

Research paper

Correlation of medial temporal lobe atrophy with seizures in Alzheimer's disease and mild cognitive impairment: A case control study



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ABSTRACT

Background: Seizures are common accompaniment of neurodegenerative disease. Though, Alzheimer's disease (AD) is the most common cause, but seizures also occasionally occur in mild cognitive impairment (MCI).

Material & methods: We studied patients of Subjective Memory Complaints coming to the Department of Neurology of a Tertiary Care Hospital in Northern India from July 2012 to July 2015. A total of 171 patients were studied. Those with a diagnosis of AD/MCI with seizures were taken for the current study. A total of 30 controls with chronic diseases were taken for comparison. Medial Temporal Lobe Atrophy (MTA) Rating was done using Sheleton's Visual Rating Scale.

Results: A total of 256 patients were screened and 171 had dementia of Alzheimer's type ($n = 75$; M:F = 60:15) and 96 patients had MCI (M:F = 76:20). The mean MMSE of those with AD was 18.5 ± 3.3 and that of the MCI was 26.6 ± 2.4 . A total of 9 cases with AD had seizures and 6 had seizures in MCI group (total $n = 15$). Moderately strong correlation was obtained between MMSE of AD patients having seizures and MTA scoring.

Conclusions: Seizures are common in dementia of Alzheimer's type and not uncommon in MCI. They have the potential to worsen the cognitive profile of the patient and need attention in these patients.

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1. Introduction

Late life seizures occur in patients with Alzheimer' disease (AD)¹ and Mild Cognitive Impairment (MCI). It has been observed that seizure occurrence in AD is more common than previously thought.² Notably, advanced age carries a higher risk for development of seizures in patients with AD.² In the absence of proper drug management, seizures have the potential to cause deterioration of dementia³.

AD is the most common cause of dementia while MCI is a precursor to dementia.³ Patients with AD are at a high risk of developing seizures, upto 10 folds.² Ongoing seizures can worsen the cognitive status in these patients. It has been observed that AD and other neurodegenerative conditions are the presumed etiology of upto 10% of New onset Epilepsy in patients older than 65 years.³ Also, the lifetime prevalence of seizures in AD has been estimated

to be 1.5–64%.⁴ Appearance of a new onset seizure is associated with cognitive worsening and seizures also contribute amnesic wandering.⁵ Though AD is common in Indian elderly, but no systematic study is there on seizures in AD/MCI patients.⁶ The present study was done to study the frequency and factors associated with seizures in patients with AD/MCI. Also, an attempt was made to correlate Medial Temporal Lobe Atrophy (MTA) with various predictors in patients of AD/MCI.

2. Material & methods

Patients attending to the Department of Neurology of a Tertiary Care Hospital in Northern India from July 2012 to July 2015 were enrolled for the present study. The study represents >6000-person-years of observations. A total number 256 with memory complains were screened in last 3-years. The patients were selected randomly from the outpatient department of Neurology and were asked to attend the specialized memory clinic. Those selected underwent through general physical, neurological and neuropsychological evaluation. The diagnosis of MCI and dementias was made as per the established criteria (Clinical Dementia Rating score = 0.5 for MCI and Diagnostic & Statistical Manual DSM-

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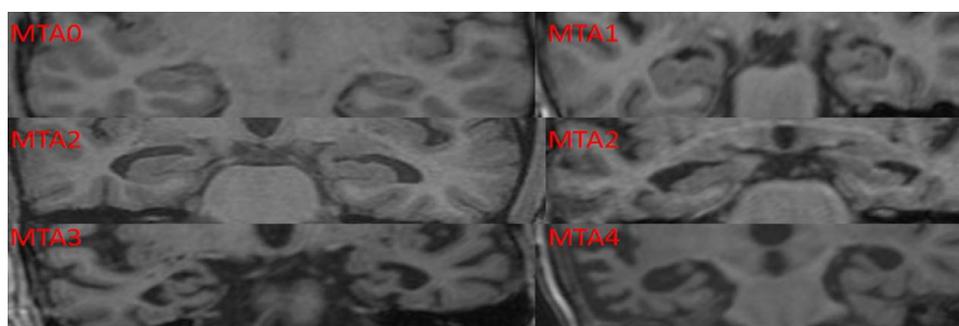


Fig. 1. Sheletens Medial Tempal Lobe Atrophy (MTA) Rating Scale. Scoring was done as follows (0) (0) scores on left and right sided were given if there was no visible atrophy on T1 weighted coronal MRI images. The scores of (1) (1) left sided were given to those with minimal atrophy. Those with moderate atrophy were rated as (2) (2) left and right sided respectively. Those with moderate atrophy were given the score of (3) (3) and scores of (4) (4) were given to those with marked atrophy.

V criteria for diagnosis of dementias respectively).⁷ A total of 171 patients with diagnosis M:F (136:35) with mean age 71 ± 0.6 years and the mean duration of illnesses 3.2 ± 0.3 years were recruited for the present study. The MTA rating was done using Sheleten Visual Rating Scale.⁸ This scale has a high inter and intra-rater reliability. For the purpose of the study, the standardization of rating was performed using the figures given below (Fig. 1). T1 oblique coronal image was used for MTA rating and confirmed using T2 weighted coronal images. A total of 30 controls with chronic diseases were taken for comparison. Comparison with controls was done to know the relative risk of seizures in controls and diseased group and also to see if there is any correlation that exists in between controls and diseased group and MTA.

The controls ($n=30$) were the patients with Osteoporosis ($n=12$), Diabetes and Hypertension ($n=6$), and Psychiatric illnesses which included anxiety disorders, depression and psychosomatic disorders ($n=12$). Mean duration of illness in case of controls was 3.5 ± 0.6 years. The mean age of controls was 56 ± 5.53 years.

3. Results

A total of 75 patients had dementia of Alzheimer's type and 96 patients had MCI out of the total number 256 screened in last 3-years (Tables 1 & 2). The duration of illness in AD was 3.6 ± 0.3 years and that of the MCI was 2.8 ± 0.2 years. The mean MMSE of those with AD was 18.5 ± 3.3 and that of the MCI was 26.6 ± 2.4 The MMSE of those with AD having seizures has been plotted using Box and Whisker plot (Fig. 2). There were a total of 15 cases with seizures in this study sample [(AD=9, MCI=6), Fig. 3].

There was a significant difference between the MMSE of MCI, AD without seizures and AD with seizures were statistically different using one way ANOVA (p -value = <0.001).

The prevalence rate of the Alzheimer's disease was 2.08%. It was calculated as the total number of AD cases during last 3 years divided by the number of elderly at risk (>60 years) reporting to the neurology outpatient department during this period (July 2012–July 2015), multiplied by 100. This prevalence rate is not significantly different from the prevalence rate of dementias reported from urban Indian population.² Likewise, the prevalence rate for seizures in AD was calculated to be $9/75 \times 100 = 12\%$, which is in range with the reported prevalence rate for seizures in AD (1–64%).⁴ The odds ratio (OR) at 95% confidence interval in AD was almost twice to that in MCI group (OR=1.94, 95% confidence interval = 0.6545–5.6327). That means, patients with AD are twice more likely to have seizures compared to those with MCI. Likewise, the OR of having seizures in patients with AD was 7.6 compared to controls (95% confidence interval = 0.4331–136.0228). Similarly, OR in MCI compared to controls was 4.1 (95% confidence

Table 1

Demographic features of the patients in the present study.

Category	Sample size (n = 171)	Mean Age (years)	Sex Ratio	MMSE
AD	75	75 ± 5	60:15	18.5 ± 3.3
MCI	96	67 ± 7	76:20	26.6 ± 2.4

Table 2

Breakup of screened cases of cognitive impairment/dementia from July 2012 to July 2015.

Type of Cognitive Impairment/Dementia (n = 256)	Sample size (n)
MCI	96
AD	75
Vascular dementia	30
Dementia with Levy Body	6
Mixed dementias	12
Fronto-temporal dementias	8
Normal pressure hydrocephalous	4
Pseudodementias	3
Thyroid dementias	5
B12 deficiency	5
Drug-Induced dementias	5
Crutzfelt-Jacob's disease	2
Corticobasal dementias	1

interval = 0.2249–75.0607). A total of 7 patients in the AD group had generalized seizures and 2 had partial seizures; in the MCI group a total of 4 had generalized seizures and 2 had partial seizures. The mean duration of seizures was 3.2 ± 0.3 years in AD and 2.5 ± 0.3 years in MCI respectively.

The mean and standard deviation of MTA rating score was 2.40 ± 0.63 and 0.87 ± 0.35 in AD with seizures compared to those without seizures ($p < 0.001$). There was no significant correlation between the MMSE and MTA ratings in MCI group (Pearson Correlation Coefficient = 0.19, p -value = >0.05). However, correlation between MMSE and MTA rating in the AD group was significant (Pearson Correlation Coefficient = 0.59, p -value = <0.05).

The mean duration of antiseizure treatment in patients with AD/MCI in the current study was 2.9 ± 0.3 years. All ($n = 15$) but 2 cases had controlled seizures in the current study population of AD/MCI. Two cases, one with MCI, another with AD had breakthrough seizures while being on antiseizure drugs. A total of 7 cases were taking sodium valproate (1000 mg/day) and two cases were on levetiracetam (1000 mg/day) in AD group, and 4 cases in MCI group were on sodium valproate (1000 mg/day) compared to 2 cases who were on levetiracetam (1000 mg/day).

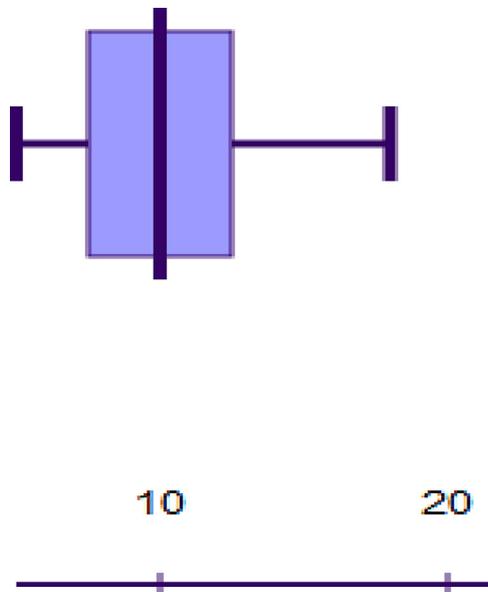


Fig. 2. Box and Whisker plot of MMSE of the patients with Seizures in the current study (n = 15).

4. Discussion

Alzheimer's disease and Mild Cognitive Impairment are related disorders, and hence have been studied together here. There is a significant conversion from MCI to AD and this makes MCI an extension of AD in a sizable number of cases.

The present study has given the frequency of seizures in AD/MCI in Indian population. The pubmed search using the website www.pubmed.com did not yield any article on the area using the search terms such as "Alzheimer's disease and India and Seizures". The study has, apart from the frequency, estimated the prevalence, which is near to the reported prevalence of dementia from the urban population.² Some of the characteristic features associated with seizures in AD/MCI have been seen. To our knowledge, this is the first study that has linked MTA with the seizures in AD/MCI patients using T1 weighted images of MRI brain. Our group had previously reported the occurrence of hippocampal atrophy in an uncontrolled study of 38 patients, where 7 had seizures and all of them had hippocampal volume loss.¹ The present study, on the other hand is a case-control comparative study of sufficiently large sample.

Most of the results of our study are in agreement with limited number of international studies done in this area. The mean duration of anti-seizure treatment in patients with AD MCI in the current study was 2.9 ± 0.3 years. Most cases had controlled seizures but two cases who experienced breakthrough seizures. Seizures are more common in patients with mutations in *PSEN1*, *PSEN2*, or *APP*, as well as with *APP* duplication.⁷ Also, the amyloid- β possible is a possible link between AD and seizures.³ It has been

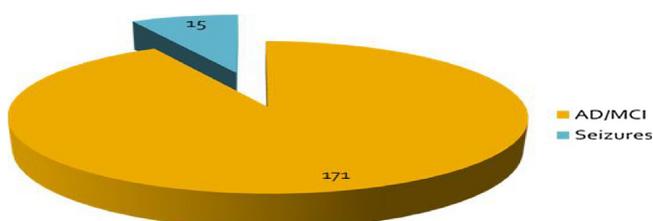


Fig. 3. Proportion of cases with seizures in a sample of 171.

seen that antiepileptic drugs rescue cognitive deficits in AD mouse models and human patients.^{7–8} AD is clinically characterized by insidious onset of memory and cognitive impairments, which are also presented in patients with temporal lobe epilepsy.⁹

Several questions remain unanswered about the occurrence of seizures in AD. Like for example, do epilepsy and AD share pathophysiology? The diagnosis of seizures in AD is also not easy and overlooking the subtle manifestations of seizures can lead to underestimation. Likewise, "funny" or "unusual" behaviors of demented patients with seizures may lead to overestimation of seizure rates. To add to the diagnostic confusion, in patients with AD some nonepileptic episodes of inattention or confusion as well as syncope or near-syncope can also occur. Generalized seizures are the most common type of seizures that occur in AD followed by partial seizures. It has been seen that the seizure prevalence increase with AD duration. Observationally, it has been seen that in patients with AD, the onset of seizures occur in the later stages of the disease. The Choice of antiepileptics in these patients is empirical and is based on side effect profiles.

In the present study, seizures have occurred both late (n = 5) and early (n = 4) in the course of disease AD, while were seen early in MCI (n = 4). Most cases have responded to the drug treatment i.e. seizures were controlled. In a meta-analysis of 10 pooled studies showed predictors like younger age, greater degree of cognitive impairment, and history of antipsychotic use were independent risk factors for new-onset seizures in AD.¹⁰ In the present study, increasing duration of dementia, severity, and smaller medial temporal lobe volumes were correlated with seizures. We could not find an association of young age with seizures in the current study, as most of our patients are brought to the hospital in later stages rather than young due to lack of awareness. Seizures in AD are more common than general population.¹¹ Reported prevalence and incidence of seizures in patients with AD is quite variable¹² with reported lifetime prevalence rates of 1.5–64%.⁴ The prevalence of seizures in MCI is currently unknown. This is the first study to our knowledge giving the prevalence of seizures in MCI; else, the seizures in MCI are grouped under the "elderly seizures". Since there were 6 cases of seizures with MCI in a population of 96 over the 3 years in the memory clinic; the prevalence comes out to be 1.04%. Since this is a hospital based study, so the prevalence data should be interpreted with caution. However, this gives a hint about the prevalence of this important condition in MCI. In the absence of any other study available on the subject from India, however, this data can be used as a reference.

Only recently has some information about the predictors of seizures in AD become available. Population based study has highlighted the importance of duration of disease as a risk factor for seizures in AD.¹³ More needs to be learnt about the seizure predictors in this population.¹⁴ In the present study, MTA¹⁵ was marked in all patients with seizures, and is greater compared to controls.¹ Our group has previously published the sensitivity and specificity of MTA.¹⁵ This result of the present study i.e. MTA more in seizures with AD compared to those without is in agreement with our study¹ done earlier (n = 7). However, this was a very small study, and there were no controls. The medial temporal lobe atrophy has been used as an alternative to the hippocampal volumetry and its usefulness has been demonstrated only in AD but in other dementias like dementia with Lewy body as well.¹⁶ Additionally, the MTA has been correlated with behavioral and psychological disturbances of dementias¹⁷ and depression.¹⁵ Ours is the first study correlating it with seizures in AD/MCI. MTA has been underreported but its importance is now increasing.^{18–19} Epileptic activity associated with AD¹⁸ deserves increased attention because it has a harmful impact on these patients, can easily go unrecognized and untreated, and may reflect pathogenic processes that also contribute to other aspects of the illness.²⁰

Seizure activity in AD has been widely interpreted as a secondary process resulting from advanced stages of neurodegeneration, perhaps in combination with other age-related factors. However, recent findings have challenged this notion, raising the possibility that aberrant excitatory neuronal activity represents a primary mechanism that may contribute to cognitive deficits. Patients with sporadic AD have an increased incidence of seizures that appears to be independent of disease stage and highest in cases with early onset.^{21–22} Some cases of episodic amnesic wandering and disorientation in AD are associated with epileptiform activity and can be prevented with antiepileptic drugs.^{23–24}

Though the current study has confirmed the prevalence of seizures in AD, given the prevalence of seizures in MCI in a limited hospital setting; it has several limitations. Not all cases coming to the general outpatient department reported to the memory clinic. Hence, there is a dropout rate of 20%, which should be taken into account as well. Moreover, we have not taken the antipsychotic usage into account. This has been reported to be one of the predictors of seizures activity in elderly.¹⁹ Additionally, the study has relied on the clinical acumen of the senior neurologists in diagnosing the seizures in AD and rather than strict diagnostic criteria. Despite these drawbacks of cross sectional study in mind, the current study still provides a framework for the prevalence data; and also, the MTA rating that can easily be performed in a busy clinic. Large community based studies could be done to confirm the finding of this study.

5. Conclusions

Seizures are common in dementia of Alzheimer's type and not uncommon in MCI too. They have the potential to worsen the cognitive profile of the patient and need appropriate attention in these patients.

Conflict of interest statement

None.

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