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Clinical Study

Total intracranial and lateral ventricle volumes measurement in Alzheimer's disease: A methodological study

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ABSTRACT

Measuring of brain and its compartments' sizes from magnetic resonance (MR) images is an effective way to assess disease progression in neurodegenerative disorders, particularly Alzheimer's disease (AD). The objective of this study was to compare total intracranial volume (TIV) and lateral ventricle volume (LVV) in patients with Alzheimer's disease with those in elderly control subjects, and to compare an automated method (automatic lateral ventricle delineation [ALVIN]) and a manual method (ImageJ). MRI of the brain was performed on 20 patients with Alzheimer's disease and 18 control subjects. The TIV was calculated by a manual method and the LVV was calculated by using two methods: an automated and manual method. We found a significant increase in LVVs in Alzheimer's disease patients compared to control subjects, but no difference in TIV between the two groups. A perfect agreement, with 0.989 (0.973–0.996) intraclass correlation coefficient (ICC) and 0.978 (0.946–0.991) concordance correlation coefficient (CCC), was observed between the manual and automatic lateral ventricle measurements in Alzheimer patients. The results revealed that LVV measure has predictive performance in AD. We demonstrated that ALVIN and ImageJ are both effective in determining lateral ventricular volume, providing an objective tool for quantitative assessment of AD.

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and is characterized by a progressive decline in cognitive function, which typically begins with deterioration in memory. AD prevalence is set to rise in the coming decades [1] and there is still no currently accepted early diagnosis for AD. It is widely believed that the way to early and effective treatment for AD requires the development of early diagnostic markers that are both sensitive and specific. Two complementary modalities, imaging and cerebrospinal fluid (CSF) biomarkers are promising antecedent markers for AD [2]. A variety of neuroimaging techniques have been developed for early detection of individuals at risk of developing AD-related neurodegeneration. These techniques include structural MRI, positron emission tomography (PET), and functional Magnetic resonance imaging (MRI). In particular, structural MRI has provided insight into the neuroanatomical profile of pre-clinical and early AD and its progression [3].

Some imaging studies in literature compared brain structures of patients with AD and healthy elderly individuals. Although some of these investigations indeed revealed atrophic brain changes in geriatric depression, the results of these studies were, however, partly contradictory [4–7]. These conflict results may be explained by the use of different morphometric methods; furthermore, most of these studies were limited because they were performed by planimetric methods or visual inspection of atrophy rather than by a direct volumetric approach. MRI in combination with appropriate computer software provides the advantage of directly measuring volumes of particular brain structures and therefore allows more precise investigation of volume changes in region of interest.

Research efforts for the purpose of rating dementia based on neuro-imaging findings have focused on the atrophy of the brain parenchyma and other key structures such as the lateral ventricle (LV) and hippocampus. Research has shown that pathological changes in these areas have strong correlations with Alzheimer's

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disease. These studies have frequently shown a reduction on the total brain volume and atrophy on the hippocampus region by using different methods which utilized various programs [8–13].

Neuroimaging techniques such as Computed tomography (CT) scans and MRI indicated loss of brain tissue, especially gray matter, and increased cerebrospinal fluid in AD [14–16].

The lateral ventricle volume (LVV) measurements have usually been performed using computer-assisted manual tracing methods, semiautomatic algorithms, and fully automated methods [17–19]. Manual tracing methods are commonly applied on three-dimensional (3D) MRI on each slice of the series. This process can be time consuming when the amount of data is large. Unlike the 2D MRI sequences, the acquisition of the 3D images and the following post-processing are two operations that need time and thoroughness. Automatic segmentation algorithms usually require a 3D template MRI for the registration step that may need a considerable time too, even on powerful machines. 3D MRI acquisitions are generally long time-taking due to phase encoding in two directions, thus they are very sensitive to patient motion. As a result, 3D approach is limited in clinical practice when subjects are patients with neurodegenerative diseases who cannot remain in a stable condition for long durations due to movement and shaking troubles. Motion leads to artifacts such as blurring or ghosting on 3D images resulting in difficulty in image processing and likely extraction of false information.

A novel algorithm for segmentation of the lateral ventricles, named ALVIN (automatic lateral ventricle delineation), uses 'unified segmentation' in standard Statistical Parametric Mapping (SPM) [20,21]. Unified segmentation produces grey matter, white matter, and CSF images from MRI data but does not segment subcortical structures. ALVIN works by applying a binary mask to spatially normalized CSF segmented images produced using unified segmentation. In SPM analysis, MRI images are normalized into a standardized template and spatially smoothed. The set of pooled data are then assessed on a voxel-by-voxel basis, to identify the profile of voxels that significantly changes between conditions.

In this study, we utilized computer-based technique (manual, ImageJ software) to obtain volumetric measures of total intracranial volume (TIV) and lateral ventricles in patients with AD and compared the results with healthy volunteers. The predictive performances of lateral ventricle manual (LVM) and TIV in identifying Alzheimer's disease and the repeatability and reliability of the manual LVV measurements were assessed statistically. In addition, we used MATLAB-based SPM toolbox for data pre-processing and tissue segmentation (ALVIN) in automatic LVV estimation of AD patients and we also used ImageJ software to measure LVV, aiming to show its accuracy in comparison to ALVIN.

2. Materials and methods

2.1. Subjects

Total number of 38 subjects participated in MRI including 20 clinically diagnosed AD patients (age range, 67–81 years; mean age, 74.75 years) and 18 control cases (age range, 68–80 years; mean age, 73.22 years). AD patients, who were involved in the study, were referred from the neurology clinic of our institution. They fulfilled the criteria for probable AD dementia with documented decline of National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [22]. Healthy elderly control subjects without any significant neurologic, psychiatric or systemic disease were recruited by the fliers posted in the community areas. Mini mental state examination (MMSE) of the participants were between 10 and 23 for the patient group and higher than 23 for the control group. All participants were over 65 years. The patient group had mild or moderate degree disease according to Clinical Dementia Rating [23] and did not have any other neurologic, psychiatric illness or any significant unstable systemic illness. The clinical characteristics of the population under investigation are shown in Table 1.

No statistically significant difference was found between the two groups with regard to age or gender examinations ($p > 0.05$). This study was approved by the institutional review board, and written informed consent was obtained from all the subjects and from the caregivers of AD patients.

2.2. MRI procedure

MRI was performed at 1.5 T scanner (Philips Gyroscan Intera, Best, Netherlands). The protocol consisted of axial T2-weighted MRI, fluid-attenuated inversion recovery (FLAIR), and 3D T1-weighted turbo field echo (TR = 25 ms, TE = 4.6 ms, Flip angle = 30°, FOV = 256 × 196 mm, with isotropic voxel size 1 mm).

2.3. Volume estimation techniques

T1-weighted MRI images were used for volume estimation. TIV was calculated from MRI images using ImageJ software. TIV was estimated by summating the volumes of both hemispheres including all ventricles, subarachnoid space, cerebellum, and brainstem. LVV calculation was performed both manually (ImageJ) and automatically (ALVIN) on MRI images.

2.4. 1-Manual measurement with ImageJ

TIVs and LVVs were calculated from MRI images. We used ImageJ software (version 1.33) for volume calculation. ImageJ is a freely downloadable image analysis software package developed at the National Institute of Health to assist in clinical and scientific image analyses. The applicability of ImageJ for LVV measurement has not been addressed before.

The analysis included the following steps: The DICOM files were transformed into a "stack" using the function "Convert Images to Stack" in the submenu "Stacks". The region of interest (ROI) relevant for the present study is the LV. Before outlining an ROI on each LV border, the ROI manager in the pull-down menu "Analyse > Tools" was opened. The right and left LV border were manually outlined using the "Polygon selection tool". This tool can create an irregularly shaped selection defined by a series of line segments [24]. The respective ROI of each slice was added to the ROI manager with the function "Add" in the ROI manager menu. To calculate the areas, all the ROIs must be selected in the ROI manager. The area of each ROI was calculated with the function "Measure" in the ROI manager menu. All images were created as masked images and image sequences saved in a BMP format. The outer boundaries of the LV were delineated using threshold tool and then the wand tool was used to delineate the boundaries of the LV (Fig. 1). The sectional cut surface of the structure of interest was measured by the software automatically. The LVV was estimated

Table 1
Group characteristics of patients with Alzheimer's disease and healthy control subjects

	Alzheimer Patients	Control Subjects
No. of subjects	20	18
Age range	67–81	68–80
Age, mean ± SD	74.75 ± 4.48	73.22 ± 3.91
Men/Women	13/7	10/8
MMSE score, mean ± SD	17.95 ± 2.18	27.77 ± 1.06

MMSE = mini mental state examination, SD = standard deviation.