Objective: We used three-dimensional stereotactic surface projection (3D-SSP) technique to analyze 123I-Iomazenil single-photon emission computed tomographic (IMZ-SPECT) images in temporal lobe epilepsy (mTLE) resulting from hippocampal sclerosis, to assess the usefulness of 3D-SPP in identifying epileptic focus and demonstrating the relationship between IMZ uptake distribution and clinical profile.

Methods: We compared the 3D-SSP images with the original IMZ-SPECT visual images in 26 cases. We assessed IMZ uptake quantitatively in each brain region in all patients and investigated the influence of laterality (involved or non-involved side), a past history of secondary generalized seizure (SGS), and treatment with benzodiazepine on IMZ uptake in each region.

Results: 3D-SSP showed significantly decreased IMZ uptake in the amygdale-hippocampus region on the involved side in
23 of 26 cases, while visual inspection by epileptologists identified correct focus laterality in 17 of 26 cases. The IMZ uptake in the temporal and frontal cortex as well as the amygdala on the non-involved side was significantly greater than that on the involved side. A past history of SGS and benzodiazepines treatment had no apparent effect on IMZ uptake in any region.

Discussion: 3D-SSP was more useful than visual inspection in identifying epileptic focus and showing the distribution of IMZ uptake objectively and accurately. IMZ-SPECT using 3D-SSP not only facilitates detection of epileptic focus but also elucidation of the spread of pathological BZD receptors in the whole brain.

Introduction
In epilepsy, imaging diagnosis using nuclear medicine is equally important as electrophysiological tests such as electroencephalography (EEG). In practice, magnetoencephalography (MEG), magnetic resonance imaging (MRI) and measurements of blood circulation and sugar metabolism using single photon emission computed tomography (SPECT) and positron emission tomography are widely employed in the diagnosis of epilepsy.

In Japan, $^{123}$I-Iomazenil (ethyl-5,6-dihydro-7-ido-5-methyl-6-oxo-4H-imidazo[1,5a][1,4]benzodiazepine-3-carboxylate; C$_{15}$H$_{14}$N$_3$O$_3$I, IMZ), which binds central type benzodiazepine receptors (BZR), has been developed as a radioligand for SPECT. IMZ (Benzodine®, Nihon Medi-Physics Co. Ltd, Tokyo, Japan) has been available in Japan since September 2004 as a means of identifying epileptic focus. IMZ-SPECT was introduced as the first BZR-imaging SPECT, and IMZ uptake in an epileptic focus decreases during interictal periods. Its value in localizing epileptic foci is well established [1-3]. However, an accurate assessment of the focus by visual inspection alone, which is the usual method of evaluation in IMZ-SPECT, is sometimes difficult, because abnormal uptake tends to be less severe and smaller than the virtual finding.

To solve this problem, statistical image analysis based on the development of computed processing techniques has been developed. In neurodegenerative brain disorders such as dementia, statistical image analysis based on a database of normal brains reflects the severity and extent of changes in dynamic blood circulation and metabolism objectively and accurately. Superimposing the images of the patient’s brain on images from the Talairach atlas facilitates lesion diagnosis and selection of excision targets in epilepsy [4].

To date, statistical image analysis using IMZ-SPECT has not been reported in epilepsy. We used image analysis technique to identify the epileptic focus and the extent of pathological change in the whole brain in patients with mesial temporal lobe epilepsy (mTLE) resulting from hippocampal sclerosis (HS).
Patients and Methods

1. Patient Selection

We studied 26 patients (14 females, 12 males) with intractable mTLE resulting from HS. The onset age ranged from 1 to 45 years [mean ± standard deviation (SD): 10.5 ± 9.92 years], age at the time of IMZ-SPECT was 12 to 48 years (mean ± SD: 28.2 ± 9.05 years), and the period from disease onset to IMZ-SPECT examination was 3 to 33 years (mean ± SD: 17.8 ± 7.61 years). Eighteen patients had febrile seizures (FS). There was a family history of FS in five patients and of afebrile convulsions in three. Complex partial seizures occurred in all patients, simple partial seizures in 19, and secondary generalized seizures (SGS) in 17 cases. Eleven patients were taking benzodiazepines (BZDs) at the time of IMZ-SPECT.

To localize the epileptic focus, all patients underwent long-term simultaneous closed circuit television observation and EEG (CCTV/EEG) recording, brain MRI and CT. SPECT was done to assess blood circulation. Neuropsychological tests including the Wada test were also performed. Intracranial EEG was performed in three patients, because pre-operative tests failed to adequately localize the focus. By combining the results of all tests, the focus was identified in all cases. All patients underwent selective amygdale-hippocampectomy. According to Engel’s classification [5] determined 2 years after surgery, 22 of the 26 patients were class I and 3 were class II. One patient was lost to follow up 12 months after surgery.

The control group consisted of 21 normal volunteers (aged 19-20 years, 11 females, 10 males), whose images provided reference data for the three-dimensional section displays.

The methods and conditions for IMZ-SPECT were as described in our previous study [6], except for injection of appropriately reduced MBq in pediatric cases and a cut-off of 0.35 cycles/pixel in the Butterworth filter. IMZ-SPECT was performed during the interictal period, 165-195 minutes after the injection of IMZ.

The images obtained were analyzed statistically using the software “iSSP5 iNEURO-STAT++ for windows” (distributed by Nihon Medi-Physics Co. Ltd) based on three-dimensional stereo-tactic surface projection (3D-SSP) developed by Minoshima et al [7]. The location of the mid-sagittal plane of the brain was determined from a SPECT image set and the bicommissural AC-PC line was located on the mid-sagittal plane by automated methods. The AC-PC line was estimated from four computer-derived landmarks; the frontal pole, the inferior aspect of the anterior corpus callosum, the subthalamic point and the occipital pole. The center of the estimated AC-PC line was matched to the center of the atlas brain. The matched SPECT image was corrected for individual brain size based on the standard dimensions of the atlas brain by linear and non-linear corrections. In linear correction, the anteroposterior length and width of the brain were measured on the SPECT images, and the brain height was estimated by a contour-matching procedure using
the mid-sagittal plane. In non-linear correction, individual gray matter locations were matched with those of a standard brain by maximizing correlation coefficients of regional profile curves determined between predefined stretching centers (predominantly in white matter) and the gray matter landmarks. In image processing, we constructed and used an original template based on the distribution of IMZ instead of the usual template based on FDG-PET. Then cortical radioactivity was extrapolated to stereotactic surface pixels covering the entire cortex of the brain.

For comparing the IMZ-SPECT images obtained from the patients, the difference in radioactivity uptake was shown as a Z-score. Z-score was calculated for each pixel using the following formula; 

\[ Z\text{-score} = \frac{[\text{normal mean}] - [\text{individual value}]}{\text{normal standard deviation}}. \]

A decreased uptake with a Z-score over 2 was defined as significant, and such areas in the 3D sections of the Talairach brain were superimposed on the patient’s MRI image of the brain. Significantly decreased uptake was observed in the amygdale-hippocampus (A-H) regions on both the involved and the non-involved sides. Our definition of the A-H region was limited to amygdale and hippocampus.

With regard to visual inspection, the involved side was determined through discussions among multiple physicians or neurosurgeons who are board certified epilepsy specialists. We compared the results of visual examination with the results of 3D-SSP images assessed by Z-score in each case to assess the usefulness of 3D-SSP for detecting epileptic foci.

We estimated radioisotope (RI) uptake in each brain region by obtaining the ratio of RI count in each region to the average RI count calculated for all regions in the cerebrum or whole brain (cerebrum and brain stem), because there was individual variation in the degree of general RI uptake. We evaluated the following regions: frontal association cortex (FAC), temporal association cortex (TAC), parietal association cortex (PAC), occipital association cortex (OAC), posterior cingulated cortex (PCC), anterior cingulated cortex (ACC), medial frontal cortex (MFC), medial parietal cortex (MPC), primary sensorimotor cortex (PSC), primary visual cortex (PVC), caudate nucleus (CN), cerebellar hemisphere (CH), cerebellar vermis (CV), putamen (Pu), parahippocampus gyrus (PG), amygdala (Ag) and thalamus (TH) (Figure 1).

Subsequently, we analyzed the effect of laterality (involved or non-involved side), a past history of SGS, and BZDs treatment on IMZ uptake in each region. Intergroup differences in the rate of significantly decreased uptake were analyzed by chi-square and Student’s t-test. Significance was defined as p<0.05. The ethics review committee of our institute approved this study.

Results

The 3D-SSP showed decreased uptake in the A-H region on the involved side in 23 (23/26: 88.5%) patients, and on the non-
involved side in 1 (1/26: 3.8%) patient, while visual inspection by the epileptologists concluded that there was apparent decrease in uptake on the involved side in only 17 (17/26: 65.4%) cases. However, the difference between 3D-SSP and visual examination was not statistically significant (p = 0.09). A representative case is shown in Figure 2. In contrast, brain MRI showed abnormalities in the A-H region on the involved side in all patients.

Comparing the mean IMZ uptake (mean ± standard deviation) between the involved and the non-involved sides in 26 patients, there was a significant difference in TAC (involved vs. non-involved: 0.985 ± 0.048 vs. 1.021 ± 0.044, p = 0.007), FAC (1.036 ± 0.028 vs. 1.054 ± 0.026, p = 0.02), PG (0.523 ± 0.039 vs. 0.598 ± 0.048, p < 0.001) and Ag (0.604 ± 0.057 vs. 0.656 ± 0.053, p = 0.001). No significant difference in all regions were detected between patients with a past history of SGS and those without. Compared with patients not treated with BZDs (n = 15), patients treated with BZDs (n = 11) had a significantly higher IMZ uptake in PAC on the non-involved side (1.164 ± 0.025 vs. 1.134 ± 0.033, p = 0.021), but a significantly lower uptake in TAC on the involved side (0.958 ± 0.046: 1.005 ± 0.039, p = 0.009).

Discussion

This is the first report of brain regions with decreased IMZ uptake in subjects with mTLE identified by statistical image analysis of IMZ-SPECT images. Assessing abnormal IMZ uptake by direct visual inspection is sometimes difficult because the drawings of mesial temporal lobe structures are often inadequate for the assessment. However, 3D-SSP with images superimposed over a modeled brain provides highly specific evidence of decreased uptake.

Holls et al. [8] used IMZ-SPECT clinically for the first time. In epilepsy, Bartenstein et al. [9] first reported the use of IMZ-SPECT in patients with localization-related epilepsy. Thereafter, several authors reported decreased uptake on IMZ-SPECT images in epileptic foci, although they used visual inspection or statistic analysis of regions of interests in their analyses [6, 10, 11]. Matheja et al. [3] analyzed BZR function in TLE using asymmetry values of IMZ uptake between the involved and non-involved sides. In the present study, we analyzed the whole brain of subjects with mTLE by IMZ-SPECT using 3D-SSP for the first time. In 3D-SSP, standard deviation, is calculated from normal controls for each pixel of the whole brain, meaning that the uptake change in each pixel can be assessed by 3D-SSP.

We used 3D-SSP to analyze IMZ-SPECT images in mTLE resulting from HS, and confirmed significantly decreased IMZ uptake in the involved A-H region in most cases. 3D-SSP is likely to be more useful than visual inspection in detecting epileptic foci. However brain MRI is superior to IMZ-SPECT because it demonstrated lesions in all cases. Further evaluation is necessary to establish
the most appropriate Z-score in 3D-SSP to define a significantly decreased uptake.

This study revealed that IMZ uptake in FAC, TAC, PG and Ag on the involved side were significantly lower than that on the non-involved side. In particular, the low accumulation of IMZ in FAC on the involved side was interesting, and has not been reported previously in patients with mTLE. This might imply sclerosis not only in TAC and A-H region, but also in FAC as background pathological tissues in mTLE.

There was no significant difference in IMZ uptake in all regions between the group with and that without a past history of SGS. Although the spread of repetitive epileptic discharges has been considered to bring about histopathological changes, our study did not support that conclusion.

It is necessary to consider whether BZR imaging is affected by the administration of BZDs. Kuki et al. [11] reported that identifying low uptake sites in IMZ-SPECT was more difficult and the RI count was lower in patients administered BZDs for over 2 months compared to those administered for less than 2 months. Meanwhile, Duncan et al. [12] found no qualitative or quantitative differences between adult patients who received clobazam and those who did not. In our study, 11 patients were treated with clobazam at the time of examination, but no consistent trend was observed. As mentioned above, different results were reported for different methods and different age groups. Considering all the available data, it remains unclear whether the assessment of IMZ-SPECT is affected by administration of BZDs.

IMZ-SPECT using 3D-SSP is very helpful not only in the diagnosis of HS-associated mTLE but also in elucidating the spread of pathological BZR in the whole brain. Definite localization of the epileptic focus and other regions with reduced IMZ uptake could be a valuable guide for further treatment in any epileptic syndrome. In the future, IMZ-SPECT and statistical image analysis will be applied not only to epilepsy but also to other disorders with a presumed relationship to pathological BZR [13, 14].

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Figure 1: Drawing of regions of interest.
a: frontal association cortex (FAC), b: temporal association cortex (TAC), c: parietal association cortex (PAC), d: occipital association cortex (OAC), e: anterior cingulated cortex (ACC), f: posterior cingulated cortex (PCC), g: medial frontal cortex (MFC), h: medial parietal cortex (MPC), i: primary sensorimotor cortex (PSC), j: primary visual cortex (PVC), k: cerebellar hemisphere (CH), l: cerebellar vermis (CV)
**Figure 2:** IMZ-SPECT findings of a representative case (12 year-old female). The focus laterality cannot be determined by visual inspection (upper). However, 3D-SSP shows lesions with decreased uptake in right (involved) amygdale-hippocampus region and basal temporal lobes (lower).
References


