SPECT IMAGING OF BRAIN AND TINNITUS-NEUROTOLOGIC/NEUROLOGIC IMPLICATIONS

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ABSTRACT

Single Photon Emission Computed Tomography (SPECT) of brain with technetium-99m hexamethyl propyleneamine oxine (Tc-HMPAO) is an imaging technique which has been introduced for the identification of abnormalities of regional cerebral blood flow (rCBF) in patients with a central type of subjective idiopathic tinnitus, which was characterized as severe and disabling. These patients demonstrate a negative clinical history, physical examination does not evidence central nervous system disease, and CT/MRI studies of brain were negative. Two typical cases are presented which demonstrate significant regional abnormalities in cerebral perfusion bilateral of temporal, frontal, parietal and hippocampal amygdala regions when compared with normative Tc-HMPAO SPECT of brain data.

Neurotologic and neurologic implications are suggested which include cerebrovascular disease, neurodegenerative disorder and dementia, and neuropsychiatric mood disorder. SPECT results of brain demonstrate for the first time the in vivo significance of the organicity of brain for a central type of tinnitus.

Key Words

Single Photon Emission Tomography (SPECT), Tinnitus, Clinical Types of Tinnitus, CNS Disease, Central Type Tinnitus, Attributes of Hearing, Tinnitus

GENERAL PRINCIPLES

Tinnitus is a perceptual disorder of auditory function clinically identified to have both sensory and affect components. Clinical types of tinnitus have been identified with a Medical Audiologic Tinnitus Patient Protocol

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(MATPP).¹ The MATPP is a unified diagnosis and treatment strategy for tinnitus.

Cerebral single photon emission computed tomography (SPECT) perfusion scintigraphy has been applied for tinnitus diagnosis in tinnitus patients with no evidence of central nervous system (CNS) disease, negative CT and/or magnetic resonance imaging (MRI) studies of the brain, and a central type of subjective idiopathic tinnitus (SIT) described as severe and disabling. Since 1990, 22 patients with severe disabling tinnitus of the central type and absence of CNS Disease, including negative CT and/or MRI studies, have completed SPECT imaging of the brain. These patients were seen for initial consultation in the Tinnitus Clinic of the Health Sciences Center at Brooklyn-State University of New York and referred for this examination.

SPECT imaging technique of the brain is an objective analytical detection method which provides information on regional cerebral perfusion of the brain. Cerebral blood flow has been correlated with function.²⁻⁸ In the determination of local brain function, the variables to be considered are cerebral blood flow (CBF) and cerebral metabolic rate (CMR). SPECT data may reflect the physiologic test mapping of the metabolic rate of cerebral function for a particular region of interest. In this way, SPECT reflects local neuronal activity.9-11 The availability for SPECT of specific receptorbinding radio tracers, which bind at a specific particular site of lesion within the CNS, may thus be identified.

Previously reported analytic localization techniques for tinnitus have included electrophysiologic testing for cochleovestibular function including auditory brain stem response for the recording of auditory evoked potentials.¹² SPECT provides a measurable regional metabolic correlation. Quantitative SPECT can potentially provide measures of structure and function, which can assist in both the diagnosis and monitoring of therapy.

Organicity of brain in tinnitus patients was first reported in a preliminary study of 10 patients, who, upon completion of an MATPP, were identified to have a predominantly central type tinnitus. Normative data (n = 5) demonstrated no significant variation between right and left for any region of interest (p < 0.05). Significant tinnitus patient asymmetries (n = 10) of rCBF, bilateral left greater than right, were demonstrated and quantified (p < 0.005) (Tables I and II).¹³ This preliminary study demonstrated for the first time in vivo the significance of organicity in the brain of patients presenting the central type of tinnitus.

Two representative cases are presented to illustrate the organicity observed in patients with a central type of tinnitus and to speculate on the implications of SPECT in neurotologic and neurologic disease, as exemplified by cerebrovascular, diseases, neurodegenerative and neuropsychiatric mood disorders.

METHOD Patient Selection

The patient selection criteria for SPECT brain imaging included the following: (1) Presence of subjective SIT of a duration in excess of 1 year (median, 18 months); (2) completion of an MATPP to identify the clinical types of tinnitus; (3) the clinical identification of a predominantly central type tinnitus; (4) MRI and/or CT of brain reported negative; and (5) absence of CNS Disease based on the limits of history and physical examination.

Materials and Methods— SPECT Technique¹⁴

The single-photon cerebral perfusion tracer (Tc-99m HMPAO) was used in all patients in this SPECT study. Cross-sectional images of radiotracer distributions were analyzed and provided a direct measure of regional organ function of the brain. An HMPAO dose of 25 mCi was administered intravenously in patient 1; and 23 mCi in patient 2, while the patient was at the basal-physiologic state, that is, with eyes and ears open. Triad, that is, a state-of-the-art, tripleheaded, Anger-type gamma camera with a dedicated computer for acquisition and processing—was used to acquire a 64-frame, 360° study.

Raw data used for quantification of brain SPECT regions of interest in the three orthogonal planes of examination (i.e. transaxial, coronal, and sagittal) were computed and graphically demonstrated areas of hypo- or hyperfusion. Perfusion images of the brain were obtained with a spatial resolution of 6.8 mm in the plane of the slice.

Quantification and the Quantification Curve—Analysis of Cerebral Perfusion Data

The method of analysis was reported in the original study.¹³ In that study, distribution data of HMPAO cerebral activity (i.e. hypo- or hyperactivity) was based on quantitative information graphically displayed, derived from single-pixel, thick-slide data. Symmetry and asymmetries in selected right and left regions of interest (ROIs) in each of the three orthogonal planes of examination, (i.e., transaxial, coronal, and sagittal) were quantified using a technique similar to that used in myocardial function determination. Operator modified semi-automatic ROIs of frontal, parietal, occipital, temporal lobes, and cerebellum, in three orthogonal planes, were compared in two groups, normals (n = 5) and abnormals (n = 10) to determine the side-to-side incidence of asymmetry (i.e., percentage); and the degree of asymmetry in each ROI (i.e., asymmetry index). Counting statistics for each ROI were derived by standard methods, and expressed as the mean number of counts. Absolute counts per pixel with identically sized regions of interest were first analyzed. Significant side-to-side count differences were determined by standard statistical analysis.

Normal Data/Patterns

Normal brain SPECT studies in the preliminary study¹³ demonstrated bilateral symmetrical activity in anatomic regions of interest of cortical and central gray matter (Fig. 1A–C). Our normative qualitative data were obtained in five patients with hearing within normal ranges for speech frequencies. In general, symmetry was identifiable for all five patients in all cerebral lobes. One patient did demonstrate right asymmetry in the temporal lobe.



Fig. 1a. Normal SPECT/brain. Three orthogonal imaging planes coronal (upper left), sagittal (upper right), transaxial (lower left), raw data (lower right)



Fig. 1b. Normal SPECT/brain - coronal images. Right(r), left(l)
upper left (r): 1-putamen 2-frontal 3-temporal lobe
upper right (l): 1-putamen/caudate 2-frontal 3-temporal/amygdala
lower left (r): 1-thalamus 2-amygdala/hippocampus 3-primary auditory cortex
lower right (l): 1-thalamus 2-hippocampus/parahippocampus 3-parietal 4-cingulate



Fig. 1c. Normal SPECT/brain - sagittal images. Right(r), left(l)
 upper left—dorsolateral(r) lower left - dorsolateral(l)
 1-primary auditory cortex 2-posterior speech center 3-anterior speech center
 upper right - parasaggital(r) lower right - parasaggital(l)
 4-thalamus 5-frontal inferior gyrus 6-cerebellum

RESULTS

In patient 1, we noted the following deviations in distribution of HMPAO from the normal pattern:

(1) bifrontal symmetrical hypoactivity—severe;(2) temporal lobe posterior roof asymmetry left greater than right;

(3) hypoperfusion primary auditory cortex left greater than right with loss of contour and expansion of the right parietal lobe;

(4) hippocampal amygdala complex, hypoactivity bilateral;

(5) anterior speech center (Broca)—

hypoperfusion bilateral. The finding of relative normal deposition in the subcortical areas, motor strip cortex, and cerebellum was of interest.

In patient 2, a different pattern included:

(1) Frontal lobe—bilateral hypoperfusion in frontal lobe maximal in the inferior gyrus

(2) Temporal lobe—bilateral hypoperfusion involving primary auditory cortex, and associative auditory cortex

(3) Parietal lobe—bilateral hypoperfusion with left greater than right

(4) hippocampal amygdala complex—

hypoactivity bilateral with left greater than right

(5) Posterior speech center (Wernicke) hypoperfusion of left greater than right

(6) Thalamus—hypoperfusion bilateral on right greater than left

(7) Anterior speech center (Broca)-

hypoperfusion bilateral with left greater than right.

CASE REPORTS

Case 1

D.R., age 44, was seen in original consultation 7/7/87 with the chief complaint of severe disabling tinnitus. Brain SPECT was performed 7/13/90. This symptom had been present since December 1986, following ear cleaning for wax removal. The tinnitus parameters of identification include tinnitus location in left ear greater than in right; quality of a *hiss* and *tea kettle* as well as a *tickling sensation*; fluctuant intensity; constant duration; hypercusis, and a tinnitus intensity index of 7 (on a

scale of 0 to 7 with 0 reflecting no tinnitus and 7 representing the most severe intensity). Associated complaints included ear blockage greater on left than on right, dysequilibrium, and cognitive and memory deficits. Significant past history included antecedent psychiatric history with hospitalization in 1986 and 1987 for depression, a sleep disorder stated by the patient to be related to tinnitus, and periodic marijuana use in 1970 to 1972. Family history was positive for alcoholism.

Audiologic findings are presented in Figure 2. Electrical high frequency audiometry revealed positive responses of 1000 to 3000 Hz, absent at 3000 to 20000 Hz to the limits of the audiometer 60 dB sound pressure level (SPL). Auditory brain stem response (ABR) testing revealed latency increase inter-peak P1 to P5 with left greater than right; amplitude increase P3 ipsilaterally on right; and dysynchrony ipsilaterally and contralaterally on left P3 and contralaterally P1, P2 on right. Central speech testing revealed an abnormality in the competing sentence test: right primary message, left competing message 60%; left primary message, right competing message 30%. The vestibular test battery (computerized rotary chair and pursuit tracking test) was clinically interpreted as a primarily central oculomotor dysfunction; with a reduced vestibular response of the peripheral vestibular labyrinth right.

On tinnitus evaluation the primary sound the patient had described as that of a tea kettle was matched with a 9000 Hz pure tone of 70 dB in the right ear and 70 dB in the left ear; the secondary sound, described as hissing was matched with a 9000 Hz narrow band noise of 55 dB in the right ear, and the 53 dB in the left ear. Residual inhibition was measured binaurally at 10 dB re threshold of the matching 9000 Hz tone and then a 9000 Hz narrow band noise. Tonal testing revealed negative residual inhibition on the right and a rebound effect on the left. Narrow band masking curves were performed and yielded Type IV distance curves ipsilaterally and contralaterally. This is interpreted to indicate that although the tinnitus was maskable, an intensity level of at least 20 dB above the threshold would be needed to produce this effect.

The neurotologic diagnoses of 7/7/87 based on a correlation of the clinical history,







Fig. 3. Pure Tone Audiogram

cochleovestibular test battery, neurotologic examination, and tinnitus evaluation clinically identified the tinnitus to be predominantly of the cochlear type with a significant central component bilaterally. Computerized tomograph scan of head and brain performed in 1986 was reported to be negative. A follow-up neurologic examination on 7/31/87 reported this right handed patient to be completely normal except for a possible slight heel-knee-shin ataxia, which was considered marginal. Laboratory work including complete blood count, sequential multiple Analyzer Computer (SMAC) 25, thyroid examination, fluorescent treponemal antibody (FTA)-all reported normal.

Attempted tinnitus control between 7/7/87 and 11/16/90 was based upon a

combined medical/audiologic team approach of otology, neuropsychiatry, and social work. For the sensory component, treatment was directed at factors known to influence tinnitus which included fluctuation in aeration of the middle ears, secondary endolymphatic hydrops right, and a trial of acoustical masking (10/87 until)7/78), external electrical stimulation (4/88), and middle ear electrical stimulation 2/90. Tinnitus masking had been attempted before the initial consultation of 7/7/87 with a reported rebound phenomenon. The tinnitus masker was reported to be of some relief in the period between 10/87and 7/89 following control of secondary endolymphatic hydrops right and maintenance of middle ear aeration. For the affect component, psychiatric consultation for control of anxiety and depression included therapy with car-



Fig. 4. Case 1 Abnormal SPECT brain three orthogonal imaging planes: coronal (upper left), sagittal (upper right), transaxial (lower left), raw data (lower right)



Fig. 5. Case 1 coronal images right(r), left(l)
1 - relative high perfusion 2 - 4 asymmetry(r)(l), hypoperfusion
upper left (r) 1 - putamen 2 - frontal 3 - temporal lobe
upper right (l) 1 - putamen/caudate 2 - frontal 3 - temporal/amygdala
lower left (r) 1 - thalamus 2 - amygdala/hippocampus 3 - primary auditory cortex
lower right (l) 1 - thalamus 2 - hippocampus/parahippocampus 3 - parietal 4 - cingulate



Fig. 6. Case 1 sagittal images right(r), left(l)
1-5 asymmetry, hypoperfusion 6 high perfusion
upper left - dorsolateral(r) lower left - dorsolateral(l)
1 - primary auditory cortex 2 - posterior speech center 3 - anterior speech center
upper right - parasaggital(r) lower right - parasaggital(l)
4 - thalamus 5 - frontal inferior gyrus 6 - cerebellum

bamazepine and clonazepam, with amitriptyline and flurazepam for sleep. The degree of tinnitus control was reported to be minimal and of short duration.

A gradual worsening in the severity of the tinnitus complaint commenced 8/89. Interference in speech expression and memory was reported in November, 1989. Interval examinations between 8/89 and 11/90 revealed no spontaneous sign(s) of labyrinthine irritation, an increase in hearing loss with audiometric testing, and no sign(s) of neurologic disease. Repeated neurologic examinations were reported to be satisfactory except for anxiety/depression.

Repeat site of lesion impedance and pure tone audiometry as they were done on 1/23/91 are reported in Figure 3 as essentially unchanged in right ear, but with a significant reduction in speech discrimination in left ear.

Persistence of the increased tinnitus complaint with associated memory and cognitive complaints since 2/90 was followed with brain SPECT done in July 1990. This revealed (Figures 4 to 6):

(1) Severe symmetrical bifrontal hypoactivity

(2) Posterior roof temporal lobe asymmetry left greater than right

(3) Hypoperfusion primary auditory cortex of left greater than right with loss of contour and expansion of right posterior parietal lobe

(4) Hypoperfusion of hippocampal amygdala complex bilaterally

(5) Anterior speech center (Broca)—hypoperfusion bilateral.

The finding of a relatively normal deposition in the subcortical areas, motor strip cortex, and cerebellum was judged significant.

Neuropsychologic evaluation questioned cognitive impairment; a borderline function range was impaired for fundamental tasks of visual perception, visual span and attention, visual reasoning, visual problem solving, and visual memory. The neuropsychologic profile was most consistent with significant right hemisphere abnormalities. A repeat CT scan of the brain on 6/17/91 reported only minimal cortical atrophy.

Case 2

M.W., age 72, was seen in initial consultation 2/11/92 for the chief complaint of

tinnitus of increasing intensity for at least 1 year. The parameters of tinnitus identification were described to have a quality of a *high ring*; ear in location, bilaterally left greater than right, constant duration, and fluctuant intensity. The tinnitus intensity index rating was 6 on a 0 to 7 scale (0 meaning no tinnitus and 7 greatest severity). Associated complaints included bilateral hearing loss, with left greater than right, bilateral ear blockage left worse than right, early memory dysfunction, and an occasional positional dysequilibrium. CT scan of brain was reported negative in June, 1992.

The original tinnitus onset was in 1944 after exposure to artillery in the United States' Marine Corps, and described as right ear *ring*. Tinnitus first appeared in the left ear in 1977. The intensity was described as severe and has become left greater than right for at least 3 to 5 years before the initial consultation. Review of systems revealed hypertension of 1 year's duration. Significant past history was of Dengue fever. The neurotologic diagnosis was based on correlation of the clinical history, cochleovestibular test battery, neurotologic examination, and tinnitus evaluation identified tinnitus to be primarily of the central type with a cochlear component bilaterally, with left greater than right and a clinically presumptive secondary endolymphatic hydrops (SEH) on the left. Vestibular testing revealed a vertical upbeat nystagmus in all position tests with normal caloric testing. (Fig. 7 shows audiologic findings.)

A combined program of tinnitus control was followed, based on differentiation between its sensory and affect component. For the sensory component, tinnitus control initially included treatment of a presumpted secondary endolymphatic hydrops left for 4 to 6 weeks, with a trial course of systemic vestibular suppressant anti-histamine medication and diet—in the elimination or control of salt intake. Reduction in recruitment and control of dysequilibrium was followed by a trial of instrumentation. Acoustical masking provided a minimal degree of tinnitus control. A trial of Trental therapy for the central component was recommended for persistence of tinnitus.

SPECT of brain done 8/92 revealed the following (Figs. 8 to 10):

(1) Frontal lobe—hypoperfusion bilateral with prominence in the inferior gyrus of the frontal lobe bilateral

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(2) Temporal lobe—hypoperfusion bilateral, left greater than right, primary auditory cortex, and associative auditory cortex

(3) Parietal lobe—hypoperfusion bilateral left greater than right

(4) Hippocampal amygdala complex—hypoperfusion bilateral left greater than right (5) Posterior speech center (Wernicke) hypoperfusion left greater than right

(6) Thalamus—hypoperfusion bilateral right greater than left

(7) Anterior speech center (Broca)—hypoperfusion bilateral left greater than right.



Fig. 7. Pure Tone Audiogram



Fig. 8. Case 2 three orthogonal planes coronal (upper left), sagittal (upper right), transaxial (lower left), raw data (lower right)







Fig. 10. Case 3 sagittal images right(r), left(l)
1-5 asymmetry, hypoperfusion 6 - high perfusion
upper left - dorsolateral(r), lower left - dorsolateral(l)
1 - primary auditory cortex 2 - posterior speech center 3 - anterior speech center
upper right - parasaggital(r), lower right - parasaggital(l)
4 - thalamus 5 - frontal inferior gyrus 6 - cerebellum

DISCUSSION

The findings reported in SPECT of brain performed on two patients with tinnitus of the severe disabling type reflect ongoing clinical experience with this technique. The patterns of asymmetry reported in the initial preliminary study of 10 patients were being maintained.¹³

Neurotologic Implications: • Attributes of Hearing

Diagnosis of auditory function was done using identification of attributes of hearing.

Auditory function can be considered to involve multiple neural networks reflecting various attributes of hearing.¹³ Asymmetries identified by this imaging technique may represent interruptions of normal auditory function as reflected in variations in right cerebral blood flow (CBF) that affect multiple neural networks.

Central attributes of hearing may be represented by multiple areas of the cortex now identified in part as CBF asymmetries in SIT patients with predominantly central tinnitus. Our position is that central attributes of hearing may have as one of its symptoms of dysfunction not only interference in sound perception and speech discrimination, but also tinnitus.

Attributes of hearing and the appropriate cortical representations may be theorized as follows:^{13,15}

(1) Frequency, intensity, tonotopicity primary auditory cortex (Brodmann's areas 41 and 42)

(2) Speech discrimination—cortical speech centers [(Brodmann's areas 6, 39 and 40)(Wernicke); (44 Broca)]

(3) Integration of signal—parietal lobe

(4) Attention, anxiety—apex of temporal lobe, limbic lobe, that is, to include the frontal lobe for sustained attention and globally directed behavior

(5) Memory—frontal lobe, hippocampus, amygdala

(6) Masking—cortex-associative auditory cortex; subcortical location-medial geniculate body, brain stem, reticular formation, efferent system.¹⁶

Localization of tinnitus by sensory component and the identification of attributes of tinnitus

Both are speculated to be reflected in the multiple areas of cortical asymmetries as demonstrated in this study and reported in the initial SPECT report.^{13,15} The attributes of tinnitus are considered to be as follows:

(1) Sensorium and speech discrimination frontal lobe, anterior and posterior speech centers

(2) Anxiety—temporal lobe and hippocampalamygdala complex

(3) Frequency, intensity, and tonotopicity primary auditory cortex and associative auditory cortex

(4) Masking—hippocampus and associative auditory cortex

(5) Memory—amygdala and hippocampus

(6) Integration, speed, and speech discrimination—parietal lobe

(7) Spatial orientation—cerebellum and parietal lobe.

Identification of attributes of tinnitus in different ROIs of brain and their attentional modulation in patients with tinnitus of the central type could provide a basis for increased accuracy of tinnitus diagnosis and its clinical application for treatment. It would also provide a means for correlating a specific pathology with a specific physiologic attribute of tinnitus and thus lead to the development of a neuropharmacologic approach for tinnitus of a central type(s).

Identification of the Tinnitus Affect Component and Auditory and Paradoxical Memory

Identification of the affect component of severely disabling tinnitus using SPECT demonstrates impairment in rCBF in specific regions of interest known to be related to mood and memory. Cortical and subcortical areas of asymmetries in perfusion involving frontal, parietal, and temporal lobes, and in structures of the limbic system identified for this population.¹³

The medial temporal lobe system was identified to have a memory function.^{17, 18} Reciprocal connections are presumed to exist

between the hippocampus and adjacent anatomically-related cortex, including endorhinal, perirhinal, and parahippocampal cortices. This system is speculated to have a memory-related function in two directions.^{17,18}

(1) The hippocampus system provides rapid acquisition of new information of facts and events. It is a storage site for simple memory available as conscious recollections. The role of the hippocampus system is temporary, fast, and of limited capacity.

(2) The neocortex serves as a storage site which represents a total memory. Over time the memory stored in neocortex becomes independent of the medial temporal lobe system. This allows the medial temporal lobe system to become available for the acquisition of new information. It has been conceptualized that the hippocampus and associated areas of cortex act as a binding location to neocortex, resulting in a memory for a whole event which can be reactivated even from a partially similar event.¹⁷ It is hypothesized at this time that this concept has application for the patient with tinnitus.¹⁵

As new information adds to our understanding of the anatomy and function of the limbic system, the medial temporal lobe system studies of memory, perception, and mood can be applied to the affect component of tinnitus. Clinical manifestations of alterations in the sensorium of tinnitus patients include stress, anxiety, and depression. Tinnitus is hypothesized to reflect an abnormality in affect involving auditory memory.¹⁵ The stress factor has been linked to cortisol accumulation resulting from a defect in its control at the level of the hippocampus.¹⁹ Its accumulation has been linked to changes in mood which, over time, progress from anxiety to depression. The tinnitus patient may develop a memory not only for normal auditory stimuli but also, paradoxically, for the aberrant sound, that is, tinnitus.¹⁵ It can be speculated that a short-term memory is established for tinnitus in the medial temporal-lobe memory system which becomes stored in associated areas of the neocortex.^{13,15} A paradoxical memory for tinnitus may cause the tinnitus to become clinically manifest as a severely disabling tinnitus.

It is also hypothesized that the technique of SPECT imaging of those areas of the cortex

and subcortex previously identified may provide clinical manifestations of mood alteration and its relationship to a paradoxical auditory memory as reflected in asymmetries of rCBF.

The affect component of the symptom of tinnitus reflects the emotional response of the patient to the presence of tinnitus.²⁰ Emotional responses are reflected in the neurobiologic processes occurring in the brain. PET and SPECT both measure regional blood flow which reflects biologic markers of local neuronal activity. The temporal poles have been reported to be involved in normal and pathologic forms of human anxiety,²¹ as are the parahippocampus and superior colliculus.²²

Identification of Subtypes of Central Tinnitus

The multiplicity of asymmetries in various ROIs examined in brain with SPECT imaging when correlated with present knowledge of neurotransmitter function underlying a dysynchrony in neural firing within and between neural networks suggest types and subtypes of a central tinnitus.

Neurologic Implications

Neurologic implications for tinnitus patients are suggested by the findings of perfusion asymmetries with SPECT imaging of the brain. The two cases discussed in this paper support such implications and suggest the need for further investigation.

Neurologic implications are highlighted by three categories of diagnosis: (1) cerebrovascular disease; (2) neurodegenerative disorders and associated dementia; and (3) neuropsychiatric disorders specifically dementia, schizophrenia, and the affective disorder of depression.⁷

Cerebrovascular Disease

SPECT imaging of the brain can differentiate among various stages of acute and chronic ischemia and/or cerebral infarction. Functional localization of stroke and/or the reduction in blood flow to the cerebral hemisphere depends on which of the three major arteries are involved, the laterality of the stroke, and reduced flow.

Neurogenerative Disorders and Dementia

SPECT can differentiate between Alzheimer's disease and some other types of dementia including multi-infarct dementia, hydrocephalus, progressive supranuclear palsy, and various frontal lobe dementias. The typical finding in Alzheimer's disease is a bilateral parietotemporal hypoperfusion and hypometablism, with sparing of the sensory motor and occipital regions. In a small proportion of Alzheimer's patients, SPECT abnormalities can be primarily unilateral and correspond with signs of unilateral functional disturbances found on neuropsychologic tests. In general, SPECT of the brain can be helpful in the differential diagnosis of pathophysiologic patterns seen in various forms of dementia, Alzheimer's, and other diseases.⁷

Neuropsychiatric Disorders—Dementia, Schizophrenia, Depression⁷

Neuropsychiatric disorders including the schizophrenias, and the affective disorders, including depression, can be demonstrated with SPECT imaging of the brain. In schizophrenia, the most consistent finding has been a decrease in frontal lobe size, that is, hypofrontality, and increased rCBF in the basal ganglia, specifically the caudate, often associated with positive symptoms such as delusions and hallucinations. Increases in rCBF were also demonstrated in the temporal lobes.

It has been hypothesized that there is a specific link between the thought disorder present in schizophrenia and pathologic sites in the left temporal lobe.²³ The degree of thought disorder is suggested to be related to the size of the reduction in volume of the left posterior superior temporal gyrus. Postmortem CT and MRI studies have indicated that patients with schizophrenia have anatomic abnormalities in the left temporal lobe, and also that positive symptoms are related to an enlargement of the left sylvian fissure. Three major findings reported by Shenton and colleagues²³ are (1) lateralized left-sided decrease in gray matter in the anterior hippocampus—amygdala, parahippocampal gyrus, and superior temporal gyrus with an associated

increase in the temporal horn of the lateral ventricles; and (2) a strong correlation between the degree of thought disorder and decrease in volume in the left posterior superior temporal gyrus, a region previously acknowledged to be significant as a neuroanatomic substrate for language, 24,25 and (3) a statistically significant correlation between volume reduction and neuroanatomically interconnected temporal lobe regions, which may be important in performing auditory associative memory links. This report stresses that it is not known whether similar *features* are present in patients with other diagnoses such as mood disorders with psychosis or in patients with a first episode of schizophrenia, in whom the potentially confounding effects of chronicity and medication may not have occurred.

SPECT studies of affective disorders including major depressive disorders show an overall decrease in regional rCBF especially in the frontal lobes.²⁶ This pattern is reported to be different from that seen in dementias. In depression the reduced CBF tends to normalize with clinical improvement of the patient.

Case reports

Significant involvement of hypoperfusion particularly in the frontal lobe areas has been demonstrated in our preliminary study and present case reports.

Case 1 demonstrated perfusion asymmetries in the posterior parietal, temporal, and anterior frontal lobes, with a relatively normal deposition in the subcortical areas, motor strip cortex, and cerebellum. Such findings have been reported typical of a pattern seen with dementia of the Alzheimer's type. A decrease in cognitive function was reportedly delayed years fol-lowing the onset of tinnitus in this patient. Neuropsychologic testing demonstrated inter-ference in cognitive function, which raises the question as to whether or not in this patient and in others with similar patterns of cortical asymmetry, the tinnitus may have such a medical significance. Namely, can be consider the presence of tinnitus, which precedes dementia, to be an early marker of a neurodegenerative disorder, with its initial focus in the primary auditory areas of the temporal lobe and tinnitus is the primary symptom?

Case 2 is considered to reflect patterns seen in cerebrovascular disease and the mood disorder of depression. Tinnitus in this patient may be a *soft* sign of gradually progressive cerebrovascular disease. The clinical history of an associated memory disorder accompanying intensification in tinnitus may be reflected in the hypoperfusion of the temporal lobes.

The heterogeneity of the clinical manifestations of tinnitus are considered to be reflected in the SPECT of brain imaging results obtained in our series to date and demonstrated in the two reported cases. The distribution of cortical asymmetries in the frontal, partial, temporal lobes and in particular the limbic system suggest the possibility of a neurologic basis for tinnitus particularly of the central type.

SPECULATIONS

Brain SPECT results in a particular central type SIT patient may reflect a complexity of dysfunction in neuronal networks resulting from an altered state of excitation which results in a dysynchrony in neuronal signaling, with the place of origin in the primary auditory cortex. The extension of the area of dysynchrony from the primary auditory cortex can, through interneuronal networks, extend

(1) Posteriorly to the posterior speech center (Brodmann's areas 39 and 40) for the sensory component of speech for both recognition and speech reception

(2) Anteriorly to the anterior speech center (Brodmann's 44) with interference in motor speech function and in its extreme a motor aphasia

(3) Superiorly to the superior speech center for interference in articulation (Brodmann's 6)

(4) Inferiorly to the associative auditory cortex (Brodmann's 21 and 22) with interference in auditory memory, speech discrimination, masking, tone quality and intensity

(5) Anteriorly in the temporal lobe to the hippocampal amygdala complex for involvement of the limbic system and mood alteration (6) Medially to involve the medial temporal lobe system of memory with interference in auditory memory and affect ranging from anxiety to severe depression.

In short, the degree of clinical manifestation of the sensory and/or affect component of the symptom of tinnitus by the patient may in reality reflect the extent of neuronal dysynchrony in central processing areas in the brain associated with the auditory cortex for intelligibility and comprehension of sound perception and its integration for speech function.

The underlying basic mechanism may be that of glutamate neurotoxicity. Such glutamate receptors mediate excitatory neurotransmission in the brain and are important in memory, speech and sound acquisition, learning, certain neurodegenerative disorders, neuronal plasticity, and neurotoxicity.

Tinnitus, defined as a basic dysynchrony in neuronal firing within the cochleovestibular system, may specifically result in a paradoxical auditory memory center in the hippocampal amygdala complex, and other portions of the limbic system may result in varying degrees of abnormality in affect ranging from mild anxiety to severe depression. Interference in glutamate neurotransmission is considered to interfere in neuron plasticity which is regulated for memory by processes of long-term potentiation (LTP) in the hippocampus and long-term depression (LTD) in the cerebellum.²⁴ Both of these fundamental processes are considered to underlie information storage in the brain.

In short, varying degrees of glutamate neurotoxicity involving neuronal networks leading from the primary auditory cortex to areas of brain function for auditory memory and affect may underlie the heterogeneity of the symptom of SIT. In any single patient, this neurotoxicity may be a forerunner of progressive degenerative diseases (including Alzheimer's disease), neuropsychiatric mood disorders, schizophrenias, cerebrovascular disease, and other central neurologic pathologies.

No conclusion has yet been arrived at with respect to association between SIT and a cerebrovascular, neurodegenerative, and some neuropsychiatric disorders. Such a conclusion awaits neuropathologic confirmation with attention to the demonstration of a neuropathologic correlate. The identification of subtypes of a central type tinnitus await future identification of a neuropathologic correlate which can only be accomplished by the scoring of neurons in brain, ganglion cells in the organ of Corti, and other factors.

SUMMARY AND CONCLUSIONS

SPECT imaging of brain in a patient with SIT is considered a significant advance for the neuroscience of tinnitus diagnosis. This is the first time that objective asymmetry in cortical perfusion in multiple areas of brain, consistently in the left temporal lobe, has been demonstrated in consecutive tinnitus patients clinically identified to be of the predominant central type. Tinnitus of the severely disabling type as demonstrated by SPECT imaging of the brain, may in some patients be a *soft*, and key symptom or sign of organic brain disease. Preliminary studies support this implication. Its significance requires further investigation, now ongoing.

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