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SHORT COMMUNICATION

Medial temporal lobe atrophy in Alzheimer's disease/mild cognitive impairment with depression

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Objective: Depression is common in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Patients with depression have an earlier onset and rapid progression of cognitive decline. Medial temporal lobe atrophy (MTA) is common in AD and MCI, and some degree of atrophy is found in almost all patients. In the present study, an attempt was made to know if MTA is more common in patients with AD/MCI with depression than those without it.

Methods: Patients reporting to the outpatient department of a neurology centre of a tertiary care hospital were recruited for the present study. After initial general physical and neurological examination, they were evaluated using National Institute of Neurological and Communicative Disorders and Stroke and Related Disorders Association criteria for diagnosis of AD. Clinical Dementia

rating scale was used for the diagnosis of MCI. Cornell scale for depression in dementia (CSDD) was used.

Results: We found 20 cases with depression as per CSDD out of a sample of 37 patients (male:female = 30:7). There were 26 patients with AD and 11 with MCI. The mean age of all patients was 72.33 ± 6.45 years. The mean mini mental status examination score was 19.00 ± 6.73 . The mean time since diagnosis was 4.19 ± 3.26 years. The mean Scheltens visual rating scale score for right MTA was 2.08 ± 0.95 and was 2.05 ± 0.94 for the left. Both scores did not differ statistically when analyzed using paired *t*-test ($p > 0.05$). However, difference in those with depression (2.36 ± 0.95) from those without depression (1.60 ± 0.74) was significant ($p < 0.05$).

Conclusion: MTA scores were higher in those with AD/MCI with depression than those without it.

Depression¹ is common in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Relationship between depression and cognitive decline is a complex one, and depression is both an aetiological risk factor² and comorbidity for dementia.³ Incidence and prevalence of depressive symptoms in MCI range from 15% in population-based studies to 44% in hospital-based studies.⁴ Likewise, up to two-thirds of patients with AD have been reported to have depression.⁵ Because in many studies, depression has been seen to be an early manifestation of AD, it has been suggested that it may represent a continuum⁴ from depression to MCI to AD (late-life depression → MCI → AD). Two recent meta-analyses have found that a history of depression approximately doubles an individual's risk for subsequent dementia in general and AD in particular.⁶ Depression is known to be neurotoxic to medial temporal lobe structures and can contribute to their atrophy.⁷⁻⁹ Atrophy is more so, when depression is severe or recurrent⁷ and medial temporal lobe atrophy (MTA) has a temporal association with depression.⁹ Continued treatment of depression has been shown to protect the

hippocampus from the ill effects of depression.¹⁰ Although volumetric method could be a preferred mode of measuring the hippocampal volume in AD, qualitative rating of MTA is a good alternative.¹¹ Visual rating of the hippocampal volume¹²⁻¹⁴ can be carried out using Scheltens et al¹⁵ rating scale that is based on the width of the choroid fissure, the width of the temporal horn and the height of hippocampal formation and is a quantitative scale.

METHODS AND MATERIALS

Patients reporting to the outpatient department of a neurology centre of a tertiary care hospital were recruited for the present study. Subjects were selected randomly and from the general outpatient department, and they were asked to attend a specialized memory clinic. After initial general physical and neurological examination, they were evaluated using the National Institute of Neurological and Communicative Disorders and Stroke and the Related Disorders Association (NINCDS-ARDA) criteria for the diagnosis of AD.² Clinical Dementia Rating scale⁵ was used for the diagnosis of MCI (0.5 score on Clinical Dementia

Rating scale). Cornell Scale for Depression in Dementia (CSDD) was used for assessing depression in dementia (internal consistency, 0.84; predictive validity—sensitivity, 0.90; specificity, 0.75). CSDD contains 19 items with a maximum score of 2 each, therefore, the maximum possible score is 38. The scale has high inter-rater reliability (0.67).

Depression was evaluated using CSDD, which is considered the gold standard in assessing depression in dementia. CSDD is the best-validated instrument for measuring depression in dementia⁷ and takes into account the fact that some symptoms of dementia can mimic those of depression. It involves comprehensive semi-structured interviewing approach and integrates the patient and caregiver interviews to reach a composite clinician rating. Probable depression in the present study was defined as a score of CSDD >10.

MTA described by Scheltens *et al*¹⁵ (Table 1) uses hard copies of MRI coronal sections. The scale has high inter-rater and intra-rater reliability.¹⁵ It has been validated both in linear and volumetric measures of the medial temporal lobe. Some studies indicate that the visual method of medial temporal lobe estimation is as good as detailed volumetric measurements.¹⁵

Comparisons of clinical diagnosis made by NINCDS-ARDA criteria and MTA scores were performed to know the diagnostic accuracy of the MTA scores. MTA (right and left) Scheltens visual rating using MRI brain coronal sections was carried out by an experienced neurologist with 30 years' experience.

It was found that MTA scoring had high sensitivity [88–95% confidence interval (CI) = 68–94%] and specificity (86% CI = 68–94%) in diagnosing dementia of probable Alzheimer's type using NINCDS-ARDA criteria. It is well known that definite diagnosis of AD can only be made by histopathology. However, clinical diagnosis of probable, possible and unlikely Alzheimer's can be diagnosed using NINCDS-ARDA criteria. Sensitivity and specificity calculated in this study is in agreement with data reported earlier.⁷

RESULTS

There were 26 patients with AD and 11 with MCI. The mean age of all patients was 72.33 ± 6.45 years. 20 cases with depression as per CSDD out of a sample of 37 patients (male:female = 30:7) were found (54%). The mean mini mental status examination

(MMSE) score was 19.00 ± 6.73 . Mean time since diagnosis was 4.19 ± 3.26 years. Data were checked for normalcy using inter-quartile range (IQR) for both sets (non-depressed and depressed). The IQR for the non-depressed set was 1.5 and the median was also 1.5, whereas the IQR for the depressed set was 1 and the median was 2.5. These values represent a normal distribution as there were no outliers. The latest version of SPSS® (SPSS Inc., Chicago, IL) was used for data analysis.

The mean Scheltens visual rating scale score for the right MTA was 2.08 ± 0.95 and 2.05 ± 0.94 for the left. Both of them did not differ statistically when using paired *t*-test ($p > 0.05$). However, the difference in those with depression (2.36 ± 0.95) from those without depression (1.60 ± 0.74) was significant ($p < 0.05$).

Pearson's correlation coefficient between the left and right MTA was calculated to be 0.45, and the coefficient of determination (r^2) was 0.2.

This suggests a weak relationship between the left and right MTA scores (Figure 1). This was consistent with the insignificant difference between the left and right MTA scores.

DISCUSSION

Depression is a common comorbidity seen in AD/MCI.¹¹ It can precede the development of dementia or can present along with it. The loss of hippocampal volume and memory functions observed in some elders in late-life depression suggests the possibility that depression may be a predisposing risk factor for AD in particular. Lower hippocampal volumes independently predict subsequent AD in groups of MCI and cognitively normal elderly subjects.⁷ The present study reports MTA using Scheltens visual rating scale for MTA. Smaller volume in the present study could perhaps be owing to hypercortisolemia,^{12–14} as reduced hippocampal volume may no longer be able to inhibit hypothalamic pituitary adrenal axis. An increase in cortisol notably promotes apoptosis and neurodegeneration and encourages deposition of

Figure 1. Scatter plot for correlation between the left and right medial temporal lobe atrophy scores as per Scheltens visual rating scale.

Table 1. Scheltens visual rating scale for medial temporal lobe atrophy¹⁵

Score 0: no atrophy (no atrophy)
Score 1: only widening of choroid fissure (minimal atrophy)
Score 2: also widening of temporal horn of lateral ventricle (moderate atrophy)
Score 3: moderate loss of hippocampal volume (decrease in height—severe atrophy)
Score 4: severe volume loss of hippocampus (marked atrophy)

beta-amyloid plaques. Post-mortem studies report greater hippocampal amyloid plaques and neurofibrillary tangle pathology in patients with AD with a lifetime history of depression than those without it.⁷

MTA on MRI coronal sections is considered to be the hallmark of patients with AD. Patients with AD have greater reductions in the hippocampi (10–50%), amygdalae (up to 40%) and parahippocampi (up to 40%) than do age-matched controls. There is evidence that atrophy of the hippocampus,¹⁵ parahippocampal areas and entorhinal cortex occurs in the early part of the disease. By the time the symptoms started to appear, volume loss exceeding 25% had already occurred.^{16–18} Visual rating method of MTA is an independent tool predicting conversion of MCI to AD.¹⁹

Treatment guidelines for depression in dementia are yet to fully evolve, and, perhaps, more needs to be learnt about its pathophysiology especially its relationship with cognition.¹⁵ This is because some trials report benefits¹⁸ such as slowing down of cognitive decline with antidepressants, whereas some other trials have been negative.²⁰

CONCLUSION

Depression is common in patients with AD/MCI. Depression has the potential to adversely affect the hippocampus.²¹ The present study reports greater volume loss of medial temporal lobe structures of the brain in patients with AD/MCI with depression as per CSDD than those without it. Greater attention to evaluation and treatment of depression in AD/MCI is warranted.

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