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Clinical Reasoning: A 72-Year-Old Woman with Rapidly Progressive Bilateral Hearing Loss

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Title: Clinical Reasoning: A 72-Year-Old Woman with Rapidly Progressive Bilateral Hearing Loss**Abstract:**

A 72-year-old woman presented with rapidly progressive hearing loss and neuropsychiatric symptoms without other focal neurological symptoms. Progressive sequential sensorineural hearing loss (SNHL) was demonstrated on serial audiology. A diagnostic approach to SNHL is reviewed. Lumbar puncture revealed elevated protein, low glucose, and pleocytosis with poorly differentiated cells, and a differential diagnosis is discussed. MRI brain revealed gadolinium enhancement within the internal auditory canals bilaterally as well as the left cochlea. A malignancy workup revealed right axillary lymphadenopathy. Biopsy revealed poorly differentiated breast adenocarcinoma, with identical cells to those in the cerebrospinal fluid. The patient was treated with intrathecal methotrexate with no effect on the patient's hearing. In this case, rapidly progressive SNHL was the presenting feature of widely metastatic breast adenocarcinoma with leptomeningeal carcinomatosis, highlighting the need to search for a central cause for this presentation.

Section 1:

A 72-year-old woman presented to the hospital with 5 months of rapidly progressive hearing loss, confusion, and worsening anxiety. Hearing loss, without tinnitus or vertigo, began acutely in the left ear after returning from an overseas trip then progressed to involve her right ear within one month. The patient was seen by an otolaryngologist who confirmed sensorineural hearing loss (SNHL) and she received a course of oral steroids without benefit. She had a history of hypertension and atypical lobular hyperplasia (without dysplasia) of the breast resected 12 years prior with clear margins.

On examination, vital signs were normal. She scored 20/25 on a modified Montreal cognitive assessment (profound hearing loss), with the predominant impairment being delayed recall. She was also noted to be anxious and perseverative.

Serial audiograms demonstrated progressive SNHL culminating in a profound deficit in the left ear and moderate-to-severe deficit in the right ear. Extraocular movements were normal, without nystagmus, and gait was wide-based without truncal or appendicular ataxia.

The remainder of the physical examination was non-contributory.

Question:

What are potential localizations for SNHL? Describe a diagnostic approach.

Section 2:

SNHL occurs from lesions proximal to the oval window of the cochlea. Localizations include the cochlea, cochlear nerve, cerebellopontine angle, or brainstem auditory nuclei. Proximally, ascending auditory fibers decussate extensively, leading to binaural representation. Brainstem or cortical lesions, therefore, rarely present with SNHL, with some exceptions. Lesions of the inferior colliculus or midbrain may present with bilateral deafness due to the compact auditory pathways within the midbrain¹.

Figure 1 shows an approach to the differential diagnosis of SNHL.

Four months prior to her current presentation, the patient developed a spell of situational anxiety followed by brief unresponsiveness and transient confusion. EEG at that time revealed left frontal polyspike and spike discharges over the left frontal region and she was started on levetiracetam, then cross-tapered with lamotrigine given worsening anxiety.

Question:

What is your differential diagnosis at this time?

What investigations would you order?

Section 3:

Given the patient's subacute bilateral SNHL, episode of transient unresponsiveness with epileptiform discharges on EEG, and neuropsychiatric manifestations, main considerations included infectious, toxic/metabolic, immune-mediated, neoplastic, or paraneoplastic etiologies. Infection was less likely with no fever, headache or meningismus, and subacute time course. The patient had no known exposure to potentially ototoxic substances and no risk factors for thiamine deficiency, which may present with encephalopathy, wide-based gait, and hearing loss. Hearing loss in itself may further exacerbate any encephalopathy state. Immune-mediated causes such as systemic lupus erythematosus, rheumatoid arthritis, Behcet's disease, and sarcoidosis may present with hearing loss, neuropsychiatric manifestations, or seizures. Susac syndrome would be an important consideration with SNHL and encephalopathy however does not typically occur in her age group. Bilateral cerebellopontine angle tumors could present with SNHL, but are typically associated with vestibular symptoms and other cranial nerve (VII, V, VI) involvement. Leptomeningeal carcinomatosis can also present with variable cranial nerve dysfunction and encephalopathy. Paraneoplastic cochleovestibulopathy is a rare cause of rapidly progressive SNHL with or without encephalomyelitis^{2,3}.

The patient was admitted to hospital for expedited workup. Bloodwork including a complete blood count, renal and liver function testing, and a rheumatological panel were unremarkable (**eTable 1**). Repeat EEG contained no further epileptiform discharges. MRI brain with gadolinium reported no abnormal susceptibility artifact or parenchymal or leptomeningeal enhancement. Upon re-review of the MRI, bilateral internal auditory canal enhancement and left cochlear enhancement was present (**Figure 2**). Lumbar puncture revealed glucose of 37.8 mg/dL with normal serum glucose, and white cell count of $28 \times 10^6/L$, with 83% of the cells reported as unidentifiable on hematopathology review. Protein was elevated at 92 g/dL, with an elevated IgG index.

Question:

What is the differential diagnosis for this CSF profile?

What is the most likely diagnosis and what further investigations would you like to order?

Section 4:

Hypoglycorrhachia can result from infectious and noninfectious causes. In one cohort of 87 patients with CSF glucose $<40 \text{ mg/dL}$, the most common causes were bacterial (including tuberculous), fungal, and less commonly viral meningitis, neurosyphilis, stroke, and malignancy⁴. Elevated IgG index is a nonspecific marker of intrathecal synthesis of immunoglobulins that is typically seen in inflammatory

disorders such as multiple sclerosis or sarcoidosis, but may also be present in CNS infections and leptomeningeal carcinomatosis.

The most likely diagnosis at this time was thought to be neoplastic infiltration or paraneoplastic SNHL. The patient was empirically treated with a 5-day course of IVIG without improvement. Paraneoplastic antibody panel returned positive for anti-Zic4 antibodies in the serum and CSF. Cytology further identified the abnormal cells as undifferentiated carcinoma. Flow cytometry was negative for lymphoma. MRI of the spine was negative for leptomeningeal deposits or enhancement. CT of the chest, abdomen, and pelvis revealed right axillary lymphadenopathy, initially reported to be related to recent COVID-19 vaccination. The patient underwent a lymph node biopsy which was ultimately positive for metastatic triple-negative breast adenocarcinoma. Mammography revealed a highly suspicious lesion (BI-RADS 5) in the left breast. Once the cancer diagnosis was confirmed, she began treatment with intrathecal methotrexate with moderate improvement in anxiety but no effect on hearing loss.

Discussion:

Rapidly progressive hearing loss is SNHL progressing slower than sudden deafness but faster than presbycusis, typically over days to several months. In a retrospective series, 6 of 12 patients had rapidly progressive hearing loss attributable to an intracranial lesion or systemic vasculitis⁵. Reported etiologies include viral or fungal meningitis, superficial siderosis, internal auditory metastasis, leptomeningeal metastasis, or paraneoplastic cochleovestibulopathy^{2, 5, 6, 7}. Therefore, it is essential for physicians to recognize and investigate this symptom thoroughly.

Leptomeningeal carcinomatosis (LC) is an increasingly common complication of solid organ and hematological malignancies in part due to longer patient survival. There are several mechanisms by which cancer cells enter the subarachnoid space, including hematogenous spread, direct extension from parenchymal lesions, venous spread from adjacent bony metastasis, or perineural spread⁶. It is commonly seen with lung or breast cancer⁶, but has been reported with other solid tumors^{8,9}, melanoma, and less commonly, hematological malignancies¹⁰.

Diagnosis is challenging as the clinical presentation is highly variable due to deposition of tumor cells throughout the neuraxis. More than 50% of patients with LC have cranial nerve symptoms and signs¹⁰, with one paper reporting hearing loss as a presenting symptom in approximately 4% of patients¹¹. New onset psychiatric disorders have rarely been described in LC¹². LC should be on the differential diagnosis for patients presenting with multifocal, progressive, or sequential neurological deficits. The gold standard remains detection of malignant cells in the CSF, which is highly specific but has around 60% sensitivity. Repeat CSF sampling may improve sensitivity to approximately 90%¹². Other features include elevated opening pressure and protein. Around 30% of patients have hypoglycorrhachia⁶. In cases with negative cytology, MRI with contrast is the imaging modality of choice, but has a false negative rate of up to 30% in the absence of bulky disease⁶. The entire neuraxis must be imaged to identify abnormal meningeal or cranial nerve enhancement, even in the absence of clinically obvious cranial nerve involvement, as demonstrated in our case showing facial nerve enhancement without clinical evidence of facial weakness, likely due to blood-brain barrier disruption from tumor cell microdeposits. In addition, nodular enhancement may be present, usually in the cauda equina, basal cisterns, cerebellar folia, and cerebral sulci.

Leptomeningeal metastasis reflects a poor prognosis, with median survival of 4 weeks to 4 months¹². Therapy consists of intrathecal and systemic chemotherapy. Typical agents are methotrexate, cytarabine, and thiopeta. BRAF inhibitors such as bevacizumab are also used in breast cancer and melanoma with LC¹². Novel therapeutic regimens with immune checkpoint inhibitors and intrathecal tumor-infiltrating lymphocyte therapy are under investigation as potential treatment targets for LC¹³. Radiation is typically reserved for relief from focal or nodular symptomatic lesions.

Paraneoplastic cochleovestibulopathy is a rare, recently characterized manifestation presenting with rapidly progressive hearing loss with or without vestibular dysfunction, refractory to high dose oral or

intratympanic steroids³. In a recent review by Hammami et al.², SNHL was the initial presenting feature in 15 of 26 patients and preceded the diagnosis of cancer by a median of 5 months. SNHL was bilateral, asymmetrically progressive, and occurred with or without tinnitus, vestibular, or cerebellar symptoms². It is associated with antibodies against KLHL11 (+/- coexisting LUZP4), ANNA1, and amphiphysin. In our patient, antibodies against Zic4 were detected. The ZIC family of genes is involved in cerebellar, and in animal models, inner ear development^{14,15}. Presence of Zic4 antibody in the CSF may represent an epiphenomenon from the immune response towards tumor cell deposits¹⁵. Varying combinations of IVIG, corticosteroids, and immunosuppression have been used but none have been effective for the treatment of paraneoplastic cochleovestibulopathy. Treatment of underlying malignancy remains paramount.

In this case, rapidly progressive SNHL was the presenting feature of widely metastatic breast adenocarcinoma with leptomeningeal carcinomatosis, highlighting the need to search for a central cause for this presentation.

Figures - Legends:

Figure 1: Differential diagnosis of SNHL

Figure 2: Magnetic resonance imaging, T1 post-gadolinium axial (A), sagittal (B) and coronal (C) views, demonstrating abnormal enhancement of both facial and vestibulocochlear nerves within the internal auditory canals bilaterally (A: small arrows), extending to the cochlear nerves with abnormal enhancement of the entire left cochlea (B,C: large arrows).

Table 1: Laboratory results

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