Dement Neurocogn Disord. 2024 Apr;23(2):95-106
https://doi.org/10.12779/dnd.2024.23.2.95
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Original Article

Impact of the Ventricle Size on Alzheimer's Disease Progression: A Retrospective Longitudinal Study

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Received: Jan 16, 2024
Revised: Mar 4, 2024
Accepted: Mar 11, 2024
Published online: Mar 27, 2024

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Funding
This research was supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) and Korea Dementia Research Center

ABSTRACT

Background and Purpose: Ventricle enlargement has been implicated in the pathophysiology of Alzheimer's disease (AD). We studied the relationship between ventricular size and cognitive function in patients with AD. We focused on the effect of the initial ventricle size on the rate of cognitive decline in patients with AD.
Methods: A retrospective analysis of probable clinical AD participants with more than 2 magnetic resonance imaging images was performed. To measure ventricle size, we used visual rating scales of (1) Cardiovascular Health Study (CHS) score and (2) conventional linear measurement method.
Results: Increased clinical dementia rating (CDR) was correlated with a decreased Mini-Mental Status Examination (MMSE) score, and increased medial temporal lobe atrophy (MTLA) and global ventricle size (p<0.001, p<0.001, p=0.021, respectively). There was a significant correlation between the change in cognitive function in the group (70%–100%ile) with a large initial ventricle size (p=0.021 for ΔCDR, p=0.01 for ΔMMSE), while the median ventricle size (30%–70%ile) showed correlation with other brain structural changes (MTLA, frontal atrophy [FA], and white matter) (p=0.036 for initial MTLA, p=0.034 for FA).
Conclusions: In this study, the initial ventricle size may be a potential new imaging biomarker for initial cognitive function and clinical progression in AD. We found a relationship between the initial ventricle size and initial AD-related brain structural biomarkers.

Keywords: Alzheimer's Disease (AD); Cerebral Ventricles; Cognitive Impairments; Diagnostic Imaging; Retrospective Studies

INTRODUCTION

Alzheimer's disease (AD), the most common type of dementia, is a progressive, irreversible, and degenerative brain disorder that induces memory, thinking, and cognition impairment.[1] AD is pathologically characterized by amyloid-β (Aβ) accumulation which disturbs normal synaptic transmissions, and tau protein which disrupts axonal transport, causing loss of signal transmission and axon death.[2] Therefore, a waste clearance system is required for the brain.[3] The role of cerebrospinal fluid (CSF), secreted by the choroid plexus and filling the ventricle system, functioning as one of the waste clearance systems, is to regulate the

(KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: HU22C0118).

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim HJ; Data curation: Lee JS, Heo DY, Choi KH, Kim HJ; Methodology: Kim HJ; Project administration: Kim HJ; Resources: Lee JS, Heo DY, Choi KH, Kim HJ; Supervision: Kim HJ; Writing - original draft: Lee JS, Heo DY; Writing - review & editing: Lee JS, Heo DY.

transport of nutrients and waste in the brain and to protect the brain.[4] Hence, interruption of CSF flow may trigger neurodegenerative diseases that are accompanied by abnormal expansion of the brain ventricular system.[5]

Ventricle enlargement has been implicated in the pathophysiology of AD.[6] Although the ventricles themselves do not have a direct role in cognition impairment, their enlargement may affect brain structure globally which results in the possibility of AD-related pathologies.[7] White matter (WM) changes, common in patients with AD, are correlated with expansion of the ventricle's volume.[8]

The prognostic factor of AD is complicated and much remains elucidated.[9] Imaging tests, such as magnetic resonance imaging (MRI) for evaluating medial temporal lobe atrophy (MTLA), are under development to identify the progression from prodromal to clinical AD.[10] In several studies, the use of ventricular volume as a measure of AD progression has been supported.[11] Here, we found a relationship between ventricle size and cognitive function through cross-sectional and longitudinal studies. (1) First, we extracted the demographic data of AD patients tracked for 14 years. (2) Secondly, we found a correlation between initial ventricle size and cognitive decline. (3) To determine a regionally specific section of the ventricle that may affect cognitive function as AD progresses, we observed the correlation of ventricle size changes with changes in cognitive function and changes in AD-related brain structure.

METHODS

Participant enrollments

We filtered 966 patients from past medical records of the neurology department at a tertiary university hospital (**Fig. 1**). Among the participants, enrolment was specified for clinically probable AD patients based on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association[12] and 356 participants were selected. Of these participants, 88 underwent MRIs more than twice. The final eligible study participants consisted of 74 participants, excluding 12 whose images were unclear due to reasons such as being taken in an emergency, less than a year of MRI imaging, or images that could not be used with our evaluation method. Next, we collected all the score data of the Mini-Mental Status Examination (MMSE)[13] and the clinical dementia rating (CDR)[13] scale as a measurement of cognitive function in these 74 patients. Specifically, the first year of MRI scans was 2007, and the final year of MRI scans was 2020. We checked all MMSE and CDR scores for 14 years.

Imaging analysis

Image acquisition MRI was carried out using a 3.0-T Achieva system (Phillips, Best, The Netherlands) equipped with a standard quadrature head coil. All visual scales were measured under Flair T2 Weighed image. All the MRI FLAIR images from 74 patients were screened and evaluated in 3 ways: (1) Cardiovascular Health Study (CHS) score,[14] (2) Conventional linear measurement of method,[15] and (3) brain structural changes. All imaging scales were checked on both the initial and follow-up images.

CHS

CHS score originally indicated the relationship between cardiovascular diseases, such as hypertension, and brain ventricle enlargement.[14] Hence, we selected the CHS scale to

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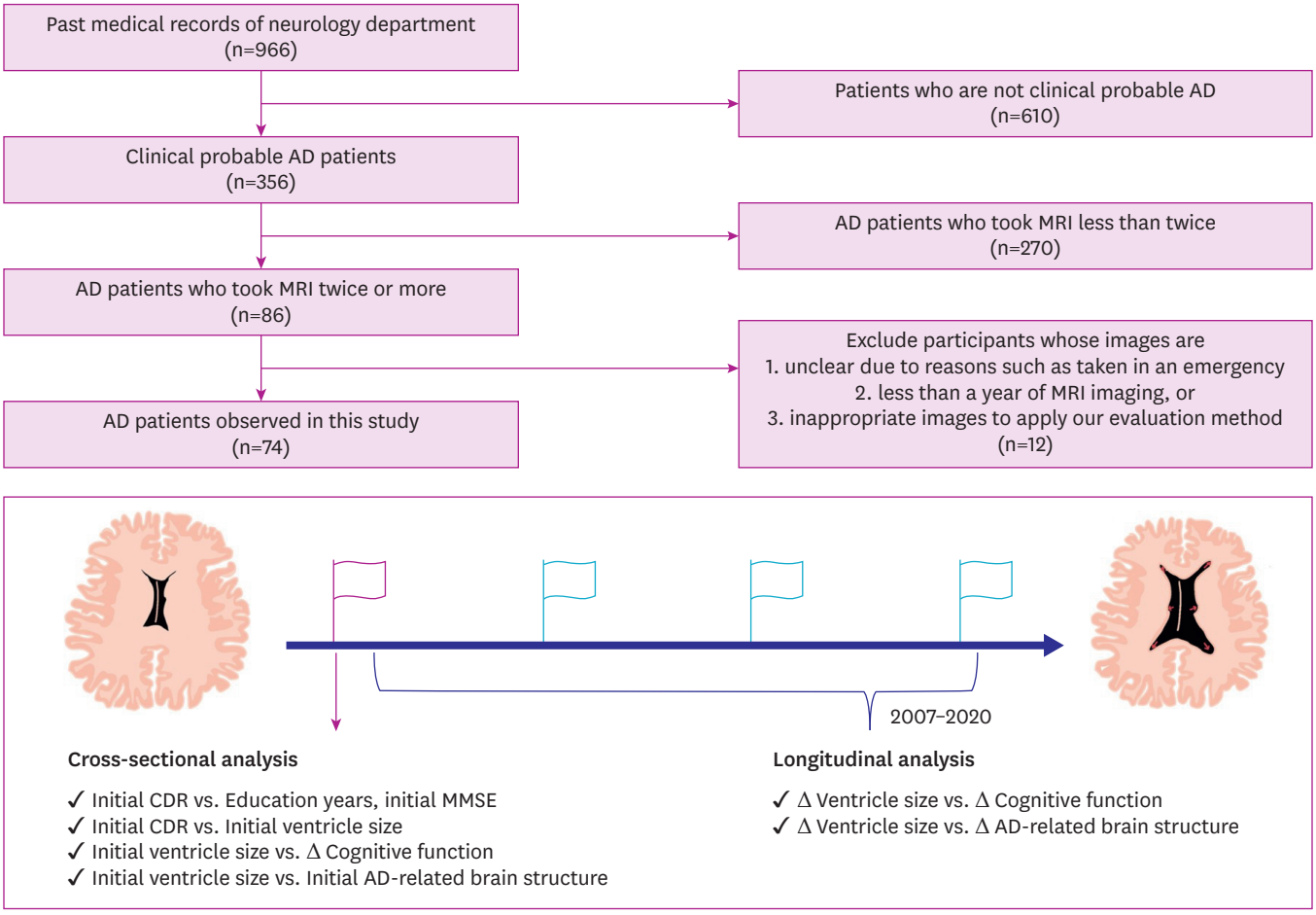

Fig. 1. Participant enrollment and experimental scheme for the study. In this study, we selected AD patients who took MRI twice or more and have appropriate images for the study from the tertiary university hospital neurology department medical records. The diagram illustrates the process of this study. We extract demographic data composed of AD patients tracked for 14 years. We analyzed initial ventricle size with initial cognitive function and initial AD-related brain structure cross-sectionally. Next, we analyzed changes in ventricle size with changes in cognitive function and changes in AD-related brain structure, longitudinally.
AD: Alzheimer's disease, MRI: magnetic resonance imaging, CDR: clinical dementia rating.

measure ventricle enlargement. Images were categorized into 8 grades. The more the score increases from 1 to 8, the greater the degree of expansion of the ventricle global size and the more WM changes increase (**Supplementary Fig. 1A**).[14]

Conventional linear measurement method

The conventional linear measurement method was used to represent ventricle size in detail and analyze the enlargement of the ventricle in more detail about the effect on the lobes of the brain.[15] In this method, several parameters have been set to indicate a specific length of the brain, and we selected 7 parameters that we needed. The parameters were from A to H (**Supplementary Fig. 1B**).[15]

A: greatest distance between the anterior horns
B: distance between the caudate nuclei
C: distance between the choroid plexuses
D: distance between the posterior horns
E: greatest distance between the lateral walls of the ventricles at the cell-media level

https://doi.org/10.12779/dnd.2024.23.2.95

F: sum of the distances between the Sylvian fissure and the third ventricle
*MH: maximum internal width of the skull

We modified this method, as it was originally used to evaluate computed tomography (CT) scans. Parameters A, B, C, D, E, and F were measured in the same layer. The H parameter which means whole brain size was redefined as MH to be measured at the same level as parameter E because of the irregularity of the MRI scan gap. Using these 7 parameters, we recorded A to MH for each MRI image. We finally used parameters from A to F divided by MH to adjust for factors such as whole brain size.

Brain structural changes

We evaluated 3 brain structural changes, MTLA,[16] WM change,[17] and frontal atrophy (FA),[18] that indicated the pathological impacts of AD. For the atrophy in the medial temporal lobe, the grade of MTLA was categorized into grade 0 to grade 4 according to the scale of A, C, and D parameters of the hippocampus in the coronal plane.[16] In each image, the grade of MTLA was recorded for both the left and right hemispheres according to Shelton's grade.[16] For the WM changes, it was graded on 2 scales, deep white matter (DWM, D) lesion and periventricular white matter (PWM, P) lesion, respectively.[19] Each grade was categorized into grades 0 to 3, and the grades of the DWM and PWM lesions were recorded for each image. For atrophy in the frontal lobe (FA), the grade of FA was categorized into grade 0 to grade 3 according to the degree of enlargement in the subarachnoid spaces and loss of brain tissue volume.[20] FA grade was recorded for each image.

Statistical analysis

We used descriptive statistics for the mean analysis of the initial diagnostic age, years of education, and initial MMSE scores of the group, divided by CDR values of 0.5, 1, and >2, in the demographic data. Repeated measures analysis of variance (ANOVA) was also applied to determine significant differences between the groups. In addition, we utilized both descriptive statistics and repeated measures ANOVA in the analysis of the initial MRI findings and ventricular measurements.

Second, we divided the patients into 2 groups based on the CDR value: the first group with a CDR value of less than 2, regarded as mild AD, and the second group with a CDR value of more than 2, which indicates severe AD. The initial ventricle was compared, and a *t*-test was used for the mean analysis between the 2 groups.

Next, the participants were divided into 3 groups based on their initial CHS size: the bottom 30%, 30% to 70%, and the top 30%. For these groups, we observed a correlation between the initial values of the MMSE and CDR scores, and brain structural scores. We also found a correlation between the delta (Δ) values of MMSE and CDR and the initial brain structural scores. For this analysis, Pearson's correlation coefficients were used to determine statistically significant correlations. The delta value used here was defined by the following equation: Simple linear regression was used in the graph.

$$\Delta\text{Scores} = \frac{\Delta The\ Final\ Scores - \Delta The\ Initial\ Scores}{\Delta The\ Year\ of\ the\ Final\ Scores - \Delta The\ Year\ of\ the\ Initial\ Scores}$$

Finally, the Pearson correlation coefficient method was used to obtain a significant correlation between the delta values of the cognitive function score and the brain structure

https://doi.org/10.12779/dnd.2024.23.2.95

scales and delta values of region-specific ventricle size. Simple linear regression was used in the graph. The confounding factors were also included.

SPSS version 28.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Mechanical significance was set at $p<0.05$, $p<0.005$, and $p<0.001$. GraphPad Prism 9.4.1(GraphPad Software, Inc., San Diego, CA, USA) was used for the statistical graph in repeated measures ANOVA of demographic data.

RESULTS

Demographic data

Seventy-four total patients with AD (male: female=23:49) were enrolled in this study. We divided them into 3 groups with initial CDR scores of 0.5, 1, and >2. The numbers in each group were 20, 43, and 11, respectively (**Table 1**).

The average age of the subjects was 73.73±8.18 years, and the average of each group was 70.65±8.19, 74.98±6.55, and 74.45±12.45 years, corresponding to CDR 0.5, 1, and more than 2, respectively. Age did not significantly differ according to the CDR scores. The average number of years of education in all groups was 6.11±5.49 years, and the average number of years of education in each group was 8.26±5.82, 5.79±5.56, and 3.36±4.0, respectively. This showed a significant correlation with the CDR value ($p=0.05$) (**Supplementary Fig. 2A**). The average of the initial MMSE scores of the entire group was 18.86±5.66 points, with 23±4.34, 18.46±5.04, and 12.91±4.2 points for each group. The CDR value and initial MMSE score were negatively correlated and showed a high level of significance ($p<0.001$) (**Supplementary Fig. 2B**).

Table 1. Demographic data

Characteristics	CDR0.5 (n=20)	CDR1 (n=43)	CDR ≥2 (n=11)	Total (n=74)	*p*-value
Age (yr)	70.65±8.19	74.98±6.55	74.45±12.45	73.73±8.18	0.141
Sex (Male: Female)	9:11	11:32	3:08	23:51	
Education (yr)	8.26±5.82	5.79±5.56	3.36±4.00	6.11±5.49	**0.058**
Initial MMSE	23.00±4.34	18.46±5.04	12.91±4.20	18.86±5.66	**<0.001*****
Initial MRI finding					
MTLA(L)	1.70±1.26	2.72±1.03	3.00±0.77	2.48±1.16	**<0.001*****
MTLA(R)	1.75±1.33	2.70±1.03	3.09±0.83	2.51±1.15	**<0.001*****
FA	1.35±0.59	1.48±0.76	1.45±0.69	1.44±0.69	0.761
D	0.85±0.93	1.13±0.89	1.00±1.18	1.04±0.94	0.525
P	11.00±0.85	1.32±0.84	1.73±1.01	1.32±0.877	0.164
Initial ventricle					
CHS	3.40±1.53	4.48±1.77	5.09±1.92	4.28±1.81	**0.021***
A/H	0.2517±0.0393	0.2740±0.0445	0.2818±0.0415	0.2692±0.0436	0.096
B/H	0.1449±0.0364	0.1558±0.0412	0.1625±0.0401	0.1538±0.0397	0.446
C/H	0.1577±0.0237	0.1601±0.0260	0.1750±0.0445	0.1611±0.0291	0.413
D/H	0.4353±0.0517	0.4236±0.0582	0.4010±0.0578	0.4234±0.0568	0.278
E/H	0.2004±0.0405	0.2034±0.0557	0.2361±0.0432	0.2074±0.0512	0.127
F/H	0.5693±0.0326	0.5603±0.0449	0.5467±0.0299	0.5607±0.0401	0.327

Repeated measures analysis of variance. Significant correlations are highlighted in bold (*$p<0.05$, ***$p<0.001$).
CDR: clinical dementia rating, MMSE: Mini-Mental Status Examination, MTLA: medial temporal lobe atrophy, L: left, R: right, FA: frontal atrophy, D: deep white matter, P: periventricular white matter, CHS: Cardiovascular Health Study, A: greatest distance between the anterior horns, B: distance between the caudate nuclei, C: distance between the choroid plexuses, D: distance between the posterior horns, E: greatest distance between the lateral walls of the ventricles at the cell-media level, F: sum of the distances between the Sylvian fissure and the third ventricle, H: maximum internal width of the skull (MH).

https://doi.org/10.12779/dnd.2024.23.2.95

In terms of brain structure, MTLA scores on both left and right sides increase as the group's CDR value increases, and their positive correlation is highly significant (p<0.001, both left and right). (**Supplementary Fig. 2C and D**) In terms of initial ventricle size, the initial CHS score, regarded as a measurement of global ventricle size, increases as the group's CDR value increases. The average of the initial CHS scores of the entire group was 4.28±1.81 points, and each group had 3.4±1.53, 4.48±1.77, and 5.09±1.92 points, respectively. This positive correlation was significant (p=0.021) (**Supplementary Fig. 2E**).

There were also increases or decreases in other initial brain structures and initial ventricle sizes, but no correlation was found.

Initial ventricle size tends to indicate early cognitive function in AD progression

Initial global ventricle size and initial distance of lateral walls of ventricles tend to indicate early cognitive function in AD progression. We divided the participants into 2 groups with initial CDR; less than 2 and >2, as each group was generally represented as mild and moderate AD, respectively (**Table 2**). When divided into 2 groups, only the initial CHS, global ventricle size measurement, and initial E/H, the distance of the lateral walls of the ventricle had a tendency toward initial CDR and early cognitive function (p=0.087 and p=0.063, respectively). However, except for these 2 measures, when divided into groups, no significant correlations were found between the initial CDR and other initial ventricle sizes.

Initial global ventricle size affects AD-related brain structure size and cognition impairment

Initial global ventricle size affects initial AD-related brain structure size and cognitive function impairment as AD progresses. The participants were divided into 3 groups according to the initial CHS scales or global ventricle size measurements: <30%, 30%–70%, and >70%, depending on their values (Groups 1, 2, and 3, respectively) (**Supplementary Fig. 3**). We observed a correlation between the initial cognitive function and initial brain structure between the groups. Furthermore, we identified changes in cognitive function as AD progressed. In this analysis, age, years of education, and sex were included as confounding factors.

Concerning the cross-sectional study, the initial median size of the ventricle, indicated as Group 2 (initial ventricle size above 30% and less than 70% among the participants), was correlated with the initial AD-related brain structure. Specifically, both sides of the MTLA, commonly represented in AD progression, correlated with the median size of the initial global ventricle (left and right, p=0.036, p=0.034, and R=0.44, R=0.444, respectively)

Table 2. Correlations between initial CDR groups and initial ventricle size

Initial ventricle	CDR group						p-value
	CDR <2 (n=65)		CDR ≥2 (n=11)		Total (n=76)		
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
CHS	4.10±1.74	4.09	5.09±1.92	5.00	4.23±1.79	4.00	**0.087**
A/H	0.2671±0.0431	0.2671	0.2819±0.0414	0.2879	0.2692±0.4309	0.2678	0.295
B/H	0.1513±0.0396	0.1513	0.1624±0.0401	0.1575	0.1529±0.0396	0.1515	0.395
C/H	0.1607±0.0265	0.1607	0.1718±0.0446	0.1543	0.1623±0.0297	0.1607	0.257
D/H	0.4279±0.0553	0.4279	0.4010±0.0578	0.4229	0.4240±0.0561	0.4316	0.143
E/H	0.2047±0.0525	0.2047	0.2362±0.0432	0.2384	0.2093±0.0522	0.256	**0.063**
F/H	0.5640±0.0412	0.564	0.5467±0.0299	0.5444	0.2615±0.0400	0.5599	0.189

Independence t-test. Tendencies are highlighted in bold.
CDR: clinical dementia rating, SD: standard deviation, CHS: Cardiovascular Health Study, A: greatest distance between the anterior horns, B: distance between the caudate nuclei, C: distance between the choroid plexuses, D: distance between the posterior horns, E: greatest distance between the lateral walls of the ventricles at the cell-media level, F: sum of the distances between the Sylvian fissure and the third ventricle, H: maximum internal width of the skull (MH).

https://doi.org/10.12779/dnd.2024.23.2.95

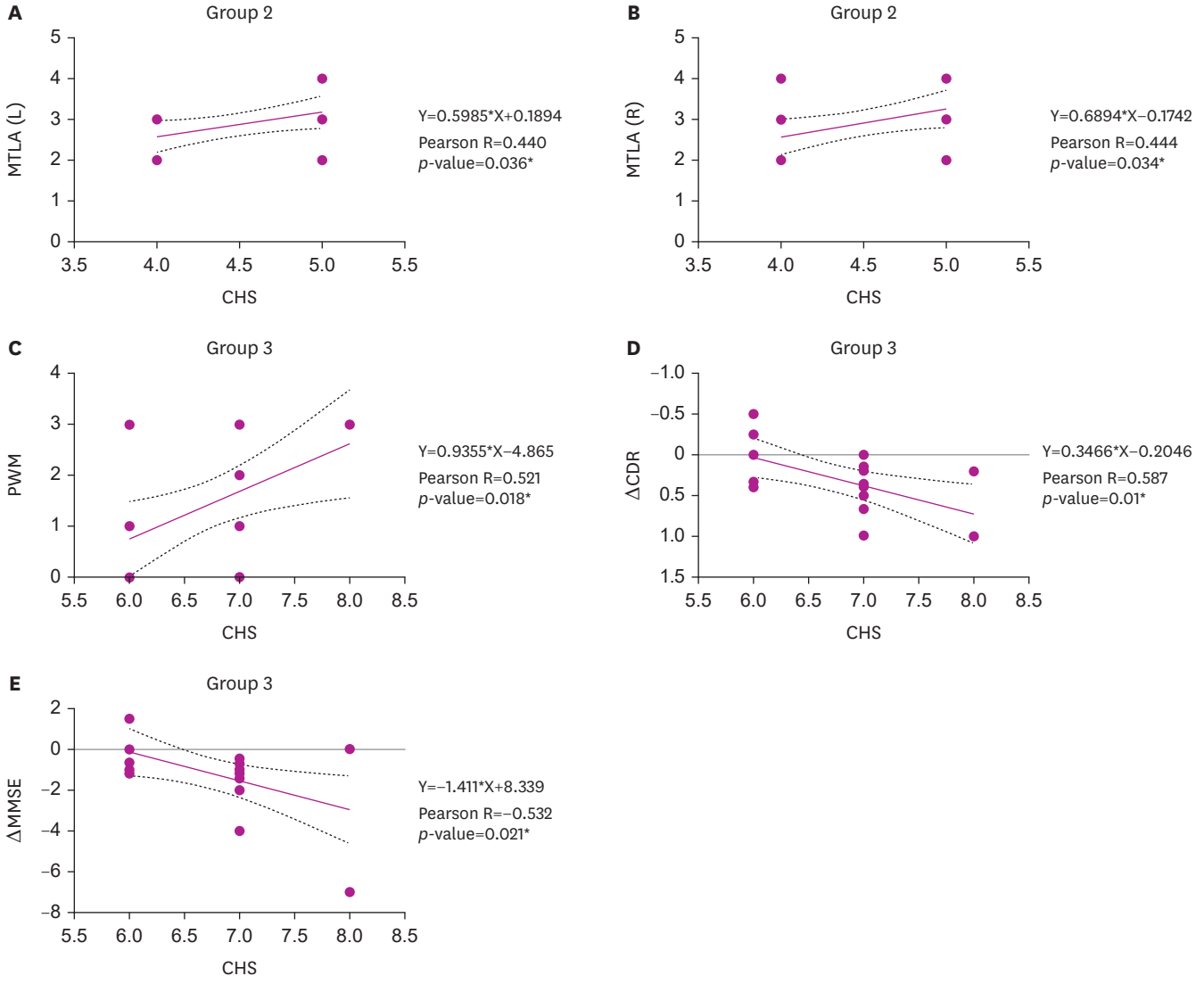

Fig. 2. Initial ventricle size and their specific effects according to the size of the groups. According to the initial CHS scores, groups are divided into 3. Group 2 (30%–70%) indicates the intermediate size of the global ventricle, and Group 3 (70%–100%) implicates the enlarged size of the global ventricle. (A, B) AD patients with intermediate size of ventricles have a positive correlation with both sides of MTLA. (C-E) AD patients with enlarged ventricle size positively correlate with PWM scales, and negatively correlate with cognitive function.
CHS: Cardiovascular Health Study, AD: Alzheimer's disease, MTLA: medial temporal lobe atrophy, PWM: periventricular white matter, CDR: clinical dementia rating, MMSE: Mini-Mental Status Examination.

(**Fig. 2A and B**). In Group 3 (initial ventricle size above 70% of the participants), initial scales of P were correlated with initial global ventricle size (p=0.018, R=0.521) (**Fig. 2C**).

In contrast, in AD progression, Group 3 showed a correlation with changes in cognitive impairment, represented as ΔCDR and ΔMMSE (p=0.021, p=0.01, and R=0.587, R=−0.532, respectively). (**Fig. 2D and E**) Through this analysis, the largely expanded initial ventricle size causes worse cognitive function impairment as AD progresses.

Ventricle size changes are regional and specifically related to AD progression

Ventricle size changes are regional and specifically related to cognitive function impairment and changes in brain structure related to AD progression. We analyzed the correlations

https://doi.org/10.12779/dnd.2024.23.2.95

Table 3. Region-specific ventricle changes are correlated with cognitive function changes and brain structure changes

Variance	Section of ventricle	Correlation with	*p*-value
ΔCHS	Global ventricle size	ΔMMSE	**0.011***
		ΔMTLA(R)	**0.007***
ΔA/H	Distance between the anterior horns	ΔD	**0.015***
ΔB/H	Distance between the caudate nuclei	ΔFA	**0.008***
ΔC/H	Distance between the choroid plexuses	ΔD	**0.010***
ΔE/H	Distance between the lateral walls of the ventricles	ΔMMSE	**0.021***
ΔF/H	The sum of the distances between Sylvian fissures and the third ventricle	ΔMMSE	**0.016***
		ΔFA	**0.030***

Pearson correlation. Significant correlations are highlighted in bold (*$p<0.05$).
CHS: Cardiovascular Health Study, MMSE: Mini-Mental Status Examination, MTLA: medial temporal lobe atrophy; R: right, FA: frontal atrophy, D: deep white matter, A: greatest distance between the anterior horns, B: distance between the caudate nuclei, C: distance between the choroid plexuses, D: distance between the posterior horns, E: greatest distance between the lateral walls of the ventricles at the cell-media level, F: sum of the distances between the Sylvian fissure and the third ventricle, H: maximum internal width of the skull (MH).

between changes in ventricle size (Δventricle size) and changes in cognitive function and AD-related brain structure (**Supplementary Tables 1** and **2**).

Changes in CHS, or global ventricle size changes, correlated with ΔMMSE with the negative slope (p=0.011, R=−0.317). In addition, these were positively correlated with ΔMTLA(R) (p=0.007, R=0.313). With respect to regional changes in ventricles, ΔA/H, changes in the greatest distance between the anterior horn of the ventricle, were negatively correlated with ΔD (p=0.014, R=−0.281). In ΔB/H, the distance between caudate nuclei was positively correlated with ΔFA (p=0.008, R=0.307). ΔC/H, which indicates the distance between the choroid plexuses, showed a positive correlation with ΔD (p=0.01, R=0.298). However, in the case of ΔD/H, the distance between the posterior horns did not correlate with changes in cognitive function and AD-related brain structure. ΔE/H, the greatest distance between the lateral walls of the ventricles, was positively correlated with ΔFA (p=0.021, R=0.267). Finally, ΔF/H, the sum of the distances between the Sylvian fissure and the third ventricle, was positively correlated with cognitive function, ΔMMSE (p=0.016, R=0.299), and negatively correlated with ΔFA and ΔD (p=0.03, p=0.014, and R=−0.253, R=−0.285, respectively) (**Table 3**, **Supplementary Tables 1** and **2**).

Changes in ventricle size are regional and specifically correlated with changes in cognitive function and brain structure as AD progresses.

DISCUSSION

We started this retrospective observational follow-up study of 74 patients with AD to determine the significance of ventricle enlargement in AD. We aimed to determine how the clinical ventricle size and its changes affect AD progression. Here, we confirmed that (1) the larger the initial size of the ventricle, the more severe the progression of AD. In addition, (2) we observed that the initial ventricular size was related to cognitive function deterioration in AD patients with an enlarged ventricle size (70%–100%). (3) We found that ventricle size was correlated with anatomical AD structures such as MTLA in the median ventricle size group (30%–70%). (4) The global ventricle and the distance between the lateral walls were larger than those in the moderate AD group compared to severe one. We determined the region-specific sections of the ventricle that affect changes in cognitive function and AD pathological

https://doi.org/10.12779/dnd.2024.23.2.95

brain structure. Changes in global ventricle size was correlated with ΔMMSE and ΔMTLA. Changes in region-specific ventricle size was correlated with ΔFA, ΔD, and ΔMMSE.

In patients with AD, the fastest rate of atrophy occurs in the medial temporal lobe.[20] Specifically in patients with AD gray matter volume loss appears at a deteriorated and accelerated rate of atrophy.[21] This brain tissue volume loss is replaced by fluid and is demonstrated by ventricular enlargement.[22] As ventricle enlargement is due to the loss of brain tissue, the volume of CSF in the lateral ventricles and the surrounding brain expands to fill the space within the fixed volume of the skull.[23]

Conversely, the brain waste clearance system through the CSF, which fulfils the brain ventricle, is essential to maintain brain homeostasis, such as brain volume regulation and removal of its waste products.[23] The brain waste clearance system, mainly via the CSF, removes a substantial amount of toxic metabolic by-product/interstitial waste products, including Aβ and tau protein, for maintaining brain homeostasis.[3] BBB removes interstitial solutes by transporting proteins which are then removed via the bloodstream.[24] However, due to the large distance between interstitial solutes and the BBB, CSF which can exchange with interstitial fluid, fulfilling the ventricle system, must be utilized.[24]

Interrupted CSF flow co-occurs with the abnormal expansion of the brain ventricle system and may induce neurodegenerative diseases.[5] In several studies, the use of ventricular volume as a measure of AD progression has been supported.[25] Normal pressure hydrocephalus (NPH) is a syndrome associated with CSF malabsorption due to intracranial CSF volume in idiopathic NPH being significantly enlarged.[26] NPH causes gait dysfunction and cognitive deficits in the frontal and subcortical lobes.[26] Especially, a high prevalence of AD and NPH has been found, which is represented by neurodegenerative changes consistent with AD.[27]

In conclusion, for patients with AD, early ventricular measurements are important, as clinically implicating future cognitive function and motor symptom.[28] We verified the new finding that changes in ventricle size could be a prognostic index of AD progression. In patients with early AD, the initial ventricle should be observed with interest through MRI and CT images to predict and prevent AD progression.

A limitation of this study is that it was a retrospective study that identified the relationship between AD and ventricle size. For this reason, there were other inevitable limitations, including irregularities in the year of MRI scans, MMSE, and CDR. First, patients who did not satisfy our study criteria were excluded from the 74 study subjects. Next, irregularities in the year of the MRI scan were statistically resolved.

In future studies, ventricular measurements should be made more precisely above the visual rating by measuring the volume itself. In addition, a prospective follow-up study is required for a more accurate analysis.

ACKNOWLEDGEMENTS

This study was conducted under ‘Clinical evaluation of high-efficiency technology of BBB penetration for dementia therapeutics by anti-transferrin receptor(anti-TfR) antibody

engineering.' Doyun Heo, co-author of the study, was a trainee of the Medical Scientist Training Program at Hanyang University, College of Medicine.

We would like to thank Editage (www.editage.co.kr) for English language editing.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Correlations of initial CHS groups between initial cognition function, initial brain structure, delta cognition function and delta brain structure

Supplementary Table 2

Correlations of changes in ventricle size between cognition function changes and brain structural changes

Supplementary Fig. 1

Method of ventricle measurement. (A) Cardiovascular Health study score, originally indicates the relationship between cardiovascular diseases, such as hypertension, and brain ventricle enlargement level. The more the score increases from 1 to 8, the more the degree of expansion of the ventricle global size and the more white-matter changes increase. (B) Conventional linear measurement. Each parameter indicates as follows; A: greatest distance between the anterior horns; B: distance between the caudate nuclei; C: distance between the choroid plexuses; D: distance between the posterior horns; E: greatest distance between the lateral walls of the ventricles at the level of the cell-media; F: the sum of the distances between the Sylvian fissures and the third ventricle; *H: maxima internal width of the skull (MH).

Supplementary Fig. 2

Demographic data graph. (A) Demographic characteristics show initial CDR tends with education years. (B) In this demographic group, initial CDR has a negative correlation with initial MMSE. (C, D) Initial CDR positively correlates with both sides of initial MTLA. (E) Initial CDR positively correlates with the initial CHS scales and global ventricle size.

Supplementary Fig. 3

Regional-specific ventricle changes have relations with changes in anatomical brain changes and cognitive function. (A, B) changes in CHS are correlated with changes in MMSE and MTLA(R). (C-I) Each regional specific ventricle changes reflect AD-anatomical changes or cognitive decline, respectively.

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