Applied Radiation and Isotopes 67 (2009) 1377–1381

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Voxel-based analysis of Tc-99 m ECD brain perfusion SPECT in patients with normal pressure hydrocephalus

Bora Yoon [a], Dong-Won Yang [a,*], Yong-Soo Shim [a], Sung-Woo Chung [a], Kook-Jin Ahn [b], Joo-Hyun O [b], Sung-Hoon Kim [b], Hyung-Sun Sohn [b], Soo-Kyo Chung [b], Yong-An Chung [b,c,**]

[a] Department of Neurology, The College of Medicine, The Catholic University of Korea, Seoul 137-701, South Korea
[b] Department of Radiology, The College of Medicine, The Catholic University of Korea, Seoul 137-701, South Korea
[c] East-West Research Institute of Translational Medicine (EWTM), Incheon St. Mary's Hospital, Incheon 403-720, South Korea

ARTICLE INFO

Keywords:
Idiopathic normal pressure hydrocephalus
Regional cerebral blood flow (rCBF)
Statistical parametric mapping (SPM)
Dementia

ABSTRACT

Idiopathic normal pressure hydrocephalus (iNPH) is a reversible dementia characterized by gait disturbance, incontinence and dementia. This study investigates the neuropsychological characteristics and changes of regional cerebral blood flow (rCBF) in patients with iNPH. Ten patients who met the criteria of probable iNPH and 13 normal control subjects were evaluated. The general cognitive function and detailed neuropsychological functions were measured by K-MMSE and comprehensive neuropsychological battery. Tc-99m-ethyl cysteinate dimmer (Tc-99m-ECD) single photon emission computed tomography (SPECT) was performed to measure the rCBF and statistical parametric mapping (SPM) and statistical probabilistic brain anatomic map (SPAM) was applied to the objective analysis of SPECT data. On the neuropsychological examination, all the patients showed abnormality in memory, psychomotor speed and frontal executive function. SPM analysis of SPECT images revealed that rCBF in bilateral thalami, right prefrontal area, bilateral anterior and posterior cingulate gyri, right caudate nucleus, and left parahippocampal gyrus was significantly decreased in patients with iNPH compared to normal controls (uncorrected $P<0.005$). In SPAM analysis, rCBF reduction was observed in bilateral prefrontal area, anterior, posterior cingulate gyri and caudate nuclei. We have found that rCBF changes occurred predominantly in prefrontal and subcortical areas, the changes were associated with frontal subcortical circuit, and the affected frontal subcortical circuit may contribute to the cognitive decline seen in the iNPH patients. The reduction of rCBF and clinical cognitive impairment are closely connected in patients with iNPH.

1. Introduction

The syndrome of normal pressure hydrocephalus (NPH), first described by Adams et al. (1965), is characterized by the clinical triad of gait disturbance, dementia, and urinary incontinence. NPH is divided into two subcategories, one is idiopathic NPH (iNPH) and the other is secondary NPH. Secondary NPH is related to a clear cause, such as subarachnoid or intraventricular hemorrhage, meningitis, head trauma, basilar artery ectasia, chronic aqueduct stenosis or intracranial surgery. Since iNPH is primarily a condition of the elderly and is reversible, many clinicians have been interested in diagnostic and therapeutic approaches. None the less, the characteristics and pathophysiology of the disease are not well documented. There is some evidence, especially in iNPH, to suggest that the cerebral vasculature may have a role in the pathogenesis of NPH (Bradley et al., 1991; Greitz et al., 1994). Thus, as significant efforts have focused on the study of cerebral blood flow (CBF), the pattern of regional CBF (rCBF) in NPH has been investigated by means of positron emission tomography (PET) and single photon computed tomography (SPECT) (Chang et al., 1999; Larsson et al., 1994; Mamo et al., 1987; Owler and Pickard, 2001; Sasaki et al., 2007; Tanaka et al., 1997). Unfortunately, the studies reported heterogeneity and inconsistency in the reduction of rCBF and no report has been able to demonstrate a typical CBF pattern. Moreover, only a few studies have assessed cognitive impairment that could be related to the frontal lobe dysfunction in patients with iNPH (Boon et al., 1997; Iddon et al., 1999). Therefore, both the relationship and correlation between the reduction in rCBF and the clinical cognitive impairment are not established.

This study investigated the neuropsychological characteristics by performing comprehensive neuropsychological battery tests

* Corresponding author. Tel.: +82 2 3779 1378; fax: +82 2 783 9532.
** Corresponding author at: Department of Radiology, The College of Medicine, The Catholic University of Korea, 505, Banpo-dong, Seocho-gu, Seoul 137-701, South Korea. Tel.: +82 2 3779 2340; fax: +82 2 784 6869.
E-mail addresses: neuroman@catholic.ac.kr (D.-W. Yang), nm@catholic.ac.kr (Y.-A. Chung).

0969-8043/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.apradiso.2009.02.080

and observed the changes of rCBF by performing Tc-99m-ethyl cysteinate dimmer (Tc-99m-ECD) SPECT in patients with iNPH. Two analytic methods, statistical parametric mapping (SPM) and a statistical probabilistic brain anatomic map (SPAM) were adopted for objective and quantitative evaluation of brain perfusion SPECT. The aim of the present study was to compare the pattern of rCBF between SPM and SPAM analysis in iNPH patients and to assess the relationship between clinical cognitive impairment and the pattern of rCBF.

2. Experimental

2.1. Subjects and neuropsychological assessments

10 patients with iNPH were recruited from the dementia clinic of St. Mary's Hospital. They fulfilled the criteria for diagnosis of probable iNPH according to the Clinical Guidelines for iNPH (Ishikawa, 2004). The criteria are: (1) over 60 years old in age; (2) having one or more symptoms of gait disturbance, dementia or urinary incontinence; (3) ventricular dilatation (Evans index >0.3) and narrow CSF space in the superior convexity; (4) CSF pressure lower than 20 cm H_2O with normal properties of CSF cell counts and protein level; (5) having no other diseases that may account for symptoms; (6) no other previous illness that causes ventricular dilatation and (7) positive spinal tap test. All patients underwent the spinal tap test, SPECT and brain magnetic resonance imaging (Br-MRI).

Thirteen healthy volunteers were selected as the controls. They were interviewed, assessed for neurological and cognitive function, evaluated for the 29 illnesses proposed by Christensen et al. (1991), which may be associated with cognitive impairment and underwent SPECT and Br-MRI following the same protocol as the patient group.

General cognitive function was evaluated by using the Korean version of mini-mental status examination (K-MMSE) and clinical dementia rating (CDR) scale. Detailed neurocognitive functions were evaluated by the Seoul neuropsychological screening battery (SNSB) (Kang, 1998) including verbal, visual memory, visio-spatial function, attention and frontal executive function tests such as motor performance tasks, digit span backward, Stroop color reading, and word fluency tests. This study was approved by the Ethics Committee of the Catholic University Hospital of Korea.

2.2. SPECT scanning

SPECT imaging was initiated 20 min after intravenous injection of approximately 740–925 MBq of Tc-99m-ECD using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. The head unit consisted of two rotating rings of 59 probe-type detectors. Data were reconstructed in a 128×128 matrix with a pixel size of $3.9 \times 3.9 \times 3.9$ mm (FOV $= 240$ mm, slices thickness $= 7$ mm) and a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after back-projection using a Butterworth filter (cutoff frequency 0.4 cycles/pixel, order 5) to reduce statistical noise. Tc-99m-ECD images were corrected for tissue attenuation using a standard commercial correction routine (Siemens Inc., Erlangen, Germany), assuming uniform attenuation and a circular head shape.

2.3. Image preprocessing

All subsequent image manipulation and data analyses were performed on an IBM personal computer running a Windows XP operating system. The software for image manipulation included Matlab version 5.3 (Mathworks, Inc., Natick, MA) and SPM99 (Institute of Neurology, University College of London, UK). The SPECT data with attenuation and scatter correction were converted into ANALYZE format (Mayo Foundation, Baltimore, MD, USA) having voxel dimensions of 3.9 mm in each spatial dimension. The mean pixel intensity across all slices of the imaging volume was calculated. Pixel threshold was set to 80% of this value to eliminate background noise and partial volume effects at the edge of the brain. Each SPECT scan was then spatially normalized using a 12-parameter affine warping and tri-linear interpolation to the SPECT template brain from the Montreal Neurological Institute, reformatted to a 16-bit image having a size of $79 \times 95 \times 68$ voxels and a $2 \times 2 \times 2$ mm voxel dimension. These images were smoothed with a Gaussian filter of 16 mm full-width at half maximum (FWHM). Normalized rCBF values were calculated by dividing CBF at each voxel by global CBF in each individual.

A SPAM (Lee et al., 2004) of the International Consortium for Brain Mapping was applied to objectively draw voxel of interests (VOIs). SPAM consists of 98 VOIs in a single image, where each voxel has the probability of belonging to a specific VOI. After spatial normalization, the counts of each SPECT image were normalized using proportional scaling, with the mean counts of the cerebellum set at 50. The normalized counts were multiplied by the probability of the SPAM and were determined as the count of each VOI. The cerebral lobar counts were then calculated by averaging the counts of the VOIs that had been reclassified into each lobe.

2.4. Statistical analysis

Intensity-normalized SPECT data from the iNPH group were compared with similarly normalized data from the 13 healthy subjects. Group contrasts in rCBF were estimated at each voxel using the general linear model of SPM99. A two-sample t-test model was fitted, and a t-statistic image was constructed and then threshold at $t>8.01$, corresponding to an uncorrected p-value <0.005, in conjunction with a cluster filter of 100 voxels in the reformatted, template imaging space. This combined application of a statistical threshold and cluster filter has previously been shown to reduce substantially the false positive identification of activated pixels at any given threshold (Forman et al., 1995). For the visualization of the results, the clusters of a voxel with significance were projected onto the standard high-resolution MRI images. This fusion images illustrated anatomic localization of the SPM analysis. To identify precise anatomical location of the results, we entered the values of x, y, z of the cluster of a statistical significance into the software program, and finally obtained anatomical locations and Brodmann areas of the results. In SPAM data, a Mann–Whitney test was performed to compare iNPH and control groups. A value of $P<0.01$ was considered significant.

3. Results

3.1. Demographics and neuropsychological results

In iNPH patients group, there were six men and four women, the mean age was 71.90 ± 4.93 years old (range: 62–76 years), the educational year was 10.80 ± 4.39 years, and the mean duration of symptoms was 28 ± 22 months (range: 12–78 months). The distribution of the subjects' gender, age, and the educational level between the iNPH group and the control group was not different.