K. Ishii  
M. Sasaki  
M. Matsui  
S. Sakamoto  
S. Yamaji  
N. Hayashi  
T. Mori  
H. Kitagaki  
N. Hirono  
E. Mori

A diagnostic method for suspected Alzheimer’s disease using H215O positron emission tomography perfusion Z score

**Abstract** We developed cerebral perfusion Z score map (Z map) images using H215O and positron emission tomography (PET), and examined their use in diagnosing Alzheimer’s disease (AD). Cerebral blood flow (CBF) images were obtained using the PET and H215O autoradiographic method. The best region for normalising the CBF value to remove individual variation was determined. Then CBF images were transformed to Talairach’s standard space, and each pixel value of an individual’s image set was normalized to the mean value of the sensorimotor area. Based on the CBF images of 20 normal volunteers, normative mean and standard deviation (SD) CBF images were constructed. Then, each pixel value of the axial CBF images in 28 patients with probable AD and 10 further normal volunteers was converted to a Z score (Z = (normal mean – individual value)/normal SD). A Z map, showing pixels exceeding a threshold of Z score > 2 on MRI of standardised anatomical space was demonstrated. These 38 Z maps were interpreted by four radiologists. When regions in the temporoparietal area were found with Z scores > 2, the subject was diagnosed as having AD. A receiver operating characteristic (ROC) analysis was performed to compare the conventional CBF images and Z maps. The diagnostic performance of the Z map was superior to that of visual inspection of conventional CBF images (mean areas under the ROC curve of the four radiologists were 0.946 and 0.584, respectively). These results indicate that a Z map obtained in this way is superior to conventional PET for diagnosing AD.

**Key words** Alzheimer’s disease  
Blood flow, cerebral  
Positron emission tomography

**Introduction**

Early diagnosis of Alzheimer’s disease (AD) has been investigated with various modalities, including MRI, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). An early study with 15O-labelled water (H215O) and a low-resolution PET scanner failed to detect abnormalities characteristic of AD [1]. Several PET studies with 2-[18F] fluoro-2-deoxy-D-glucose (FDG) [2, 3] or H215O [4] demonstrated characteristic abnormalities in patients thought to have AD, including abnormalities of the posterior cingulate gyrus. A difficulty in interpreting PET is that there are minimal perfusion and/or metabolic changes in the mild stage of late-onset AD [5, 6]. Moreover, age-related changes, frequently seen in healthy aged people should be discriminated from minimal disease-specific change. Visual inspection of PET is thus unreliable and inaccurate. To improve the diagnostic efficacy of nuclear medicine images, we have introduced the idea of converting the original image to a probability map which represents deviations from the
normal. A technique was developed which normalises an individual to a standard brain and, by voxel-by-voxel comparison, facilitates interpretation of the images [2, 3]. On the probability map, the areas which deviate significantly from the normal, regarded as affected, should be easily identified. As degenerative diseases such as AD have disease-specific sites, i.e., sites that are most likely to be affected, the probability map might be useful in diagnosing them. We developed a probability map conversion technique for H215O-PET for diagnosis of AD, and evaluated its diagnostic value.

Methods

A reference appropriate for normalisation should be determined to remove individual variations in cerebral blood flow (CBF) [7]. The following conditions should apply: 1. the regional CBF is representative of an individual’s baseline CBF; 2. the region is less affected by the disease; 3. the normalized data are less variable; and 4. the normalisation can discriminate the disease.

We studied 20 healthy volunteers (NC) recruited from the community (mean age 64.6 ± 7.1 years, 18 women, two men) and 20 patients who fulfilled the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD [8] (mean age = 67.9 ± 10.8 years, 17 women, three men). All patients were examined by both neurologists and psychiatrists, and received routine laboratory tests, brain MRI, MRA of the neck and head, an EEG and neuropsychological examinations including the Mini-mental state examination (MMSE) and Alzheimer’s disease assessment scale (ADAS) (mean MMSE score = 20.5 ± 3.9, mean ADAS score = 20.7 ± 7.0) (Table 1). All healthy volunteers had no neurological or psychiatric history or abnormality on MRI and achieved 28 or more on the MMSE.

Prior to the examination, written informed consent was obtained from all the patients (or agreement from their relatives) and from all NC according to the Declaration of Human Rights, Helsinki, 1975. The PET procedure was strictly according to the PET drug usage manual in our institute, and was approved by the internal ethics committee.

Before PET, all patients and NC had MRI for diagnosis and PET positioning; the detailed procedure is described elsewhere [9]. We used a PET scanner with four rings 15 mm apart, yielding axial resolution of 4.5 mm full-width-half-maximum (FWHM) [10]; slice thickness was 11 mm and slice interval 6.5 mm when the z-motion mode was used. The images were obtained parallel to the commissural or orbitomeatal plane [11, 12]. A transmission scan was performed using a 68Ga-68Ge pin source for absorption correction. Studies were performed with the subjects supine with eyes closed and ears unplugged. The detailed CBF measurement is described elsewhere [13–15]. In brief, CBF was calculated by an autoradiographic technique using a look-up table procedure over a 90 s accumulation after intravenous injection of H215O [16]. The usual amount of tracer was 5 ml and the dose of H215O 740-1110 MBq. Image data analysis was performed on a workstation and a personal computer.

We nominated six regions for normalisation reference: the pons, cerebellum, basal ganglia, thalamus, occipital lobe and sensorimotor area, which are reportedly less vulnerable in AD, and examined them in each of the candidates. At least three circular 10 mm diameter regions of interest (ROI) were placed on them. The CBF in each region of each side was averaged. To examine the appropriateness of a regional CBF for use as an individual’s baseline CBF, we calculated the correlation coefficient between the CBF of each region and the cortical CBF (an average of 84 ROI on the whole brain cortex) in the NC. The variability of the normalised data was examined by coefficients of variation (CV) of the parietal lobe/each region ratio in the NC. To verify the resistance of the region to the disease, the difference in the mean CBF between the NC and the patients was examined by using the Student’s t test. To test the discriminative value, the ratio of the parietal lobe to each region was compared between groups using the Student’s t test.

The original image data were transformed into a standard stereotactic space using SPM95 software [12, 17, 18]. Pixel values of an individual’s image set were then normalised to the sensorimotor value before analysis. Pixels with significantly decreased CBF (P = 0.05), obtained from a comparison of the two groups (20 patients and 20 NC) were plotted on a standard axial MRI co-ordinated to the Talairach space [12] (Prototype AD map).

Next, another ten NC underwent H215O-PET performed as above. The mean age of the four women and six men was 59.4 ± 9.4 years. Their CBF images were obtained without arterial blood sampling. For the patient group, another 28 consecutive patients (21 women, 7 men) with mild to moderate probable AD also underwent H215O-PET as described. Their mean age was 67.1 ± 7.9 years, mean MMSE score 21.8 ± 3.6 and mean ADAS score 16.1 ± 6.4 (Table 1). A Z score was calculated for each pixel of each subject: Z = (normal mean) – (individual value))/(normal SD). A normal database was constructed by averaging, on a pixel-by-pixel basis, the image sets of the first 20 NC. Pixels exceeding a threshold of Z > 2.0 was displayed on a standard MRI and used as a Z map image (Fig. 1).

Comparison of conventional CBF images and Z maps

For evaluation of diagnostic utility, visual and Z map inspections were performed. Each image was displayed on the colour monitor of a personal computer with a 32-level colour scale. For visual inspection, the colour display level of a conventional CBF image obtained by H215O-PET without arterial blood sampling was individually adjusted so that 10% of the maximum activity was deleted to eliminate background noise. Both conventional CBF and Z map images were reviewed by four observers who knew the criteria for abnormality, but who were blinded to the clinical data. The conventional CBF and Z map images were classified as: 1: definite; 2: probable NC; 3: indeterminate; 4: probable; 5: definite AD.

In inspecting the conventional images, we used the following criteria for a positive diagnosis of AD: bi- or unilateral parietotemporal CBF reduction with or without frontal reduction, posterior cingulate gyrus reduction, and relatively normal CBF in the sensorimotor and occipital cortex, thalamus, basal ganglia and cerebellum. Each individual’s Z map image was reviewed by referring to the Prototype AD map, and the classification was determined according to the distribution of significant pixels. Bi- or unilateral temporoparietal and/or posterior cingulate significant pixels were considered to indicate a high probability of AD (4 or 5), while such pixels in other regions were considered to indicate of score 2–4. The cases with no significant pixels were placed in group 1. Significant pixels abutting the ventricles were ignored because they may be artefacts caused by normalisation to the standard brain. We performed a receiver operating characteristic (ROC) analysis, to compare the sensitivity of visual analysis of conventional CBF images and a Z map. The areas under the curves and their standard errors (SE) were calculated using ROC curve analyzer software. To assess the difference in the areas under the ROC curves derived from the same set of patients, we calculated a z value [19].