PET imaging of cerebral metabolic change in tinnitus using ^{18}F-FDG

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Abstract Tinnitus is an auditory disorder hardly assessable by clinical technology. PET imaging of the brain in 13 cases with and 10 without tinnitus was undertaken at 40 min after injection of 280~440 MBq ^{18}F-FDG. To ensure the quality of the PET study, all cases followed a normalized procedure with visual and auditory blockage. CT/MRI imaging and routine acoustic tests were carried out in all subjects. PET revealed that an increased uptake of ^{18}F-FDG at left med-temporal lobe (primary auditory center, PAC) present exclusively in tinnitus, regardless the side of hearing hallucination. Significant asymmetry was noted between left and right PAC, but not at other cortex area. While control cases showed no asymmetric uptake between two hemispheres. The abnormal PAC uptake did not respond to external pure sound stimulus, nor did it relate to the severity of hearing loss assessed by acoustic tests. No anatomical or morphological alteration could be proven on CT/MRI. In conclusion, PET/^{18}F-FDG objectively revealed an increased metabolic change at left PAC in tinnitus, which is of diagnostic value; and there is evidence suggesting tinnitus is most likely induced by a functional change in the brain.

Keywords PET/F18-FDG functional imaging, Tinnitus, Cerebral metabolism

CLC numbers R817.4, R814.4, R764.45

1 INTRODUCTION

Tinnitus is a hearing disorder characterized by periodic or continuous auditory hallucination in one or both ear without real sound source. Over 90% of tinnitus are associated with cochlear dysfunction such as hearing loss. The sensory disorder varies in severity. In the worst case, it induces unbearable noise in ear(s), even interfering with sleep and daily life. However, tinnitus is also a kind of "subjective" abnormality, because no morphological or functional alteration could be demonstrated so far by most diagnostic modalities currently used in otolaryngology. The difficulty in diagnosing and classifying tinnitus results in uncertainty in clinical management of the patients. Recently, a new technology, positron emission tomography (PET), has been introduced clinically useful in revealing in-vivo metabolic status of tissue, especially in brain where metabolism closely couples with neural function, making many difficult diagnosis easier[1]. We tried to use the imaging technology to depict the functional change in brain caused by tinnitus.

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2 MATERIALS AND METHODS

2.1 Subjects

Eleven men, 2 women, all suffering severe tinnitus for 1~10 year, were referred to PET study. In 4 cases, tinnitus was noted in left ear, another 4 in right, and the rest in both sides. Eleven cases had hearing abnormality, and 2 had normal hearing function. The patients aged from 17 year to 71 year, with a mean age of 42.8. 10 subjects, including 2 with hearing loss and 8 normal volunteers, 6 males and 4 females, aging 21~58, acted as control in this study. All patients and controls are right handed individuals with no history or clinical sign of hypertension, circulation disorder, diabetes, or other systemic disease. Brain abnormality was ruled out by CT/MRI. All subjects also underwent routine acoustic tests in a dedicated hearing Lab.

2.2 PET study

The subjects were asked to lie on bed quietly for at least 30minutes in a dim-lit room, with an eye-shade put on the closed eyes and a pair of ear-plug to block hearing, before a dose of 5.55 MBq/kg ^{18}F-FDG was injected intravenously. The patients were also asked to concentrate on their tinnitus. 40 minutes after injection, patients were positioned supine on examination table with their head rested on a head holder. A 2D acquisition over head, 25minutes emission and 5 minutes transmission, and OSEM reconstruction with attenuation correction was carried out on ECAT EXACT HR+ scanner(Siemens/CTI, USA). The visual/hearing block was put on till the end of PET study.

2.3 Data analysis

The set of PET images was resliced into OML paralleled transaxial, sagittal and coronal slices. On reviewing the transaxial images, the slice that showed the upper part of thalamus was selected. Three ROIs (region of interest), 3×3 pixels in size, were drawn on frontal, temporal, parietal, occipital lobes, basal ganglia, and cerebellum of both sides of brain. The count per pixel was normalized on the basis of patient's body weight and injected dose, and the average value from 3 ROIs on each part of brain was used to calculate the asymmetric index ($AI = (L - R)/(L + R)/2\times100\%$). The data from each group of subjects was compared using student's t-test.

2.4 Hearing function assessment

All patients underwent routine otoneurologic and audiologic evaluations before PET study. The acoustic tests included pure-tone and speech audiometry, pitch and loudness matching, auditory evoked potentials (ABR, EcochG), and otoacoustic emission measuring, etc. All the tests were undertaken in a dedicated acoustic lab located in department of otolaryngology.

3 RESULTS

3.1 Normal PET images

At 40 minutes after injection, PET revealed clear uptake of ^{18}F-FDG in the cerebral cortex, subcortical gray matter structures, and cerebellum. The activities of two hemispheres were principally symmetric. The shape and extent of ^{18}F-FDG uptake, at the opposite structures on two sides of the brain were substantially mirroring each other. The most obvious uptake was noted at basal ganglia, followed by occipital, cerebellum and mid temple regions. No abnormally high uptake was found at any known auditory center or any specific region of the brain. The normal *AI* of each cerebral lobe was listed in Table 1.

Table 1 Asymmetric index of tinnitus and control groups (%)

	Controls	Tinnitus	p
Frontal	3.8±3.2	4.0±3.7	ns
Parietal	2.2±2.0	2.4±1.9	ns
Temporal	14.9±5.8	4.9±2.8	<0.001
Occipital	4.9±4.9	3.8±3.0	ns
Basal ganglia	2.7±1.9	3.4±3.0	ns
Cerebellum	3.0±3.0	3.4±2.7	ns

3.2 PET findings in patients

The most striking finding of tinnitus brain was a high uptake of ^{18}F-FDG at medal-temporal region (superior and transverse gyrus, Brodmann area 41 and 42) on the left hemisphere, Fig.1, regardless the side of subjective sensation of tinnitus. 11/13 cases showed the abnormality, 1 case equivocal, only 1 case was negative, see Table 1 and Fig.2. A few cases also showed slighter change at other small regions, such as posterior temporal and lower occipital, but with no definite side preference. The *AI* of temporal lobe in tinnitus group was significantly higher than that of control group. But no difference was found at other regions of brain.

3.3 Other findings

None of the subjects showed any anatomical or morphological abnormality on CT/MRI. Interestingly, 11 cases of tinnitus and 2 controls had almost the same degree of hearing loss, but the abnormal increase of ^{18}F-FDG uptake at left medial-temporal region was found exclusively in 10/11 cases with tinnitus. In order to verify the relationship between hearing function and PET finding, 4 cases of tinnitus and 2 normal control repeated PET study with bilateral mono-tune sound stimulation. Two normal subjects responded, showing increased uptake at left PAC region like that of tinnitus, Fig.3 (a) and (b), while 4 tinnitus patients showed no change on their ^{18}F-FDG uptake pattern.

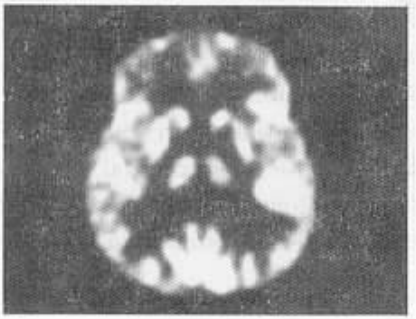

Fig.1 Cerbral metabolic imaging in this 46 year woman of tinnitus.
She suffered sudden hearing loss 1 year ago. Severe hearing loss was noted in acoustic test. Matching test indicated a 9 kHz, 75 dB, PET showed an increase of activity at left PAC, *AI* was 23.4

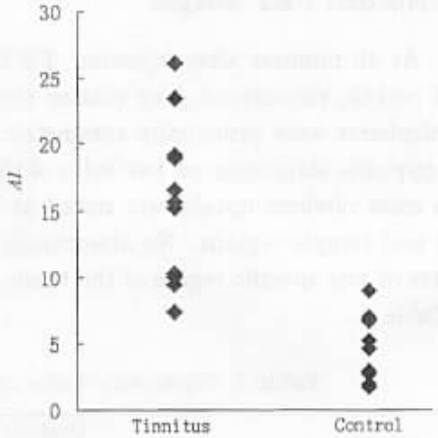

Fig.2 Comparison of *AI* distribution in tinnitus and control group

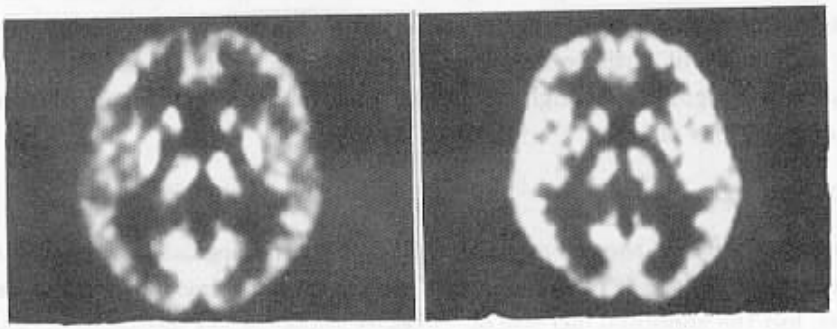

Fig.3 Normal control, male, 42 year, right handed
(a) PET image with visual and hearing block (b) repeated PET with 6kHz, 45dB pure-tune sound input from both ears. It was noted that PAC response looked like tinnitus PET image

4 DISCUSSION

Tinnitus is one clinical challenge to otolaryngologist because of its subjective nature. No one but the patients could tell the strange, sometimes stubborn, torturing sound in their ears. The origin of the "sound" is so far unknown, though some authors did suggest that over action or spontaneous firing in cochlea, or along auditory pathway, or at synaptic junction might account for the creation of the acoustic disorder[2,3]. However, no evidence was ever found to support the theories, or to enable the clinicians to assess or to prove the sensory abnormality. The only available test for tinnitus is a matching sound, as pitch and tune, test. Until an objective measurement is available, the understanding, diagnosis, and management for tinnitus would by no means be accessible, leaving the patients in continuous sufferings.

Positron emission tomography(PET) is an imaging modality by which various biological process inside human body can be revealed and quantitatively assessed, provided a proper radioactive tracer, such as ^{18}F-FDG, *is available.* ^{18}F-FDG, *a de-oxylated analogue of glucose, behaving almost the same as glucose in-vivo, is trapped in neuron, and its concentration has already been proven closely correlated to the functional status of* the neuron. PET imaging, employing ^{18}F-FDG as a tracer, was reported of great value and potential in neurological, psychological, and psychiatric studies. *Since neural activity, whether it is originated peripherally or centrally, causes metabolic alteration at the corresponding cortex region, it is obvious that tinnitus could possibly be detected* and measured objectively via the imaging technology. Indeed, in our study, abnormal high uptake of ^{18}F-FDG, i.e. hypermetabolic change, *was found at primary auditory center(PAC) on the medial-temporal lobe of the tinnitus patients, which differed significantly to controls. The difference was evident both by bare-eye review and by semi-quantitative* analysis as asymmetric ratio between left PAC and right. Since PET study was carried out with restrict visual and auditory blockage, the increased regional uptake of ^{18}F-FDG was unlikely caused by external sound input to the brain. In addition, other part of brain showed neither asymmetry between two hemispheres, nor difference to control, serving as an inner reference of quality assurance of the study. Thereby, the obvious high activity at PAC on left side of brain was considered a reliable diagnostic sign for tinnitus.

The similar finding had been reported by other investigators. Arnold[4] compared 11 tinnitus to 14 controls using PET/^{18}F-FDG investigation, his images proved increased activity at left PAC in tinnitus patients[4]. Other studies using PET or SPECT revealed an abnormal high uptake at left middle temporal, left transverse temporal gyri, hippocampus and thalamus. Only one study reported the right-sided abnormal uptake in tinnitus[5]. Nevertheless, most of the evidences supported the assumption that the primary auditory cortex, and the cerebral structure(s) connected with it, might be the core for tinnitus etiology.

Even though PET imaging showed illustrative alteration at left PAC, no structural or morphological abnormality was ever found by CT/MRI correspondingly. Cacace used fMRI to investigate several tinnitus patients, abnormal signal in the upper brainstem

and frontal lobe was found in 2/3 patients, but no anatomical anomaly was found by ordinary MRI. The discrepancy between PET and MRI suggested the functional nature of the disorder. It was of interest to notice that in tinnitus patients, no change on ^{18}F-FDG distribution in response to external sound stimulation could be evoked. While increase of tracer uptake was quite evident after pure-tune sound stimulation in normal volunteers. It was not clear whether the phenomena indicated overlap of real acoustic and hallucinated sound sensation in the specific area of brain. The fact, along with another fact that increased activity was on left PAC of patients, no matter the side of tinnitus or the severity of hearing loss, suggest the possibility that tinnitus is most likely induced in CNS, not from peripheral structures. However, because of the limited number of cases in the current study, the meaning of those findings need further verification.

5 CONCLUSION

PET/^{18}F-FDG imaging revealed an increase accumulation of radioactivity at PAC on left medial- temporal cortex in tinnitus patients, regardless the side of symptom or the severity of hearing loss. The high concentration of ^{18}F-FDG at PAC, in contrast to control, was demonstrative and diagnostic for this subjective auditory disorder, thus was of clinical and academic value for future study and management of tinnitus. The preliminary evidence derived from the current study suggested that tinnitus is most likely originated centrally in brain region which shows functionally abnormal metabolism but no detectable anatomical change.

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