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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).