Hearing loss as the initial presentation of Creutzfeldt-Jakob disease

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Abstract
Creutzfeldt-Jakob disease is a rare type of spongiform encephalopathy. Affected patients present with constitutional symptoms, which progress to severe mental deterioration and movement disorders. Dizziness is the most common early otologic symptom. Few reports in the literature describe patients with Creutzfeldt-Jakob disease who present with sudden-onset hearing loss as their primary symptom for seeking treatment. This paper discusses one such patient and reviews the clinical presentation, treatment options, and relevant literature.

Introduction
Prion-associated encephalopathies are characterized by requiring a protein component (prion) for communicability. One such encephalopathy, Creutzfeldt-Jakob disease (CJD), has been recognized for more than a century. However, few reports in the literature describe patients who first present with otolaryngologic symptoms and signs. This prodromal complex may include symptoms such as dizziness or hearing loss in addition to the more commonly associated signs of progressive dementia, visual field defects, and ataxia.

With this vague clinical picture, CJD can cause considerable diagnostic perplexity. In this article, we describe one patient with CJD who first presented with otolaryngologic symptoms and review the literature on this subject.

Case report
A 74-year-old woman presented to the otolaryngology clinic with a history of sudden-onset, right-sided hearing loss of 2 weeks’ duration. Her history also included symptoms of sudden memory loss, ataxia, and diplopia. A poor historian, the patient was accompanied by a brother and sister who provided the history. Prior to her current illness, she lived independently. The patient’s siblings were unaware of any history of vertigo or prior occurrence of similar symptoms. The patient developed progressive imbalance and had fallen three times in the 2 weeks prior to presentation. Her family also noted that she had scanning speech. The presumptive diagnosis after evaluation in a local urgent care department was Ménière’s disease. The patient’s past medical history was unremarkable except for abdominal lysis of adhesions and cataract surgery.

On physical examination, the patient exhibited poor eye tracking, shuffling gait, and truncal ataxia with intention tremor. Audiometric testing (figure 1) revealed moderate-to-severe bilateral sensorineural hearing loss with poorer word recognition than would be predicted by the degree of hearing loss.

The patient was admitted for further evaluation with a possible diagnosis of cerebrovascular accident. Several blood tests (erythrocyte sedimentation rate, angiotensin-converting enzyme I levels, Lyme titer, folate, vitamin B₁₂, ceruloplasmin, CSF analysis, thyroid panel, CHEM-7, and CBC) were ordered, all of which were negative or within normal limits. Magnetic resonance imaging of the brain (figure 2) indicated some periventricular white matter change; magnetic resonance angiography and carotid ultrasound were normal. In the first 2 weeks after her admission, the patient began to develop involuntary jerking of the upper extremities and increased tremor and startle myoclonus. Her symptoms continued to progress, and she developed aphasia and apraxia. An auditory brainstem response test was attempted, but waveforms were not reproducible. Electroencephalography was nonspecific, with background slowing and occasional triphasic waves (figure 3), indicating a global encephalopathy with lack of periodicity. A right frontal brain biopsy confirmed CJD by Western blot analysis with the presence of protease-resistant prion protein.

Following the initial workup, the patient was admitted to a rehabilitation unit to begin physical therapy. The patient’s dementia and level of consciousness deteriorated rapidly, and she expired less than 2 months from her original date of admission.

Discussion
Creutzfeldt-Jakob disease is a rare disorder of transmissible spongiform encephalopathy characterized by progressive...
dementia. It is a prion disease requiring a protein component (prion) for transmissibility, similar to kuru, bovine spongiform encephalopathy (mad cow disease), and scrapie. Creutzfeldt and Jakob, independently, first described the disease. The first published description was of a 22-year-old woman with a 1-year history of progressive dementia, spasticity, ataxia, and startle myoclonus. Simultaneously, Jakob identified 3 patients with a unique syndrome. All were older than Creutzfeldt’s patient and demonstrated a destructive process in the cerebral cortex, especially in the rolandic region, caudate, putamen, and thalamus. The first name for this disease was “spastic pseudosclerosis” because of its similarity to other diseases, such as multiple sclerosis and amyotrophic lateral sclerosis. A family with the disease was then described in the early to mid-1900s in which 11 members of the family had died of the same process.

Multiple forms of CJD have been recognized. The first is the typical form, otherwise known as subacute spongiform encephalopathy. Variants are described on the basis of localization of the disease process and presenting symptoms. Familial fatal insomnia involves the thalamus, and Heidenhain’s variant involves the occipital lobes. Related prion disorders include Gerstmann-Straussler-Scheinker syndrome, which is marked by cerebellar ataxia; and prion protein (PrP) and atypical forms of CJD caused by other mutations of the PrP gene (PRNP).

The typical form of CJD has a mean age at onset of 60 ± 9 years. This is in contrast to Alzheimer’s disease, the incidence of which increases markedly after age 60. There is no reported sex predilection for the disease. The annual incidence is 0.5 to 2 cases per million. Approximately 15% of cases are familial, caused by a mutation on the gene encoding the PrP, and are transmitted in an autosomal dominant pattern. Penetrance in familial cases also increases with age. Although 60% of familial mutations of the PRNP involve codon 200, multiple codons may be involved in members of the same family, as well as in variants of CJD. Most cases are sporadic, but iatrogenic causes have been highly publicized. These include transmission via human cadaveric pituitary growth hormone, corneal transplants, dural grafts, and EEG depth electrodes. The iatrogenic cases involving pituitary hormone occurred in patients younger than 40 years of age, serving to differentiate them from sporadic cases.

One third of patients experience prodromal constitutional symptoms, such as changes in sleeping and eating patterns and asthenia. Up to one fifth of the patients have a sudden onset of neurologic symptoms. Dizziness is the most common otorologic symptom noted. To date, only two other English-language reports of deafness as the primary presenting syndrome are published. Tobias et al reported a patient with a progressive bilateral hearing loss that was cortical in origin, as indicated by phonologic errors consistent with abnormalities in central language processing. In the second case, the patient presented with aural fullness...
and change in hearing. Our patient had a progressive increase in baseline hearing loss with dysequilibrium but no vertigo. Patients with this constellation of symptoms may be diagnosed initially with a peripheral vestibulocochlear disorder, as in the case of our patient. Other early symptoms are visuospatial or cerebellar in origin, such as visual field defects, diplopia, and ataxia.\(^1\)

Audiometric testing in these patients may reveal a poor word discrimination score that is out of proportion with the pure-tone hearing deficit. The role of imaging in the diagnosis of CJD is controversial. Computed tomography demonstrates volume loss in white matter and cortical atrophy with ventricular enlargement. In later stages of the disease, subdural fluid collections may be present. MRI, especially using higher-strength magnetic fields, may show high signals on T2 images in areas corresponding to the pathologic process, such as the basal ganglia, cortex, and periventricular white matter. Narrow-window techniques may increase the sensitivity for detecting early stages of CJD.\(^11\) Single photon emission computed tomography (SPECT) has revealed cerebral perfusion deficits in CJD that may be used to differentiate it from other dementias, such as Alzheimer’s disease. The correlation of SPECT scanning with the pathologic process behind CJD remains to be studied.\(^12\)

CJD progresses relentlessly as patients develop further mental deterioration and movement disorders, such as chorea and myoclonus. Seizures may occur, and electroencephalographic testing is performed to assist in diagnosis.\(^9\) More than 90% of patients in one series had findings of myoclonus, characteristic periodic sharp wave complexes (PSWCs), or both.\(^9\) The accuracy of these PSWCs is debatable, with one series reporting a sensitivity of 67% and a somewhat higher specificity of 86%. Serial EEGs are recommended to help increase sensitivity.\(^13\)

The ultimate diagnosis of CJD depends on neuropathologic findings in correlation with clinical history. A classic triad of spongiform change, neuronal loss, and astrocytosis has been well described (figure 4). However, spongiform change itself remains nonspecific; the only consistent location is in the head of the caudate nucleus. Spongiform change may also be absent in patients with a long duration of the disease.\(^14\) PrP immunoreactivity may be performed for confirmation but may not distinguish typical CJD from

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Figure 3. Electroencephalography demonstrates excessive diffuse slowing of theta and delta waves, and an occasional triphasic wave, suggestive of a mild diffuse encephalopathy.
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Clinical variants,\(^{15}\) and only 10% of typical cases of CJD actually contain these PrP-positive amyloid plaques.\(^6\)

CJD has a dismal outcome. Eighty percent of patients die within 1 year of onset, with the rest following a more chronic course.\(^6\) Japanese forms of CJD have a much longer duration, with patients living beyond 4 years.\(^{16}\) Little progress has been made in the search for treatment. Despite its rarity, it is important to be aware of this disease because of its significant diagnostic confusion.

**References**