy remains a hallmark of AD, where patients experience progressive cognitive decline and difficulty forming new memories. The significance of the hippocampus in cognitive functions underscores the growing demand for radiological measurements as predictive and diagnostic tools.[7] Early detection through hippocampal volume analysis not only helps differentiate MCI from AD but also provides critical insights into the risk of transition from MCI to full-blown dementia. Despite the increasing global interest in hippocampal assessment, a significant gap exists in normative data on hippocampal volumes among older Kashmiri adults. While existing data from younger and adult populations have proven valuable in epilepsy diagnostics, there remains an unmet need for comprehensive volumetric references that are directly applicable to aging-related conditions such as AD and MCI.[6]

This study assesses hippocampal volumes in cognitively healthy older adults from Kashmir and compared them with those of individuals diagnosed with dementia and mild cognitive impairment (MCI). The research is grounded in the increasing evidence that hippocampal atrophy serves as a key hallmark of dementia and a predictor of the progression from MCI to dementia. By doing so, it underscores the clinical importance of hippocampal radiological assessment and highlights its potential to become a routine component in the diagnostic evaluation of dementia and related disorders.

MATERIALS AND METHODS

This study was conducted at the Department of Radiodiagnosis and Imaging, SKIMS Medical College and Hospital Bemina, Srinagar, with the primary objective of measuring and comparing hippocampal volumes in cognitively normal older adults, patients diagnosed with dementia, and those with mild cognitive impairment (MCI). A total of 62 participants were enrolled in the study, all referred from the Department of Psychiatry for radio diagnostic evaluation. The cohort comprised 22 individuals with dementia, 15 with mild cognitive impairment (MCI), and 25 cognitively healthy controls. The study spanned from December 2022 to June 2024. Participants were selected based on predefined eligibility criteria. The inclusion criteria specified adults aged 45 to 85 years with a confirmed diagnosis of dementia or MCI by a psychiatrist, or cognitively healthy individuals undergoing routine brain imaging. Exclusion criteria encompassed a history of stroke, traumatic brain injury, major psychiatric disorders unrelated to dementia or MCI, or other significant neurological conditions. Dementia and MCI diagnoses were established by an experienced psychiatrist using standardized clinical assessments and diagnostic guidelines. Dementia was diagnosed following the DSM-5 guidelines, which require evidence of significant cognitive decline affecting daily functioning, supported by clinical evaluation and cognitive testing.[8] MCI was diagnosed using Petersen's criteria, characterized by subjective cognitive complaints, objective evidence of impairment on neuropsychological tests, preserved functional abilities, and no evidence of dementia.[9] Cognitive function was assessed using the Mini-Mental State Examination (MMSE), a well-established and validated tool for detecting cognitive impairment. MMSE scores were recorded for all participants and used for further correlation analyses with hippocampal volumes. Participants underwent brain MRI scans for various clinical reasons. Patients with dementia and MCI were referred to for imaging due to memory loss, cognitive decline, or other neurological symptoms, primarily to assess brain structures and rule out other causes of cognitive dysfunction. Cognitively healthy controls were selected from individuals undergoing MRI for reasons such as headache evaluation, wellness screening, or investigation of minor nonspecific complaints, with no prior or current evidence of cognitive decline.

All imaging procedures were performed using a 1.5 Tesla MRI scanner, utilizing high-resolution T1-weighted sequences for volumetric assessment of the hippocampus. Hippocampal volumes were manually segmented using Siemens syngo software and measured independently by two radiologists. Inter-rater agreement was calculated using Cohen's kappa, with discrepancies defined as differences in hippocampal measurements exceeding 5%. Hippocampal atrophy was characterized as a hippocampal volume that deviated by ±2 standard deviations from the means of the control group. Statistical analysis was conducted using SPSS. ANOVA was employed to compare hippocampal volumes across groups, with post hoc Tukey's HSD for pairwise comparisons. Pearson's correlation coefficient was used to evaluate the association between hippocampal volumes and MMSE scores, with statistical significance set at $p \leq 0.05$.

RESULTS

The DEM group had the highest mean age (73 ± 6.6 years) and lowest MMSE scores (13.49 ± 4.2). The duration of illness was longest in the DEM group (2.98 ± 0.85 years) compared to the MCI group (2.01 ± 1.9 years). Healthy controls had the highest MMSE scores (28 ± 0.93). ANOVA showed significant differences in MMSE scores ($p < 0.005$). Pairwise comparisons revealed no significant difference between DEM and MCI ($p = 0.32$), but both DEM ($p = 0.003$) and MCI ($p = 0.024$) had significantly lower scores than the healthy group. These findings indicate a cognitive decline from MCI to dementia.

In the DEM group, hippocampal volume showed a significant positive correlation with MMSE scores ($r = 0.55$, $p < 0.05$), indicating that greater atrophy was associated with lower cognitive performance. A similar trend was observed in both the DEM and MCI groups, where re-

duced hippocampal volume corresponded with declining MMSE scores.

Table 1: Demographic and Clinical Aspects of Study Participants

Diagnosis	Mean Age (years)	Duration of Illness (years)	MMSE	Between Group Comparison (ANOVA; p-value)	Pairwise Comparison (Independent t-test; P-value)		
					DEM vs. MCI	DEM vs. Healthy	MCI vs. Healthy
DEM (N=22)	73 ± 6.6	2.98 ± 0.85	13.49 ± 4.2	<0.005	0.32	0.003	0.024
MCI (N=15)	71 ± 5.1	2.01 ± 1.9	26.97 ± 2.21				
Healthy (N=25)	65.81 ±8.9	NA	28 ± 0.93				

Table 2: Correlation of Hippocampal Volume (HV) with Cognitive and Demographic Variables

Group/s	Variables	Pearson Correlation Coefficient (r)	P Value
DEM	MMSE and HV	r = 0.55	< 0.05
MCI	MMSE and HV	r = 0.25	> 0.05
DEM/MCI	Education and HV	r = 0.22	> 0.05
DEM/MCI	Age and HV	r = 0.31	> 0.05
Healthy	Age and HV	r = 0.32	> 0.05
Healthy	MMSE and HV	r = 0.22	> 0.05

Table 3: Comparison of Hippocampal Volumes Across Study Groups

Group	DEM (N=22)	MCI (N=15)	Healthy (N=25)	P Value Between Groups (ANOVA)
Right Hippocampal Volume (cm^3)	1.69 ± 0.47	2.12 ± 0.23	2.64 ± 0.33	<0.0001
Left Hippocampal Volume (cm^3)	1.67 ± 0.49	2.14 ± 0.21	2.6± 0.42	<0.0001

However, this association was not evident in the healthy group. Hippocampal atrophy was defined as a volume deviation of ±2 standard deviations from the mean. Among the 22 DEM patients, 12 (54%) exhibited hippocampal atrophy[6]. However, correlations between hippocampal volume and MMSE, education, or age were not statistically significant in the MCI, DEM/MCI, and healthy groups.

The right hippocampal volume was observed to be lowest in the DEM group (1.69 ± 0.47 cm^3), followed by MCI (2.12 ± 0.23 cm^3), and highest in the Healthy group (2.64 ± 0.33 cm^3). A similar pattern was noted for left hippocampal volumes, with values recorded at 1.67 ± 0.49 cm^3 for DEM, 2.14 ± 0.21 cm^3 for MCI, and 2.60 ± 0.42 cm^3 for Healthy participants. ANOVA results indicated statistically significant differences across groups for both right and left hippocampal volumes ($p < 0.0001$). In the MCI group, hippocampal atrophy was observed in only one of the 15 patients (odds ratio [OR] = 6.5, 95% confidence interval [CI] = 0.9474–54.12), whereas no cases of atrophy were detected among the healthy participants. Compared to healthy individuals, hippocampal volume loss in DEM patients was 49%, and in MCI patients, it was 16.3%, indicating a 34.7% volume loss progression from MCI to DEM. High intra- and inter-rater agreement was achieved between two independent raters (Cohen's kappa = 0.71). Agreement was defined as differences in hippocampal volume measurements of less than 5%; discrepancies exceeding this threshold were considered disagreements.

Table 4 provides the results of post-hoc Tukey HSD tests for pairwise comparisons. Significant differences in right hippocampal volume were found between DEM and MCI ($p \leq 0.0024$), DEM and Healthy ($p < 0.001$), and MCI and Healthy ($p < 0.01$). Similarly, left hippocampal volume showed significant differences across groups: DEM vs. MCI ($p = 0.003$), DEM vs. Healthy ($p < 0.001$), and MCI vs. Healthy ($p < 0.001$). These findings highlight a progressive reduction in hippocampal volumes across the groups, with DEM participants exhibiting the smallest volumes, further underscoring the structural changes associated with cognitive impairment.

Table 4: Post-Hoc Tukey HSD Analysis for Hippocampal Volumes

Comparison	Right Hippocampal Volume (p-value)	Left Hippocampal Volume (p-value)
DEM vs. MCI	≤0.0024	0.003
DEM vs. Healthy	<0.001	<0.001
MCI vs. Healthy	<0.01	<0.001

DISCUSSION

The hippocampus and its volume loss have gained importance in diagnosing and predicting neurocognitive disorders. Hippocampal volume aids in differentiating cognitively healthy older adults from those with dementia, facilitates drug trials, and forecasts the progression from MCI to dementia. It also differentiates dementia from pseudodementia and various dementia types when combined with clinical data. While automated measurement techniques are faster, manual methods remain the gold standard. Although normative hippocampal volume data exist globally, such information for older Indian adults is currently lacking. Hippocampal damage is influenced by factors such as depression, stress, seizures,

hypertension, and diabetes, along with biochemical markers like vitamin D3, serum cortisol, and homocysteine. This study examined individuals with normal biochemical and clinical profiles to compare hippocampal volumes in healthy older adults, MCI, and AD cases, emphasizing volume loss in the absence of known contributing factors.

The findings of this study indicate that patients in the AD group had the highest mean age (73 ± 6.6 years) and the lowest MMSE scores (13.49 ± 4.2), highlighting the progressive cognitive decline associated with DEM. The longer duration of illness in the DEM group (2.98 ± 0.85 years) compared to the MCI group (2.01 ± 1.9 years) aligns with the typical clinical trajectory from MCI to more severe dementia stages, as documented in previous studies (Duff K et al., 2014; Petersen et al., 2014).[9,10] Healthy controls exhibited the highest MMSE scores (28 ± 0.93), reflecting preserved cognitive function in the absence of neurodegenerative pathology. The significant variation in MMSE scores among the groups ($P < 0.005$, ANOVA) corroborates previous literature indicating that cognitive assessment tools like MMSE are effective in differentiating between healthy aging, MCI, and DEM (Folstein et al., 1975).[11] These results are inconsonance with the reports by Petersen et al. (2014), who observed significant cognitive differences between MCI and DEM patients and emphasized the importance of early diagnosis to slow disease progression.[9] Additionally, the relatively shorter duration of illness in the MCI group suggests an opportunity for timely interventions, which have been linked to a slower progression of cognitive decline (Ritchie et al., 2015).[12]

This study revealed important insights into hippocampal volume changes among individuals with DEM, MCI, and healthy individuals. The findings indicated a progressive reduction in hippocampal volume from healthy individuals to those with MCI and DEM, with significant variations evident between these groups ($P < 0.0001$). These results align with established literature underscoring hippocampal atrophy as a hallmark of neurodegenerative conditions, particularly in dementia-related diseases (Jack et al., 2010; Schuff et al., 2009).[13,14] The findings showed a 49% reduction in hippocampal volume in DEM patients compared to healthy controls, while patients with MCI exhibited a 16.3% reduction in hippocampal volume. This gradual loss from MCI to DEM (a 34.7% progression) highlights the pivotal role of hippocampal degeneration in cognitive decline. Studies by Apostolova et al. (2010) and Morra et al. (2009) similarly documented that hippocampal atrophy starts in the early stages of cognitive impairment, with measurable changes present even before clinical symptoms of dementia become pronounced.[15,16]

The association between hippocampal volume and MMSE scores supports the link between structural changes and cognitive decline. In the DEM group, a significant positive correlation ($r = 0.55$, $p < 0.05$) was observed, indicating that greater hippocampal atrophy corresponds to lower cognitive function. This finding indicates that lower hippocampal volumes are associated with poorer cognitive performance, consistent with prior research linking hippocampal atrophy to disease severity in dementia (Dickerson & Eichenbaum, 2010; Schuff et al., 2009).[14,17] In contrast, MMSE scores showed no significant correlation with hippocampal volume in the MCI and healthy groups. This lack of association may suggest that hippocampal degeneration in MCI is less extensive or not yet severe enough to produce measurable cognitive deficits. Alternatively, other brain regions beyond the hippocampus may play a more dominant role in early cognitive changes during MCI (Petersen et al., 1999).[9] Furthermore, the absence of statistically significant correlations between hippocampal volume and demographic factors such as age and education in the DEM and MCI groups diverges from some earlier studies (Raz et al., 2005).[18] This discrepancy may be due to the greater influence of pathological changes in dementia, which overshadow the effects of aging or cognitive reserve factors such as education.

The observation that 54% of DEM patients exhibited hippocampal atrophy, compared to only one case in the MCI group (OR = 6.5, 95% CI = 0.9474–54.12), highlights the specificity of hippocampal atrophy in advanced cognitive decline. None of the healthy participants showed signs of hippocampal atrophy, reinforcing its association with pathological cognitive deterioration. Apostolova et al. (2010) similarly noted that hippocampal atrophy serves as a reliable biomarker for differentiating between healthy aging, MCI, and dementia.[15] Tukey's HSD post hoc analysis showed significantly lower hippocampal volumes in DEM and MCI patients compared to healthy individuals ($P \leq 0.01$). This reinforces the clinical utility of hippocampal volume assessment as a diagnostic tool. The strong intra- and inter-rater agreement (Cohen's kappa = 0.71) further underscores the reliability of manual segmentation methods employed in the study. The clinical implications of these findings are significant. Early detection of hippocampal atrophy in MCI may offer a window for therapeutic interventions aimed at slowing disease progression. Recent studies have suggested that volumetric assessments of the hippocampus, combined with neuropsychological testing, can improve diagnostic accuracy and predict conversion from MCI to dementia (Schuff et al., 2009; Morra et al., 2009).[14,16]

CONCLUSION

This study highlights the critical role of hippocampal atrophy in cognitive decline, with a progressive reduction in hippocampal volume observed from healthy individuals to those with MCI and dementia. The significant association between hippocampal volume and cognitive performance, particularly in the DEM group, underscores its value as a potential biomarker for disease severity and progression. Although no significant correlations were found between hippocampal volume and demographic variables such as age or education, the findings

suggest that structural changes in the hippocampus may precede and contribute to cognitive deficits. Future studies should explore longitudinal changes in hippocampal volume and examine other brain regions involved in cognitive decline to better understand the progression from MCI to dementia.

Author Contribution: SB contributed to the study conception, study design, and manuscript preparation. **GH** was involved in study design and data collection. **MFM** participated in study conception, study design, and manuscript preparation. **SR** contributed to study design.

REFERENCES

1. Burje S, Rungta S, Shukla A. Detection and classification of MRI brain images for head/brain injury using soft computing techniques. Research Journal of Pharmacy and Technology. 2017 Mar 1;10(3):715. DOI: https://doi.org/10.5958/0974-360X.2017.00134.2
2. Huisman TA, Tekes A. Advanced MR brain imaging. Why?. Pediatric radiology. 2008 Jun;38:415-32. DOI: https://doi.org/10.1007/s00247-008-0895-9 PMid:18470451
3. Blamire AM. The technology of MRI-the next 10 years?. The British journal of radiology. 2008 Aug 1;81(968):601-17. DOI: https://doi.org/10.1259/bjr/96872829 PMid:18628329
4. Assam M, Kanwal H, Farooq U, Shah SK, Mehmood A, Choi GS. An efficient classification of MRI brain images. IEEE Access. 2021; 9:33313-22. DOI: https://doi.org/10.1109/ACCESS.2021.3061487
5. Gordon E. Brain imaging technologies: how, what, when and why?. Australian & New Zealand Journal of Psychiatry. 1999 Apr;33(2): 187-96. DOI: https://doi.org/10.1046/j.1440-1614.1999.00557.x
6. Mohandas AN, Bharath RD, Prathyusha PV, Gupta AK. Hippocampal volumetry: Normative data in the Indian population. Ann Indian Acad Neurol 2014;17:267-71. DOI: https://doi.org/10.4103/0972-2327.138482 PMid:25221393 PMCid:PMC4162010
7. Dhikav V, Anand K. Potential predictors of hippocampal atrophy in Alzheimer's disease. Drugs Aging 2011;28:1-11. DOI: https://doi.org/10.2165/11586390-000000000-00000 PMid:21174483
8. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014 Aug;30(3):421-42. DOI: https://doi.org/10.1016/j.cger.2014.04.001 PMid:25037289 PMCid:PMC4104432
9. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275(3):214-28. DOI: https://doi.org/10.1111/joim.12190 PMid:24605806 PMCid:PMC3967548
10. Duff K. Mild Cognitive Impairment and Dementia: Definitions, Diagnosis, and Treatment. Arch Clin Neuropsychol. 2014 Nov; 29(7): 691-2. DOI: https://doi.org/10.1093/arclin/acu034
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. DOI: https://doi.org/10.1016/0022-3956(75)90026-6 PMid:1202204
12. Ritchie K, Ritchie CW, Yaffe K, Skoog I, Scarmeas N. Is late-onset Alzheimer's disease really a disease of midlife? Alzheimers Dement (N Y). 2015 Jul 26;1(2):122-130. DOI: https://doi.org/10.1016/j.trci.2015.06.004 PMid:29854932 PMCid:PMC5975058
13. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010 Jan;9(1):119-28. DOI: https://doi.org/10.1016/S1474-4422(09)70299-6 PMid:20083042
14. Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, Thompson PM, Jack Jr CR, Weiner MW, Alzheimer's; Disease Neuroimaging Initiative. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain. 2009 Apr 1;132(4):1067-77. DOI: https://doi.org/10.1093/brain/awp007 PMid:19251758 PMCid:PMC2668943
15. Apostolova LG, Mosconi L, Thompson PM, Green AE, Hwang KS, Ramirez A, Mistur R, Tsui WH, de Leon MJ. Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. Neurobiology of aging. 2010 Jul 1;31(7):1077-88. DOI: https://doi.org/10.1016/j.neurobiolaging.2008.08.008 PMid:18814937 PMCid:PMC2873083
16. Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, Parikshak N, Toga AW, Jack CR Jr, Schuff N, Weiner MW, Thompson PM; Alzheimer's Disease Neuroimaging Initiative. Automated mapping of hippocampal atrophy in 1-year repeat MRI data from 490 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Neuroimage. 2009;45(1 Suppl): S3-15. DOI: https://doi.org/10.1016/j.neuroimage.2008.10.043
17. Dickerson BC, Eichenbaum H. The episodic memory system: neurocircuitry and disorders. Neuropsychopharmacology. 2010 Jan;35(1):86-104. DOI: https://doi.org/10.1038/npp.2009.126 PMid:19776728 PMCid:PMC2882963
18. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral cortex. 2005 Nov 1;15(11):1676-89. DOI: https://doi.org/10.1093/cercor/bhi044 PMid:15703252