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Original Articles

Left Superior Temporal Blood Flow Increases in Schizophrenic and Schizophreniform Patients with Auditory Hallucination: A Longitudinal Case Study Using ^{123}I-IMP SPECT

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Summary. Serial assessments of regional cerebral blood flow were performed using ^{123}I-IMP SPECT in two schizophrenic and three schizophreniform patients with persistent auditory hallucination. The initial SPECT study in the period with prominent auditory hallucination revealed an increased accumulation of ^{123}I-IMP in the left superior temporal area which corresponded to the auditory association cortex. In the follow-up SPECT study performed after clinical improvement, the distribution of ^{123}I-IMP had normalized. One of the case with schizophrenia showed a similar increased uptake of ^{123}I-IMP in the left superior temporal area in the third SPECT scan performed when a psychotic relapse with auditory hallucination occurred. MRI scans in two of the five patients demonstrated reduced volume of the temporal lobes. These findings suggest that the auditory hallucinations in schizophrenia may be involved in functional hyperactivity in the left superior temporal cortex which might be based partly on structural abnormalities in the temporal lobes.

Key words: ^{123}I-IMP SPECT – Left superior temporal gyrus – Auditory hallucination – Schizophrenia

Introduction

Recent advances in brain imaging techniques have provided useful tools to identify the anatomic, metabolic, and neurochemical substrates of mental illnesses and to understand the underlying neural mechanisms of clinical symptoms. With regard to schizophrenia, Ingvar and Frenzén (1974) first demonstrated the abnormal distribution of regional cerebral blood flow (rCBF) in the left hemisphere of chronic schizophrenics. Thereafter, functional brain activities in schizophrenia have been explored in many studies using ^{133}Xe clearance method, single photon emission computed tomography (SPECT), and positron emission tomography (PET). In previous studies with the two-dimensional ^{133}Xe inhalation technique (Kurachi et al. 1985, 1987; Suzuki et al. 1992), we also confirmed a decreased blood flow in the left frontal region in patients with schizophrenia, and found that the reduced frontal blood flow correlated with some of the negative symptoms including blunted affect, emotional withdrawal, avolition-apathy, and attentional deficit.

Concerning auditory hallucination, which is one of the cardinal symptoms of schizophrenia, a few reports have suggested that it might be involved in increased functional activities in the temporal lobes, especially on the left side (Kurachi et al. 1985; Matsuda et al. 1988a, 1989). However, few longitudinal studies have examined the regional brain activities in periods both with and without auditory hallucination in the same patients (Matsuda et al. 1989; Notardonato et al. 1989).

N-isopropyl-[^{123}I]p-iodoamphetamine (^{123}I-IMP) is a lipophilic compound which is highly trapped on first pass through brain when injected and is washed out slowly (Winchell et al. 1980). Therefore the initial distribution of ^{123}I-IMP reflects rCBF (Kuhl et al. 1982). We performed serial assessments of rCBF using SPECT and ^{123}I-IMP in two schizophrenic and three schizophreniform patients with persistent auditory hallucination and after clinical improvement.

Subjects and Methods

Subjects

Five patients participated and were recruited in this study from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. Two patients (one male and one female) fulfilled DSM-III-R criteria for schizophrenia and three (two males and one female) for schizophreniform disorder (American Psychiatric Association 1987). All patients were right-handed. Their mean age was 30.6,

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Table 1. Characteristics of each patient

Case no.	Age at 1st SPECT scan (years)	Sex	DSM-III-R diagnosis	Neuroleptic treatments at 1st SPECT scan (mg/day)	Neuroleptic treatments at 2nd SPECT scan (mg/day)	Interval between 1st and 2nd SPECT scans (months)
1	26	Male	Schizophrenia	Sultopride 300	Sultopride 300	3.5
2	36	Female	Schizophreniform disorder	Haloperidol 2.25	Haloperidol 9	1
3	28	Male	Schizophreniform disorder	–	Nemonapride 6	1.5
4	26	Male	Schizophreniform disorder	Haloperidol 1.5	Haloperidol 1.5	3.2
5	37	Female	Schizophrenia	Bromperidol 6	Pipamerone 250	6.5

SD 5.5 years. No patient with a history of alcohol or other drug abuse, brain injury, or any other neurologic disease was included. Routine laboratory data and electroencephalograms were unremarkable in all subjects. Table 1 describes the characteristics of each subject. The purpose and procedures were explained to the subjects, and informed consent was obtained.

Serial SPECT studies were performed. All patients had persistent auditory hallucination in the period of the first SPECT study. One patient (case 3) had never received neuroleptic medication before the first SPECT scan. Four patients were taking neuroleptic medication at the time of the first SPECT scan, and the duration of medication before the first SPECT scan ranged from 3 days to 4 years. When the auditory hallucinations were clinically improved with neuroleptic treatments, follow-up studies were performed. The mean interval between the first and second SPECT scans was 3.1 months. In case 5, a third SPECT study was performed when a psychotic relapse with auditory hallucination occurred 1.5 years after the second SPECT scan. Magnetic resonance imaging (MRI) scans were obtained in cases 1–4, and X-ray computed tomography (CT) scan in case 5.

SPECT Procedures

Measurements were carried out in a quiet and dimly lit room with the subjects at rest in the supine position and with their eyes open. In cases 1–3, SPECT imaging was performed using a three-head rotating gamma camera (GCA9300A; Toshiba, Tokyo) with high resolution collimators interfaced to a minicomputer (GMS550U; Toshiba, Tokyo). The resolution is 8 mm full width half maximum, and the computer slice width is 6.8 mm. The SPECT data were obtained in a 128 × 128 format for 30 angles in a 120° arc for each camera with 60 s per angle. The study was initiated 15 min after the intravenous injection of 111 MBq (3 mCi) of ^{123}I-IMP, and the total periods of data acquisition were 30 min. In cases 4 and 5, a single-head rotating gamma camera (GE Maxi Camera 400A/T; General Electric Company, Milwaukee, WI) with middle energy collimators combined with a minicomputer (GE Maxi Star; General Electric Company, Milwaukee, WI) was used. The resolution is 25 mm full width half maximum, and the computer slice width is 6 mm. Data were accumulated in a 64 × 64 format for 64 angles with 30 s per angle. Acquisition of projection data was started from 30 min after intravenous injection of 111 MBq of ^{123}I-IMP and lasted for 32 min. The filtered backprojection method was used for image reconstruction after preprocessing projection data with a Butterworth filter. A series of slices was reconstructed to be parallel to the orbitomeatal line. The resultant transaxial sections were reoriented to create coronal and sagittal plane images.

Tomographic images of all subjects were visually evaluated. For semiquantitative analysis, a region of interest (ROI) was drawn over the left superior temporal area in the transaxial slice showing the most pronounced accumulation in the first scan and over the corresponding region in the second scan. The ratio between counts/voxel of ROI and counts/voxel of the whole slice in the same plane was calculated, and the mean ratio in the first SPECT scan was compared with that in the second SPECT scan using paired *t*-test.

Results

The first SPECT scans in all patients demonstrated a focal area of increased uptake of ^{123}I-IMP in the left superior temporal cortex (Fig. 1A, Fig. 2A and 2D, Fig. 3A and 3C). The ^{123}I-IMP uptake in the anterior cingulate area was also increased in cases 4 and 5 (Fig. 3A and 3C). There was no remarkable increase or decrease in ^{123}I-IMP accumulation except in the left superior temporal area in cases 1–3. In the follow-up SPECT scans when the auditory hallucinations were clinically improved, the distribution of ^{123}I-IMP in the left temporal cortex was significantly normalized in all cases (Fig. 1B, Fig. 2B and 2E, Fig. 3B and 3D). In cases 4, the ^{123}I-IMP uptake was normalized in the anterior cingulate area as well as in the left temporal area (Fig. 3B). In case 5, however, the increased accumulation of ^{123}I-IMP in the anterior cingulate area persisted (Fig. 3D). The third SPECT scan in case 5 with psychotic relapse replicated the findings of increased ^{123}I-IMP uptake in the left superior temporal

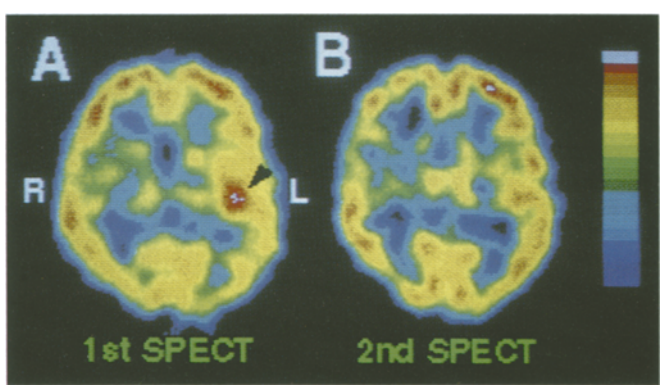

Fig. 1. Transaxial SPECT images through the superior temporal cortex in case 1: The first SPECT scan in the period with auditory hallucination *(A)* illustrates an increased uptake of ^{123}I-IMP in the left superior temporal area *(arrowhead)*, while the second SPECT scan in the period without auditory hallucination *(B)* shows normal ^{123}I-IMP distribution

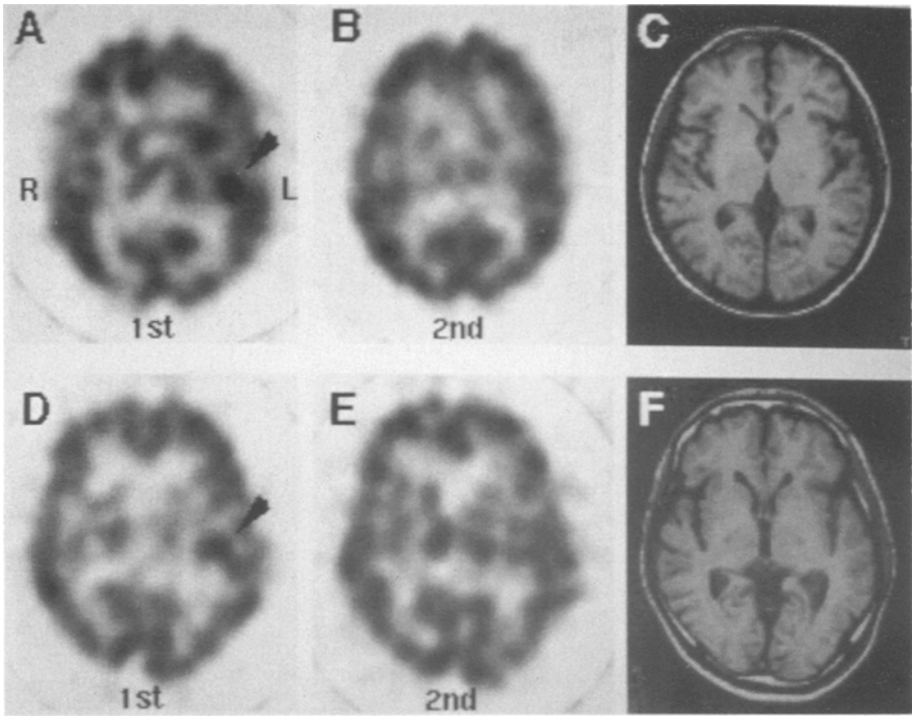

Fig. 2. Transaxial SPECT images and T1-weighted MRI images in case 2 (top row) and case 3 (bottom row): In both patients, the first SPECT scans *(A, D)* demonstrate an increased accumulation of ^{123}I-IMP in the left superior temporal area *(arrowheads)*. The second SPECT scans *(B, E)* show normal rCBF pattern. The MRI scans *(C, F)* reveal enlargement of the Sylvian fissure and reduced volume of the temporal lobes

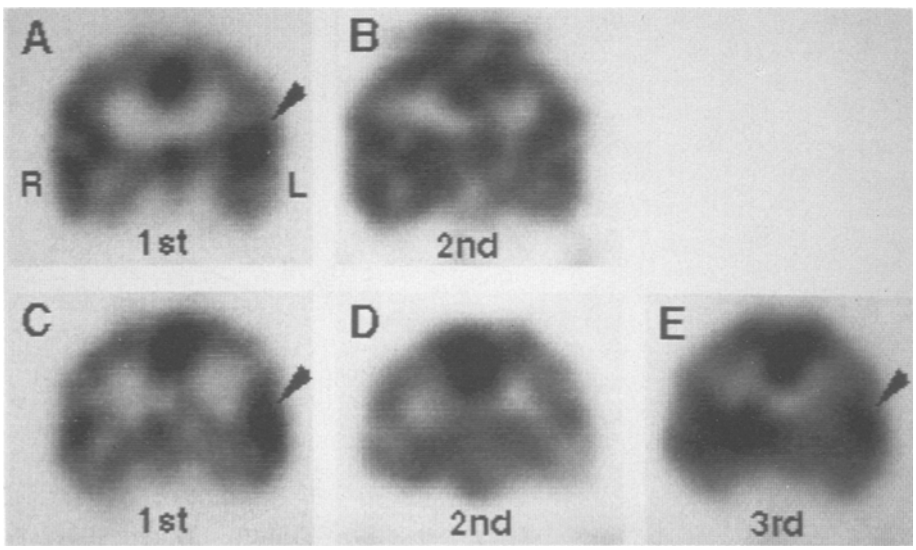

Fig. 3. Coronal SPECT images in case 4 (top row) and case 5 (bottom row): In case 4, the increased uptake of ^{123}I-IMP in the left superior temporal *(arrowhead)* and anterior cingulate areas in the first scan *(A)* has normalized in the second scan *(B)*. In case 5, an increased ^{123}I-IMP uptake is illustrated in the left superior temporal *(arrowhead)* and anterior cingulate areas in the first scan *(C)*, in the anterior cingulate area in the second scan *(D)*, and in the left superior temporal *(arrowhead)* and anterior cingulate areas, as well as in the right superior temporal area and basal ganglia in the third scan *(E)*

and anterior cingulate areas which were seen in the first scan, and also showed increased accumulation of ^{123}I-IMP in the right superior temporal area and basal ganglia (Fig. 3E).

Figure 4 demonstrates changes in the ROI measurements between the first and second SPECT scans. The mean ratio between ROI and the whole slice was 1.26, SD 0.07 in the first scan and 1.09, SD 0.07 in the second scan. This difference was statistically significant ($P=0.04$, paired t-test).

MRI and CT scans in all patients did not show any area of abnormal signal intensity or of abnormal density in the brain. The MRI scans in cases 2 and 3 revealed slightly enlarged ventricles, cortical sulci and Sylvian fissures, and moderately reduced temporal cortical volume (Fig. 2C and 2F). The MRI scan in case 4 showed a slight enlargement of the lateral ventricles. The MRI scan in case 1 and CT scan in case 5 were unremarkable.

Discussion

In the present study, schizophrenic and schizophreniform patients with persistent auditory hallucination showed increased accumulation of ^{123}I-IMP in the left superior temporal area which disappeared in association with the

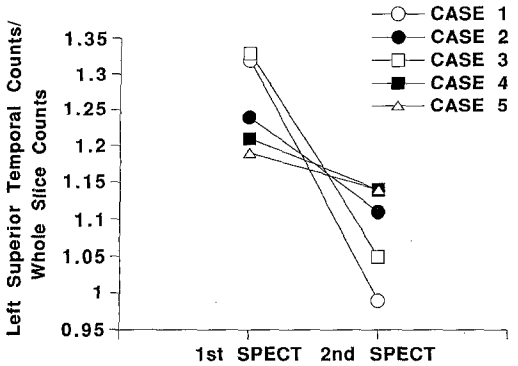

Fig. 4. Comparison of the left superior temporal counts/whole slice counts in the first and second SPECT scans in each patient: The mean ratio in the second scans was significantly reduced compared with that in the first scans ($P = 0.04$, paired t-test)

remission of auditory hallucination. The area with the increased uptake of ^{123}I-IMP roughly corresponds to the auditory association cortex of the dominant hemisphere. In normal subjects, auditory stimulations produce increased glucose consumption in the temporal lobes (Mazziotta et al. 1982). Penfield and Perot (1963) electrically stimulated multiple brain areas of epileptic subjects and found that auditory hallucinations were elicited in the area of the superior temporal gyrus. Andreasen (1988) has postulated that auditory hallucinations could arise from aberrations in any part of the auditory neural system, or in other systems connected to it. Our present results are consistent with this hypothesis.

A few caveats need to be considered before concluding that the auditory hallucination in schizophrenics is involved in aberrant functional activity in the left temporal lobe. First, this is an uncontrolled case study with small samples. Second, the accumulation of ^{123}I-IMP in the left superior temporal cortex may not be related to the auditory hallucination alone, since the changes between the first and second SPECT measurements were accompanied by not only the disappearance of auditory hallucination but also changes in other state variables. Given these considerations, further controlled study with larger samples is needed to confirm and extend our findings.

To our knowledge, only two case reports have examined rCBF during the presence or absence of auditory hallucination in the same patients. Matsuda et al. (1989) reported a schizophrenic patient with auditory hallucination in whom the first SPECT scan revealed an increased ^{123}I-IMP accumulation in the left auditory area, which was normalized in the second scan performed 6 weeks later with remission of auditory hallucination. Notardonato et al. (1989) also described the longitudinal course of a patient with schizophrenia who showed a increased uptake of ^{123}I-IMP in the right temporal lobe, contralateral to the side of the auditory hallucination, and caudate nuclei in SPECT. After clinical recovery, the follow-up SPECT scan demonstrated significant improvement in the distribution of ^{123}I-IMP.

Our results are also in agreement with previous cross-sectional studies. In our earlier study with ^{133}Xe inhalation technique (Kurachi et al. 1985), schizophrenic patients with auditory hallucination showed a significantly increased blood flow predominantly in the left temporal region compared with patients without hallucination and normal controls. Matsuda et al. (1989) demonstrated using SPECT that increased uptake of ^{123}I-IMP in the left superior temporal area was observed in 20 of the 22 schizophrenic patients with auditory hallucination, while it was seen in only 4 of the 20 patients without hallucination. A PET study by Cleghorn et al. (1990) failed to find any difference in regional glucose metabolism between hallucinating and non-hallucinating patients, but a pattern of significant correlations of metabolic activity among language-related areas including Broca's area, left superior temporal cortex, and anterior cingulate cortex was observed in the former.

Our findings appear to be not specific to schizophrenia, because a few authors have reported that increased rCBF in the temporal region is also seen in psychiatric conditions with auditory hallucination other than schizophrenia (Berglund and Risberg 1981; Matsuda et al. 1988b, 1989).

It is of interest that MRI in two of the five patients revealed moderately reduced volume of the temporal lobes. MRI studies (Suddath et al. 1989, 1990) and postmortem neuropathological studies (Bogerts et al. 1985; Jakob and Beckmann 1986) have provided increasing evidence suggestive of subtle deviations in the size and cytoarchitecture of temporal lobe structures in schizophrenic patients. Barta et al. (1990) reported that schizophrenic patients have a smaller volume of the superior temporal gyrus and of the left amygdala, and shrinkage of the left superior temporal gyrus correlated with the severity of auditory hallucinations. It is unclear whether these anatomical abnormalities lead to functional hyperactivity or hypoactivity. However, taken together, the previous reports cited and our present study raise the possibility that the auditory hallucinations might be involved in the functional hyperactivity based at least partly on a structural abnormality in the left superior temporal gyrus. Structural abnormality and metabolic hyperactivity in the same brain region have also been reported in the hippocampal formation (Bogerts et al. 1985; Suddath et al. 1990; Kawasaki et al. 1992) and globus pallidus (Bogerts et al. 1985; Early et al. 1987). The precise relationship between changes in brain structure and function, and clinical symptoms remains to be elucidated by further studies.

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