

Basal serum cortisol levels, Depression and Medial Temporal Lobe Atrophy in patients with Mild Cognitive Impairment and Alzheimer's disease

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Abstract:

Objectives: Changes in serum cortisol levels have been reported in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). Atrophy of Medial Temporal Lobes (MTLs) is common in both conditions. Glucocorticoids are known to be neurotoxic and have been believed to cause damage to memory mechanisms in the brains; whether the same is applicable to AD/MCI is not known. Also, they have long been hypothesized to cause atrophy of MTLs but the proof of the same is lacking. The present study was performed to delineate correlations between serum Cortisol levels, Depression in Dementia and Medial Temporal Lobe Atrophy in patients with AD/MCI.

Methods: We randomly recruited 28 patients out of a total of 65 presenting with subjective memory complaints to the Department of Neurology, at a tertiary care institute during the study period (July 2014-2015). Morning serum Cortisol levels (8 AM) were analyzed in all patients (n=28) who met the diagnostic criteria for diagnosis of probable AD e.g. National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's disease related Disease Association criteria (NINCDS-ARDA) and Clinical Dementia Rating (CDR) for AD and MCI respectively. The Cornell Scale for Depression in Dementia (CSDD) was used to evaluate Depression. Visual Rating of Medial Temporal Lobe Atrophy (MTLA) was done using the Scheltens Visual Rating Scale. An association between the Depression and MTLA was evaluated using Pearson correlation coefficient.

Results: A total of 28 Patients (M: F=24:4, AD=13, MCI=15) were recruited for the present study. The mean age was 73.39 ±7.6 years and mean duration of illness was 3.4±3 years. Mean Mini Mental State Examination (MMSE) score was 21.7±7.4. A total of 4 patients (14%) had a high basal serum cortisol. Only one case out of these 4 had MCI and the rest had AD. There was a statistically significant correlation between serum Cortisol levels and MTLA (Pearson Correlation Coefficient=0.39, p<0.05). Similarly, a statistically significant correlation was found between serum Cortisol levels and CSDD scores (Pearson Correlation Coefficient=0.49, p<0.05). Likewise, there was a statistically significant negative correlation between MMSE and CSDD (Pearson Correlation Coefficient=-0.48, p<0.001).

Conclusion : Statistically significant correlation between Serum Cortisol and MTA Scores as assessed by Scheltens Visual Rating Scores was found (Pearson Correlation Coefficient=0.39, p<0.05; 95% confidence interval=0.02 to 0.66). Similarly, a significantly correlation was present between serum cortisol and CSDD Scores (Pearson Correlation Coefficient=0.49, p<0.05; 95% confidence interval=0.144 to 0.729). This suggests that glucocorticoids and depression and MTA in AD/MCI are inter-related and points towards the possible role that increase in endogenous glucocorticoids may play in pathophysiology of AD/MCI.

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Introduction

Alteration of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in patients with Alzheimer's disease (AD)¹⁻⁵. Changes in Cortisol levels in patients with AD prompted the hypothesis that stress and glucocorticoids are involved in the development or maintenance of AD⁶. Glucocorticoids might also influence amyloid beta levels and their deposition in patients with AD⁶. A small study (n=9) conducted almost a decade ago demonstrated that serum cortisol is mildly elevated in AD and could be related to disease progression^{7,8}. The association between apolipoprotein E Epsilon 4 (APOE ε4) and serum cortisol also suggests that the two common pathophysiological links i.e. amyloid beta and APOE ε4 are interrelated⁹. Prior studies have demonstrated that Medial Temporal Lobe (MTL) could be affected by AD/MCI. The importance of Medial Temporal Lobe Atrophy (MTLA) with respect to cognitive decline is further established by hippocampus's role in memory formation¹⁰⁻¹¹.

Chronically elevated cortisol levels have been associated with increased blood pressure and cerebral atrophy¹⁰ but its relationship with cognition seems to be a complex one. In one study of older adults (n=27), significant correlation between the HPA axis hyperactivity and frontal lobe atrophy¹⁰ was observed.

MTLA is more common in patients with AD/MCI with comorbid depression compared to those without². There is an elevation of serum cortisol in some patients with AD and in major depression as well⁹. Hippocampal area, the major component of the medial temporal lobe is sensitive to the toxic effects of glucocorticoids and undergoes atrophy under the influence of its chronic elevation. Therefore, the relationship between MTLA, serum cortisol and depression seems plausible. In the

present study, an attempt was made to see if a correlation exists between basal Serum Cortisol, Depression and Medial Temporal Lobe Atrophy Visual Rating Scores in patients with AD/MCI.

Material and Methods

Screening

We screened 60 patients with complaints of subjective memory impairment presenting to the Department of Neurology at a tertiary care centre starting from July 2012 to July 2015 and enrolled 28 of them into the study. These patients met the diagnostic Criteria for diagnosis of Dementia of Probable Alzheimer's disease [(National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's disease related Disease Association criteria (NINCDS-ARDA)]. For the diagnosis of MCI, Clinical Dementia Rating Scale (CDR Score=0.5) was used. Dementias other than AD were excluded from the study.

Patient Selection and Diagnostic Evaluation

Selected patients underwent detailed neuropsychological, radiological and neurological examination for diagnosis of AD. A detailed general physical examination was conducted in all cases to rule out systemic diseases that could have accounted for the cognitive impairment besides AD. Routine laboratory examination and work up to rule out other types of dementias was also done.

A written and informed consent was obtained from all study participants. The study was approved by institutional ethics committee.

Study Design

This is a cross sectional and observational study in which recruited patients with AD/MCI were subjected

to Magnetic Resonance Imaging of the Brain and serum cortisol measurement. Serum cortisol was then

Table-1: Methodology of Scheltens Visual Rating for Medial Temporal Rating Scale

| Scoring | Interpretation |
|---------|------------------|
| 0 | No atrophy |
| 1 | Minimal atrophy |
| 2 | Mild atrophy |
| 3 | Moderate atrophy |
| 4 | Severe atrophy |

correlated to MTLA and depression. Selected patients were free from concurrent neurological or mental disorders. All were but 3 were past non-smokers and non-alcoholics. Serum cortisol levels for patients with depression were assessed before starting them on antidepressants or any other treatments/s for dementias (e.g. anticholinesterases). Later on, patients with depression were treated with antidepressants (e.g. escitalopram/sertraline) or with anticholinesterases (e.g. donepezil/rivastigmine).

Scales

1. Mini Mental Status Examination (MMSE): to cognitive screen and categorise patients into mild, moderate and severe cognitive impairment. MMSE is a tool that is used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language.
2. Scheltens Visual Rating of Medial Temporal Lobe Atrophy: The visual rating of MTLA was done using

this scale⁵ by obtaining T1 weighted coronal section image on MRI scan of the brain. This rating does not require any special radiological training and can be done easily using hard copies of T1 weighted coronal sections of the brain

3. MRI. It has a diagnostic accuracy of over 80% in diagnosing dementia of Alzheimer's type (Table-1).
3. Cornell Scale for Depression in Dementia (CSDD): considered to be the Gold Standard for assessment of depression in Dementia. This scale is the best validated instrument for assessing depression in dementia and takes into account that some of the symptoms of dementia can mimic those of depression. CSDD involves a comprehensive semi-structured interview to reach a composite clinical rating. Depression was evaluated using CSDD. Those with AD/MCI and CSDD scores greater than 10 were included for cortisol level estimation (10 is the cut off score for depression in dementia).
4. Clinical Dementia Rating Scale: The Clinical Dementia Rating is a five-point scale in which CDR-0 connotes no cognitive impairment, and then the remaining four points are for various stages of dementia: The CDR 0.5 is considered to be mild cognitive impairment.

All the scales used in the current study have been well validated and extensively used in Indian patients^{2,22-24}.

Radiology Protocol

MTLA was assessed using a template based on Scheltens Visual Rating Scale (Figure-1). MRI scans were done using 1.5 Tesla Magnetic Resonance (Megnatom Symphony 1.5T scanner). T1 weighted Coronal sections were used for rating MTLA.

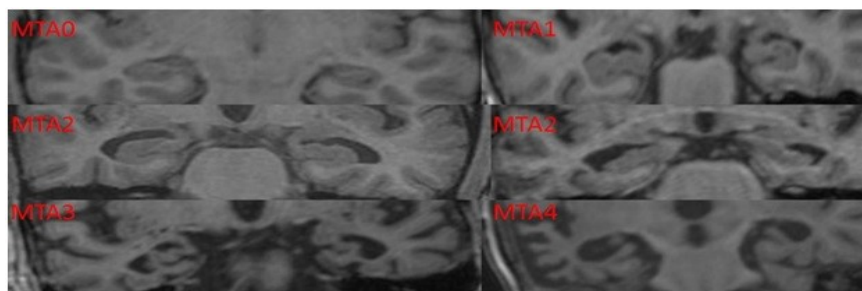


Figure-1: Scheltens Visual Rating Scale used in the current study to assess the medial temporal lobe atrophy rating scores.

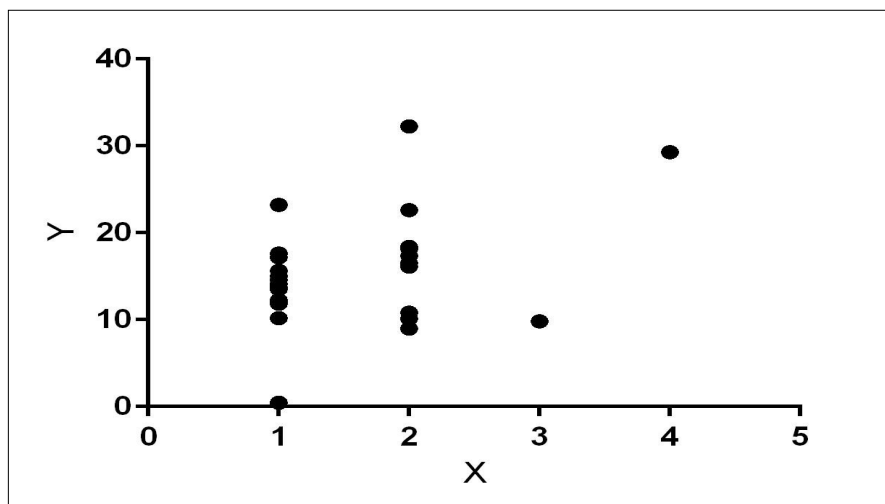


Figure-2: Linear regression showing correlation between serum cortisol (y) and MTA scores (x).

Biochemical Analysis

After an overnight fasting, morning samples (8 AM) of 5 ml whole blood were withdrawn from the antecubital vein. A total of 3 ml serum was extracted and estimation was done using Chemiluminescence based competitive assay. A reference range of 10-20 microgram/dl was used as normal. This study was approved by the Institutional Ethical Committee.

Statistical Analysis

The latest version of Statistical Package for Social Sciences (SPSS®-SPSS Inc., Chicago, IL) was used for data analysis. Normality of data was checked using Q-Q plot. Correlations and Pearson Correlation Coefficients were assessed for various variables. Linear regression was done. Differences between left and right medial temporal lobe ratings were compared using *paired t-test*. Two tailed *p-value* <0.05 was used to test the level of significance. Confidence interval (95%) was calculating using value of Pearson Correlation Coefficient (r).

Results

A total of 28 Patients (M=24: F=4) presenting with subjective memory complaints/cognitive abnormalities to the Department of Neurology of a tertiary care hospital in India were assessed. These included 15 patients with MCI and 13 with AD. The mean age was 73.39 ±7.6 years and mean duration of illness was 3.4±3 years. The mean MMSE Score was 21.7±7.4. Mean CSDD score was 11.6±6 and mean MTLA scores of both sides were 1.5±0.74.

There was no statistical difference between left and right MTLA scores ($p>0.05$) using *paired t test*. Mean basal serum cortisol level was 15.3±6.3 microgram/dl for all patients and 18±7 microgram/dl for patients with AD. Four patients (14%) had a high morning serum cortisol. Only one case out of those 4 was MCI, rest three had AD (mean MMSE=15.3±3).

There was a significantly positive correlation (Figure-2) between serum cortisol level and MTLA scores (Pearson Correlation Coefficient=0.39, $p<0.05$). Similarly, a significantly positive correlation was present between serum cortisol and CSDD Scores (Pearson Correlation Coefficient=0.49, $p<0.05$).

There was a significantly negative correlation between MMSE and MTA scores (Pearson Correlation Coefficient=0.60, $p<0.0001$). No significant correlation between age and MTA scores was observed. A positive correlation between CSDD and MMSE was also present ($r=0.40$, $p<0.05$). One way Analysis of Variances (ANOVA) test was performed using standard weighted-means analysis to see if the groups with MMSE scores, MTA scores, serum cortisol and CSDD scores were significantly different from each other. ANOVA showed a highly significant difference between groups ($p<0.0001$). Tukey's Honestly Significant Difference Test showed that all 4 independent groups at alpha level of significance (0.05) were significantly different from each other. Odds ratio of serum cortisol in AD/MCI was 3.4 (95% confidence interval=0.3197 to 37.4751), however the *p-value* was not significant.

Discussion

Alteration in serum cortisol has been observed in prior studies involving AD patients¹. This cortisol elevation could possibly happen as a response to stress. Dysregulated hypothalamic-adrenal-pituitary axis can cause damage to the Hippocampus, a structure located in medial temporal lobe, important for learning and memory. Poor memory and mis-communication² may propound stress. A greater severity of dementia is associated with rise in serum cortisol³. In our study as well, high serum cortisol was found in 14% of the patients with AD/MCI. Earlier studies have demonstrated that higher/rising serum cortisol is associated with rapid disease progression⁴. It has been postulated that the negative feedback of the shrunken hippocampus becomes weak and is unable to exert its inhibitory effect and hence leads to hypercortisolemia².

Qualitative visual assessment of Temporal Lobe Atrophy on MRI has high sensitivity in distinguishing AD from normal aging, depression, and vascular dementia^{2,9-10}. Atrophy of the MTL is particularly important because it can be detected earlier than generalized atrophy in patients with AD^{2, 11-13}. No prior studies have correlated serum cortisol levels with MTLA scores, although they have been correlated with hippocampal volumes in the past¹⁴. We wanted to see if the same correlation can be observed using a visual rating scale as well. This is important as MTLA can be assessed quickly using the visual rating as a bedside tool in busy clinics. Mild elevation of serum cortisol has been observed in patients with AD in the previous studies¹. We observed 4 patients with cortisol elevation in this series. Since we had more number of patients with MCI than AD; therefore frank hyper-cortisolemia was not seen. Moreover, our patients had moderate AD (mean MMSE=15.3±3) rather than severe AD which are more likely to have higher cortisol levels³⁻⁵. In general MCI patients do not have very high serum cortisol levels. In fact patients with MCI might have even lower than normal adult levels of serum cortisol which makes the association between cortisol and AD/MCI a complex one¹⁵. Some of the findings of this study are similar to our earlier study, where we demonstrated that MTLA is more common in patients with AD/MCI with depression compared to those without². In this study, there was a negative correlation between MMSE and CSDD

suggesting that patients with decreased cognition (severe dementias) are more likely to have depression.

A silico-model of hippocampal dysfunction correlated hippocampal activity (HA) and serum cortisol. This model predicted that aging induces a 12% decrease in HA. Acute and chronic elevations in cortisol decreased the HA further to 30% and 40% respectively. A biological intervention used in the study attenuated the cortisol induced decrease in HA by 2% in the acute cortisol simulation and by 8% in the chronic simulation¹⁶. This suggests that higher serum cortisol levels may potentially have a negative consequence for hippocampus and for disease in general. How much of this is applicable to AD/MCI currently remains unknown¹⁶.

In a recent study of 155 patients, serum cortisol was found to have distinct ability to differentiate AD patients from healthy controls¹⁷. However, the contributory effect of serum cortisol towards cognitive decline remains uncertain¹⁸⁻²¹. In the present study, cortisol levels of patients with AD were higher than the mean of all patients (AD+MCI) combined together (18±7 microgram/dl) and yet the levels were within normal range. Our results are in agreement with the Rotterdam study where serum cortisol of larger number of patients was studied (n=90)¹⁹. Our study also confirms the findings of a study² that observed correlations between MTLA and depression. In addition, we have shown correlation between serum cortisol and MTLA. Correlation between serum cortisol and MTA seems in accordance with animal data and the proposed hypothesis that higher cortisol might contribute to MTLA³⁻⁵. However, larger study with greater sample size could be done to confirm these findings.

Present study also highlights an important issue related to depression in Dementia. The findings are in accordance with those of a previous study in patients with AD having comorbid depression² and further, this correlation can be confirmed using biochemical means as well. A negative correlation between MSSE and CSDD scores is also an interesting finding which points towards the fact that decreased cognition (as observed in Dementia), increases the possibility of depression. Conversely, a higher level of depression might contribute to decreased cognition. The study also establishes a strong negative correlation between MMSE and MTA

scores (Pearson Correlation Coefficient=0.60, $p<0.0001$). This confirms that an increasing severity of dementia is associated with greater MTLA. A sex bias²²⁻²⁴ can be seen in the present study and can limit the external validity of the study apart from the small sample size. This sex bias is typical of memory disorders in several developing countries² where females are hardly brought in for treatment.

The issue of depression in AD/MCI and MTA is getting increasing attention. For example, a recent large study ($n=366$) showed that hippocampal atrophy was more pronounced among patients having MCI with depressive symptoms. These findings suggest that different mechanisms underlie depression in older people with and without AD and may explain some of the inconsistent observations in previous studies²⁵. Additionally, the Leukoaraiosis and Disability in the elderly (LADIS) study²⁶ which was another large study ($n=639$) that showed that the depressive symptoms are associated with an increase risk of cognitive decline, independent of the effect of white matter lesions in brain, probably due to an additive or synergistic effect. In this context, depressive symptoms probably represent a subtle ongoing organic dysfunction. A small pilot study also suggested that amnesic MCI (aMCI) can be distinguished from late life depression based on cerebral atrophy measures and that the hippocampal and entorhinal atrophy in aMCI varies according to the presence or absence of depressive symptoms²⁷. The latter suggests that not only can MTLA be used to distinguish different types of dementias, but it is also valuable as a bedside tool to differentiate aMCI from late life depression.

Conclusion

A statistically significant correlation between serum Cortisol and MTA Scores as well as between MTA Scores and CSDD scores highlights the importance of glucocorticoids as a potential contributor towards Medial Temporal lobe Atrophy in patients with AD/MCI.

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