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The Protean Neuropsychiatric and Vestibuloauditory Manifestations of Neurosarcoidosis

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Keywords
Neurosarcoidosis · Sarcoidosis · Cochlear implants · Cochlear implantation · Psychotic disorders · Cochlear diseases · Labyrinthine diseases · Autoimmune inner ear diseases

Abstract
Background: A rare subset of sarcoidosis, neurosarcoidosis, is reported to occur in 5–7% of sarcoid patients and can manifest in a variety of ways. The most common are facial paralysis and optic neuritis, less commonly causing cochleovestibulopathy, blindness, anosmia, and other cranial nerve (CN) palsies. The sensory deficit may be severe and psychiatric symptoms may result from the effects of the disease or steroid treatment. Although MRI-compatible cochlear implants are now available, concerns about the feasibility of recoverable hearing with cochlear implantation in these patients as well as the practical difficulty of disease monitoring due to implant artifact must be considered. Results: We present 3 recent cases from different institutions. The first is a 39-year-old man with a history of progressively worsening hearing loss, followed by visual loss, delusions, agitation, ataxia, and musical auditory hallucinations, diffuse leptomeningeal enhancement on MRI with a normal serum angiotensin-converting enzyme (ACE) level but elevated cerebrospinal fluid (CSF) ACE levels, suggesting neurosarcoidosis, was treated with corticosteroids, and underwent successful cochlear implantation. The second is a 36-year-old woman with rapid-onset horizontal diplopia, left mixed severe sensorineural hearing loss (SNHL) and tinnitus, diffuse leptomeningeal enhancement on MRI, and progressive palsy of the left CNs IV, VI, VII, IX, X and XI, with altered mental status requiring admission following high-dose intravenous corticosteroids. The third is a 15-year-old boy who presented with sudden, bilateral, profound SNHL, recurrent headaches, and left facial weakness refractory to antivirals, ultimately diagnosed with neurosarcoidosis following an aborted cochlear implantation where diffuse inflammation was found, and histopathology revealed Schaumann bodies; he was treated with methotrexate and later underwent successful cochlear implantation. Conclusions: Neurosarcoidosis is an elusive
diagnosis and can cause hearing loss and psychiatric symptoms. Cochlear implantation for patients with severe hearing loss should be considered once the diagnosis is confirmed, as it is possible to achieve a successful level of hearing. Psychiatric symptoms can manifest with the onset of neurosarcoidosis, result from CN deficits, or develop as a side effect from long-term, high-dose corticosteroids, and should be monitored carefully in patients with neurosarcoidosis.

Introduction

Neurosarcoidosis is a subset of the multisystem granulomatous disease that normally has a propensity for the lungs but may affect the nervous system in 5–15% of affected patients [Hoitsma et al., 2010; Loor et al., 2012]. Cranial neuropathies most commonly include the facial nerve (cranial nerve [CN] VII) and optic nerve (CN II). Rarely, neurosarcoidosis can affect the vestibulocochlear nerve (CN VIII), leading to loss of hearing and balance function [Carlson et al., 2015; Hoitsma et al., 2010; Zajicek et al., 1999]. Disease onset can be insidious and the progression of cranial neuropathies including facial palsy, optic neuritis, sensorineural hearing loss (SNHL), blindness, and anosmia can fluctuate, rendering diagnosis difficult. Psychiatric symptoms from the disease, sensory deficit, and steroid treatment may be severe, and can confound the diagnosis. Severe-to-profound hearing loss following neurosarcoidosis is generally not amenable to amplification with conventional hearing aids. Previous studies have recommended against cochlear implantation for SNHL from neurosarcoidosis due to the concerns of irreversible cochlear damage from disease progression. These recommendations are primarily based on histopathologic studies of a neurosarcoidosis patient autopsy by Babin et al. [1984] which demonstrated diffuse cochlear destruction, and on imaging and auditory brainstem response testing by Cama et al. [2011] that revealed a cochlear site of pathology in these patients. There is also a historic concern that cochlear implantation could interfere with disease monitoring by means of MRI.

In this report, we present 3 examples of patients with sudden SNHL and other cranial neuropathies secondary to neurosarcoidosis, and 2 patients that received cochlear implants with a successful recovery of functional hearing that exceeded expectations. We discuss the management dilemma of monitoring disease progress with MRI precluding cochlear implantation, even with the latest MRI-compatible cochlear implants. We also describe the psychiatric complications of neurosarcoidosis that can complicate diagnosis and treatment. Written informed consent was obtained from all 3 patients for the publication of their case reports and any accompanying images (available for review from the Editor-in-Chief of this journal).

Case Reports

Patient 1

A 39-year-old African-American male with mild developmental delay, otherwise previously healthy and living independently, presented in December 2014 with 8 months of progressively worsening bilateral hearing loss, 5 months of progressive vision loss, 1 month of gait imbalance, and, most recently, increasing agitation and confusion. He had previously been evaluated at another facility and diagnosed with a stroke, and so was discharged with a statin and aspirin. He was readmitted to the outside facility for worsening mental status and musical auditory hallucinations, and was treated with Halodol in the psychiatric ward. His family brought him to Northwestern for a second opinion because of the unclear etiology of his worsening vision and his deafness, and because his agitation was difficult to manage at home, at times requiring 4-point soft restraints.

On physical exam, he was uncooperative, agitated, could not walk, and could only see large letters written with a sharpie pen. He wrote a note for the inpatient team, stating “HELP ME.” It was difficult to assess if the auditory hallucinations were ongoing at that point. He had bilateral optic nerve palsy but was unable to cooperate for a formal vision exam. His extracocular movements and CNs were otherwise intact. Audiogram demonstrated a profound SNHL on the left and severe mixed hearing loss on the right (Fig. 1A). Word recognition scores were not tested.

Initial lumbar puncture showed lymphocytic predominance with cerebrospinal fluid (CSF) angiotensin-converting enzyme (ACE) above detectable level (7 U/L) but still within the normal range. Evidence of central nervous system (CNS) inflammation was demonstrated by lumbar puncture studies: CSF IgG was 22 mg/dL (high), quantitative CSF IgG was 1,110 mg/dL (normal), and cerebrospinal fluid (CSF) angiotensin-converting enzyme (ACE) above detectable level (7 U/L) but still within the normal range. Evidence of central nervous system (CNS) inflammation was demonstrated by lumbar puncture studies: CSF IgG was 22 mg/dL (high), quantitative CSF IgG was 1,110 mg/dL (normal), and CSF angiotensin-converting enzyme (ACE) above detectable level (7 U/L) but still within the normal range.

Fig. 1. Case 1: a 39-year-old man with progressive profound hearing loss, visual loss, delusions, agitation, ataxia, and musical auditory hallucinations was treated successfully with corticosteroids after a diagnosis of neurosarcoidosis, and experienced successful restoration of hearing after a cochlear implantation. A Audiogram on presentation demonstrated profound SNHL on the left, and severe mixed hearing loss on the right. B Aided sound-field testing 1 month after implantation revealed thresholds in the range of 30–35 dB HL and 250–4,000 Hz, suggesting adequate audibility across the frequency range, far exceeding expectations. C–F Gadolinium-enhanced T1-weighted MRI revealed diffuse symmetrical leptomeningeal enhancement with basilar predominance, and abnormal enhancement of the optic chiasm, CN V, CN VII, and CN VIII. No corpus callosum lesions were detected, decreasing the likelihood of Susac syndrome.

(For figure see next page.)
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A standard mastoidectomy and posterior tympanotomy approach was used. Intraoperative impedance field telemetry (IFT)

measurements were measured on all electrodes during closure of the incision and before the electrically evoked compound action potential measurements. IFT measurements, which provide an objective evaluation of the integrity of the implant electrode contacts and leads as well as the status of the electrode contact/tissue interface, show that all of impedances across the 12 intracochlear electrode array are in normal range relative to the reference electrode (Fig. 2A) and ensure that the device is functioning properly. The auditory nerve response telemetry (ART) platform was used to record the electrically evoked compound action potential (ECAP) of the auditory nerve in response to electrical stimulation from the MED-EL cochlear implant system. An ART was measured with the MAESTRO software system (MED-EL) intraoperatively. As shown in Figure 2B, there were no ECAP responses measured intraoperatively (Fig. 2Bb: an example of positive ECAP responses for the reader’s reference).

Six days postoperatively, the patient came back for the first electrode activation and an electrode mapping. The IFT measurements once again ensured that the device was functioning properly (Fig. 2C). MAESTRO software measurements for determining the most comfortable level (MCL) on the same day are shown in Figure 2D. MCL is defined as the maximum level of stimulation that is perceived as very loud, but not uncomfortable or painful with the user volume set to 100%.

The MCLs were able to be measured across all 12 electrodes, indicating that these stimuli were now audible to the patient. It should also be noted that most MED-EL implants have MCL values between 5 and 25 charge units (c.u.). Figure 2D indicates that the MCLs were between 31.01 (channel #1) and 44.42 c.u. (channel #12), much higher than normal. This suggests that a higher stimulus current requirement was necessary to obtain the MCL for this particular patient.

Speech testing on 25 October 2016 indicated 54% on the AzBio sentences test [Spahr and Dorman, 2004] and 46% on the consonant-nucleus-consonant (CNC) monosyllabic words test [Peterson and Lehiste, 1962] in silence at a 50-dB hearing level (HL), indicating that he was doing fairly well with his cochlear implant. The MCL at initial activation started at 35.19 c.u. on the apical electrode and increased to 40.14 c.u. on the basal electrode. As he wore the processor more and got accustomed to the sound quality, they increased to 35.19 and 42.58 c.u. on the apical and basal electrodes, respectively.

Finally, aided sound-field testing utilizing warble tones was performed 1 month after the initial activation, and revealed thresholds in the range of: 30–35 dB HL and 250–4,000 Hz (frequency) (Fig. 1B). Results suggest adequate audibility across the frequency range, far exceeding expectations. Aided speech testing in the sound field at 60 dB HL was revealed as 51% on the AzBio sentences test and 52% on the CNC words test.

During the drafting of this paper, the patient was contacted regarding his permission for publication and was able to answer the phone personally. Most exciting of all, the patient himself answered the phone. He readily granted his permission, and thanked the senior author (A.J.M.) for all his help. He also stated that he is driving and ready to go back to work, and that soon after the cochlear implant had been activated, the musical hallucinations had diminished. His mother confirmed that no further psychiatric symptoms were noted.

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Patient 2
A 36-year-old woman presented in 2013 with headaches and worsening diplopia and multiple cranial neuropathies, predominantly on the left side, over several months (palsy of CNs IV, VI, VII, IX, X, and XI). She was initially found to have a left CN VI palsy causing diplopia, then later developed left-side hearing loss, dysphagia, vocal cord paresis, and facial paresis. She responded symptomatically to oral and intratympanic steroids, but the symptoms would return after the cessation of the steroids. She had 3 lumbar punctures with normal CSF studies, a negative brain CT scan, and normal labs (i.e., a normal erythrocyte sedimentation rate [ESR], antinuclear antibodies [ANA], RPR, HbA1c, calcium, ACE, antineutrophil cytoplasmic antibodies), and tested negative for Lyme disease and celiac disease.

MRI demonstrated dural enhancement consistent with meningeal inflammation, and enhancement of multiple CNs but no localized lesion. Repeat MRI demonstrated left-sided progression of patchy leptomeningeal enhancement, predominantly around CNs VI and VIII as well as the cerebellum, falk cerebri, and cavernous sinus. A gallium scan demonstrated left lacrimal gland and left lung uptake suggesting granulomatosis with polyangiitis, lymphoma, or sarcoïdosis. A lung biopsy of these lesions confirmed noncaseating granulomas consistent with sarcoïdosis.

The patient’s audiogram revealed a moderate-to-severe mixed left hearing loss (Fig. 3) with a type B tympanogram correlating with her known left tympanic membrane perforation (not depicted), which was later repaired with a paper-patch myringoplasty followed by a tympanoplasty. Her videoystagmography demonstrated bilateral hypofunction, indicating bilateral vestibular loss and injury to CN VIII caused by the neurosarcoidosis.

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The patient was initially treated with intravenous (i.v.) steroids (with an oral taper), with some improvement to her cranial neuropathies apart from the photosensitivity headaches and hearing loss. She was also treated with hydrochlorothiazide (25 mg orally daily) with a potassium supplement, which mildly helped her symptoms. She was evaluated by the rheumatology department and began immunosuppressants (mycophenolate mofetil [MMF]) while tapering off the oral steroids, but decreasing the steroids led to worsening of her balance, tinnitus, and hyperacusis symptoms.

The patient unfortunately experienced depression, agitation, and insomnia, likely as side effects of the steroids. In order to try to spare her the consequences of long-term steroids, the MMF dose...
was increased, and she was also started on monthly Remicade which provided some temporary relief from her symptoms. However, she relapsed the following month with bilateral tinnitus, vision changes, and headaches, and so was restarted on steroids. She was found to have steroid-induced central serous choriorretinopathy without evidence of ocular sarcoidosis (i.e., uveitis, choroiditis, or papillitis). Again, the steroids were tapered to 30 mg daily, but her cranial neuropathies would then return. Repeat audiograms demonstrated a stable left-sided hearing loss, but she still experienced hyperacusis and fluctuating tinnitus. She tried a hearing aid for her left ear but experienced no benefit.

Approximately 1 year following the diagnosis, the patient’s MRI demonstrated no enhancement of bilateral internal auditory canals or cerebellopontine angle cistern, a normal facial nerve and canal, and no meningeal enhancement, with no evidence of neurosarcoidosis. The patient was on a regimen of prednisone (12 mg/day on a slower taper), CellCept (MMF, 2 g/day), infliximab (5 mg/kg, initially every 4 weeks and then every 6 weeks), famvir, valtrex, and clonazepam. A repeat videonystagmography demonstrated a great improvement with bilateral robust responses.

In September of 2014, the patient noted an abrupt worsening of her hyperacusis, tinnitus, balance and gait issues, fatigue, and agitation, and made multiple visits to the emergency room. She described feeling “in a fog,” “not myself,” and that she was experiencing “sensory overload.” She was treated with pulse Solu-MEDROL and an increase to her CellCept and prednisone dose to 60 mg daily, which temporarily improved her symptoms but these would then return within a few days.

Following 5 days of high-dose i.v. steroids, she presented to the emergency room in October 2014 with shortness of breath, chest pain, worsening neurologic symptoms, and depression. She was monitored for this change in mental status and evaluated by the neurology department for potential infectious etiology; this included a lumbar puncture that produced negative results for VDRL testing, CSF culture, cryptococcal antigen, herpes simplex and cytomegalovirus PCR, and CSF ACE. It was noted that after the lumbar puncture, her disequilibrium and headache improved, suggesting that she had had high CSF pressure. The patient was noted to have persistent hypokalemia and hyponatremia requiring i.v. replacement. She was examined by the nephrology department for renal involvement of sarcoidosis and was started on amiloride and Di-amox. She was also started on rituximab in addition to CellCept, prednisone, Neurontin, clonazepam, Navigil, and Ability, with an improvement of her neurologic and depressive symptoms. Serial brain MRI was negative for any evidence of the return of the neurosarcoidosis. By June of 2015, the patient was on minimal prednisone (1.5 mg daily), still had tinnitus, and experienced hearing difficulty in loud environments which is partially improved by hearing aids. She also has chronic fatigue and mild balance issues for which she has completed vestibular rehabilitation and vision therapy.

**Patient 3**

A 15-year-old, previously healthy African-American male presented with sudden, bilateral, profound SNHL, recurrent headaches, and left facial weakness refractory to antivirals, was ultimately diagnosed with neurosarcoidosis following an aborted cochlear implantation where diffuse inflammation was found and histopathology revealed Schaumann bodies. He was treated with methotrexate and later underwent successful cochlear implantation. A 36-year-old woman with rapid-onset horizontal diplopia, left mixed severe SNHL and tinnitus, diffuse leptomeningeal enhancement on MRI, and progressive left cranial nerve IV, VI, VII, IX, X, and XI palsies, with altered mental status required admission following high-dose i.v. corticosteroids. Audiogram demonstrates a moderate-to-severe mixed left hearing loss with an air bone gap of 40–60 dB. The patient also had a type B tympanogram (not depicted).
2 weeks, his symptoms returned and did not respond to steroid or antiviral treatment. He was admitted for workup and found to have mildly elevated ESR, serum ACE (106 U/L) and positive Mycoplasma IgM. All other laboratory testing was normal or negative (complete blood count, CMP ANA, RPR/VDRL, Lyme disease, herpes simplex, and varicella). The CSF demonstrated few lymphocytes and an otherwise normal profile negative for malignant cells. At a repeat serum ACE test, the level had returned to normal (44 U/L). Brain MRI demonstrated persistent enhancement of the right CN VI and bilateral CN VII, and the CN VIII within the internal auditory canal suggested possible viral neuritis (Fig. 4C, D). Subtle enhancement of the right cochlea was also apparent, suggesting labyrinthitis. A bilateral increased T2 signal in the mastoid air cells was consistent with chronic mastoiditis (the right worse than the left) but there was no evidence of cholesteatoma or abscess.

The patient was treated with i.v. steroids and acyclovir which completely resolved the facial weakness after 1 month. After 3 weeks of treatment, the deafness in the right ear remained, and it worsened from moderate to profound in the left ear (Fig. 4). Given his persistent hearing loss, he was scheduled for a left cochlear implantation, but this was aborted intraoperatively due to significant granulation tissue in the middle ear and mastoid cavity. Instead, the right mastoid bone was biopsied. It demonstrated predominantly chronic osteomyelitis with a foreign-body giant-cell reaction, granulomatous inflammation, and possible Schaumann bodies, and was negative for fungal or TB stains (Fig. 5A, B). A von Kossa stain for calcium and an AE1/AE3 immunostain for squamous epithelium were negative, i.e., not supporting calcium or squamous inclusions in the multinucleated giant cells. These inclusions also did not polarize, so did not support a crystalline nature (foreign material). At this point, the inclusions were deemed as possible Schaumann bodies observed in sarcoidosis. Testing was negative for fungal or TB stains.

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The patient underwent a successful right cochlear implantation 2 months later with the COCHLEAR CONTOUR ADVANCE Z60353, which is MRI-compatible. He was placed on a regimen of methotrexate (20 mg weekly), with good control of his headaches, and no recurrent facial paralysis or other symptoms. A postimplantation audiogram demonstrated good audibility, with the aided sound-field testing thresholds in a range of 15–25 dB HL and 250–8,000 Hz (Fig. 4B). The patient had to delay a year of school due to losing his hearing, but he graduated from high school and has since started college.

Fig. 5. Case 3: histopathology of the right mastoid bone demonstrates predominantly chronic osteomyelitis with a foreign-body giant-cell reaction and granulomatous inflammation (A, long arrow; B, short arrows). A Possible Schaumann bodies (long arrow). A von Kossa stain for calcium and AE1/AE3 immunostaining for squamous epithelium were negative, i.e., not supporting calcium or squamous inclusions in the multinucleated giant stains. These inclusions also did not polarize, so did not support a crystalline nature (foreign material). At this point, the inclusions were deemed as possible Schaumann bodies observed in sarcoidosis. Testing was negative for fungal or TB stains.

Discussion

Differential Diagnosis

Neurosarcoidosis remains an elusive disease and a diagnostic challenge. Workup for neurosarcoidosis often includes a gadolinium-enhanced MRI, among a panel of other infectious and immunologic tests to rule out a wide differential of neoplastic and nonneoplastic etiologies. An overlap of symptoms can occur, between neurosarcoidosis and other syndromes like multiple sclerosis with optic nerve, brain, or spinal cord involvement, Lyme disease with facial palsy, granulomatosis with polyangiitis, Behçet’s disease, meningeval carcinomatosis, TB, and CNS lymphoma [Hoitsma et al., 2010]. It is critical to recognize that neurosarcoidosis does not always coincide with systemic sarcoidosis, and can present solely with SNHL or other neurocognitive deficits [Souliere et al., 1991]. In a retrospective study of 305 patients with suspected neuro-
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Neurosarcoidosis, 38% presented with isolated neurosarcoidosis with no pulmonary or other systemic manifestations of sarcoidosis [Carlson et al., 2015].

Hearing loss in neurosarcoidosis is an even rarer presentation than optic or facial nerve involvement. In a retrospective study on 68 patients with neurosarcoidosis, 7% had CN VIII involvement, compared to 38% with optic nerve involvement and 19% with facial palsy [Zajicek et al., 1999]. Given the wide differential for hearing loss, this can confound the diagnosis of neurosarcoidosis. Sudden-onset SNHL can be caused by a variety of pathologies, most commonly idiopathic hearing loss, or chronic age-related changes that are unnoticed by the patient, and, less commonly, viral labyrinthitis, congenital malformations such as an enlarged vestibular aqueduct, or, even more rarely in patients with asymmetric SNHL, a cerebellopontine angle tumor such as an acoustic neuroma is discovered. Nonneoplastic causes of asymmetric SNHL may include labyrinthitis, chronic pachymeningitis, intralabyrinthine hemorrhage, and otospongiosis. In a retrospective study on 3,000 patients with asymmetric SNHL, 3 were found to have chronic pachymeningitis based on MRI, either linear or hypertrophic T1 enhancement of the pachymeninges (dura mater) as opposed to the leptomeninges (pia and arachnoid mater); this is what is typically enhanced in neurosarcoidosis [Oghalai et al., 2004]. The 2 pathologies are not distinct, as chronic pachymeningitis may be caused by viral, bacterial, or fungal meningitis, parasitic and other infections, malignancy, idiopathic etiology, or autoimmune diseases including neurosarcoidosis [Oghalai et al., 2004]. In 1 study, idiopathic chronic pachymeningitis causing bilateral SNHL and facial weakness was only distinguished from neurosarcoidosis once a dural biopsy had been performed and found negative for granulomas [Christakis et al., 2012]. Neurosarcoidosis presented as leptomeningeal enhancement on T1-weighted postcontrast MRI in 67% of patients, or as distinct from multiple granulomas that mimicked neoplastic masses in 17% [Carlson et al., 2015]. In other case reports of neurosarcoidosis, the hearing loss was initially unilateral and then became bilateral [Loor et al., 2012; Rose et al., 2014].

Zajicek et al. [1999] described the diagnostic criteria for neurosarcoidosis: "definite" which includes positive neural tissue histology, "probable" which includes evidence of CSF inflammation (increased protein or oligoclonal bands), MRI findings of neurosarcoidosis (white matter lesions, leptomeningeal enhancement, or CN enhancement) and evidence of systemic sarcoidosis (positive histology, elevated serum ACE, and at least 2 of the following: a positive Gallium scan, and chest imaging demonstrating bilateral hilar lymphadenopathy or serum ACE), and "possible" where evidence suggests neurosarcoidosis but the previous criteria are not met. Patients with neurosarcoidosis do tend to have multiple cranial neuropathies, most commonly involving CN II and less often, CN VII and CN VI, as well as gait ataxia, cognitive decline, and meningeal symptoms.

Meeting the “definite” diagnostic criteria for neurosarcoidosis remains a challenge, as biopsy-proven granulomas of CNS tissue can be both difficult and morbid [Valeyre et al., 2014]. There is no single test to diagnose neurosarcoidosis [Carlson et al., 2015], and even laboratory evidence of systemic sarcoidosis can suggest multiple etiologies, as serum ACE can be elevated in other disorders such as TB, multiple sclerosis, and Guillain-Barré syndrome [Rose et al., 2014]. In the study by Zajicek et al. [1999], elevated CSF ACE was noted in 6 of the 18 patients tested, but the authors felt that an elevated CSF ACE was only helpful if it was raised out of proportion to serum ACE. Tahmoush et al. [2002] found the CSF-ACE level a useful biochemical marker in patients with probable neurosarcoidosis, with sensitivity and specificity of 55 and 94%, respectively, in their group of 11 patients with probable neurosarcoidosis versus 207 normal controls. However, Bridel et al. [2015] found CSF-ACE to have low specificity and sensitivity in diagnosing neurosarcoidosis, providing a cohort of 440 patients with suspected neurosarcoidosis and 9 with a confirmed diagnosis by histology. Despite the controversy regarding diagnosis, there seems to be consensus that any patient with multiple cranial neuropathies, whether they are simultaneous, or sequential as in our patients, should raise suspicion for neurosarcoidosis [Carlson et al., 2015; Loor et al., 2012; Rose et al., 2014].

By the diagnostic criteria of Zajicek et al. [1999] for neurosarcoidosis, case 1 was diagnosed with “possible” neurosarcoidosis, given the lack of systemic sarcoidosis, but it was strongly suggested by his clinical presentation, detectable CSF ACE, elevated CSF protein and IgG, and MRI findings. Though he had evidence of CNS inflammation, he lacked evidence of systemic sarcoidosis, as his serum ACE level was normal and hilar lymph node biopsy was negative for granulomas. Although Susac syndrome was on the differential, given his concomitant vision loss, the lack of corpus callosum and retinal involvement decreased the likelihood, according to the consulting ophthalmology and neurology services.

Case 2 would merit “probable” neurosarcoidosis, as she had a positive gallium scan demonstrating left lacri-
mal gland and left lung uptake, and biopsy of these lesions confirmed sarcoidosis normal serum and CSF ACE, along with her clinical presentation, and MRI suggested a CNS inflammatory process.

Case 3 would fall under “possible” neurosarcoidosis, as he was not diagnosed until the histopathology of his mastoidectomy demonstrated noncaseating granulomas with Schaumann bodies, although on imaging he had also demonstrated an inflammatory process surrounding multiple CNs. Although it is possible that this patient simply had chronic mastoiditis following a Mycoplasma infection, the noncaseating granulomas suggested a possible granulomatous disease. Apart from sarcoidosis, granulomatosis with polyangiitis or Churg-Strauss syndrome are possible granulomatous pathologies, but these ultimately did not match his clinical presentation. Schaumann bodies can also be found in patients with TB, chronic beryllium, or Crohn’s disease, but he tested negative (for TB) and did not fit these clinical scenarios.

**Psychiatric Symptoms of Neurosarcoidosis**

Case 1 presented with frank auditory hallucinations, agitation and psychosis, whether from the neurosarcoidosis itself, the side effects of treatment, or severe sensory deficit remains unclear. It was the primary reason his family brought him to Northwestern as, at times, he was requiring 4-point restraints at home, but prior to his illness he had been fully functional and living independently. Case 2 had a more fluctuating course of symptoms and her psychiatric symptoms did not truly manifest until the episode of suicidality, where she described feeling “in a fog” and a “sensory overload.” Again, whether her psychiatric symptoms were treatment (steroid)-induced or as a result of the neurosarcoidosis remains difficult to distinguish.

Neurosarcoidosis can present with a variety of psychiatric symptoms from depression, dementia, delirium, delusions, hallucinations, or frank psychosis. Given the rarity of neurosarcoidosis, this diagnosis is often confused with other psychiatric conditions and correct treatment is delayed. One case report described a 54-year-old, previously healthy man who developed sudden, bilateral SNHL, followed several years later by "command” hallucinations from a deceased relative [Steriade et al., 2014]. This patient was treated with various antipsychotics and electroconvulsive therapy over the course of several years, with worsening psychiatric symptoms, and he developed neuroleptic malignant syndrome from the medical therapy; eventually it was noted that he had axillary and hilar lymphadenopathy which, upon biopsy, revealed noncaseating granulomas. The patient was successfully treated with high-dose corticosteroids with no recurrence of psychosis.

There are several isolated case reports of neurosarcoidosis causing psychosis. One detailed a 36-year-old man with multiple psychiatric admissions for auditory and visual hallucinations, disorganized thoughts, and combative behavior over >10 years; treatment with antipsychotics provided little improvement [Bona et al., 1998]. Initial medical workup including brain CT scan and MRI returned normal, as did the laboratory workup. Finally, when it was noted he had chronic hilar lymphadenopathy, and biopsy revealed noncaseating granulomas, repeat brain MRI revealed leptomeningeal enhancement. This patient was treated with high-dose corticosteroids, and was eventually discharged home to his family with a significant improvement in his psychiatric symptoms.

In another case report, a 40-year-old male patient presented with headaches, diplopia, and progressive paranoid delusions that did not improve with antipsychotics [Westhout and Linskey, 2008]. Brain MRI revealed aqueductal stenosis without any visible obstructive masses or lesions, and other medical and laboratory workups were normal including the CSF studies. His diplopia resolved with ventriculoperitoneal shunting but his paranoid delusions worsened, requiring admission for 6 months. Eventually, due to the severity of his disease, a meningeal biopsy was performed and revealed noncaseating granulomas consistent with neurosarcoidosis. He improved on corticosteroid therapy and his psychiatric symptoms resolved.

Another case report detailed isolated neurosarcoidosis that caused recurrent, violent psychotic episodes over the course of 3 years without any pulmonary or extracranial symptoms apart from mild papilledema and severe headache in a previously healthy 30-year-old woman [Rudkin et al., 2007]. The patient was only successfully diagnosed once a repeat MRI showed subtle meningeal enhancement with contrast that was then biopsied, and revealed noncaseating granulomas; she was successfully treated with corticosteroids.

Without histopathologic evidence of neurosarcoidosis, it can be difficult to definitively diagnose, and also to conclusively rule out schizophrenia, steroid-induced psychosis, or psychosis secondary to the hypercalcemia commonly caused by systemic sarcoidosis. In a case study on a 31-year-old woman with known systemic sarcoidosis, and onset of auditory and visual hallucinations, the patient was concomitantly treated with antipsychotics and...
high-dose steroids and her symptoms improved, although, per the authors, it is unclear which medication truly helped her and thus whether she had schizophrenia or neurosarcoidosis [Spiegel et al., 2012].

In another case report, a previously healthy 32-year-old female developed paranoia, fatigue, headache, and persecutory delusions. There was an initial negative medical workup but diffuse basal meningeal enhancement on MRI; however, meningeal biopsy was negative for granulomas [Sabaawi et al., 1992]. She was hospitalized in the psychiatric ward for several months, and was found to have a normal chest X-ray, gallium body scan, serum ACE, and salivary gland biopsy. Eventually, a conjunctival biopsy demonstrated sarcoid granulomas and so she was treated with high-dose steroids, with an improvement in her mental state.

Steriade et al. [2014] discuss the difficulty of diagnostically separating neurosarcoidosis from schizophrenia, and state that later age of onset of psychiatric symptoms, preserved affect, lack of thought disorder, and multimodal hallucinations all suggest psychosis secondary to a medical condition. In our study, both cases 1 and 2 experienced psychiatric symptoms, from musical hallucinations to suicidality, which improved with treatment of their neurosarcoidosis. It is difficult to tell if the psychiatric symptoms were due solely to the neurosarcoidosis disease process itself, or from the CN deficits, steroid treatment, or other baseline psychiatric issues.

**Etiology/Pathophysiology**

Clinical symptoms do not necessarily correlate well with CN enhancement on MRI [Carlson et al., 2015; Shah et al., 2009]. Indeed, in this study, case 1 had enhancement of CN V and CN VII even though they were intact clinically. Imaging changes, however, can correlate with clinical progression, and imaging abnormalities like those of the CNs, are more likely to respond to immunosuppressive therapy than dural or parenchymal lesions [Sugaya et al., 1996]. The initial histopathologic evidence of audiovestibular neurosarcoidosis was initially described by Babin et al. [1984], after an autopsy of a deaf patient with neurosarcoidosis revealed perivasculard lymphocytic and granulomatous inflammation, especially within CN VII and CN VIII. Near cochlear degeneration without any degree of infiltration or inflammation suggested vascular occlusion or ischemia. Cranial neuropathies may be the result of ischemic axonal degeneration and demyelination due to local pressure from epineural and perineural granulomas and granulomatous vasculitis. Increased intracranial pressure or inflammation surrounding the basilar meninges may also contribute to injury [Carlson et al., 2015]. Hearing loss may also be the result of toxemia to the organ of Corti [Sugaya et al., 1996]. The etiology of psychiatric symptoms resulting from neurosarcoidosis is not well understood.

**Treatment Management**

Corticosteroids are the first-line therapy for the treatment of neurosarcoidosis, and usually an initial dose of 1 mg/kg/day is recommended although in severe cases, as in case 1, high-dose i.v. methylprednisolone is used for a few days [Hoitsma et al., 2010; Jardine et al., 2015; Loor et al., 2012; Rose et al., 2014; Zajicek et al., 1999]. In many cases, patients experience stable, improved, or even complete resolution of disease although they may require long-term corticosteroids [Carlson et al., 2015; Jardine et al., 2015; Loor et al., 2012]. In order to decrease the likelihood of side effects from chronic high-dose steroids, other immunomodulatory medications such as methotrexate, azathioprine, cyclophosphamide, and hydroxychloroquine are also used [Zajicek et al., 1999]. Cranial irradiation remains a last option in patients who have failed all other treatment [Motta et al., 2008]. Relapses can occur while tapering prednisone to 10–20 mg or less [Hoitsma et al., 2010]. In addition, symptoms of small-fiber neuropathy (sensory symptoms of pain and paresthesias, or those of autonomic dysfunction including diarrhea or sexual dysfunction), appear resistant to corticosteroids [Hoitsma et al., 2010]. Patients with refractory disease can be treated with immunomodulatory therapies or even radiation therapy, and there are case reports of a good clinical response to cranial radiation [Motta et al., 2008].

**Cochlear Implantation in Patients with Neurosarcoidosis**

Given the difficulty in diagnosing neurosarcoidosis with laboratory tests such as serum or CSF ACE, MRI has been critical to providing evidence of neurosarcoidosis. Cochlear implantation, even the modern MRI-safe cochlear implants, renders disease monitoring difficult due to implant artifact. The histopathologic studies showing diffuse cochlear destruction [Babin et al., 1984] as well as the imaging and auditory brainstem response testing revealing a cochlear site of pathology [Cama et al., 2011] led to the general belief that, once profound deafness occurs in patients with neurosarcoidosis, cochlear implantation would not restore hearing and they would be counseled accordingly. However, this study shows, in cases 1 and 3, that cochlear implantation was successful beyond expectations despite the preexisting severe hearing loss and...
suspected intracochlear involvement. Cochlear implantation appears to be a viable option and should be offered to patients for the treatment of hearing loss due to neurosarcoidosis.

There are reports of labyrinthitis ossificans following neurosarcoidosis with hearing loss. Dhanjal et al. [2014] claimed that early imaging and cochlear implantation is highly recommended. In their study, a 40-year-old male patient with initially left, then bilateral, profound SNHL, headaches, hilar lymphadenopathy on chest X-ray, and elevated serum ACE, was diagnosed with neurosarcoidosis, and treated with high-dose corticosteroids which helped with the headaches, but with no improvement to his hearing so cochlear implantation was recommended. However, intraoperatively, he was found to have cochlear ossificans on the right, with blockage of the scala tympani, and so the posterior tympanotomy was extended, the ossicles removed, and the cochlear implant was inserted into the scala vestibule. He had average postimplantation audiometric thresholds values.

Conclusion

Neurosarcoidosis is an elusive diagnosis and can cause hearing loss and psychiatric symptoms. Once diagnosis is confirmed, cochlear implantation for patients with hearing loss should be considered due to the risk of labyrinthitis ossificans. Cochlear implantation can achieve a successful level of hearing beyond previous expectations. As a result of CN deficits or long-term high-dose corticosteroid treatment, psychiatric symptoms can be manifest with the onset of neurosarcoidosis and should be monitored carefully.

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Statement of Ethics

Written informed consent was obtained from all patients for publication of this case report and any accompanying images.

Disclosure Statement

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J.J.G. and A.J.M. (lead authors responsible for manuscript draft and treating physicians for case 1), I.C.N. and J.M.P. (contributing authors for case 3), K.T.N. (contributing author for case 1), L.W. (consulting audiologist for case 1 and contribution for audiology data analysis), J.P.H. (treating physician for case 2, and substantial involvement in authorship, preparation, and interpretation of the manuscript). All authors read and approved the final manuscript.

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