Original Article

Prevalence of hippocampal morphologic variants between healthy elderly subjects and patients with Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disease with atrophic changes in the temporal lobe. Enlargement of cerebrospinal fluid (CSF) spaces, hippocampal sulcus (HS) enlargement, or an increase in the number or size of hippocampal cavities (HCs) could be associated with medial temporal lobe atrophy (MTA). In this study, we assessed the relation of these CSF spaces with AD.

Materials and Methods: A total 36 demented patients with diagnosis of Alzheimer (Mini-Mental State Examination (MMSE) ≤25) and 36 non-demented elderly individuals were referred for basic magnetic resonance imaging (MRI) before initiating anti-dementia therapy in the demented group. Two observers assessed the maximal HS width, as well as the occurrence, number, and size of HCs, and the visual rating score of MTA on magnified coronal high-resolution T1-weighted MR images.

Results: The findings of our study indicate that the presence of hippocampal cavity (HC) (especially in the left side) and medial temporal lobe atrophy in demented patients was significantly higher in comparison with non-demented elderly subjects ($P \leq 0.05$). There was a significant relationship between MTA and HS width ($P = 0.003$, $r = 0.00323$), and it also had a trend to be significant with size of HCs ($P = 0.08$, $r = 0.00314$). A correlation between MTA and number of HCs was not detected.

Conclusion: HS width is associated with MTA in patients with AD. It may serve as a measure to evaluate MTA for identifying individuals at particularly high risk for Alzheimer progression, and could be employed for selecting subjects for clinical trials or for treatment decisions.

Key Words: Alzheimer's disease, hippocampal cavities, hippocampal sulcus, magnetic resonance imaging

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Received: 13.10.2012, **Accepted:** 21.10.2012

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.125817

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that primarily affects the elderly. Selective memory impairment and dementia are the main clinical manifestations of AD. AD is characteristically a disease of the elderly. Prevalence of AD in patients younger than 60 is uncommon. Women are affected with AD slightly more common than men, with a relative risk of 1.5.[1,2]

How to cite this article: Hekmatnia A, Basiratnia R, Koohi R, Barekatein M, Ahrar H, Hekmatnia F, *et al*. Prevalence of hippocampal morphologic variants between healthy elderly subjects and patients with Alzheimer's disease. Adv Biomed Res 2014;3:59.

At present, AD afflicts 10% of individuals over 65 years old, and more than 50% of persons over 80 years old. Approximately every 5 years between the ages of 65 and 85, the risk of developing AD doubles. Therefore, the aging demographics suggest a great necessity to accurate diagnosis of AD and to specifically differentiate it from several other possible causes of cognitive impairment.[3]

The earliest manifestation of AD, which is an essential characteristic for the disease, is memory impairment. There is a distinctive pattern of memory impairment. Declarative memory for facts and events (episodic and semantic memory), which is processed by the medial temporal lobe, neocortical structures, entorhinal cortex, and related structures in the mesial lobe, is profoundly affected in AD, whereas subcortical systems supporting procedural memory and motor learning are relatively spared until quite late during the disease.[3-5]

AD is definitively diagnosed based on specific pathological lesions observed in cadavers, including intra-cellular neurofibrillary tangles (NFTs), β-amyloid deposition in the extra-cellular senile plaques and blood vessel deposits, synapse dysfunction, and synapse loss.[6,7] Both NFTs and amyloid plaques are related to diffuse synaptic loss (i.e. loss of connections between neurons) in AD patients' brains, with 30%-90% decrease depending on the brain regions observed.[4,8,9]

Magnetic resonance imaging (MRI) studies in AD patients have demonstrated that as the disease progresses, cortical atrophy also occurs in defined sequences, comparable to both extent of NFT pathology and magnitude of synapse loss.[10-12] Most MRI studies show that in mild AD patients, severe entorhinal cortex and hippocampal atrophy is consistently found, whereas volume reductions in the cortical regions, specially parieto-temporal, posterior cingulate/precuneus, and frontal cortices, can be shown in moderate-to-severe AD.[13-15]

Enlarged cerebrospinal fluid (CSF) spaces in the hippocampus have been shown in MRI studies of the medial temporal lobe among elderly and AD patients.[16,17] These spaces include the peri-hippocampal fissures, uncal sulcus, and the hippocampal sulcus (HS) residual cavity (HC). HCs are generally considered residual cysts resulting from lack of hippocampal fissure obliteration. Some investigators believe HCs are regularly found in routine MRI studies and represent a normal variant reflecting CSF collection.[18-20]

Considering that structural neuroimaging AD is focused on detection of medial temporal lobe atrophy (MTA), particularly of the hippocampus, Para hippocampal gyrus (including the entorhinal cortex), and amygdale and on the other hand brain atrophy results in enlargement of the CSF spaces, so it seems that either HS enlargement or an increase in the number or size of hippocampal cavities (HCs) could be associated with MTA occurring in AD. In addition, it will be useful to assess MRI in early diagnosis of AD; therefore the aim of this case-control study was to determine the relation between presence and enlargement (size) of the HS and HCs, comparing with a control group.

MATERIALS AND METHODS

A total 36 patients (22 men, 14 women) (demented patients with diagnosis of AD (According to the National Institute of Neurologic, Communicative Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for probable AD)) were referred by their neuropsychiatrist for basic MRI (to the MRI department of Al-Zahra Hospital, Isfahan, Iran) before initiating anti-dementia therapy.[21] Mini-mental state examination (MMSE) was done to evaluate cognitive function..[22]

A total 36 subjects (19 men, 17 women) in a control group were non-demented elderly individuals who were referred by the same neuropsychiatrist for evaluation by MRI (to the same MRI department, within same time period) for complaints other than dementia (like headache, vertigo, dizziness) with normal MMSE. The control group are age-matched with the patient group.

In both groups, lacunar infarction, hydrocephalus, or demyelinating disease were excluded from the study.

A supraconductive magnet operating 1.5-T system and a routine imaging protocol for both group were used in MRI examination. in addition, other features of MRI were high-resolution three-dimensional(3D) T1 weighted gradient echo sequence.

Two observers assessed the maximal HS width by means of fimbriosubicular distance at the anterior part of the hippocampal body, as well as the occurrence, number, and size of HCs, and the visual rating score of MTA on magnified coronal high-resolution T1-weighted MR images. Our observers were unaware about the patient's clinical data.

The HS is a shallow groove just below the fimbria and above the subiculum. Fimbriosubicular distance as an indicator of HS width is a linear measurement perpendicular to the long axis of the temporal lobe in

high-resolution coronal T1-weighted images [Figure 1].

HCs are defined as sharply demarcated cystic structures (iso-intense with CSF) localized at the apex of the hippocampal fold. The greatest dimension of each of the HCs is determined on coronal T1-weighted images [Figures 2 and 3].

We also used a visual rating scale to evaluate MTA[23] on coronal T1-weighted images (possible range of scores for each side, 0-4) [Table 1]. The degree of MTA was ascertained with a ranking procedure and was validated by linear measurements of the medial temporal lobe, including the hippocampal formation and surrounding spaces occupied by the CSF.

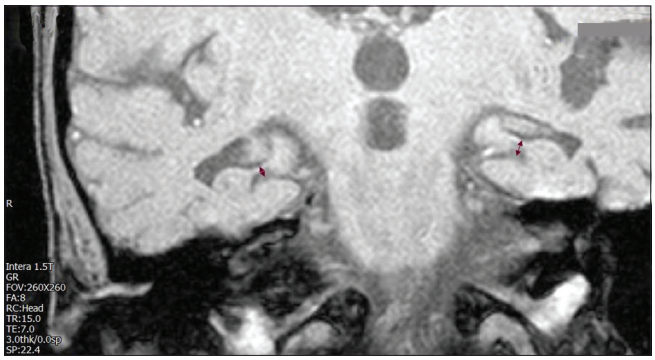

Figure 1: Fimbriosubicular distance as an indicator of HS width is a linear measurement perpendicular to the long axis of the temporal lobe in high-resolution coronal T1-weighted images

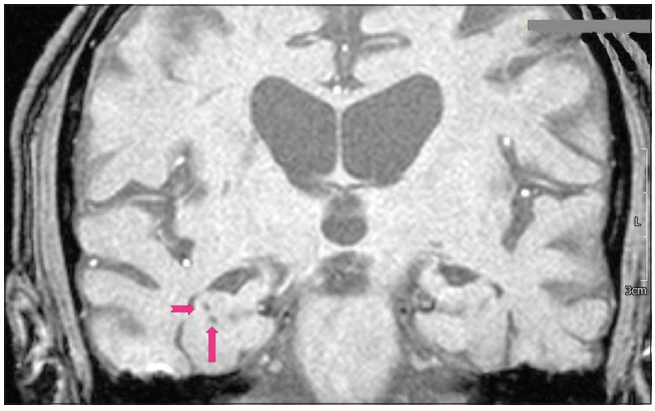

Figure 2: A high-resolution coronal T1-weighted image at the level of the hippocampus. HCs (long arrows) are defined as sharply demarcated cystic structures (iso-intense with CSF) localized at the apex of the hippocampal fold

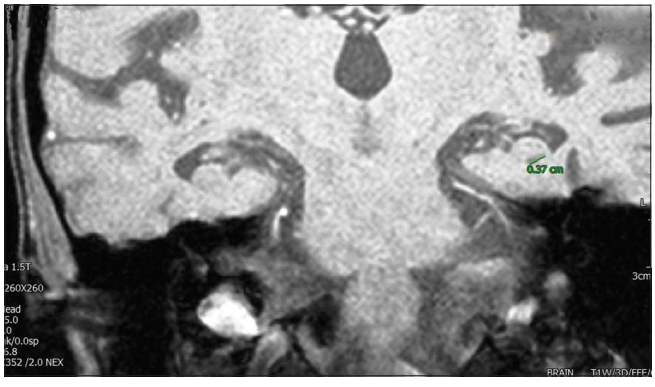

Figure 3: An HC with a diameter of 0.37 cm in the left hippocampus is noted in the T1-weighted image at the level of the hippocampus

The relation between prevalence, size of HCs, and HS width and MTA score has been examined by independent *t*-test and χ^2-test. To assess inter-observer agreement, we used the kappa coefficient for numerical variables. The whole analysis was performed by using SPSS 15.0.

RESULT

The findings of our study indicate that the presence of HC (especially in the left side) in patients with AD in comparison with non-demented elderly control subjects was significantly higher ($P \leq 0.05$) [Table 2].

Patients with AD had higher grades of MTA than the control group and inter-observer agreement for MTA was significant (Mann-Whitney test).

Table 1: Visual rating of medial temporal lobe atrophy

Score	Width of choroidal fissure	Width of temporal horn	Height of hippocampal formation
0	*N*	*N*	*N*
1	↑	*N*	*N*
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

MTA: Medial temporal lobe atrophy

Table 2: Characteristics of patients with Alzheimer's disease and non-demented elderly control subject, including age, Mini-Mental State examination, hippocampal sulcus, width, number, and size of hippocampal cavities

Characteristic	Mean (SD)		*P* value
	AD patients	Control subjects	
Age	62.8+8.7	57.5+6.8	0.005
Male/female	22/14	17/19	0.24
MMSE score	20.1+3.4	27.6+1.6	≤0.0001
HCN-RI	0.7+0.8	0.44+0.7	0.1
HCN-LI	0.6+0.6	0.3+0.6	0.1
HCS-RI	0.2+0.1	0.17+0.4	0.2
HCS-LI	0.2+0.8	0.2+0.2	0.9
HS-RI	0.2+0.7	0.18+0.9	0.1
HS-LI	0.2+0.8	0.17+0.7	0.05
HCN-R2	0.6+0.6	0.6+0.8	0.8
HCN-L2	0.6+0.4	0.3+0.4	0.01
HCS-R2	0.2+0.9	0.015+0.7	0.07
HCS-L2	0.2+0.8	0.12+0.6	0.002

AD: Alzheimer's disease, HC: Hippocampal cavity, HS: Hippocampal sulcus, MMSE: Mini-mental state examination

There was a significant relationship between MTA and HS width ($P = 0.003$, $r = 0.00323$) and it also had a trend to be significant with size of HC (HCS) ($P = 0.08$, $r = 0.00314$). A correlation between MTA and number of HCs (HCN) was not detected.

Although inter-observer agreement was not significant for some indices such as HCS-L1 and HCS-L2, HS-R1 and HS-R2, and HS-L1 and HS-L2, inter-observer agreement for the presence of HS on the right and left side was 91.7% ($P \leq 0.05$) and 88.9% ($P \leq 0.05$).

There were no relation between mentioned variables and age in control group. the correlation was significant between HS,HCN and MTA, and age, but it was not between HCS and age.

DISCUSSION

Different reports have been published in this field, but our results were comparable to the report of Bastos-Leite's relation between HS enlargement and increase in the number or size of HCs with MTA occurring in AD was significant in both studies. They concluded that enlargement of the HS, assessed by the fimbriosubicular distance, was associated with MTA disease, but enlargement of the HCs were not, which was similar to our results. They reported that the observers neither found significant differences between patients with AD and non-demented subjects with respect to occurrence, number, or size of HCs, nor did they find a significant correlation between the number or size of HCs and MTA.[5] However, because in our study occurrence of HCs was higher in the case group, a discrepancy between two observers has been created. The differences may be ethnic, environmental, and methodological, and to reach more conclusive results, a larger sample size will be needed.

MTA can be assessed by using visual rating scales, linear measurements of temporal lobe structures, and volumetry of the hippocampus.[24,5] Previous studies using computed tomography (CT) axial thin sections parallel to the long axis of the temporal lobe found enlargement of the choroidal–hippocampal fissure complex in AD, assessed either by visual rating of the medial hippocampal lucency or by using a quantitative stereological approach.[17,22,25] Other studies found linear measurement of the temporal horn width to be reliable for detection of AD.[26,27] Bastos-Leite *et al*. used a linear measurement between the fimbria and the subiculum on magnified coronal high-resolution T1-weighted images to estimate maximal HS width. They also used a visual rating scale for MTA, based on subjective evaluation of choroidal fissure width, temporal horn width, and hippocampal height.[24,5] They reported that the fimbriosubicular distance is significantly larger in patients with AD than in control cases with similar MTA scores. Because both the fimbria and the subiculum are part of hippocampal structures, this measurement may reflect purely hippocampal atrophy better than choroidal fissure width or temporal horn width, both surrounded superiorly and laterally by white matter of the temporal lobe.[5] Similarly, in our study higher grades of MTA were presented in patients with AD and also there was a significant correlation between MTA and HS. No significant correlation between MTA and HCS was found, but it had a trend to be significant.

HCs are usually defined as cystic remnants of the primitive hippocampal fissure, although some authors believe they actually represent enlarged peri-vascular (Virchow-Robin) spaces.[18,19,28] Their presence, increased number, or enlargement could reflect focal hippocampal atrophy.[29,30] They could be associated with white matter lesions and cognitive impairment.[31] In our study, although occurrence of HCs was higher in patients with AD, we did not find a significant difference between patients with AD and non-demented subjects with respect to their number or size. We also did not find a significant correlation between number or size of HCs and MTA. Our results were similar to the findings of Bastos-Leite *et al*.[16,32]

The current study indicated that there was no relation between the studied variables and age in the control group. In the case group, the mean age of patients with HC was higher than those without HC, but this difference was not statistically significant. Li *et al*. recently concluded that HC was poorly correlated with age and was not related to hippocampal atrophy.

All in all, the findings in this report represent that enlargement of the HS is associated with MTA in patients with AD and may serve as a measure to evaluate MTA or AD, and it is useful in identifying individuals particularly those at high risk for progression, and could readily be employed for selecting subjects for clinical trials or treatment decision, in the case of future improved medications.

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Source of Support: Isfahan University of Medical Sciences, **Conflict of Interest:** None declared.