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Neuroimaging

Characterizing biomarker features of cognitively normal individuals with ventriculomegaly

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Abstract

Introduction: The clinical significance of ventriculomegaly in cognitively normal elderly individuals remains unclear.

Methods: We selected cognitively normal individuals (n = 425) from the Alzheimer's Disease Neuroimaging Initiative database and calculated Evans index (EI) based on the ratio of the frontal horn and skull diameter. We defined ventriculomegaly as EI $\geq$ 0.30, and the participants were stratified into EI $\geq$ 0.30 group and EI $<$ 0.30 group. Neuropsychological, imaging, and fluid biomarker profiles between the two groups were then compared using regression models.

Results: A total of 96 (22.5%) individuals who had ventriculomegaly performed worse on the cognitive tests; showed smaller hippocampal volume but larger caudate, cingulate, and paracentral gyrus volumes; and displayed lower positron emission tomography [^{18}F]fluorodeoxyglucose standardized uptake value ratio but higher amyloid burden represented by higher [^{18}F]florbetapir standardized uptake value ratio and lower cerebrospinal fluid amyloid β 1–42 levels compared to those without ventriculomegaly.

Discussion: Asymptomatic ventriculomegaly might be an early imaging signature of preclinical Alzheimer's disease and/or normal pressure hydrocephalus.

Keywords: Ventriculomegaly; Neuropsychological test; Biomarker; Alzheimer's disease; Idiopathic normal pressure hydrocephalus

1. Introduction

Ventriculomegaly, defined as the enlargement of cerebral ventricles, is an objective and sensitive neuropathological feature associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1,2]. Theoretically, ventriculomegaly can be caused by either two different pathophysiological processes: brain atrophy or hydrocephalus. The former is commonly observed in AD and other neurodegenerative diseases, often in the advanced stages and sometimes in mild stage [2–4]. The latter can be due to congenital [5] or adult hydrocephalus

Conflict of interest: The authors have no conflicts of interest to report.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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[6], which has more cerebrospinal fluid (CSF) in ventricles. In MCI and AD studies, ventriculomegaly is commonly attributed to brain atrophy due to neuronal loss [2–4]. With the wide use of computed tomography (CT) and magnetic resonance imaging (MRI) brain scans in clinical practice, ventriculomegaly has been increasingly observed in cognitively normal individuals, especially in elders. However, the clinical significance of the incidental finding of ventriculomegaly in asymptomatic individuals remains elusive.

Here, we stratified cognitively normal individuals into two groups, the presence or absence of ventriculomegaly using the Evan's index (EI) $\geq$ 0.30 [7] and investigated the neuropsychological and biomarker characteristics of ventriculomegaly in cognitively asymptomatic subjects.

2. Methods

2.1. Study sample

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Further information can be found at http://www.adni-info.org. The ADNI also recruits cognitively normal participants with regular follow-up for neuropsychological assessments, neuroimaging such as MRI, [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]florbetapir PET scans, as well as CSF evaluations for amyloid β 1–42 ($A\beta_{1-42}$), total tau (t-tau), and phosphorylated tau (p-tau).

In this study, we selected cognitively normal individuals who had baseline Clinical Dementia Rating (CDR) testing, Mini-Mental Status Examination (MMSE), Montreal cognitive test (MoCA), neuropsychological battery, MRI, lumbar puncture, [^{18}F]FDG and [^{18}F]florbetapir PET imaging. We defined cognitively normal individuals as those with a MMSE score of $\geq$24, CDR = 0, and absence of any neuropsychiatric diseases such as depression, MCI, and dementia.

2.2. Standard protocol approvals, registrations, and patient consents

The ADNI study was approved by the Institutional Review Boards of all the participating institutions. Informed written consent was obtained from all participants at each site.

2.3. Measurement of frontal horn diameter and skull diameter and calculate EI

Images downloaded from ADNI database were transformed to the Montreal Neurological Institute space using six-parameter affine transformations preserving the structural heterogeneities. The measurements of the frontal horn and the skull were acquired by an expert neurologist using the image visualization software JIV2 (http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization/JIV2). The maximum diameter of the frontal horns of the lateral ventricles (LVs) and the maximum inner diameter of the skull in the same section were recorded in millimeter. EI was calculated as the ratio between the maximum diameter of the frontal horns of the LVs and the maximum inner diameter of the skull in the same section. This index has been widely accepted as an indicator of enlargement of cerebral ventricles [8–10] and has close correlation with ventricular volume [11,12]. Generally, EI $\geq$ 0.30 is regarded as ventriculomegaly in guidelines of hydrocephalus [9,10].

2.4. Groups segregation

According to the EI values, subjects with normal cognition were stratified into two groups: those with ventriculomegaly were defined as EI $\geq$ 0.30 group and those without ventriculomegaly as EI $<$ 0.30 group. Neuropsychological scores, brain structure volumes, [^{18}F]FDG standardized uptake value ratio (SUVR), [^{18}F]florbetapir SUVR, CSF $A\beta_{1-42}$, t-tau, and p-tau were compared between the two groups.

2.5. Neuropsychological assessments

The neuropsychological assessments were performed by certified raters using standardized ADNI protocols. CDR, MMSE, MoCA, AD Assessment Scale-Cognition (ADAS-Cog), neuropsychological battery, and ADNI-Mem and ADNI-EF data sets used in this study were obtained from the ADNI files "CDR.csv", "MOCA.csv", "MMSE.csv", "NEUROBAT.csv", "ADASSCORES.csv", and "UWNPSYCHSUM_04_22_16.csv", respectively. ADNI-Mem and ADNI-EF are validated composite memory and executive scores, respectively, derived using data from the ADNI neuropsychological battery [13,14]. The Rey Auditory Verbal Learning Test (AVLT), ADAS-Cog, MMSE, and Logical Memory tests were analyzed using a modern psychometric approach to obtain the composite memory score (ADNI-Mem) [13]. Based on WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing, ADNI-EF, the composite executive function measure, appears to be a useful composite measure of executive function in MCI, as good as or better than any of its composite parts [14]. Lower ADNI-Mem and ADNI-EF scores reflect a poorer performance in memory and executive function, respectively. The details of the ADNI protocols for the neuropsychological assessments and the methods for developing the ADNI-Mem and ADNI-EF can be found at www.adni-info.org (accessed January 2017).

2.6. CSF data

CSF $A\beta_{1-42}$, t-tau, and p-tau at threonine 181 were measured by using Innogenetics (INNO-BIA AlzBio3) immunoassay kit–based reagents in the multiplex xMAPLuminex platform (Luminex) as previously described [15]. The CSF data used in this study were obtained from the ADNI files "UPENNBIOMK5-8.csv". Further details of ADNI methods for CSF acquisition and measurements and quality control procedures can be found at www.adni-info.org (accessed January 2017). CSF $A\beta_{1-42}$ concentration $\leq$192 pg/mL was regarded as having AD risk [15].

2.7. Neuroimaging data

The neuroimaging data, including structural volume in MRI, cerebral glucose metabolism in [^{18F}]FDG PET, and cortical Aβ burden using [^{18F}]florbetapir PET SUVRs were obtained from the ADNI file "UCSFFSL_11_02_15", "UCSFFSX51_11_02_15_V2", "UCD_ADNI2_WMH_10_26_15", "UCBERKELEYFDG_07_30_15.csv", and "UCBERKELEYAV45_06_15_16.csv", respectively. The neuroimaging techniques used by ADNI have been reported previously [16–18]. Briefly, cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu). Each PET scan is coregistered to the corresponding MRI, and the mean isotope uptake within the cortical and reference regions is calculated. To investigate the regional cerebral glucose metabolism and Aβ deposition, [^{18F}]FDG SUVR values from five brain regions (left angular gyrus, right angular gyrus, bilateral posterior cingulum gyrus, left temporal gyrus, and right temporal gyrus) and [^{18F}]florbetapir SUVR values from four regions (frontal, cingulate, parietal, and temporal) were analyzed, respectively. Further details regarding ADNI image acquisition and processing can be found at www.adni-info.org/methods. (accessed January 2017).

2.8. Statistical methods

Statistical analyzes were performed using the R Statistical Software Package, version 3.3.017. Demographic data (age, gender, educational level, and apolipoprotein E [*APOE*] status), cognitive scores, MR volumes, SUVR and CSF biomarker values were summarized. Between the two groups, gender and *APOE* status were compared using chi square tests for categorical variables, while age, educational level, cognitive scores, MR volumes, SUVR, and CSF biomarker values were compared using the independent samples t-test for continuous variables. Statistical models (cognitive scores, MR volumes, SUVR, and CSF biomarker values) were corrected for age, gender, education, and *APOE* ε4 status using analysis of variance. $P < .05$ was adopted and regarded to the significance.

3. Results

3.1. Demographic data of the subjects

Out of the 425 cognitively normal individuals, 96 (22.5%) had ventriculomegaly. The individuals with ventriculomegaly were older (mean age ± standard deviation) (76.0 ± 5.6 vs. 72.0 ± 6.4 years, $P < .001$) and had more males (70.8% vs. 41.0%, $P < .001$) as compared to the group without ventriculomegaly (Table 1). There was no significant difference in the education level and the number of *APOE* ε4 carriers between the two groups.

3.2. Measurement of diameters of frontal horn and skull

The mean diameters of frontal horn and skull in the group with ventriculomegaly compared to the group without ventriculomegaly were 45.13 ± 2.89 mm versus 36.91 ± 3.42 mm, $P < .01$ and 139.18 ± 3.27 mm versus 140.97 ± 3.30 mm, $P < .01$, respectively. The maximum EI in group with ventriculomegaly was 0.43, and in the group without ventriculomegaly, EI < 0.30 was 0.29. The mean EI in the two groups were 0.32 ± 0.02 and 0.26 ± 0.02, respectively.

3.3. Neuropsychological scores

Participants with ventriculomegaly performed worse in the domains of global, attention, delayed recall memory and executive function on the neuropsychological assessments compared to those without ventriculomegaly. For example, the mean neuropsychological scores measuring global cognition in MoCA were 24.83 ± 2.72 versus 25.88 ± 2.52 ($P < .001$). In the neuropsychological assessment measuring the executive function, participants with ventriculomegaly took longer time (worse performance) to finish the Trail Making Test part B than those without ventriculomegaly. In the assessment measuring memory, participants with ventriculomegaly had worse performance than those without ventriculomegaly in the Logical Memory Test and Rey AVLT. These findings were also consistent using the ADNI-Mem and ADNI-EF scores. In the assessments that measured language, there were no significant differences in the category fluency animals and Boston

Table 1
Demographics of subjects

Characteristics	EI ≥ 0.30	EI < 0.30	*P* value
Numbers	96	329	
Percentage (%)	22.59	77.41	
Age (years)	76.0 ± 5.6	72.0 ± 6.4	<.001*
Males, n (%)	68 (70.8)	135 (41.0)	<.001*
Education, year	16.8 ± 2.5	16.4 ± 2.6	.21
APOE ε4 n (%)			.44
2	2 (2.1)	6 (1.8)	
1	23 (24)	101 (30.7)	
0	71 (74.0)	222 (67.5)	

*Statistically significant.

Table 2
Neuropsychological scores

Scale	EI ≥ 0.30 (n = 96)	EI < 0.30 (n = 329)	*P* value
MoCA	24.83 ± 2.72	25.88 ± 2.52	<.001*
MMSE	28.59 ± 1.46	29.08 ± 1.13	<.001*
ADAS-Cog11	6.93 ± 3.16	5.30 ± 2.79	<.001*
Clock score	4.54 ± 0.75	4.73 ± 0.63	.01*
BNTSpont	28.19 ± 1.97	28.20 ± 2.28	.98
CATANIMSC	20.03 ± 4.98	21.14 ± 5.31	.06
TRAA	35.77 ± 17.86	33.27 ± 24.41	.35
TRAB	90.44 ± 45.35	77.00 ± 38.01	.003*
LIMM Total	13.02 ± 4.23	14.91 ± 3.78	.003*
RAVLT-immediate	4.05 ± 10.52	4.48 ± 10.99	<.001*
ADNI-Mem	0.84 ± 0.68	1.17 ± 0.69	<.001*
ADNI-EF	0.62 ± 0.77	0.89 ± 0.73	<.001*

*Statistically significant.

naming tests. There were also no significant differences in the Trail Making Test part A scores (Table 2).

3.4. Volumes of brain structures

Compared to the group without ventriculomegaly, the individuals in ventriculomegaly group had substantially larger intracranial volume (cc) (1465.95 ± 111.32 vs. 1393.34 ± 124.06, $P < .001$), larger CSF volume (379.43 ± 45.06 vs. 321.06 ± 44.80, $P < .001$) and larger gray matter volumes (607.19 ± 42.08 vs. 590.26 ± 50.95, $P = .008$). The volumes (mm^3) of some structures in the group with ventriculomegaly were substantially different compared with those in the group without ventriculomegaly. Concerning specific structures, some were significantly bigger, such as bilateral caudate, paracentral gyrus, rostral anterior cingulate gyrus, choroid plexus, and inferior LVs, whereas others were significantly smaller, such as central part of corpus callosum (CC) and hippocampus gyrus. There was no significant difference in the volumes of entorhinal gyrus, anterior and posterior CC, caudal anterior cingulate, and posterior cingulate (Table 3 and Fig. 1).

3.5. FDG uptake

The ventriculomegaly group had substantially lower [^{18}F]FDG SUVR in bilateral angular gyrus and posterior cingulate compared to the group without ventriculomegaly, for example, left angular gyrus 1.28 ± 0.14 versus 1.33 ± 0.14 ($P = .004$). There was no significant difference in the [^{18}F]FDG SUVR in the temporal regions between the two groups (Table 4).

3.6. Biomarkers of Aβ and tau pathologies

The group with ventriculomegaly had higher [^{18}F]florbetapir SUVR in the frontal and parietal regions compared to the group without ventriculomegaly. There was no significant difference in the [^{18}F]florbetapir SUVR in the cingulate and temporal regions between the two groups. The

Table 3
Volume of specific brain structures

Structure	Volume (mean ± SD) (mm^3)		*P* value
	EI ≥ 0.30 (n = 42)	EI < 0.30 (n = 179)	
CC_ANTERIOR	745.48 ± 143.60	773.56 ± 138.27	.22
CC_CENTRAL	338.17 ± 55.57	372.22 ± 66.33	.001*
CC_MID_ANTERIOR	343.90 ± 77.86	377.56 ± 71.43	.005*
CC_MID_POSTERIOR	314.00 ± 65.39	348.10 ± 78.52	.007*
CC_POSTERIOR	895.81 ± 149.23	912.93 ± 150.72	.49
L _ENTORHINAL	1909.55 ± 332.59	1974.13 ± 394.60	.31
R _ENTORHINAL	1747.26 ± 335.01	1862.46 ± 375.59	.06
L _PARACENTRAL	3261.90 ± 509.84	3061.12 ± 484.20	.011*
R _PARACENTRAL	3642.02 ± 546.14	3412.67 ± 559.98	.0002*
L _ROSTRAL ANTERIOR CINGULATE	2653.64 ± 480.90	2386.81 ± 453.94	<.001*
R _ROSTRAL ANTERIOR CINGULATE	2122.62 ± 448.44	1911.63 ± 441.98	.006*
L _CAUDAL ANTERIOR CINGULATE	2299.50 ± 382.72	2228.93 ± 396.65	.28
R _CAUDAL ANTERIOR CINGULATE	2016.67 ± 460.23	1998.87 ± 403.93	.80
L_POSTERIOR CINGULATE	2975.93 ± 431.04	2922.83 ± 431.24	.47
R _POSTERIOR CINGULATE	3031.24 ± 402.62	2889.69 ± 386.92	.06
L _ISTHMUS CINGULATE	2530.17 ± 419.09	2357.06 ± 404.41	.01*
R _ISTHMUS CINGULATE	2313.07 ± 335.19	2172.47 ± 360.28	.02*
L_CAUDATE	3487.02 ± 528.39	3290.77 ± 509.44	.03*
R_CAUDATE	3608.76 ± 573.00	3372.68 ± 555.31	.01*
L_HIPPO	3519.77 ± 460.25	3741.25 ± 416.66	.002*
R_HIPPO	3640.09 ± 499.51	3798.25 ± 457.51	.03*
L_CHOROID_PLEXUS	2079.14 ± 399.95	1746.74 ± 351.68	<.001*
R_CHOROID_PLEXUS	2513.24 ± 443.22	2052.38 ± 417.55	<.001*
L_INF_LAT_VENT	1195.57 ± 709.44	553.39 ± 399.36	<.001*
R_INF_LAT_VENT	912.90 ± 598.90	480.80 ± 394.13	<.001*

Abbreviations: CC, corpus callosum; HIPPO, hippocampus; INF, inferior; L, left; LAT, lateral; MID, middle; R, right; VENT, ventricles; SD, standard deviation.
*Statistically significant.

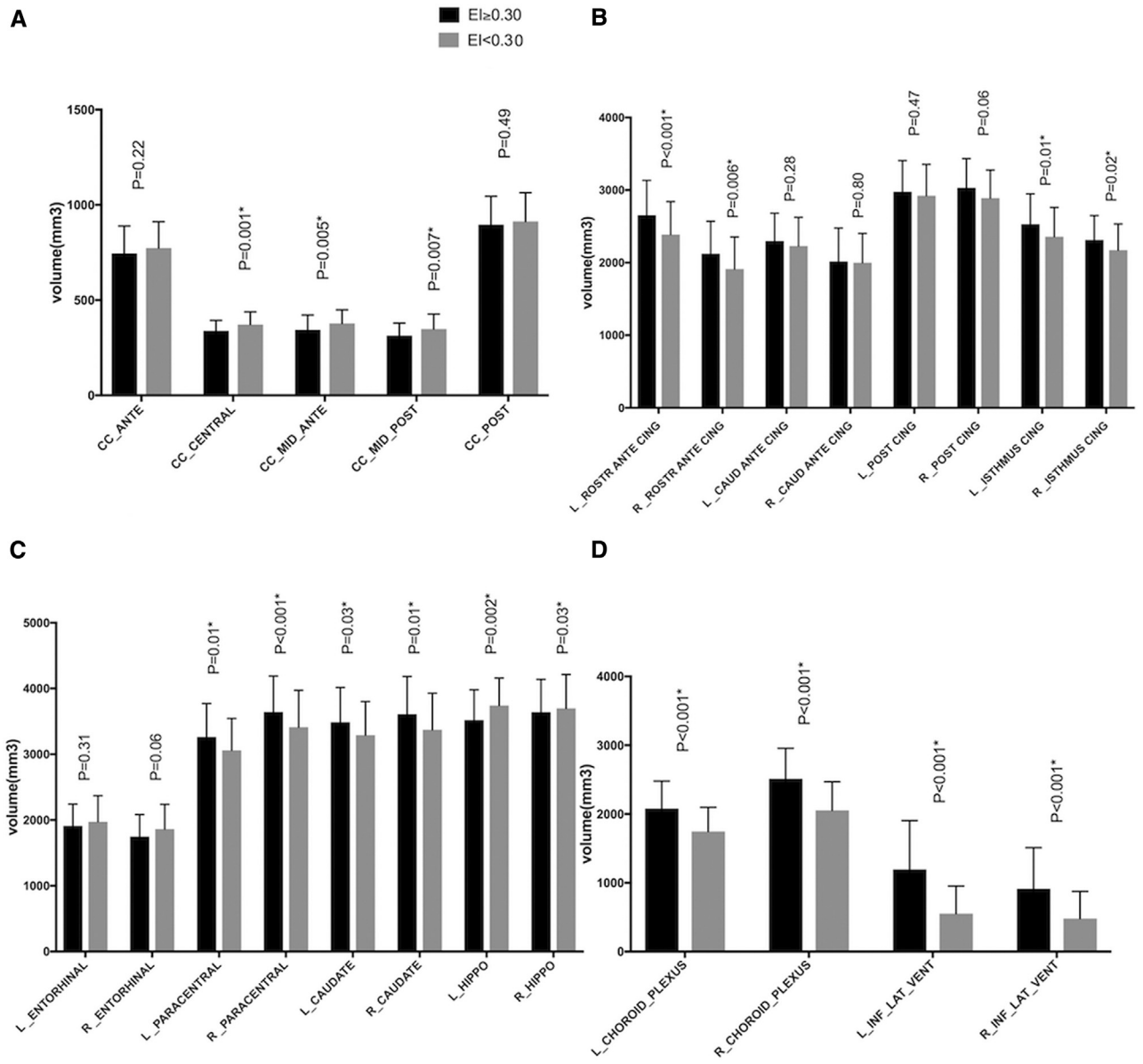

Fig. 1. Brain structure volumes. (A) corpus callosum; (B) cingulate gyrus; (C) entorhinal, paracentral, caudate, hippocampus gyrus; and (D) choroid plexus and inferior lateral ventricles. Abbreviations: ANTE, anterior; CAUD, caudal; CC, corpus callosum; CING, cingulate; HIPPO, hippocampus; L, left; LAT, lateral; MID, middle; R, right; ROSTR, rostral; POST, posterior; VENT, ventricles.

Table 4
FDG uptake analysis

	FDG SUVR		
Brain region	EI ≥ 0.30 (n = 75)	EI < 0.30 (n = 245)	*P* value
Angular left	1.28 ± 0.14	1.33 ± 0.14	.004*
Angular right	1.28 ± 0.14	1.33 ± 0.12	.005*
Cingulumpost bilateral	1.33 ± 0.14	1.43 ± 0.14	<.001*
Temporal left	1.26 ± 0.13	1.27 ± 0.12	.36
Temporal right	1.24 ± 0.11	1.25 ± 0.11	.38

Abbreviations: Cingulumpost bilateral, bilateral posterior cingulate cortex; FDG, fluorodeoxyglucose.

*Statistically significant.

ventriculomegaly group had lower CSF $A\beta_{1-42}$ level. There was no significant difference in CSF t-tau and p-tau values between the two groups. There was higher percentage of subjects with CSF $A\beta_{1-42} \leq 192$ pg/mL in ventriculomegaly group than that without ventriculomegaly, 60.6% versus 38.0% (Table 5).

4. Discussion

In this study, we found that cognitively normal individuals with ventriculomegaly had worse delayed memory and executive function, more gray matter and CSF volumes, disproportionately changed volumes of brain structures, less

Table 5
F18-PET-AV45 SUVR, CSF Aβ, and tau biomarkers

Brain region	Value		*P* value
	EI ≥ 0.30	EI < 0.30	
FRONTAL	1.33 ± 0.28 (n = 92)	1.27 ± 0.25 (n = 302)	.04*
CINGULATE	1.44 ± 0.28 (n = 92)	1.40 ± 0.27 (n = 302)	.12
PARIETAL	1.35 ± 0.29 (n = 92)	1.29 ± 0.25 (n = 302)	.03*
TEMPORAL	1.24 ± 0.23 (n = 92)	1.21 ± 0.22 (n = 302)	.20
CSF $A\beta_{1-42}$ (pg/mL)	177.08 ± 48.57 (n = 62)	203.03 ± 49.96 (n = 229)	<.001*
CSF $A\beta_{1-42}$ ≤192 pg/mL; n (%)	40 (60.6)	87 (38.0)	<.001*
CSF Tau(pg/mL)	67.38 ± 29.36 (n = 59)	69.77 ± 35.44 (n = 223)	.49
CSF P-Tau(pg/mL)	39.72 ± 19.68 (n = 62)	37.21 ± 20.47 (n = 228)	.999

Abbreviations: Aβ, amyloid β; CSF, cerebrospinal fluid; SUVR, standardized uptake value ratio.
*Statistically significant.

FDG SUVR and more Aβ deposition in the neocortex with specific distribution pattern, and less CSF $A\beta_{1-42}$ level with unchanged CSF tau, compared to the cognitively normal individuals without ventriculomegaly. Until now, the characteristics of neuropsychological and biomarker profiles of ventriculomegaly in cognitively normal elderly individuals and its implication are poorly understood. Our findings have shed light on this issue showing for the first time that cognitively normal individuals with ventriculomegaly shown neuropsychological and multiple biomarker abnormalities that can be identified before clear clinical presentation.

EI is an indicator of the enlargement of LVs and traditionally used in the diagnosis of normal pressure hydrocephalus (NPH). Idiopathic NPH (iNPH) was first described by Hakim and Adams in 1965, with a typical clinical triad of gait disturbance, cognitive impairment, and urinary incontinence in the elderly patients who showed the association with the enlargement of the cerebral ventricular system and good response to shunt surgery [19]. Some researchers found that EI more than 0.30 should be indicative of ventriculomegaly [7]. Following this criterion, our demographics data showed that 22.5% of cognitively normal individuals in the selected ADNI cohort had ventriculomegaly. Only gender and age were significantly different between the two groups. Individuals with asymptomatic ventriculomegaly tended to be older (76.0 ± 5.6) and of male gender (70.8%). Although ventriculomegaly is common in both AD and NPH, the male predominance has been observed in NPH epidemiological study [20,21], whereas gender predominance in AD is uncertain [22,23] even with female predominance is reported in AD studies [24,25]. Hence, our findings suggested that male cognitively intact elders with ventriculomegaly concord more with the early spectrum of iNPH although this needs to be confirmed in future longitudinal studies.

MoCA, MMSE, ADAS-Cog, and Clock Drawing scores reflect global cognitive function. The scores in these scales all suggested that the subjects with ventriculomegaly had consistently worse cognitive functions compared to those without ventriculomegaly although they were still cognitively normal. This finding is consistent with the scores of Logical Memory Test and Rey AVLT. Furthermore, the scores of ADNI-Mem and ADNI-EF also supported the framework that memory and executive function domains of individuals with asymptomatic ventriculomegaly were impaired although they remained clinically cognitively normal. Hence, subclinical memory and executive dysfunction may be the earliest neuropsychological impairments, which characterize asymptomatic ventriculomegaly.

The structural volume differences in our study showed certain characteristics that were unique for asymptomatic ventriculomegaly. The hippocampal gyrus volume and the volumes of the CC were significantly smaller in the individuals with asymptomatic ventriculomegaly than individuals without ventriculomegaly. Atrophy of these structures is regarded as a typical finding in AD. However, our findings showed that the gray matter volumes in ventriculomegaly group were significantly larger. As the increased ventricular volume in AD is commonly caused by the loss of brain tissue or brain atrophy [26,27], this enlargement of gray matter makes brain atrophy as the underlying cause for ventriculomegaly in cognitively normal individuals less likely. In this study, we also found some unique phenomena such as smaller middle part of CC, posterior cingulate gyrus and entorhinal gyrus without significant difference, and the larger anterior cingulate volume, while they are uncommon in early AD, where the most involved part of CC should be the anterior [28] or posterior/splenium region [29,30,31], the posterior cingulate gyrus and entorhinal gyrus [32,33] are often involved and the anterior cingulate volume is often unaffected [27]. In addition, we observed that the bilateral caudate, paracentral gyrus, and isthmus cingulate volumes were also larger in these individuals. These features, at least, make the manifestation unlike typical AD. As these enlarged brain structures were located near the LVs: caudate is medial to the LV; paracentral gyrus is superior and medial to the LV; and isthmus cingulate is medial to LV, we speculate that the enlargement of these structures may be caused by increase of water content or some kind of compensation mechanism, rather than brain atrophy [34,35]. Nevertheless, the decreased

hippocampal volume is not consistent with our speculation as this structure is also near the LV though atrophy of hippocampus has been observed in NPH [36]. We suppose that this can be due to the position of this structure, which is inferior and medial to the LV, while the previously described brain structures with increased volumes are superior and medial to the LV. Perhaps, the decreased hippocampal volume is still an indicator of AD. As such, this finding of disproportionately changed brain structure volumes may further characterize the asymptomatic ventriculomegaly framework.

In iNPH, the disproportionate enlargement of subarachnoid space (DESH) was observed by Hajime in 1998 and was proposed as a preclinical state of iNPH in an epidemiological study [37]. Both the convexity and the medial subarachnoid spaces were significantly smaller in most of the patients with iNPH than those with AD while the sylvian fissure was larger in iNPH than in AD [38]. However, the underlying pathophysiology of DESH is unknown. Our finding of a disproportionate enlargement of the brain structures is consistent with the proposed framework of DESH. Essentially, brain regions with enlarged subarachnoid space in NPH have structures with decreased volumes (hippocampus), and brain regions with decreased area (tight convexity) have structures with increased volume (paracentral gyrus and caudate). Significantly larger inferior LVs and choroid plexus may also suggest NPH tendency, and the enlargement of inferior LVs may exert pressure on the medial part of temporal lobe, resulting in the decreased hippocampal volume. The enlargement of LVs can also exert pressure on the CC, which results in the reduction of the volume of CC, a common MRI finding in iNPH [39]. As iNPH has been reported frequently in comorbidity with AD [40–42], our NPH-like structural findings further support our claim that these individuals with asymptomatic ventriculomegaly may be an early signature of AD and/or preclinical spectrum of iNPH.

The caudate plays a key role in supporting the planning and execution of behavior needed to achieve complex goals [43]. In preclinical familial AD studies, the volumes of the both caudates have been shown to be decreased [44]. Therefore, our finding of the enlargement of bilateral caudates cannot be explained by the AD pathophysiology. However, this finding cannot be completely explained by NPH pathophysiology, either, as one NPH study has reported smaller caudate volume in NPH compared with normal control [45]. Hence, while we propose that the disproportionate enlargement of brain structural volumes characterizes asymptomatic ventriculomegaly, future longitudinal studies are needed to test this hypothesis and further elucidate the underlying pathophysiology of this observed phenomenon.

We found that the [^{18}F]FDG SUVR was decreased in the bilateral angular gyri and posterior cingulate gyri of the individuals with asymptomatic ventriculomegaly compared to those without ventriculomegaly. As hypometabolism in posterior cingulate was reported to be obvious [46], this metabolic signature indicates that this population with ventriculomegaly has some features of AD. However, there was no significant difference in [^{18}F]FDG SUVR in temporal gyrus between the two groups. It has been reported that medial temporal regions were also often affected in AD [47]. The decreased [^{18}F]FDG uptake in both the angular and posterior cingulate regions, not in the temporal area, in the group with ventriculomegaly made this biomarker profile look unlike typical AD.

We also found that [^{18}F]florbetapir SUVR was increased in the neocortex (frontal and parietal), and the CSF $A\beta_{1–42}$ level was decreased in the individuals with asymptomatic ventriculomegaly compared to those without ventriculomegaly. This finding is consistent with the Aβ biomarker signature of AD [16]. Taking CSF $A\beta_{1–42} \leq 192$ pg/mL as a cutoff value for having AD risk [15], asymptomatic ventriculomegaly group had higher risk of AD according to the recent definition of asymptomatic at AD risk [48]. CSF biomarker changes are evident over two decades before the individual's expected age at symptom onset, as determined by their parental age at onset [49]. Reduced concentrations of CSF $A\beta_{1–42}$ and increased concentrations of CSF tau were detected at 25 and 15 years from the expected symptom onset, respectively. However, there was no significant difference in the [^{18}F]florbetapir SUVR in cingulate and temporal areas between the groups in our study, which is not consistent with the typical AD feature [50,51]. CSF t-tau and p-tau had no significant difference either. Unsurprisingly, this phenomenon can be found in AD as decrease of Aβ in CSF can happen earlier than increased level of tau. Meanwhile, this feature is also in concordance with iNPH as total secreted amyloid precursor protein (APP), soluble APP α and $A\beta_{1–42}$ have been shown to decrease in the CSF of NPH patients without change of t-tau or p-tau [52]. Therefore, Aβ and tau biomarker features of asymptomatic ventriculomegaly could be early AD or preclinical NPH spectrum.

Altogether, asymptomatic individuals with ventriculomegaly are ostensibly cognitively normal, however, they have worse memory and execution compared with those with normal ventricles, therefore, special attention should be paid to these individuals. This study showed that asymptomatic individuals with ventriculomegaly have smaller hippocampal volumes, less FDG uptake, more Aβ deposition in the neocortex, and less CSF $A\beta_{1–42}$ level, which are characteristics of preclinical AD [16]. However, relatively bigger posterior cingulate gyrus and uninvolved entorhinal gyrus are not supportive of preclinical AD. Besides these, interestingly, it has also been found that these specific individuals have bigger volumes of gray matter, paracentral gyrus, and caudate with unchanged CSF tau levels. The pattern of MRI structural volumes implies the disproportionate change of brain structures, which concords with DESH feature of iNPH. Some researchers suggest that less CSF $A\beta_{1–42}$ level and unchanged CSF tau levels may be features of iNPH [52]. Therefore, cognitively normal individuals with ventriculomegaly may constitute a unique group of people. Here, we just reported this interesting finding. There is limitation

in this study. The self-selected group of participants in the ADNI limits the generalizability of our results. The follow-up is not long enough. Our findings will require further validation in a larger population-based longitudinal study and a longer follow-up. Furthermore, future work should be carried out to answer questions such as "what triggers this phenomenon?", "what is the underlying pathophysiologic process?", "How about the prognosis?", and "Are there interacting mechanisms between AD and NPH?"

5. Conclusions

Ventriculomegaly is common among cognitively normal individuals. The characterization of the neuropsychological and biomarker profiles in these individuals implies that it may be an early imaging signature of preclinical AD and/or have comorbidity of iNPH and more research should be performed.

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RESEARCH IN CONTEXT

1. Systematic review: Quite a few research studies have suggested that ventriculomegaly in mild cognitive impairment (MCI) and Alzheimer's disease (AD) is possibly attributed to the brain atrophy. In clinical practice, ventriculomegaly can be more and more frequently observed in asymptomatic subjects, however, the prevalence of the neuropsychiatric and biomarker features of ventriculomegaly in cognitively normal subjects is unclear.
2. Interpretation: Ventriculomegaly in cognitively normal subjects is not uncommon, and overall neuropsychological and biomarker profiles imply a kind of atypical preclinical AD or have comorbidity of preclinical iNPH.
3. Future directions: Other plasma or cerebrospinal fluid biomarkers should be investigated to see their relationships with ventriculomegaly. In ADNI, the cognitively normal control group might contain different types of preclinical comorbidities of other brain disorders. This should be taken into consideration to understand if there are interacting mechanisms between underlying neurodegenerative disorders and ventriculomegaly.

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