Hippocampal Magnetic Resonance Neurochemistry and Quantitative Neuromorphometry in clinically diagnosed Dementia patients

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Aims and objectives

The global prevalence of dementia is estimated to be 24 million and likely to double every 20 years. [1] AD (Alzheimer's disease) is the most common primary neurodegenerative disease but usually coexists with other pathologies associated with aging and dementia, most commonly cerebral small vessel disease. [2] Less common but important causes of dementia are vascular dementia, DLB (dementia with Lewi bodies) and FTD (fronto-temporal dementia).

Considering the expected burden of dementia in future, it is important to diagnose the condition as early as possible. There are various complex causes of dementia and it is important to differentiate the various types of dementia to start appropriate treatment.

In vivo structural changes of demented brains have been studied using magnetic resonance imaging (MRI) with increasing frequency. Magnetic resonance imaging can provide detailed anatomic information in multiple imaging sections with excellent tissue contrast and spatial resolution. There is no ionized radiation with the MRI technique, which makes it the modality of choice for repeated measurements in longitudinal studies. [3]

Several literatures have shown that hippocampal MR volumetry and H1 MRS (Proton Magnetic Resonance Spectroscopy) can be helpful in diagnosing and differentiating the various types of dementia. [4-10] However, there is not enough data available on south Asian population. Our study was an attempt to study our dementia patient population for the volumetric and spectroscopic changes in hippocampus.
Methods and materials

Patient population:

Cross-sectional study with Institutional review board approval, was performed for 32 clinically diagnosed dementia cases by department of psychiatry VIMS & RC, Bengaluru and 32 aged matched controls with no evidence of clinical dementia. Informed consent was obtained from all the subjects.

Patients attending to the Memory and Dementia Clinic of department of Psychiatry who consented for the study were included in the study by purposive random sampling. Diagnosis of Dementia was made as per ICD 10 classification of mental and behavioral disorders by WHO by a consultant Psychiatrist and cognitive function was evaluated in all participants by using Mini Mental Status Examination (MMSE). Since majority of our subjects did not belong to highly educated group, a score of 24 was taken as normal and a score less than 24 was included in the study.[11,12]

MR volumetry was performed for bilateral hippocampi and total hippocampal volume was generated in both cases and controls for comparison among cases and controls. H1 MRS was performed for bilateral hippocampi and NAA/Cr,

ml/Cr and Cho/Cr ratios were calculated which were compared between case and controls.

Data acquisition and analysis:

MR images were acquired with a 1.5-T MR unit Philips, Achieva scanner (Philips Medical system, Netherlands) using a standard head coil. The imaging protocol consist of a tilted coronal T1-weighted IR (delay 400 ms) sequence with slice thickness 2 mm, repetition time 3811 ms, echo time 15 ms, flip angle 25°, and matrix 512 x 512. On coronal viewing, the most anterior slice is the slice on which the hippocampus is first visible. This is seen as a notch in the medial border of the temporal horn of the lateral ventricle; the border between the amygdala and the hippocampus. The structure of the hippocampus was followed with the white matter of the alveus as a border between the hippocampus and the amygdala. The uncal apex of the hippocampus was then visible. Sometimes the hippocampus appeared to be in two parts-if so, both parts were included. Care was taken not to include choroid plexus. The tail of the caudate nucleus, the optical tract, and the lateral geniculate nucleus as well as the more posterior part of the pulvinar are grey matter structures that were not included.

When atrophic, the hippocampus being mostly surrounded by CSF. In the most posterior slices, the fimbria continues into the fornix. A straight horizontal line was drawn through the fimbria/fornix at the dorsal border (the greyer appearing part) of the hippocampus.
The last, most posterior, slice to measure was the first slice on which the total length of the crus of the fornix was seen. The regions were manually marked on successive MR images, and the volume was calculated by software. Total hippocampal volume was calculated by summing up right and left hippocampal volumes.

H1 Magnetic Resonance Spectroscopy: The single-voxel 1H MRS studies were performed with Point-Resolved Spectroscopy (PRESS) Pulse Sequence with an echo time (TE) of 144 milliseconds (ms) and repetition time (TR) of 2000 ms. The VOI was placed in the most gray matter zone of hippocampus. The 1H-MRS parameters analyzed in this study were NAA/Cr, ml/Cr and Cho/Cr.

Statistical analysis:

Data were analyzed using SPSS version 20 for windows. The data were tested for normality and were found to vary significantly from normal distribution on Shapiro Wilks Test. Hence we did a non parametric Mann Whitney test to compare hippocampal volumes and spectroscopy values between dementia and controls.

Within dementia group we compared the hippocampal volumes and spectroscopy between various clinical dementias -- Alzheimer's, Vascular, Frontotemporal and Parkinson's disease using One-Way ANOVA with post hoc Tukey's test. Bivariate relationships between MMSE score and age were compared with hippocampal volumes and spectroscopy using Pearson's Correlation Analysis.
Results

Largest group of dementia subtype found in our study was Alzheimer's (62.5%). All the patients and controls were within the age group of 50-80 yrs. All pts were left handed.

There was a significant decrease in hippocampal volume, \((z=0.89, p<0.001)\) in patients with dementia compared to controls on non-parametric independent samples Man Whitney Test [Table 1]. Among the different types of dementias most significant decrease was found in Alzheimer's and vascular dementia [table 2].

There was a significant decrease in NAA/Cr ratio \((p<0.001)\) in dementia pts as compared to controls [table 3]. The change was most significant with Alzheimer's and vascular dementia group. There was a significant increase in Mi/Cr in Alzheimer's disease \((p<0.001)\) and vascular dementia \((p=0.007)\) compared to controls on the Rt Hippocampus. There was no significant change in Cho/Cr ratio in these dementia subtypes compared to control group on post Hoc Tukeys test [table 4].

Bivariate relationships:

There was a significant positive correlation between mini mental state examination and hippocampal volume and NAA/Cr ratios in dementia [right hippocampal volume \((r=0.74, p<0.001)\), left hippocampal volume \((r=0.75, p<0.001)\) total volume \((0.49, p<0.001)\) and right and left NAA/Cr ratio \((r=0.49, p<0.001)\)].

Limitations:

The study had relatively small sample size, especially for Parkinson's dementia \((n=3)\) and unspecified dementia \((n=3)\), which is a limiting, factor in our study.
Fig. 1

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Fig. 2: Volumetry in a normal subject and a case of alzheimer's.
**Fig. 3:** Dementia - MRI volumetry and MRS

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<table>
<thead>
<tr>
<th>GROUP</th>
<th>Rt Hippo Vol (cm³) Mean ±SD</th>
<th>Lt Hippo Vol (cm³) Mean ±SD</th>
<th>Total Vol (cm³) Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia, N=32</td>
<td>2.0 ± 0.13**</td>
<td>1.96 ± 0.24***</td>
<td>3.95 ± 0.27***</td>
</tr>
<tr>
<td>Controls, N=32</td>
<td>2.30 ± 0.24</td>
<td>2.34 ± 0.25</td>
<td>4.64 ± 0.47</td>
</tr>
</tbody>
</table>

***p<0.001 on Mann Whitney Test

**Table 1:** Volumetry Dementia vs Controls

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**Table 2:** Volumetry-Dementia subtypes

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<table>
<thead>
<tr>
<th>Group</th>
<th>Rt Hippo Vol cm³ Mean±SD</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Controls, N=32</td>
<td>2.30±0.24</td>
<td>2.34±0.25</td>
<td>4.64±0.47</td>
</tr>
<tr>
<td>Alzheimers, N=20</td>
<td>1.94±0.09***</td>
<td>1.95±0.13***</td>
<td>3.89±0.19***</td>
</tr>
<tr>
<td>Parkinsons, N=3</td>
<td>2.06±0.10</td>
<td>2.08±0.03</td>
<td>4.13±0.10</td>
</tr>
<tr>
<td>Vascular, N=6</td>
<td>2.11±0.15</td>
<td>1.84±0.50</td>
<td>3.93±0.44**</td>
</tr>
<tr>
<td>Unspecified D, N=3</td>
<td>2.07±0.17</td>
<td>2.13±0.12</td>
<td>4.20±0.29</td>
</tr>
</tbody>
</table>

Comparison of hippocampal volumetry in individual dementia subtypes with controls. ***p<0.001, **p<0.01 on post hoc Tukeys test

**Table 3:** MRS- Dementia vs controls.

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<table>
<thead>
<tr>
<th>Group</th>
<th>Rt NAA/Cr Mean±SD</th>
<th>Lt NAA/Cr Mean±SD</th>
<th>Rt Cho/Cr Mean±SD</th>
<th>Lt Cho/Cr Mean±SD</th>
<th>Rt Mi/Cr Mean±SD</th>
<th>Lt Mi/Cr Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia n32</td>
<td>1.18±0.30***</td>
<td>1.11±0.32***</td>
<td>1.32±0.44***</td>
<td>1.39±0.42</td>
<td>0.51±0.33***</td>
<td>0.32±0.76</td>
</tr>
<tr>
<td>Controls n32</td>
<td>1.57±0.41</td>
<td>1.67±0.37</td>
<td>1.37±0.34</td>
<td>1.37±0.29</td>
<td>0.14±0.06</td>
<td>0.15±0.06</td>
</tr>
</tbody>
</table>

***p<0.001 on Mann Whitney Test
<table>
<thead>
<tr>
<th>Dementia Subtype</th>
<th>Rt NAA/Cr Mean±SD</th>
<th>Lt NAA/Cr Mean±SD</th>
<th>Rt Cho/Cr Mean±SD</th>
<th>Lt Cho/Cr Mean±SD</th>
<th>Rt Mi/Cr Mean±SD</th>
<th>Lt Mi/Cr Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimers n20</td>
<td>1.13±0.32***</td>
<td>1.08±0.39***</td>
<td>1.27±0.41</td>
<td>1.41±0.39</td>
<td>0.58±0.34***</td>
<td>0.43±0.96</td>
</tr>
<tr>
<td>Parkinsons n3</td>
<td>1.24±0.16</td>
<td>1.30±0.04</td>
<td>1.55±0.38</td>
<td>1.47±0.49</td>
<td>0.08±0.06</td>
<td>0.12±0.07</td>
</tr>
<tr>
<td>Vascular n6</td>
<td>1.24±0.26**</td>
<td>1.09±0.15**</td>
<td>1.37±0.56</td>
<td>1.27±0.37</td>
<td>0.49±0.33**</td>
<td>0.15±0.05</td>
</tr>
<tr>
<td>Unspecified n3</td>
<td>1.35±0.36</td>
<td>1.13±0.29</td>
<td>1.31±0.63</td>
<td>1.40±0.76</td>
<td>0.49±0.05</td>
<td>0.16±0.08</td>
</tr>
</tbody>
</table>

**p<0.001, ***p<0.01 on post hoc Tukeys test

**Table 4:** MRS-Dementia subtypes

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Conclusion

The purpose of this study was to examine with the help MRI and H1 MRS the relationship between different types of dementia and hippocampal volume and biochemical changes. It was concluded that there is decrease in the total hippocampal volume in dementia as compared to normal individuals.

The hippocampal volume reduction is more pronounced Alzheimer’s disease, the most common cause of dementia followed by vascular dementia, as compared other subtypes of dementia. It was also found that there is reduction in NAA/Cr ratio bilaterally in dementia cases and increase in ml/Cr especially in Alzheimer’s and vascular dementia.

It was also found that MMSE score had a strong positive correlation with hippocampal volume and NAA/Cr ratio. These results should be validated in a larger group of patients and in prospective study.
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