Central Nervous System Neurodegeneration and Tinnitus: A Clinical Experience

Part I: Diagnosis

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Abstract: In an evolving clinical experience since 1979, the medical significance of the symptom of tinnitus has been identified as a “soft” sign of neurodegeneration (ND) in the central nervous system (CNS) in a particular subset of tinnitus patients diagnosed with a predominantly central-type, severe, disabling, subjective idiopathic tinnitus. To highlight this experience, a retrospective review and analysis of consecutive tinnitus patients (N = 96) was conducted. Ninety-six tinnitus patients (ages 22–90 years) were seen in neurotological consultation from November 1, 2005, to June 30, 2007, all of whom had subjective idiopathic tinnitus of the severe disabling type (SIT). Of these 96 patients, 54 had SIT of the predominantly central type and of these, 18 (ages 39–75 years) were recommended for nuclear medicine imaging (single-photon emission computed tomography [SPECT] and fluorodeoxyglucose–positron emission tomography/computed tomography [FDG-PET/CT]). Patient selection for nuclear medicine imaging fulfilled the criteria of a medical-audiological ND tinnitus profile: completion of a patient protocol that diagnosed a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus lasting in excess of 1 year, and failure of existing modalities of treatment attempting tinnitus relief. In 16 of the 18 patients, objective evidence of ND was reported in multiple neural substrates of brain obtained with SPECT or FDG-PET/CT of brain. Classification of CNS ND and tinnitus differentiated between (1) ND of nonspecific or unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (n = 11/18); and (3) neurodegenerative CNS disease consistent with nuclear medicine criteria for senile dementia of the Alzheimer’s type (n = 5/18). The diagnosis has been associated with cerebrovascular disease (n = 16/18). The identification of neurodegenerative CNS disease in a selected cohort of patients with subjective idiopathic tinnitus as a soft sign of such CNS disease has implications for diagnosis and treatment.

Key Words: central-type, severe, disabling tinnitus; inflammation; ischemia; medical-audiological neurodegenerative profile; neurodegeneration; senile dementia of the Alzheimer’s type

In this report, the term neurodegeneration (ND) designates the processes involved in the progressive damage or death of neurons. This process is reflected clinically in a gradual deterioration of and interference in function of the affected neural substrates of the nervous system.

Neurological insults result in neurotoxicity, neuronal death, and ND. Such insults include hypoxic ischemia of stroke, sustained seizures, head trauma, spinal cord injury, and profound hypoglycemia [1].

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central-type, severe, disabling, subjective idiopathic tinnitus. A retrospective review and analysis of 96 tinnitus patients was conducted. These patients (ages 22–90 years), seen in initial and consecutive neurotological consultation from November 1, 2005, to June 30, 2007, all had subjective idiopathic tinnitus of the severe disabling type (SIT). Of these 96 patients, 54 were diagnosed to have SIT of the predominantly central type and of these, 18 (ages 39–75 years) were recommended for nuclear medicine imaging via brain single-photon emission computed tomography (SPECT) or fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT).

SIT patient selection for the brain SPECT and FDG-PET/CT neuroimaging was based on (1) diagnosis of a predominantly central-type, severe, disabling SIT established by patients’ completion of a medical-audiological tinnitus patient protocol (MATPP) [2]; (2) a positive correlation (i.e., fulfillment of the criteria established in a medical-audiological ND profile of SIT patients) clinically considered to be a “soft” sign of neurodegenerative CNS disease; and (3) resistance to therapeutic modalities of medication and instrumentation attempting tinnitus relief for at least 1 year. Brain nuclear medicine imaging and interpretation of the results were completed at the State University of New York, Downstate Medical Center (SUNY/Downstate), for SPECT, whereas FDG-PET/CT was completed at the Columbia Kreitchman PET Center, Columbia University College of Physicians and Surgeons, and State University of New York/Downstate.

In a particular cohort of patients with diagnosed SIT, the medical significance of their tinnitus is that it is clinically considered to be a “soft” sign of neurodegenerative CNS disease. This clinical impression has evolved in stages as a reflection of our clinical experience with SIT. That experience originated in 1979 in the Tinnitus Clinic of the Health Science Center at Brooklyn/SUNY and has been ongoing at the Martha Entenmann Tinnitus Research Center, Inc. (METRC) since 2005. More than 10,000 patients have been seen in consultation for SIT since 1979 [2].

Initially, in stage 1 (1979–1989), the clinical impression was anecdotal, based on observation and clinical interpretation and correlation of findings revealed in tinnitus patients’ MATPPs. That instrument established a clinical diagnosis of a predominantly central-type tinnitus and identified factors influencing the clinical course of the tinnitus [3–8].

Stage 2 (1989 and ongoing) has been one of objectivity correlated with observations and clinical interpretations of patients’ MATPPs. The objectivity has been provided by progressive introductions into the MATPP: in 1985, neuroradiology with brain magnetic resonance imaging (MRI); in 1989, nuclear medicine imaging (brain SPECT); in 1999, electrophysiology (i.e., quantitative electroencephalography [QEEG]); in 2000, FDG-PET; in 2002, magnetoencephalography (MEG); and in 2005, brain FDG-PET/CT, which have respectively identified neural substrates and abnormal electrical activity in the brain, both in support of the clinical diagnosis of a predominantly central-type tinnitus [9–13].

As a result of this experience, the clinical medical-audiological profile of SIT patients in whom the medical significance of SIT suggests a soft sign of neurodegenerative CNS disease has been established.

Classification of ND in the CNS of SIT patients on the basis of brain SPECT and FDG-PET/CT has differentiated among (1) ND of nonspecific or unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (neurodegenerative disease with ischemia [NDDI]; n = 11/18); and (3) a neurodegenerative disease (NDD) of the CNS consistent with nuclear medicine criteria for senile dementia of the Alzheimer’s type (SDAT) (n = 5/18). The SDAT I designation is for primarily parietal hypoperfusion, whereas the SDAT II designation is for the combination of parietal and other regions of interest (ROI) in the brain [14–17].

The incidence of occurrence of identifying the medical significance of SIT as CNS ND (i.e., ND, NDDI, NDD/SDAT) in a particular cohort of a predominantly central-type severe disabling tinnitus has increased since the year 2000 in our one-day-a-week neurotological practice at the METRC. This increased incidence is considered to be multifactorial, reflecting an increase in the sensitivity and reliability of technologies of nuclear medicine imaging and electrophysiology and an increased complexity and heterogeneity of a predominantly central-type SIT in the tinnitus population seeking our neurotological consultation, as well as an increase in the aging population.

Since 1989, more than 285 examinations consisting of nuclear medicine imaging of brain (SPECT or FDG-PET/CT) have been recommended and completed in SIT patients. Scintigraphy has been found to be essential for attempting to establish an accurate tinnitus diagnosis, its medical significance, a rationale for treatment, and a monitor for establishing the efficacy of treatment modalities attempting tinnitus relief. Perfusion asymmetries have been identified and reported in multiple ROI in the brain. Highlights of this ongoing experience include the first reports in tinnitus patients of identifying multiple neural substrates. They include a tinnitus metabolic correlate, glucose; a benzodiazepine deficiency syndrome; the identification of the GABA_A receptor as a biochemical marker for tinnitus; a hypothesis of a final common pathway for tinnitus in the brain; a receptor-targeted therapy (RTT) directed to the GABA_A receptor (RTT-GABA); and a theory for tinnitus (i.e., the
dysynchrony-synchrony theory of tinnitus, which has clinical applications for diagnosis and treatment and an electrophysiological correlate for SIT) [10,18–23].

Specifically, for NDDI, NDD-SDAT, and tinnitus, neuroradiology and nuclear medicine findings are highlighted by ischemia and brain atrophy in multiple brain ROI and in pseudotumor cerebri. Ischemia, associated with cerebrovascular disease, has been identified by (1) alterations in multiple brain structures seen on MRI and reported as white-matter changes (predominantly in frontal, periventricular, temporoparietal and, occasionally, basal ganglia areas) and brain atrophy and (2) cortical alterations in regional cerebral blood flow (rCBF) and perfusion asymmetries in multiple brain ROI (in the frontal, medial temporal, temporal, and primary auditory cortex more than in the parietal region, basal ganglia, and cerebellum) as identified with nuclear medicine FDG-PET/CT and with brain SPECT, both baseline and post-Diamox stress testing [9,10,18,24,25].

Significantly, QEEG results for all SIT patients (n = 18) revealed elevated electrical activity in the brain from multiple recording sites [9,11,12].

New cerebral PET tracers are reported to visualize amyloid plaques and neurofibrillary tangles in the brain in diagnosing Alzheimer’s disease (AD). Such molecular probes, reported to be noninvasive, include the molecule 2-(1-{6-[2-[F-18] fluoroethyl](methyl)amino]-2-naphthyl}ethylidene) malononitrile (FDDNP) and [11]-PIB (Pittsburgh compound B), which bind to plaques and neurofibrillary tangles in vitro in early stages of the disease. Future application is planned in appropriately selected SIT patients [26].

This retrospective review and analysis of nuclear medicine imaging data is an evolving experience. Two case reports of brain SPECT and FDG-PET/CT will demonstrate CNS ND and SIT (i.e., NDDI, NDD-SDAT). Included is a protocol and classification system for ND, NDDI, and NDD-SDAT diagnoses, the medical-audiological ND profile of such SIT patients, criteria for patient selection for SIT nuclear medicine imaging, and implications for diagnosis and treatment.

CLINICAL MEDICAL-AUDIOLOGICAL ND PROFILE: CNS ND AND TINNITUS

General Information and Incidence of Occurrence

The tinnitus diagnosis of a predominantly central-type SIT is established by patients’ completion of the MATPP [5]. Nuclear medicine imaging is reserved and recommended for patients who have SIT of a predominantly central type and in whom therapy with instrumentation and medication failed in attempting tinnitus relief. All referred SIT patients have a positive medical-audiological profile highlighted by central findings in their clinical history, physical examination, and cochleovestibular testing. A “normal brain MRI” result is not a contraindication for nuclear medicine imaging. The MRI demonstrates brain structure; nuclear medicine imaging reveals function. Neurological consultation should include MRI brain scan and is recommended for all SIT patients identified via nuclear medicine imaging as having a CNS etiology for the SIT or demonstrating ND, NDDI, or NDD-SDAT.

A medical-audiological profile of patients in whom SIT of the severe disabling type has been clinically suggested to be a soft sign of neurodegenerative CNS disease has been identified. The elements of the profile include the patients’ neurootological clinical history, physical examination of the head and neck, electrophysiological correlates of cochleovestibular function, spectral analysis of raw QEEG data of brain function, and brain SPECT or FDG-PET/CT. The incidence of occurrence in a cohort of SIT ND, NDDI, and NDD-SDAT patients will vary in different neurotological practices, depending on the demographics and severity of the SIT patient population seeking consultation.

History

The clinical history is the most important element of the profile. A neurootological history seeks to elicit the presence or absence of positive responses to questions about the head and neck, ear, nose, and throat, and brain function or dysfunction.

General Information

Initial questions are directed at identifying the tinnitus. They are followed by recording associative complaints reflective of cochleovestibular and brain function or dysfunction. These are followed in turn by reviewing systems, hospitalizations, medications, past illnesses, noise exposure, and family history, which focus on allergy, metabolic disease, hearing loss, and any family illness, particularly epilepsy [4,5].

Positive Reports in the Personal, Family, and Social History

From age 35 to age 60 and beyond in particular, the chief complaint of severe disabling tinnitus (SIT) onset is more sudden than gradual. Its location can be bilateral more often than unilateral, and its location is in either ear or in the head alone or in combination. It is always accompanied by an affect of anxiety or depression (or both).

Personal loss, sudden emotional stress, or trauma can trigger a preexisting non-disturbing tinnitus and increase
its intensity. Other possible triggers are metabolic disease, hyperlipidemias, thyroid disorders, diabetes, cardiovascular disease (hypertension, atrial fibrillation), and cochleovestibular complaints (e.g., hearing loss, vertigo, ear blockage, hyperacusis).

**Review of Systems**

SIT may manifest in altered sensory ability: For instance, affected patients may experience occasional interference in smell. An analysis of the cranial nerves may reveal abnormality in cranial nerves 1 and 8. A cardiovascular examination may indicate hypertension, atrial fibrillation, or coronary heart disease. Metabolic disorders may include diabetes mellitus, hyperlipidemia, or thyroid disease. Patients may report certain neuropsychiatric malfunctions, such as epilepsy or stroke; cerebrovascular disease; or, either singly or in combination, anxiety, depression, and stress or posttraumatic stress disorder. Cochleovestibular complaints often point to hearing loss, vertigo, ear blockage, and hyperacusis.

The parameters of tinnitus identification (Table 1) include quality (noise more than tone, multiple more than single); association with or separate report of an auditory hallucination (single or multiple); location—“outside the body,” in the head (particularly a right or left temporal region) or one or both ears. Additional parameters include hyperacusis, intensity (severe), duration (short [3–6 months] more frequently than a year or longer), and masking characteristic (Feldmann type 4–5 or type 1–3).

The following associated complaints, either alone or in combination, may be positive in the clinical history of the tinnitus: preexistent or recent gradual increase in hearing loss, asymmetrical or symmetrical ear blockage with or without head pressure, hyperacusis, interference in sensations of smell or body temperature fluctuation; and interference with cognitive function, speech expression, memory, coordination, motor function, and gait.

**Physical Examination**

The absence of local disease in the head and neck is first established by physical examination. Auscultation of the head and neck frequently uncovers a carotid bruit on the side of the tinnitus or reported auditory hallucination (or both). Positive tuning fork results often point to hyperacusis. Weber lateralization findings are negative. Rinne test results are positive both right and left.

Microscopical examination of the tympanic membranes at 10× magnification indicates no pulsation. Spontaneous eye movements are directed to confirm the absence of nystagmus with eyes open and Frenzel lenses. On interference of visual-vestibular interaction, ocular fixation suppression is reduced. Romberg standing test results are negative, and the Fukuda stepping test readings are positive for central dysfunction.

**Multimodality Testing Results**

**Cochleovestibular Testing**

Conventional audiometry results (250 Hz–8 kHz) show a sloping high-frequency sensorineural hearing loss. Ultrahigh-frequency audiometry (10–20 kHz electrical or air, or both) indicates a hearing loss greater than expected for the age of the patient. Auditory brainstem response

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<th>Table 1. Parameters of Tinnitus Identification</th>
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FMC = Feldmann masking curves; Inc = incomplete; L = left; NC = nonclassifiable; ? = questionable; R = right.
(ABR) results in short latencies confirm an abnormality, particularly in interpeak P1–P5. A low-amplitude P1, P3, or P5 suggests a slow brain-wave syndrome [27, 28]. The rotary chair reading would be positive for central dys-function; tinnitus intensity is altered with rotation [29].

Tinnitus Evaluation

The parameters of tinnitus identification (see Table 1) include quality (noise more than tone, high-frequency more than low-frequency, multiple more than single); association with or separate report of an auditory hallucination (single or multiple); location (bilateral more than unilateral, particularly “outside the body,” in the head [particularly the right or left temporal region] or one or both ears); intensity (severe); duration (short [3–6 months] more frequently than a year or longer); and masking characteristic (Feldmann type 4–5). In addition, loudness discomfort levels are abnormal.

Quantitative Electroencephalography

QEEG results indicate elevated electrical activity: delta higher than beta in the frontotemporal electrode recording sites [11,12].

Brain MRI with Gadolinium

Brain MRI with gadolinium is useful for revealing brain atrophy in the cortex, particularly the frontal and temporal lobes. It also can reveal any white-matter change in the periventricular frontal, temporoparietal, and (occasionally) basal ganglia areas consistent with small-vessel disease. Ischemic effects would occasionally include pseudotumor cerebri secondary to brain atrophy.

Nuclear Medicine Imaging

Alterations in the rCBF are identified via SPECT, both baseline and post-Diamox stress testing. Alterations in cerebral metabolism can be identified with FDG-PET/CT in the frontal, temporal, and medial temporal lobe systems, primary auditory cortex, the parietal lobe, basal ganglia, and cerebellum (Table 2).

Clinical Medical-Audiological ND Profile Summary

The accuracy of the diagnosis is critical for establishing the medical significance of the tinnitus and its subsequent treatment. Completion of the MATPP establishes the clinical diagnosis of a predominantly central-type tinnitus and a basis for SIT selection for brain SPECT and FDG-PET/CT. In a selected cohort of SIT patients, SPECT identification of ND, NDD-SDAT, and NDDI supports the medical significance of the disorder as a soft sign of CNS disease (Table 3).

RESULTS

Incidence

Our clinical experience with ND in the CNS has suggested it as a significant soft sign of the symptom of tinnitus (see Tables 1–3).

<table>
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<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>FDG-PET/CT</th>
<th>SPECT</th>
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<td>1</td>
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<td>Biparietal, bitemporal MTLS reduced: SDAT</td>
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<td>Biparietal, bitemporal MTLS reduced: SDAT</td>
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<td>Bitemporal MTLS reduced, PAC L increased: NDDI</td>
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<td>Bitemporal MTLS reduced, PAC R increased: NDDI</td>
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<td>Bitemporal MTLS reduced: NDDI</td>
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<td>Bitemporal MTLS reduced: NDDI</td>
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<td>Bitemporal MTLS reduced, PAC R increased: NDDI</td>
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<td>10</td>
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<td>Hemispheric reduction L, bilateral temporal reduction L&gt;R; MTLS reduction L&gt;R; PAC increase R: NDDI</td>
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<td>11</td>
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<td>Bifrontal-parietal, bitemporal MTLS reduced; thalami reduced L&gt;R: NDD-SDAT</td>
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FDG-PET/CT = fluorodeoxyglucose–positron emission tomography/computed tomography; L = left; MTLS = medial temporal lobe system; NDDI = neurodegenerative disease with ischemia; PAC = primary auditory cortex; R = right; SDAT = senile dementia, Alzheimer’s type; SPECT = single-photon emission computed tomography.
Stage 1: 1979–1989
Our clinical MATPP diagnosis of a predominantly central-type tinnitus occurred in approximately 20–25% of affected patients. The medical significance of the SIT as a soft sign of CNS disease was approximately 5%.

Stage 2: 1989 and Ongoing
Overall, in stage 2, our clinical diagnosis of a predominantly central-type tinnitus has been approximately 60–70%. Its medical significance as a soft sign of CNS disease (supported by nuclear medicine imaging) has been greater than 15–20%. A cerebrovascular diagnosis has predominated.

Analysis of Current Cohort: November 1, 2005, to June 30, 2007
The total number of patients with whom we consulted and reported here was 96. From November 1, 2005, to December 30, 2006, we worked with 68 patients (group A), and from January 1, 2007, to June 30, 2007, we worked with 28 (group B) (see Table 1).

The age range of the group A patients was 22–86 years (average, 49.5 years). In group B, patient ages ranged from 32 to 90 years (average, 49.46 years). The mean age of all patients (N = 96) was 49.3 years.

In group A, male patients numbered 43 of 68 (63.2%), whereas in group B they totaled 19 of 28 (67.9%). Overall, male patients represented 62 of the 96 patients (64.6%). The total number of female patients in group A was 20 of 68 (29.4%) and, in group B, 9 of 28 (32.1%). The overall number of female patients was 29 of 96 (30.2%).

The numbers of those affected patients who successfully completed the MATPP included 54 of 68 (79.4%) in group A and 19 of 28 (67.9%) in group B.

Clinical diagnosis of predominantly central-type tinnitus was made in 45 of 68 patients (66.2%) in group A, whereas this diagnosis was made in 14 of 28 patients (50.0%) in group B. Overall, the diagnosis established a predominantly central-type tinnitus in 59 of the 96 patients (61.4%).

The diagnosis of cerebrovascular disease applied to 16 of 18 patients (88.9%). Their ages ranged from 39 to 75 years (14 male, 4 female). Ten patients exhibited hypertension; of these, NDDI was present in seven and NDD-SDAT in three.

Nuclear Medicine Imaging of Brain: SPECT and FDG-PET/CT
From November 1, 2005, to June 30, 2007, 96 consecutive SIT patients were seen in neurotological consultation and, on completion of the MATPP, 54 of the 96 were given a diagnosis of a predominantly central-type SIT (Figs. 1, 2; see Tables 2, 3). We recommended that 18 SIT patients undergo brain SPECT or FDG-PET/CT examinations. Positive findings consistent with ND, NDDI, or NDD-SDAT were reported in 16 of the 18. Abnormalities in brain regions of reduced rCBF were reported in the frontal, temporal, and medial temporal lobe systems, the parietal lobe, and the basal ganglia.

Brain MRI with gadolinium contrast had been obtained in 8 of 18 patients prior to neurotological consultation and SPECT and FDG-PET/CT. Atrophy or ischemia (or both) were reported in 4, whereas the remaining 4 had normal readings (see Table 3).

In the cohort of 18 of 96 SIT patients, no clinical association has been identified at this time between SIT and established neurodegenerative CNS disease (i.e., AD or frontotemporal degeneration or both). Brain FDG-PET/CT identified NDD-SDAT in 5 of the 18 patients. Additionally, brain FDG-PET/CT identified ischemia (NDDI) in 11 of the 18 patients. Ischemia associated with NDD-SDAT was disclosed via brain MRI, FDG-PET/CT, and SPECT in three of the five NDD-SDAT patients.

The diagnosis of cerebrovascular disease was established in 16 of the 18 patients by combining findings of history, incidence of hypertension, and brain SPECT and FDG-PET/CT imaging. Long-term longitudinal studies of different clinical types of a predominantly central-type tinnitus will determine the relationship, between SIT and ND, NDDI, and NDD-SDAT.

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<th>Case No.</th>
<th>Age</th>
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FDG-PET/CT = fluorodeoxyglucose–positron emission tomography/computed tomography; HHD = hypertensive heart disease; MRI = magnetic resonance imaging; NDDI = neurodegenerative disease with ischemia; NDD-SDAT = neurodegenerative disease with senile dementia, Alzheimer’s-type; SPECT = single-photon emission computed tomography.
Figure 1. Neurodegenerative disease of the senile-dementia, Alzheimer’s type (NDD-SDAT).
A, B: PET-CT image fusion in transaxial, sagittal, coronal, and surface-rendered projections demonstrating, from left to right, (A) hypometabolism in the frontal, parietal, and medial temporal lobes bilaterally and hypermetabolism in the left primary auditory cortex; and (B) hypermetabolism in the left primary auditory cortex and hypometabolism in the right primary auditory cortex. Line 1: CT scan, grayscale. Line 2: PET scan, multicolor display. Line 3: PET-CT fusion with higher-resolution CT in grayscale and PET in color overlay.
C: PET scan in transaxial, sagittal, and coronal projections and PET-CT image fusion in transaxial, sagittal, and coronal projections from left to right, demonstrating bilateral medial temporal lobe and biparietal hypometabolism and increased left primary auditory cortex metabolism.
D: PET scan in transaxial, sagittal, and coronal projections from left to right, demonstrating bilateral medial temporal lobe and biparietal hypometabolism.

Figure 2. Neurodegenerative disease with ischemia (NDDI). PET scan, transaxial (left) and coronal (right) projections, demonstrating diffuse left-hemisphere fluorodeoxyglucose hypometabolism and hydrocephalus ex vacuo secondary to brain atrophy; bilateral medial temporal lobe hypometabolism on the left more than the right; and right primary auditory cortex hypermetabolism.
CASE REPORTS
To highlight NDD-SDAT and NDDI, the following two cases illustrate ND in the CNS in SIT patients.

Patient 1
In patient 1, NDD-SDAT was diagnosed. A 43-year-old man experienced in his left ear chronic tinnitus of approximately 20 years’ duration, beginning in 1985 after a “truck” accident with associated left-ear blockage, loss of consciousness of approximately 30 minutes’ duration, and no fracture. Its intensity had increased since 2004.

Parameters of Tinnitus Identification
The history of the patient’s present illness reported the description of the tinnitus as a “high-pitched squeal” with some modulation. Its duration was constant, but intensity was intermittent and fluctuated. The tinnitus was located in and around the patient’s left ear, with maximum intensity in the center of the ear. The annoyance level was considered severe for at least 1 year prior to initial consultation (2006). The patient’s annoyance arose from the disorder’s interference with his sleep, communication, performance, concentration, and social activities.

Tinnitus intensity and annoyance had gradually increased since 1985. The initial tinnitus was reported 2–3 months after a truck accident in which the patient was a passenger. The patient lost consciousness for approximately 30 minutes as a result; no fracture was reported, but he complained of associated left-ear blockage afterward. The tinnitus was maskable, and the patient experienced no pulsation.

At consultation, the man indicated on his tinnitus intensity index (0 = gone; 7 = worst) a best of 5 (10% of the time) and a worst of 7 (90% of the time), for an average intensity of 6. Modifying factors included stress and loud noise exposure; ear blockage with or without hearing loss; anxiety; and fluctuation in middle-ear aeration accompanying upper respiratory tract infections.

Associated Complaints
Among the associated complaints reported were hearing loss greater in the left than in the right ear and right- and left-ear blockage. Other associated complaints included imbalance (i.e., “off balance”), hyperacusis, nasal obstruction, hyposmia, headache at the center of his head with a “throb” that was synchronous with his heartbeat, a foreign-body sensation in his throat, depression, “obsessive compulsive disorder,” interference in speech expression and memory, cervical spondylosis with neck pain, weakness in both legs and all toes, a diagnosis of “Ménière’s syndrome,” difficulty in space and time orientation, a sensation of falling and unsteadiness, nausea, gait “veering to the left,” and a sensation of being “pushed back to the right.”

Clinical Course: Tinnitus, Hearing Loss, Ear Blockage, and Vertigo
The patient’s tinnitus after the accident in 1985 was described as having the quality of a “high-pitched tuning fork” in the left ear. Its duration was constant and its intensity fluctuant. In 1987, the quality of the tinnitus was reported to have modulated.

The clinical course included post-accident cochleoves-tibular complaints since 1985, with a primary complaint of imbalance, fluctuant left-ear blockage and tinnitus 2–3 months later, and left-sided hearing loss since age 36. Hyperacusis in the left ear, which was reported prior to the trial of a hearing aid 10 years before consultation, was said to have increased in 2005 and to have improved within the last month prior to the 2006 consultation. Hearing loss in the patient’s right ear was reported in the last 2–3 years before consultation. Hearing status at the time of consultation was reported to be of at least 3 months’ duration.

The onset of imbalance was 1–2 months after the accident in 1985 and, at that time, was described initially as a sensation of rotation. At the time of consultation in 2006, the patient’s complaint of imbalance was characterized as “off balance,” having difficulty orienting in space and time, a sensation of falling, unsteadiness, and nausea, and as “veering to the left” and experiencing a sensation of “being pushed back to the right.” Progression within the last year was highlighted by the veer to the left and two episodes of “spin” sensation of hours’ duration 4–5 months previously.

Reduction in memory occurred within the last 2–3 years; interference in speech expression also manifested within the last 1–2 years. The patient reported pain over the last “2 years” located in his neck and right arm. He described it as “unbearable” for 2 years; since “spring ’05,” the pain extended to “mid-spine.” Depression had been present since 1992. Since 1993, as a result of that depression, psychiatric treatment had been ongoing, and the patient was considered suicidal in 2004.

Following the accident, the patient underwent a cervical spinal fusion (C5–C6) in 2005, after which he experienced a reduction in pain intensity. However, the increased imbalance, hearing loss, and tinnitus remained unchanged.

Attempts at Tinnitus Relief
Attempts at tinnitus relief included a diagnosis of “Ménière’s disease in the left ear.” Left-sided vestibular nerve section was performed in 1987, with reported improvement in rotation sensation. The patient underwent endolymphatic left-ear shunt in 1992, which produced no change in his complaints of hearing loss, tinnitus, and vertigo. At age 38, he began using a trial hearing aid and, at age 39, began to use digital hearing aids in both ears. For the last 3 months, he has had a hearing aid with an amplifier in the right ear, with reported improvement in hearing in quiet surroundings.
His tinnitus is unchanged, hyperacusis is reduced, and imbalance remains unchanged.

**Tinnitus Evaluation and Cochleovestibular Testing: 2006**

Site-of-lesion audiometry revealed sensorineural-type hearing loss, severe to profound in the left ear and mild to moderate in the right, predominantly cochlear in location, with bilateral involvement of the central auditory pathways. Speech discrimination is reduced in the right ear and absent in the left.

Recruitment was identified in the left ear. Loudness discomfort levels were negative bilaterally. The Feldmann masking curve confirmed the symptom in the left ear to be maskable but not classifiable on the basis of the Feldmann masking curve classification system; it registered as a type III in the right ear. Otoacoustic emissions testing results were abnormal. ABR short-latency responses to broad-band click stimulation revealed amplitude reduction of P1, P2, P3, and P5 in both ears. Electronystagmography results were abnormal, with a diagnosis of a peripheral and central vertigo.

Sinusoidal harmonic acceleration (rotary chair testing) evidenced labyrinthine asymmetry to the left. Optokinetic nystagmus assessment readings on the left side proved satisfactory. Saccade testing outcomes were normal. Ocular fixation suppression of the vestibulo-ocular reflex was reduced, a sign of cerebellar dysfunction. Pursuit tracking results were normal. QEEG readings showed significant CNS electrical dysfunction. FDG-PET/CT of brain on June 4, 2006, indicated hypometabolism in the frontal, parietal, and medial temporal lobes bilaterally and hypermetabolism in the left primary auditory cortex (see Fig. 1).

The clinical type of tinnitus diagnosed in this man’s case was a predominantly central type with a cervical, cochlear, and middle-ear component left and a subclinical tinnitus right. The etiology was cerebrovascular at this time, involving anterior and posterior intracerebral circulations superimposed on past noise exposure and head trauma. Factors identified as influencing the clinical course of the tinnitus included noise exposure, stress, cervical pain, secondary endolymphatic hydrops on the left, and bilateral fluctuation in aeration of the middle ears.

**Patient 2**

In patient 2, NDDI was diagnosed. A 66-year-old woman experienced tinnitus in the right ear and auditory hallucination in the right temporal head region lasting 2 years, with increased intensity in the 5–6 months prior to consultation in 2005.

**Parameters of Tinnitus Identification**

The history of the woman’s present illness showed that she described the tinnitus, located in the right ear, as a “hum, high-pitched” and of constant duration. Its intensity fluctuated, increasing in the last 5–6 months prior to the time of our initial consultation in 2005. The patient calculated her level of annoyance to be moderate, including sleep interference.

An additional symptom—an auditory sensation of “voices of older teenagers saying, ‘Help me, please help me’”—was intermittent and experienced “in the quiet.” The patient pointed to the scalp area above the anterior attachment of helix to the scalp, above her right temporomandibular joint, to pinpoint the location of both the tinnitus and the auditory hallucination. The tinnitus was “muted” by pressure applied to this area. Increased ambient sound increased the intensity of the tinnitus.

The tinnitus was maskable, and no pulsation was evident. On the tinnitus intensity index (0 = gone; 7 = worst), as of November 15, 2005, the patient indicated a best of 3 (occasional) and a worst of 6 (70% of the time), for an average intensity level of 4. Modifying factors included stress and loud noise exposure, ear blockage with hearing loss, and anxiety.

**Associated Complaints**

The patient reported hearing loss in both ears, interference with memory, and auditory hallucinations. A seizure disorder in the past was reportedly due to “alcohol withdrawal.” Also indicated was occasional otalgia in both ears, both during and when waking from sleep.

**Clinical Course: Tinnitus, Hearing Loss, Ear Blockage, Vertigo, and Auditory Hallucinations**

The onset of the right-ear tinnitus and the auditory hallucination in the right side of the head was reported as occurring after 2–4 weeks spent in the hospital recovering from a “seizure” in 2004. The patient’s husband had found the patient unconscious in the kitchen on arising. The duration of loss of consciousness reported at this time was approximately 6–8 hours. During hospitalization for diagnosis, treatment, and rehabilitation, the etiology of the woman’s seizure was reported to be “alcohol withdrawal.” The patient experienced tinnitus of increasing intensity and annoyance in the last 5–6 months prior to consultation. She had a history of alcohol abuse over 15 years’ duration, though no prior complications (i.e., delirium tremens or seizure) had been reported.

Memory interference had commenced since the seizure in 2004. There was a questionable history of childhood epilepsy at age 3–4. A medical report and possible treatment for Wolff-Parkinson-White syndrome was requested from her local medical doctor.


Attempts at tinnitus relief included tinnitus evaluation in 2005. Site-of-lesion audiometry (November 21, 2005) confirmed a mild to moderate sensorineural hearing loss, approximately...
equal on both sides and predominantly cochlear in location, with involvement of the central auditory system on the left.

High-frequency audiometry (electrical and air) revealed a hearing loss greater than expected for the age of the patient. ABR short-latency broad-band click stimulation showed a bilateral increased latency at interpeak P1–P3, P3–P5, and P1–P5, left greater than right. Interaural latency was increased at P1–P5 on the left. Otoacoustic emissions results were abnormal. Computerized sinusoidal harmonic acceleration readings and computerized pursuit tracking test results were normal, as were those from the saccade test. QEEG readings confirmed a significantly increased electrical CNS activity.

FDG-PET/CT findings revealed left-hemisphere and bitemporal hypometabolism, on the left more than on the right, and hypermetabolism in the primary auditory cortex on the right (see Fig. 2). The tinnitus type was diagnosed as a predominantly central type bilaterally, with a bilateral cochlear component and a subclinical component left.

Factors influencing the clinical course of the tinnitus included secondary endolymphatic hydrops on the left, noise exposure, stress, hypotension, anxiety, and seizures. Auditory hallucinations that occurred were reflective of CNS hyperactivity in primary and associative auditory areas.

**DISCUSSION**

General Concepts

In the evolving discipline of tinnitology, neuroscience reports of the interaction and linkage of pathophysiological processes of ischemia and inflammation with ND have found clinical translation and identification, via brain SPECT and FDG-PET/CT, that the medical significance in a selected cohort of tinnitus patients (n = 16/18) diagnosed as having a predominantly central type, severe, disabling SIT is a soft sign of CNS ND.

The medical significance of a symptom or disease process in a patient is defined as a clinical manifestation of abnormal function of a living cell, tissue, organ, or organ system [2]. The medical significance requires identification of the abnormal function’s clinical, physiological, and biochemical manifestations. The etiology of cerebrovascular disease and the pathophysiological process of ischemia have been clinically identified in the cases reported here. Inflammation is hypothesized to be linked to and to precede ischemia, leading to ND. Furthermore, for SIT patients’ disorders identified as ND, NDDI, or NDD-SDAT, inflammatory processes are hypothesized to underlie the alterations in CNS function identified via nuclear medicine imaging in this report. MRI brain techniques are planned to identify inflammatory changes in SIT patients with early sign of ND. Antiinflammatory therapies may be an option to influence the clinical course of the ND and improve attempts at SIT relief.

Alterations in rCBF and resultant perfusion asymmetries in multiple neural substrates before and after the Diamox stress test, observed via brain SPECT or FDG-PET/CT, reflect metabolic fluctuations in glucose, providing a basis for the differential clinical diagnostic criteria of ND, NDDI, and NDD-SDAT. The clinical application of neuroradiology and nuclear medicine imaging techniques to identify CNS inflammation in SIT patients is planned for the future. Nuclear medicine imaging has the availability of a normative database of brain metabolism for different neural substrates. Comparison of the established normative database for different neural substrates with abnormalities in SIT patients can identify metabolic and perfusion abnormalities reflecting specific CNS diseases (i.e., AD) [14–17].

Converging technologies of neuroradiology (brain, functional, and spectral MRI) and nuclear medicine (SPECT, FDG-PET/CT) provide methodologies to identify ischemia, inflammation, and ND. As our report states, ischemia was identified with brain MRI for structural alteration and was reported as “white-matter changes consistent with small-vessel disease and ischemia,” predominantly periventricular in frontal, temporoparietal, and, occasionally, basal ganglia areas.

**Leukoaraiosis** is a term that defines an abnormal appearance of the subcortical white matter of the brain on neuroimaging (i.e., bilateral patchy or diffuse areas of low attenuation on CT or hyperintense T2 MRI areas). Retrospective studies have demonstrated its association with stroke, and prospective studies have demonstrated a prognostic value related to the occurrence of stroke (ischemic and hemorrhagic) or the occurrence of vascular death. Leukoaraiosis is an ischemic disease and is associated with stroke but is not considered to fulfill the criteria of a risk factor for stroke [30].

**Derived Concepts**

**Neurovascular Dysfunction, Neurodegeneration, and SIT**

This report has established a link between neurovascular dysfunction and ND in SIT patients. Translation of the neurovascular hypothesis of ND for AD to SIT is a challenge to the sensorineural view of SIT, which focuses on psychophysical and psychoacoustical elements and underlying mechanisms of SIT. Specifically, CNS neurovascular dysfunction may, in a particular cohort of SIT patients, “trigger” and/or influence the clinical course of the SIT. The identification of cerebrovascular disease in 16 of 18 patients is significant and has implications for SIT diagnosis and treatment.
**ND, NDDI, and NDD-SDAT**

On the basis of current neuroimaging results, the processes of inflammation and ischemia and their localization in brain (either diffuse or localized or both) are considered significant for the diagnostic and treatment implications of SIT patients. ND patients are considered to demonstrate nonspecific patterns of ND in the brain not related to inflammation, ischemia, or a specific CNS diagnostic category (e.g., AD, frontotemporal degeneration [FTD]). The NDDI patients demonstrated primarily ND in the neural substrates of the anterior brain (i.e., frontal and temporal). Abnormal functions in patients with NDD-SDAT involved primarily the posterior neural substrates of brain (i.e., parietotemporal and frontal). In both NDDI and NDD-SDAT, the primary auditory cortex was involved in predominantly central-type tinnitus in SIT patients.

It is hypothesized that in SIT patients, the occurrence and localization of ischemia and inflammation is random in the CNS. Involvement predominantly of or arising in the neural substrates of the final common pathway (FCP) (i.e., medial temporal and frontal lobes, primary auditory cortex) can become clinically manifest with the symptom of SIT [18]. Involvement of neural substrates predominantly of the parietotemporal and frontal lobes and diagnostic of AD or basal ganglia diagnostic of Parkinson disease (PD) will not include the symptom of tinnitus. Secondary involvement of neural substrates of the FCP will become clinically manifest as SIT and will constitute an associated complaint of, for example, AD and PD. This is consistent with our clinical experience: a low incidence of occurrence of SIT in the AD and PD populations. In summary, localization of the ischemia or inflammation (or both) in the neural substrates of the FCP will determine clinically whether SIT is the primary complaint or a secondarily associated complaint with other diagnosed CNS disease (e.g., AD, PD). In AD and PD patients, the clinical manifestation of the SIT may be an extension of the primary pathophysiological process of a particular CNS disease, reflecting involvement of the FCP (e.g., AD, PD, brain tumor other than acoustic tumor). The occurrence of SIT in AD and PD patients may be a monitor for the localization and extension of the primary pathology, regardless of etiology.

Specifically to be considered in our SIT patients at this time is that the perfusion asymmetries in multiple neural substrates consistent with SDAT is not SDAT but rather a stage of early neuronal degeneration associated with ischemia in the CNS (i.e., NDDI), which may never progress to AD or FTD.

Early identification of NDDI and NDD-SDAT and long-term follow-up have significant diagnostic and treatment implications for both ND and SIT. Such studies are planned for the future.

**SPECT and PET Perfusion Asymmetries: What Are We Seeing?**

Brain SPECT and FDG-PET/CT reflect functional alterations in single and multiple neural substrates (see Figs. 1, 2). Neuroradiology (brain CT, MRI) reflects structural alterations in single and multiple ROI.

To be considered in this report is that neural substrates in brain reflect (1) multiple levels of activity, (2) different etiologies, (3) different symptoms, and (4) specific brain functions (e.g., of consciousness, perception, attention, affect, memory, or the aging process). Pathophysiological processes of ischemia and inflammation have been identified as being involved in CNS ND [31].

Age-related findings have been identified unexpectedly in younger patients. The incidence of occurrence of NDDI and NDD-SDAT and age distribution in the cases in this report suggests that neither is restricted to the geriatric age group. Ischemia continues to be identified by brain MRI, SPECT, and PET with the Diamox stress test across all age groups. Persistence or increase (or both) in hypoperfusion in brain ROI after the administration of the Diamox test with or without diaschisis is interpreted as ischemia reflecting cerebrovascular insufficiency. Diaschisis is an autoregulation system for cerebrovascular blood flow: For example, ipsilateral hypoperfusion in the medial temporal lobe system left after Diamox administration results in contralateral hypoperfusion in the cerebellum right. The action is a central servomechanism of the longitudinal sensory motor tracts (i.e., a modulator for long-tract activation). Specifically, reduced neuronal stimulation from a “stroke” patient (right ipsilateral) results in a reduced input for cerebrovascular flow in the contralateral left cerebellum. The patterns of neuronal activity in multiple brain ROI (i.e., temporoparietal and frontal) have been identified for SDAT and differentiated between SDAT I and II [14–17].

In 2007, patterns of activity (e.g., epilepsy) and brain function in specific ROI of the brain (e.g., memory, depression) and etiologies (e.g., AD) can be identified. However, future translation of advances in neuroscience, auditory science, and proteogenomics correlated with MRI spectroscopy, nuclear medicine molecular genetic imaging, and electrophysiology (e.g., QEEG) and with clinical longitudinal studies in SIT patients will clarify the significance of the perfusion asymmetries identified at this time in a selected cohort of patients of a predominantly central-type, severe, disabling SIT.

In this report, ND, NDDI, and NDD-SDAT have been identified, but not AD. The NDD-SDAT findings in SIT patients are different from those expressed clinically and via nuclear medicine imaging in classic AD patients. Long-term studies with nuclear medicine imaging will define parameters of differentiation of
(1) multiple levels of activity, (2) different etiologies, (3) different symptoms, and (4) specific brain functions (e.g., of consciousness, perception, attention, affect, memory, or the aging process).

The patterns of CNS perfusion asymmetries may reflect underlying pathophysiology and resultant cerebral dysfunctions. The etiology of cerebrovascular disease in both ND and NDD in this cohort of SIT patients and the relative lack of complaint in the literature of the symptom of tinnitus in SDAT patients is significant. This clinical disconnect is the basis for consideration that in SIT patients, early NDDI identification may provide a basis for identification and treatment of NDD-SDAT and tinnitus relief or identification of primary CNS ND (e.g., AD, FTD).

Hypertension, Leukoaraiosis, ND, and SIT
In our experience, correlation of the clinical course of tinnitus and SIT and hypertension has been observed and reported since 1979. Tinnitus was “found to be a ‘soft’ sign of cerebrovascular disease and secondary endolymphatic hydrops” [32].

Recent reports of the association between blood pressure, hypertension, and cerebral white-matter lesions provide support for these clinical observations. Specifically, increases and decreases in diastolic blood pressure were associated with more severe periventricular white-matter lesions. Increase in systolic blood pressure was associated with more severe periventricular and subcortical white-matter lesions [33]. Higher ambulatory blood pressure levels and a trend for smaller nocturnal declines in systolic and diastolic levels have been observed to be associated with greater leukoaraiosis [34]. Hypertensive patients with severe periventricular white-matter lucency are more likely to have impaired autoregulation of cerebral blood flow than are hypertensive patients [35].

In this report, a positive history of hypertension was obtained in 10 of 18 SIT patients. Brain MRI, prior to SPECT and FDG-PET/CT, was completed in 8 of the 18. The report was positive for periventricular and subcortical white-matter lesions in 3 of the 8. It is hypothesized that the periventricular and subcortical white-matter lesions are a pathological correlate of SIT in hypertensive tinnitus patients. The lesions influence the ascending-descending cochleovestibular system, with a resultant predominantly central-type tinnitus, or influence a preexisting predominantly cochlear-type tinnitus (or both). At the cortex, involvement of neural substrates of the FCP is highlighted by the medial temporal lobe result in SIT [18,36].

Brain MRI and Nuclear Medicine Imaging
Patient selection for brain SPECT and FDG-PET/CT was not predicated on completion of or positive results from a prior brain MRI. All SIT cases referred for SPECT and FDG-PET/CT had diagnosed SIT of more than 1 years’ duration that was resistant to treatment attempting tinnitus relief. The indication was to improve the SIT diagnosis by attempting to identify brain function activities in multiple ROI, to provide a rationale for an innovative RTT directed to the GABAA receptor, and to monitor efficacy of treatment attempting tinnitus relief [19].

All NDDI and NDD-SDAT patients were referred for neurological consultation to include brain MRI with gadolinium. Brain MRI with gadolinium is recommended for all SIT patients with a predominantly central-type tinnitus, particularly if it is a unilateral tinnitus located in the ear or head. Brain FDG-PET/CT is recommended for fusion of the data, to improve the accuracy of the anatomical location of the perfusion in the neural substrate involved. Brain SPECT and FDG-PET/CT are available and can also provide fusion capability.

CONCLUSIONS
ND as a pathological process in the CNS has been identified in a particular cohort of patients (n = 16/96; 16.8%) having a diagnosis of a predominantly central-type, severe, disabling subjective idiopathic tinnitus, supported by nuclear medicine imaging (i.e., brain SPECT and brain FDG-PET/CT) and evidence of early ischemic changes in multiple neural substrates reflecting early insufficiency of the anterior and posterior intracerebral circulation (n = 16/18; 88.9%). Age-related findings have been identified unexpectedly in younger patients.

A link between neurodegenerative CNS disease and cerebrovascular disease in a particular cohort of tinnitus patients is supported in this report by the diagnosis of cerebrovascular disease in 16 of 18 patients and positive history for hypertension in 10, of whom 3 were identified as having NDD-SDAT; 7 patients had diagnosed NDDI.

The medical significance of SIT, in a particular cohort of patients (n = 16/18; 88.9%), as a soft sign of neurodegenerative CNS disease is supported by clinical history, cochleovestibular testing, and objective metabolic brain SPECT and FDG-PET/CT.

Nuclear medicine imaging is recommended for patients who have a diagnosed predominantly central-type SIT, particularly when it is unilateral and located in the ear or head (or both), and in whom established protocols of instrumentation and medication attempting tinnitus relief have failed.

ND disease in SIT patients, based on brain SPECT and FDG-PET/CT, is differentiated between nonspecific ND, NDDI, and NDD-SDAT. In this report ND, NDDI, and NDD-SDAT have been identified, but not AD.
NDD-SDAT is considered to be a particular type of ND in the SIT population. Long-term studies will establish the significance of NDD-SDAT and other specific CNS neurodegenerative diseases.

The positive findings of NDDI and NDD-SDAT via nuclear medicine imaging in 16 of 18 SIT patients should alert professionals involved with such patients to consider including nuclear medicine imaging in the medical evaluation of their patients and to evaluate its clinical application, short- and long-term, for the diagnosis and treatment of SIT and ND.

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