Published in final edited form as:
Otol Neurotol. 2011 October ; 32(8): 1198–1204. doi:10.1097/MAO.0b013e31822e9665.

TEMPORAL BONE FINDINGS IN A CASE OF SUSAC'S SYNDROME

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Abstract

Objective—To describe the histopathologic findings in the temporal bones of a patient with Susac's syndrome (SS).

Background—The key clinical features of SS consist of symptoms of encephalopathy, visual defects due to occlusion of branches of the retinal artery, and sensorineural hearing loss. The otopathology in SS has not been described.

Material and Methods—A 51-year old woman was hospitalized with severe headache, rapidly progressive encephalopathy, and bilateral low frequency sensorineural hearing loss. MRI showed lesions of the corpus callosum. Fluorescein angiography of the eyes showed focal areas of irregular retinal artery caliber and leakage from small vessels. SS was diagnosed. She died of a pulmonary embolus one month after onset of symptoms. Both temporal bones were prepared in celloidin and examined by light microscopy.

Results—Findings were nearly identical in both temporal bones. The apical halves of both cochleae showed widespread atrophy of structures of the cochlear duct (inner and outer hair cells, tectorial membranes, striae vasculares, spiral ligaments and spiral limbi). The apical parts of both cochleae also showed apparent occlusion of capillaries within the stria vascularis and related areas of the cochlear duct. Cochlear neurons were present in normal numbers. There was no endolymphatic hydrops. The vestibular sense organs were normal for age.

Conclusions—This first reported otopathologic case of SS with hearing loss showed atrophy and degeneration involving the apical halves of the cochlear duct without inflammation or infection. The findings were consistent with capillary occlusion as being responsible for the atrophy.

Keywords

Susac's syndrome; sensorineural hearing loss; temporal bone histopathology; otopathology

INTRODUCTION

It is rare to have an opportunity to examine an inner ear recently ravaged by (presumed) immune mediated disease. This report describes the histopathologic findings in the temporal

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The authors do not have any conflicts of interest to disclose.

bones of a patient who succumbed to a rapidly progressive systemic vasculopathy that included neurological, auditory and visual deficits. The patient was diagnosed with Susac's syndrome.

First described in the literature by Dr. John Susac in 1979 (1), Susac's syndrome (SS) is an endotheliopathy, possibly immune-mediated, affecting pre-capillary arterioles. The resulting tissue infarction manifests as rapidly progressive encephalopathy, blindness and hearing loss (2). Women are predominantly affected, typically between 20 and 40 years of age (3,4). The rapid onset of dementia is often accompanied by severe headaches. Microinfarcts of the corpus callosum on sagittal T2 FLAIR and T1 MRI sequences are pathognomonic for SS. Additional MRI findings may include leptomeningeal enhancement and microinfarcts of other white and grey matter regions, including the internal capsule. Manifestations in the eye include branch retinal artery occlusion which is associated with complaints of photopsia, "black spots" and scintillating scotoma. Thorough retinal examination including fluorescein angiography reveals findings consistent with endothelial disruption, including multifocal fluorescence along retinal branch arteries and "Gass" plaques, which reflect extraluminal deposition of atheromatous material. Visual symptoms may occur at any time relative to CNS effects of the disease.

Sudden or rapidly progressive sensorineural hearing loss occurring in both ears synchronously or metachronously is the third protean manifestation of SS, although it may be difficult to detect in the presence of advancing dementia. The presence of nystagmus with vertigo is an indication of inner ear involvement. Hearing loss is often greatest at lower frequencies, progressing to involve higher tones with advancing disease. In less aggressive cases, hearing loss may remain mild to moderate with fluctuation and accompanying tinnitus. The concurrent onset of CNS, visual and audiovestibular manifestations of SS are rare. Visual symptoms are the most likely to first appear in isolation, or accompanied by hearing loss or encephalopathy. Subsequent symptoms may follow weeks to months later.

Early, aggressive and sustained immunosuppressive therapy has been advocated with the possibility of halting progression of disease. High-dose prednisone, cyclophosphamide, intravenous immunoglobulin (IVIG), mycophenolate mofetil and plasmapheresis have all had variable success. The course of encephalopathy lasts 1 to 2 years and may remain quiescent with minimal disability if mild and responsive to immunosuppressant therapy (3). More severe and prolonged disease, particularly with delayed therapy is more likely to result in severe irreversible damage including dementia, visual loss and deafness (5). Cochlear implantation has been successful in restoring hearing for profoundly deafened individuals (6).

CLINICAL HISTORY

A 51-year old Caucasian woman with a history of hypertension, Grave's disease, uterine fibroids and migraine headaches presented with a severe headache that was thought to be a migraine. The following morning, she was very confused, unable to walk or stand and did not recognize her husband. She was hospitalized with a diagnosis of encephalopathy. MRI of the brain showed several small diffusion-positive lesions in the white matter, consistent with microvascular disease. Lumbar puncture revealed elevated cerebrospinal protein of 193, normal glucose of 53 and rare leukocytes. Cryptococcal antigen was negative as was PCR for cytomegalovirus, Epstein Barr virus, herpes simplex virus, John Cunningham virus, and West Nile virus.

She complained of difficulty hearing a week later. An audiogram performed 10 days after initial presentation with headaches showed a bilateral severe sensorineural hearing loss with

speech reception thresholds (SRT) of 50 dB (right) and 55 dB (left), along with speech discrimination scores of 40% on the right and 28% on the left. The pure tone thresholds had a gently up-sloping pattern, consistent with a predominant low-frequency deficit. Immittance testing revealed normal middle ear pressure and compliance in both ears. Ipsilateral acoustic threshold at 1000 Hz was absent in both ears. A second and final audiogram performed 8 days later (2 weeks pre-mortem) revealed an SRT of 40 dB on the right and 55 dB on the left (Figure 1). Speech discrimination was 60% on the right and 20% on the left. The pure tone thresholds again showed an upsloping pattern. The patient had no vestibular complaints.

A second MRI on the 11th day after presentation revealed microinfarcts of the central corpus callosum. A diagnosis of Susac's syndrome was made based on these MRI findings and the presence of hearing loss. Ophthalmic examination five days later showed visual acuity of 20/50 in the right eye and 20/20 in the left eye. Dilated fundus examination showed cotton wool spots in the periphery as well as retinal and optic nerve head telangiectasis in the right fundus. Fluorescein angiography of the right eye showed focal areas of irregular retinal artery caliber and leakage from small vessels.

She was treated with high dose steroids and intravenous immune globulin for 5 consecutive days. Despite adding cyclophosphamide to her treatment, she appeared to develop worsening encephalopathy. Repeat MRI on the 27th day after presentation showed resolution of some lesions but evidence of new microinfarcts. She developed cardiac arrest on the 31st day, was resuscitated and found to have a saddle pulmonary embolus on chest CT scan. Despite immediate treatment with tissue plasminogen activator, mechanical thrombectomy and vasopressors, she succumbed to the pulmonary embolus.

TEMPORAL BONE REMOVAL AND PREPARATION

Both middle ears were injected with formalin 1 hour after death. An autopsy was performed 15 hours postmortem at which time both temporal bones were removed after cranial nerves VII and VIII were sectioned at the porus acousticus. Brain autopsy showed multiple microinfarcts of various ages within the gray and white matter of the cerebrum, as well as multiple microinfarcts within the brain stem and spinal cord. A representative section from the frontal cortex showed an acute infarct with axonal ballooning and vacuolization. Further, the arterial vessels showed marked thickening. The neuropathology was similar to what has been described in brain biopsies in SS (1–3).

A detailed description of the histopathologic findings in her eyes is reported by McLeod et al (7). In summary, there were vaso-occlusive changes in the retinal periphery, resulting in small areas of capillary dropout. Cross sections demonstrated serous-filled spaces between the retinal blood vessels and the internal limiting membrane. Lumens adjacent to these spaces appeared compressed and sometimes closed, but without thrombosis. Decreased ADPase activity in some peripheral blood vessels suggested endothelial cell dysfunction and vaso-occlusion. Transmission electron microscopy demonstrated thickened and amorphous vascular basal lamina and open endothelial cell junctions in some retinal blood vessels.

The temporal bones were processed for light microscopy using the standard method consisting of fixation in formalin, decalcification using EDTA, embedding in celloidin, serial sectioning in the horizontal plane at a section thickness of 20 microns, and staining of every tenth section using hematoxylin and eosin (8). Temporal bone sections were examined using the light microscope. Graphic reconstruction of the cochlea was performed according to the method described by Schuknecht to determine loss of various neurosensory elements such as hair cells, stria vascularis and cochlear neuronal cells (8). Cochlear neuronal cell

counts were compared with normative age-matched data reported by Schuknecht (8). The Institutional Review Board of Massachusetts Eye and Ear Infirmary approved the study.

RESULTS

Both temporal bones were nearly identical (except as noted) and are described together. The external auditory canal, tympanic membrane, ossicles, middle ear and mastoid air spaces, and the otic capsule appeared normal. Peritubal air cells were present, while the petrous apices were not pneumatized. Preservation of cytologic elements within the inner ear was excellent.

The apical halves of both cochleae (16–32 mm regions, i.e., the upper basal, middle and apical turns) showed severe atrophy and degeneration of inner and outer hair cells, tectorial membranes and the striae vasculares, as shown in cytocohleograms in Figure 1 and photomicrographs in Figure 2. The organs of Corti were completely missing or represented by a mound of supporting cells with missing hair cells. The tectorial membranes showed marked pathologic change, characterized by cellular encapsulation and detachment from the spiral limbus. Tectorial membrane pathology was more extensive in the left ear, extending further towards the base than in the right ear. The lateral cochlear walls showed near-total atrophy of the striae vasculares and severe degeneration of fibrocytes of the spiral ligament. The fibrocytes of the spiral ligament appeared to have been replaced by connective tissue cells. The spiral limbi showed patchy atrophy.

Within the basal halves of both cochleae (0–16 mm regions, i.e., the lower basal turn), the hair cells, supporting cells, tectorial membranes, spiral limbi, and spiral ligaments were generally present and appeared normal for age. The striae vasculares were generally intact except for patchy atrophy in the 3–7 mm region on the right and 0–3 mm region on the left.

Cochlear neurons were present in numbers that were normal-for-age (total count, 23,796 on right, 24,255 on left). The central axons of the spiral ganglion cells were also present. Whereas dendrites leading up to the organ of Corti were well preserved in the distal part of the osseous spiral lamina of the basal turn, they were atrophied in the middle and apical turns.

Reissner’s membrane was in normal position in both cochleae except for apical (non-pathologic) hydrops. The scalae media of the middle and apical turns showed scattered cellular debris which appeared to be the result of sloughing of cells that were degenerating from within the striae and organs of Corti. The fluid spaces did not show any hemorrhage, or deposition of fibrous tissue or new bone.

The vasculature of the cochleae was examined. Branches of the main cochlear artery within the modiolus were patent. Similarly, the external and internal radiating arterioles were also patent. However, some capillaries of the stria vascularis showed apparent occlusion of the lumen by an acellular substance or by thickening of the vessel wall. The number of capillaries appeared to be less than normal in the lateral cochlear wall of the middle and apical turns (in areas corresponding to the severe atrophic changes). The collecting venules and the posterior spiral vein appeared unremarkable.

The vestibular sense organs, including the saccules, utricles and all three semicircular canal cristae showed good populations of hair cells, supporting cells, and innervating dendrites (probably normal for age) in both ears, except for the saccular macula in the left ear which showed a diminution of type I hair cells. The membranous vestibular labyrinths were normal, without collapse or hydrops. The lumen of the saccule in both ears contained free-floating cells arranged in strands and folded strips. The origin of these cells was obscure;

they could possibly be cells that line the saccular duct and which became detached. Blood vessels supplying the vestibular labyrinths appeared normal. There was a good population of cells within Scarpa's ganglion in both ears, probably normal for age. The facial nerves and canals were normal.

The leptomeninges within both internal auditory canals showed a large number of psammoma bodies, more than what is seen on average in a normal ear. In addition, many small arterioles within the leptomeninges showed a peculiar thickening of the vessel wall to the point of occlusion. In some instances, it appeared that there was proliferation of cells within or around the wall causing the occlusion, while in other instances there was a dense basophilic material occluding the vessel lumen. There was a general absence of inflammatory cells within the vessel walls.

DISCUSSION

This is the first description of temporal bone findings in a patient with Susac's syndrome. The histopathologic abnormalities consisted primarily of atrophy and degeneration involving the apical half of the cochlear duct (inner and outer hair cells, tectorial membrane, stria vascularis, spiral ligament and spiral limbus) with preservation of the cochlear neurons. There was no evidence of inflammation or infection. These changes appeared to be rather unique in their location and distribution, unlike the otopathology in other disorders in the human.

The etiology of SS is unknown. Studies on the brain and retina have indicated that the syndrome is a microangiopathy that affects capillaries and precapillary arterioles less than 100 micrometers in diameter (2). An endotheliopathy has been hypothesized, possibly immune-mediated, with resulting ischemic injury to the tissues. Although it is difficult to evaluate the cochlear vasculature in temporal bone sections, there was a suggestion of occlusion of capillaries within the stria and other areas within the apical halves of both cochleae. There were also other histopathologic abnormalities that were consistent with a vascular insult. For example, the observed loss of dendrites within the osseous spiral lamina cannot be explained on the basis of retrograde neural degeneration because of the short time course of the illness, but can be accounted by tissue infarction. The loss of fibrocytes within the spiral ligament was another finding compatible with a vascular lesion. Published studies have shown that vascular insults to the ear often result in deposition of fibrous tissue and new bone (9), a finding not seen in the present case. It is possible that in this particular patient, there was insufficient time for formation of connective tissue and new bone.

It is notable that the degeneration within the affected areas of the cochleae was not uniform. There were islands of healthy tissue interspersed with large areas of atrophy and degeneration. In cases of documented thromboembolic occlusion of the cochlear blood supply and subsequent ischemic necrosis, one observes uniform atrophy and degeneration (9). Therefore, the changes in the present case suggest that the cochlear damage may have occurred as a result of multifocal occlusions at the capillary level, rather than an infarction of the entire apical half of the cochlea. In addition to ischemia, it is possible that additional damage may have occurred because of leakage of fluid and other materials from the affected capillaries, causing disruption of the delicate ionic homeostasis and cytokine balance of the cochlear fluids (10).

The observed otopathology of hair cell loss in the apical half of the cochlea can explain the low frequency hearing loss seen on pure tone audiometry during life. It is pertinent to note the absence of endolymphatic hydrops in her temporal bones. In other words, a low tone sensorineural hearing loss does not automatically imply a hydropic etiology. The

histopathology also demonstrates that total loss of the organ of Corti in the apical region will result in a threshold shift for the lower frequencies but not a profound loss, provided a functioning organ of Corti is present in the remainder of the cochlea. The thresholds at low frequencies can be explained on the basis of longitudinal spread of the field of excitation of the basilar membrane toward the more basal functioning areas of the cochlea (11,12). If this is indeed the case, the word recognition results would be expected to be reduced by the amount predicted by removing the low frequency contributions. Such an analysis is shown in Figure 3. Beginning with the patient's left ear (upper panel), the thresholds were removed from the audiogram apical to the boundary of absence of the tectorial membrane. These regions are also removed from the word recognition prediction, seen as the rising line in the speech intelligibility box on the left. The predicted word recognition score, with the low frequency regions removed, matched the actual word recognition score of 20% ($p < 0.05$), and supports a model where the apex was not contributory (13,14). The analysis also supports a purely peripheral mechanism for the reduced word recognition scores. The patient's right ear (lower panel) was analyzed in a similar fashion. Here, the boundary used was that of absence of the inner hair cells. The predicted word score (88%) by removing the apical areas was higher than that actually seen (60%). A number of mechanisms may have led to the lower score, including problems in the central auditory system, or damage in the periphery not seen by light microscopy.

It is unclear why the middle and apical cochlear turns were affected while the base of the cochleae were spared. Such tissue specificity may be a manifestation of the underlying disease process, such as the tendency for lesions to affect the corpus callosum in the brain, for example. Alternatively, it may be a reflection of the microanatomy of the cochlear blood supply. Experimental work has shown that microembolization of cochlear vessels by injection of particulate matter can result in degenerative changes located predominantly in the apical regions of the cochleae (15–17). The special vulnerability of the apical region to vascular lesions may be due to the end-arteriolar blood supply of the apex by the main cochlear artery in contra-distinction to the anastomotic blood supply in the base of the cochlea provided by the cochlear ramus (18). It is to be noted there are case reports of SS patients who have suffered a profound hearing loss for all frequencies. Examination of temporal bones from such individuals in the future will help to clarify the nature of the pathology affecting the base.

Acknowledgments

We thank John O. Susac MD, Robert M. Rennebohm MD and Gerard A. Lutty PhD for guidance in interpretation of the histopathology. We also thank Jon Pack for the photomicrographs. This work was supported by NIH grant U24 DC011943.

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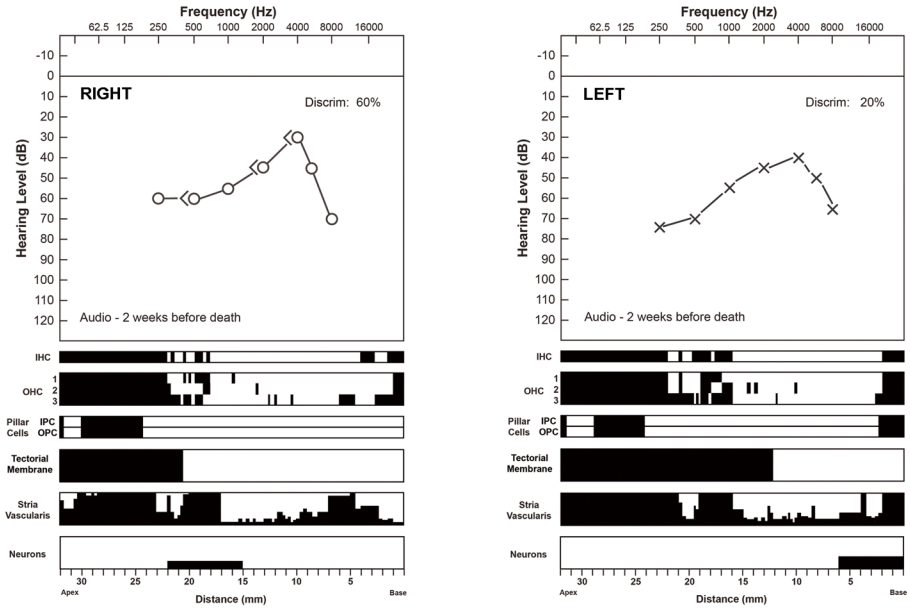

FIG. 1. Audio-cytocochleograms of the right and left ears

The audiogram was done 2 weeks before death and showed a bilateral sensorineural hearing loss with reduced speech discrimination as shown. Graphic reconstruction of the cochlear was performed in each ear according to the method described by Schuknecht (Merchant, 2010). Missing or abnormal elements are shown in black. Vertical axes of cytocochleogram boxes for the stria and neurons show percentage of loss. Neuronal loss was compared with age-matched controls. Both ears showed severe atrophy and degeneration of outer and inner hair cells, tectorial membrane, and stria vascularis in the apical halves of the cochleae. The cochlear neurons were unaffected. IHC, inner hair cell; OHC, outer hair cell; IPC, inner pillar cells; OPC, outer pillar cells.

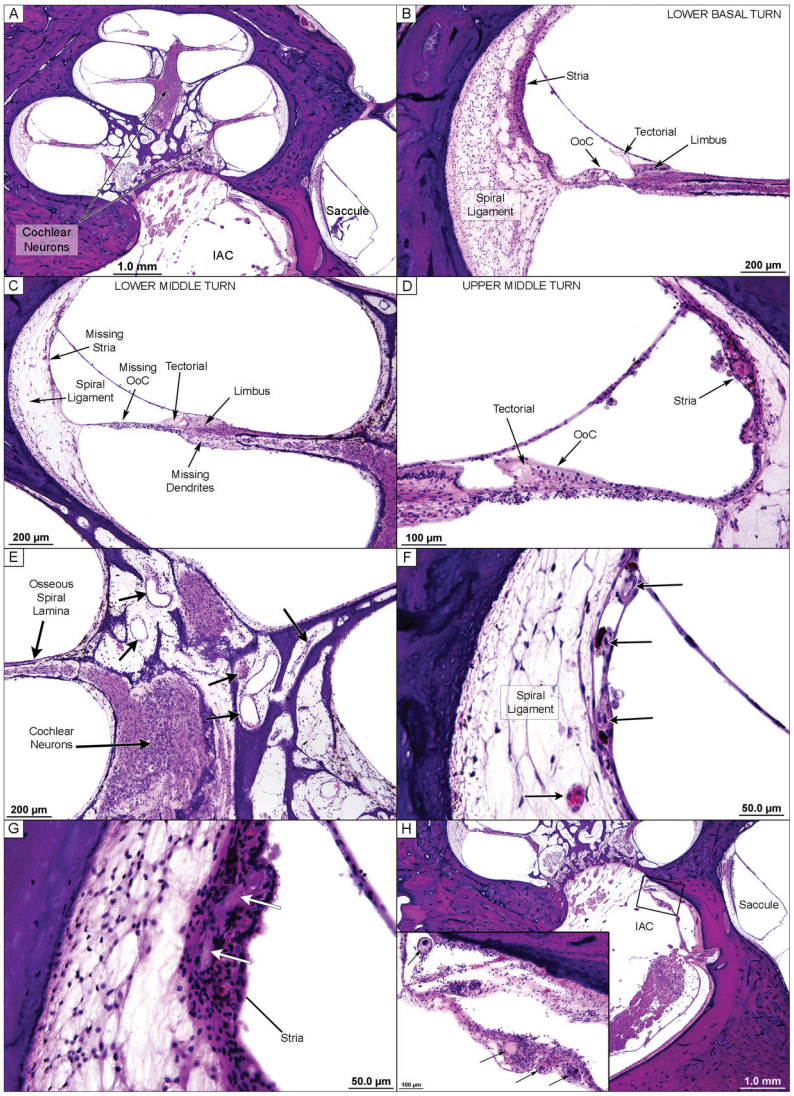

FIG. 2. Otopathologic findings in the right ear

A, Low power view of the midmodiolar section of the cochlea. Cochlear neurons, Reissner's membrane, and fluid spaces seem unremarkable. There is no endolymphatic hydrops. Note cellular debris within the saccule. IAC, internal auditory canal. *B*, Lower basal turn showing the healthy-appearing organ of Corti (OoC), tectorial membrane, spiral limbus, stria vascularis, and spiral ligament. *C*, Lower middle turn showing widespread atrophy and degeneration. The OoC was missing. The tectorial membrane was retracted and partly covered by cells. The spiral limbus showed patchy atrophy, and dendrites were missing within the osseous spiral lamina. The stria vascularis was completely atrophic. There was severe loss of fibrocytes within the spiral ligament. *D*, Upper middle turn showing widespread abnormalities, similar to C. The OoC was represented by a mound of cells. The tectorial membrane was detached from the limbus and encapsulated by cells. The stria was severely atrophic. *E*, Distal modiolus showing intact cochlear neurons and several branches of the main cochlear artery (*black arrows*). These blood vessels seemed unremarkable. *F*, Lateral cochlear wall of the middle turn showing near-total atrophy of the stria vascularis. *Arrows* pointing to the left depict 3 capillaries within the stria, which seemed to be partly occluded. *Arrow* pointing to the right shows a capillary within the spiral ligament that

seemed more normal, containing red blood cells. *G*, Middle turn showing partial atrophy of the stria vascularis and an occluded strial capillary (*white arrows*). *H*, IAC. Inset shows a higher power view of the boxed area. *Black arrows* point to 4 arterioles within the leptomeninges showing occlusion of their lumen.

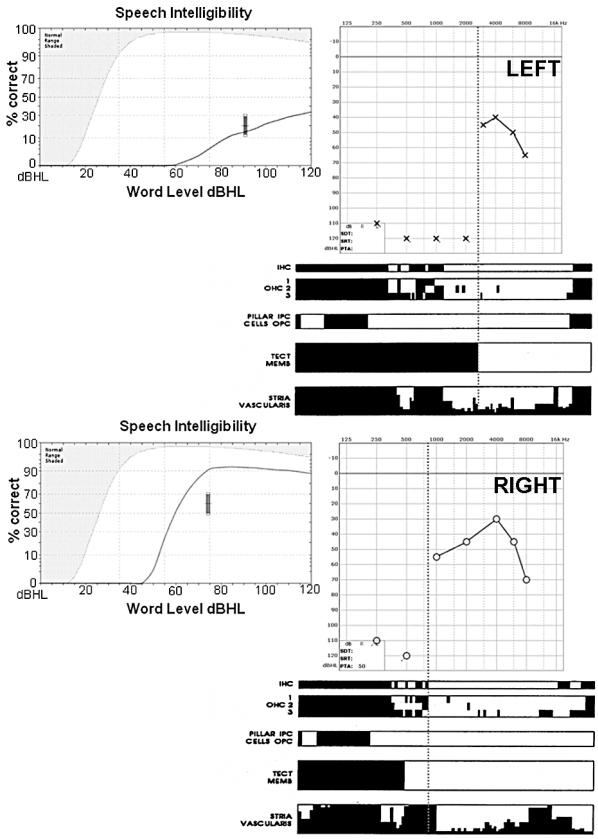

FIG. 3. Word recognition analysis of contributing regions

Standard pure tone audiograms are seen on the right, with speech intelligibility boxes for each ear on the left. The horizontal axis of these boxes is word level (dB HL), and the vertical axis is percent correct (standard monosyllable tests). The patient's score is the central tic in the rectangular data symbol (score and level), with the rectangle enclosing the 95% confidence interval. The continuous curves in each box are scores across level predicted by the Speech Intelligibility Index. Low frequencies were removed from this calculation by removing these thresholds from the audiograms. The result shows that the scores may be predicted (particularly on the left) on the basis of a lack of contribution from the apical regions of these cochleae. Also see text.