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***Retrospective Study***

**Diagnostic value of amygdala volume on structural magnetic resonance imaging in Alzheimer’s disease**

Wang DW *et al*.Amygdala volume in Alzheimer's disease

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**Abstract**

BACKGROUND

The main clinical manifestation of Alzheimer’s disease (AD) is memory loss, which can be accompanied by neuropsychiatric symptoms at different stages of the disease. Amygdala is closely related to emotion and memory.

AIM

To evaluate the diagnostic value of amygdala on structural magnetic resonance imaging (sMRI) for AD.

METHODS

In this study, 22 patients with AD and 26 controls were enrolled. Their amygdala volumes were measured by sMRI and analyzed using an automatic analysis software.

RESULTS

The bilateral amygdala volumes of AD patients were significantly lower than those of the controls and were positively correlated with the hippocampal volumes. Receiver operating characteristic curve analyses showed that the sensitivity of the left and right amygdala volumes in diagnosing AD was 80.8% and 88.5%, respectively. Subgroup analyses showed that amygdala atrophy was more serious in AD patients with neuropsychiatric symptoms, which mainly included irritability (22.73%), sleep difficulties (22.73%), apathy (18.18%), and hallucination (13.64%).

CONCLUSION

Amygdala volumes measured by sMRI can be used todiagnose AD, and amygdala atrophy is more serious in patientswith neuropsychiatric symptoms.

**Key Words:** Alzheimer’s disease; Amygdala; Structural magnetic resonance imaging; Neuropsychiatric symptoms

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**Core Tip:** Amygdala volume measured by structural magnetic resonance imaging can be used for the diagnosis of Alzheimer’s disease, and the degree of amygdala atrophy is more severe in patients with neuropsychiatric symptoms.

**INTRODUCTION**

Amygdala, a part of the medial temporal lobe, is closely related to emotion and memory, and is one of the key brain regions in the pathogenesis of Alzheimer’s disease (AD)[1,2]. Studies have shown that the dysfunction of amygdala plays an important role in the emotional disorder of AD[3,4]. The pathological changes of AD brain such as senile plaque formation, nerve fiber tangle and neuron loss can appear in the amygdala[5-8].Clinical studies have shown that injury of the amygdala can lead to agitation, irritability, anxiety, and apathy[9-11].Patients with anxiety disorder, autism, phobia,and post-traumatic stress disorder can have dysfunctionof amygdala[12,13]. Medial temporal lobe is the earliest site of brain atrophy in AD[14]. There have been a lot of studies on MRI to evaluate the degree of atrophy of medial temporal lobe, but fewstudies on amygdala[15,16].

In this study, the amygdala volumes were measured by structural magneticresonance imaging (sMRI) both in AD patients and controls to evaluate the diagnosticvalue of amygdala. The correlation between amygdala atrophy and clinical features of AD was also analyzed.

**MATERIALS AND METHODS**

***Participants***

Twenty-two patients with AD and twenty-six controls were recruited from the Second Hospital of Shandong University (Shandong, China) between May 2017 and July 2019. The average age of the AD group was 73.9 ± 7.5 years, and the ratio of male to femalewas 1:1. Among the 22 patients, 4 cases were mild AD, 10 cases were moderate AD, and 8 cases were severe AD (Table 1).Theinclusion and exclusion criteria were shown in our published article[17]. The study was approved by the Medical Research Ethics Committee of the Second Hospital of Shandong University and informed consentwas obtained from all participants.

***Neuropsychological tests***

All subjects received a cranial MRI scan and underwent neuropsychological tests including the Chinese version of the Mini Mental State examination[18], the Clinical Dementia Rating (CDR) scale(0:no dementia; 1: mild dementia; 2: moderate dementia; and 3: severe dementia)[19], the Hamilton depression scale, and neuropsychiatric inventory (NPI)[20,21].The NPI scale was used to evaluate the mental and behavioral symptoms of all AD patients and the severity of the symptoms was graded. The scale scores included the total scores of patients and psychological distress scores of caregivers. The former was obtained by multiplying the frequency of mental symptoms by the severity[20,21].

***Acquisition and processing of images***

All subjects received three-dimensionalbrain volume sequence brain MRI scans. T1-weighted image were analyzed using a set of automated analysis tools, and the steps were describedin detail in our previous article[17]. The bilateral amygdala volumes were measured both in AD patients and controls.

***Statistical analyses***

Categorical variable data are expressed as a frequency and percentage. Numerical data are presented as the mean ± standard deviation or median (interquartile range).Spearman’s rank or Pearson correlation coefficientwasused for the correlation analyses. Quantitative values were compared using theStudent’s *t*-test or Mann-Whitney *U* test. One-way analysis of variance or the Kruskal-Wallis test wasused to compare the data among three groups. The chi-square test was used to assess differences in categorical data. Diagnostic values were evaluated by receiver operating characteristic (ROC) curves and the area under the curve (AUC). *P*<0.05 was considered for a statistically significant difference. Statistical analyses were performed using SPSS Statistics (version 24.0) and GraphPad Prism version 5.0 software.

**RESULTS**

***Amygdala volume***

The left amygdala volume of the AD group was 1170.75 ± 402.63mm3, and that of the control group was 1559.65 ± 289.02mm3. The right amygdala volume of the AD group was 1342.01 ± 307.68mm3, and that of the control group was 1629.97 ± 250.24mm3. Student’s *t*-test showed that the bilateral amygdala volume in the AD group was significantly smaller than that in the control group (Figure 1, *P* < 0.01).

***Subgroup analysis***

The severity of dementia was graded by CDR score (4 mild AD, 10 moderate AD, 8 severe AD). As shown in Figure 2, the bilateral amygdala volume became smaller with the aggravation of dementia, but there was no significantstatistical differenceamong the three subgroups (Figure 2, *P*> 0.05).

Student’s *t*-test was used to compare the bilateral volume of the amygdala. There was no significant difference between the left and right amygdala (Figure 3A, *P*> 0.05). Twenty-five women and twenty-threemen were recruited in this study. Student’s *t*-test was used to observe the difference inamygdala volume between different genders. As shown in Figure 3B and C, there was no significant difference in amygdala volume between the female and male subjects (*P*> 0.05).

***Amygdala and neuropsychiatric symptoms***

NPIcan be used to evaluate the mental symptomsof dementia patients and the psychological distress of caregivers. All AD patients were divided into two groups according to mental symptoms. Thirteen patients had mental symptoms according to NPI scores(Table 2). The volumes of the bilateral amygdala were significantly different between the two groups, and the atrophy of AD patients with mental symptoms was more serious (Figure 4A, *P* = 0.0002; Figure 4B, *P* = 0.042).

As shown in Table 3, 59.1% (13/22) of the AD patients had at least one kind of neuropsychiatric symptom,the most common of which wasirritability (22.73%), sleep difficulties (22.73%), apathy (18.18%), and hallucination (13.64%). For mild AD (*n* = 4), onepatient (25%) had mental symptoms, manifested as irritability and agitation. Sixty percent (6/10) of moderate AD patients showed abnormal mental behavior, of which irritability and delusion were the most common. Seventy-five percent (6/8) of severe patients had neuropsychiatric symptom, and irritability and delusion were the most common.

Pearson correlation analysis showed that there was no significant correlation between NPI scores and amygdale volumes(Figure5A and B, *P*> 0.05). In addition, there was no correlation between the psychological distress scores of caregivers and amygdala volumes(Figure5C and D, *P*> 0.05).

***Correlation between amygdala and hippocampal volume***

Hippocampal atrophy is a characteristic imaging manifestation of AD, the amygdala attaches to its end, both of them are involved in the pathogenesis of AD.Our previous study measured the volume of hippocampus inall subjects[17]. To further evaluate the relationship between the twobrain regions, we analyzed the correlation between the volume of the amygdala and hippocampus.

Pearson correlation analysis showed that there was a significant correlation between leftamygdala and hippocampal volumes (Figure 6A, *r* = 0.562, 95%CI: 0.330-0.729, *P*< 0.001).As shown in Figure 6B, there was a significant correlation between the right amygdala volume and hippocampal volume (*r* = 0.435, 95%CI: 0.172-0.640, *P*< 0.001).

***ROC curve analysis***

To evaluate the potential of amygdala volume serving as a novel biomarker for AD, ROC curves were plotted. The AUC was 0.761for the left amygdala volume, the sensitivity was 80.8%, the specificity was 63.6%, and the cutoff point was 1358 (Figure 7A, *P* = 0.002). The AUC was 0.771 for the right amygdala volume, the sensitivity was 88.5%, the specificity was 63.6% and the cutoff point was 1472 (Figure 7B, *P* = 0.001).

**DISCUSSION**

In this study, the amygdala volumes were measured bysMRI and analyzed using a set of automated analysis tools to evaluate the diagnostic value of amygdala for AD. The results showed that the bilateral amygdala volumes of AD patients were significantly smaller than those of the controls, and were positively correlated with the hippocampal volumes, consistent with previous reports[22,23].

Poulin *et al*[16] found that amygdala atrophy was obvious in early AD and was related to the severity of dementia. Yue *et al*[15] reported that volume of the right amygdala and hippocampus in patients with subjective cognitive decline. However, none of the previous studies evaluated the diagnostic value of amygdala, and there were few studies on the correlation between amygdala atrophy and clinical characteristics. Different from previous studies, we found that the sensitivity of the left and right amygdala volumes in diagnosing AD were 80.8% and 88.5%, respectively,and the cut-off value of the amygdala volume for diagnosis of AD was obtained. Amygdala volume measured by sMRI may be used as a potential imaging marker for the diagnosis of AD.One previous study showed that the degree of amygdala atrophy is correlated with the severity of the dementia[16,24]. We found that the volume of bilateral amygdala became smaller with the aggravation of dementia through subgroup analysis, but there was no significant statistical difference.The reason may be that the sample size of this study wastoo small.

The atrophy of the amygdala was more serious in AD patients with mental symptoms in this study, consistent with previous studies[16]. About 80%-90% of patients with AD experience at least one kind of psychobehavioral symptoms, such as anxiety, agitation, irritability, aggression, disinhibition, depression, apathy, which can reduce the quality of life of patients and increase the burden of care[25-28].The amygdala is attached to the terminal part of the hippocampus and is associated with multiple brain regions to regulate multiple stages of memory formation[1,2].Some misfolded proteins such as Tau, Aβ, α-synuclein, and TAR DNA-binding protein43 are present in the amygdala in neurodegenerative diseases[29]. The decreased functional connectivity among the amygdala, inferior frontal gyrus, and medial prefrontal cortex plays an important role in the development of depression in AD patients[30,31].Previous research has shown that dysfunction of the amygdala plays an important role in the emotional disorder of AD[6-8]. The injury of amygdala can lead to agitation, irritability, anxiety,and apathy[9,10]. Other studies have indicated that patients with anxiety disorder, autism, phobia, and post-traumatic stress disorder had dysfunctionof amygdala[12,13].

NPIwas used to evaluate theseverity of mental symptoms of dementia patients and the psychological distress of caregivers in this study. Tanaka *et al*[32] reported a high frequency of apathy, depression, anxiety, and irritability in ADpatients. Different from previous studies, we found that 59.1% of AD patients had neuropsychiatric symptoms, the most common of which were irritability, sleep difficulties, apathy,and hallucination. The reason may be that the patientsrecruited in this study were mostly mild to moderate dementia, leading to a low proportion of mental symptoms.This study also showed that the more serious dementia, the higher the proportion of patients with mental symptoms. This is consistent with previous studies[26].

There weresome limitations in this study. Amygdala atrophy has also been seen in other neurodegenerative diseases, such as dementia with Lewy bodies and frontotemporal dementia[33,34]. It is necessary to compare the amygdala volume in other types of dementia in future in order to improve the specificity of amygdala in the diagnosis of AD.

**CONCLUSION**

Anyway, the amygdala volumes measured by sMRI can be used for diagnosing of AD and amygdala atrophy was more serious in those with neuropsychiatric symptoms.

**ARTICLE HIGHLIGHTS**

***Research background***

Amygdala is closely related to emotion andmemory. Thedysfunction of amygdalaplays an important role in the emotional disorder ofAlzheimer’s disease (AD).There arefew studies evaluating the degree of atrophy ofamygdalameasured by structural magneticresonance imaging (sMRI).

***Research motivation***

The purpose of this study is toevaluate the diagnosticvalue of amygdalaonsMRIforAD.

***Research objectives***

In this study, the amygdala volumes were measured by sMRIboth in AD patients and controls to evaluate the diagnosticvalue of amygdala.The correlation between amygdala atrophy and clinical features of AD was also analyzed.

***Research methods***

Twenty-two ADpatients and twenty-sixcontrols were enrolled in this study. Their amygdala volumes were measuredand analyzed usinga set of image analysis software.All subjects received a cranial MRI scan and underwent neuropsychological tests.The mental and behavioral symptoms of all AD patients and the severity of the symptoms was graded.

***Research results***

The bilateral amygdala volumes of AD patients were significantly lower than those of the controls. The sensitivity of the left and right amygdala volumes in diagnosing AD was 80.8% and 88.5%, respectively. The amygdala atrophy was more serious in AD patients with neuropsychiatric symptoms including irritability, sleepdifficulties, apathyand hallucination.

***Research conclusions***

In this study,we found that the bilateral amygdala volumes of AD patients were significantly smaller than those of the controls, and were positively correlated with the hippocampal volumes, consistent with previous reports.In addition, theatrophy of the amygdala was more serious in those withneuropsychiatric symptoms. This study confirmed that the amygdala is involved in the mental symptoms of AD.

***Research perspectives***

It is necessary to compare the amygdala volume in other types of dementia inthe future,in order to improve the specificity of amygdala for the diagnosis of AD.

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**Footnotes**

**Institutional review board statement:** The study was approved by the Medical Research Ethics Committee of the Second Hospital of Shandong University.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The author declares that there is no conflict of interest between them.

**Data sharing statement:** No additional data are available.

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**Figure Legends**



**Figure 1 Comparison of amygdala magnetic resonance imaging parameters in two groups.** The left and right amygdala volumes of Alzheimer’s disease patients were significantly lower than controls. A: Left amygdala volume; B: Right amygdala volume.



**Figure 2 Amygdala volume in different dementia severity.** There was no significant difference in the left and rightamygdala volume among the three subgroups (*P*> 0.05). A: Left amygdala volume; B: Right amygdale volume.



**Figure 3Amygdala volume between different sides and genders.**A: There was no significant difference between left and right amygdala (*P*> 0.05); B, C: There was no significant difference in amygdala volume between different genders (*P*> 0.05).



**Figure 4 Amygdala volumes between Alzheimer's disease patients with and without mental symptoms.** The left and right amygdala volumes of Alzheimer's disease patients with mental symptoms weresignificantly smaller than patients without mental symptoms. A: Left amygdala volume; B: Right amygdala volume.



**Figure 5 Correlation analyses between neuropsychiatric inventory score and bilateral amygdala.**A, B: There was no significant correlation between neuropsychiatric inventory scores and amygdala volumes (*P*> 0.05); C, D: There was no correlation between psychological distress scores of caregivers and amygdala volumes (*P*> 0.05).



**Figure 6 Correlation between amygdala and hippocampus volume. A:** There was significant correlation between left amygdala and hippocampal volumes (*P*< 0.001); B: There was a significant correlation between the right amygdala volume and hippocampal volume (*P*< 0.001).

**Figure 7 Receiver operating characteristic curve analysis of amygdala volume for diagnosis of Alzheimer’s disease.** A:Volume of left amygdala; B: Volume of right amygdala. AUC: Area under the curve.

**Table 1 Demographics characteristics of all participants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **AD,*n*=22** | **Control,*n*=26** | ***P* value** |
| Age(yr) | 74.7 ±8.9 | 70.8 ±8.5 | 0.121 |
| Gender(female/male) | 11/11 | 14/12 | 0.792 |
| Education(yr) | 5.1 (4.6-11.2) | 6.2 (3.1-10.9) | 0.853 |
| CDR (0/1/2/3) | 0/4/10/8 | 26/0/0/0 | - |
| MMSE | 13.6±8.0 | 27.8±1.5 | <0.0011 |
| Onset times (yr) | 3.8(2.5-8.5) | - | - |

1*P* values were calculated by Student’s *t*-test.2*P* values were calculated by *χ*2 test.3*P* values were calculated by Mann-Whitney *U* test.*P*<0.05 was considered statistically significant.AD: Alzheimer’s disease; CDR: Clinical Dementia Rating; MMSE: Mini Mental State examination.

**Table 2 Neuropsychiatric inventoryscore and psychological distress scores of caregivers**

|  |  |  |  |
| --- | --- | --- | --- |
| **Case** | **NPI score,points** | **Item score,points** | **Psychological distress scores of caregivers,points** |
| 1 | 27 | Hallucination 6, irritability 12, sleep difficulties 9 | 10 |
| 2 | 24 | Hallucination 12, sleep difficulties 12 | 6 |
| 3 | 14 | Agitation 6, irritable 8 | 6 |
| 4 | 20 | Disinhibition 12, sleep difficulties 8 | 9 |
| 5 | 20 | Anxiety 8, indifference 12 | 6 |
| 6 | 24 | Agitation 12，irritable 12 | 8 |
| 7 | 12 | Hallucination 12 | 5 |
| 8 | 21 | Indifference 12, irritable 9 | 7 |
| 9 | 32 | Delusion 12, aggressive 8,sleep difficulties 12 | 13 |
| 10 | 12 | Depression 12 | 4 |
| 11 | 20 | Delusion 12, irritable 8 | 9 |
| 12 | 18 | Indifference 12, sleep difficulties 6 | 8 |
| 13 | 12 | Indifference 12 | 4 |

NPI: Neuropsychiatric inventory.

**Table 3 Mental symptoms of Alzheimer’s diseasepatients, *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Symptoms** | **Total cases,*n*=22** | **Mild AD,*n*=4** | **Moderate AD,*n*=10** | **Severe AD,*n*=8** |
| Irritability | 5 (22.73) | 1 (25) | 2 (20) | 2 (25) |
| Sleep difficulties | 5 (22.73) | 0 | 4 (40) | 1 (12.5) |
| Indifference | 4 (18.18) | 0 | 3 (30) | 1 (12.5) |
| Hallucination | 3 (13.64) | 0 | 2 (20) | 1 (12.5) |
| Agitation | 2 (9.09) | 1 (25) | 1 (10) | 0 |
| Delusion | 2 (9.09) | 0 | 0 | 2 (25) |
| Disinhibition | 1 (4.55) | 0 | 0 | 1 (12.5) |
| Anxiety | 1 (4.55) | 0 | 1 (10) | 0 |
| Aggressive | 1 (4.55) | 0 | 0 | 1 (12.5) |
| Depression | 1 (4.55) | 0 | 0 | 1 (12.5) |
| At least one of the above symptoms | 13 (59.1) | 1 (25) | 6 (60) | 6 (75) |

AD: Alzheimer’s disease.