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Audiologic and Otologic Complications of Cryptococcal Meningoencephalitis in Non-HIV Previously Healthy Patients

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Abstract

Objective: To identify audiologic and otologic outcomes in previously healthy non-HIV patients with cryptococcal meningoencephalitis.

Study Design: Retrospective case review of a subset of patients recruited in a parent prospective observational study following the course of the disease in previously healthy patients who developed cryptococcal meningoencephalitis.

Setting: Tertiary referral center, National Institutes of Health Clinical Center.

Patients: Previously healthy adult patients with cryptococcal meningoencephalitis without known immunological deficiencies or on immune suppressive therapy prior to disease onset.

Interventions: Diagnostic evaluations included audiometry, acoustic immittance, otoacoustic emissions, and auditory brainstem response studies, in addition to neurotologic assessment.

Results: 29 patients (58 years) underwent audiologic evaluation between 6 months and 3.5 years after cryptococcal meningoencephalitis diagnosis; 21 patients were seen for longitudinal assessment with an average duration of follow up of 20.3 months. Nearly three-quarters (73%) of the cohort presented with hearing loss, most commonly (90%) sensorineural in origin. The most

frequent degree of loss was mild and then moderate, although some patients had severe or profound impairment. Hearing loss improved (43%) or remained stable (38%) in most cases. Hearing loss was not associated with reduced CSF glucose, CSF total protein, cryptococcal antigen or total cell count. Ears with internal auditory canal enhancement on MRI had significantly more hearing loss than those without enhancement, although a similar finding was not observed with gyral enhancement or the presence of ependymitis or ventricular volume expansion.

Conclusions: Hearing loss is a common manifestation of cryptococcal meningitis in previously healthy patients and may involve a cochlear or neural site of lesion, or both. Poorer mean hearing in ears with internal auditory canal enhancement but not CSF cryptococcal antigen, suggests a possible role for post-infectious inflammatory response syndromes in the manifestation of otologic disease in cryptococcal meningitis, although further study is required to tease out the relative roles of pathogen damage versus immune mediated damage. Routine surveillance of hearing in patients is recommended, regardless of symptomatology, to ensure early and appropriate intervention and care.

Keywords

Cryptococcus; meningoencephalitis; Audiology; Otology; pulse corticosteroids

Introduction

Cryptococcus neoformans is an opportunistic, encapsulated fungal species that, due to the control of bacterial disease through vaccination, is currently the most common etiological cause of non-viral meningitis in the United States^{1,2}. Most often, hosts are immunosuppressed following solid-organ transplant conditioning or from HIV infection, although in the U.S. nearly one-quarter of cases occur in previously healthy, HIV-negative individuals. Globally, cryptococcal meningoencephalitis (CM) accounts for 15% of AIDS-related mortality, resulting in an estimated quarter of a million deaths yearly³ and shows little decline in resource-poor settings despite widespread availability of HIV-directed anti-retroviral therapy⁴. In more developed countries such as the U.S., rates of cryptococcosis in HIV-positive patients have fallen due to effective anti-HIV therapy-driven immune reconstitution, although rates in previously healthy, HIV-negative patients have remained stubbornly persistent^{1,5}. The fungus is ubiquitous in the environment, where it is commonly found in soil and bird feces, resulting in widespread exposure. Estimates suggest that half of all people are exposed to the fungus sufficiently as young children to produce antibodies⁶, and roughly 10% maintain fungus latently throughout life⁷. Previously healthy patients have a poor prognosis and high mortality risk that is similar to immunosuppressed groups with a 30% mortality despite treatment^{8,9}. The non-HIV and non-transplant sub-population of patients affected by *Cryptococcus* makes up 17–22% of the overall population of those affected by the fungus¹⁰. While infection with *Cryptococcus* in immunocompetent hosts tends to be more localized and indolent than in immunosuppressed hosts, complications of cryptococcosis can be severe in the previously healthy population, perhaps due to delays in diagnosis in an unsuspected host group^{9,11,12}. Regardless of immune status, infection with

Cryptococcus can lead to permanent neurologic deficits, blindness, and cerebral infarctions¹¹.

Clinical presentations of cryptococcal disease can be highly variable and occur in any organ, although CNS infection leading to meningoencephalitis is particularly common. Headache is a frequent prodromal symptom, which can last for weeks to months, and may be associated with changes in behavior and mental status, fever, nausea and vomiting, lethargy, and coma¹³. Fever, however, is uncommon in non-HIV cases¹⁴. Diagnosis is established by detection of cryptococci or cryptococcal antigen in cerebrospinal fluid (CSF) and patients are treated typically with the antifungals amphotericin B, followed by fluconazole¹³. Even with effective therapy directed at the pathogen, a number of cryptococcal inflammatory syndromes complicate therapy. In HIV-related disease, an immune reconstitution inflammatory syndrome (cIRIS) is a frequent complication after effective antiretroviral therapy. Variants also occur after modifications to immune suppression in solid organ transplant recipients¹⁵ and there exists a well-described post-infectious inflammatory response syndrome (PIIRS) in previously healthy populations consisting of clinical failure in the setting of negative CSF fungal cultures, low CSF glucose with increased T cell activation and intrathecal soluble pro-inflammatory cytokines¹⁴. In each case, inflammation and resultant cerebral edema results in significant morbidity and mortality.

Otologic manifestations associated with cryptococcosis have been reported in both previously healthy and immunocompromised individuals, although the majority of the literature consists of case studies, with a few cohorts in whom hearing was not objectively assessed and reported in detail^{17–19}. Temporal bone studies have described invasion of the internal auditory canal by cryptococcal organisms, with degeneration of the cochlear and vestibular branches of the 8th cranial nerve, the organ of Corti, and the vestibular sensory organs located in the semicircular canals, saccule, and utricle²⁰. Reported clinical findings are variable but suggest a profile that is sensorineural (cochlear or neural), bilateral, and progressive or fluctuating^{17–19}. Ultimately, however, the risk of insult to and prognosis for the auditory system is poorly understood. In the present study, we present detailed otologic and audiologic data from 29 previously healthy HIV-negative patients with CM, providing further evidence that hearing loss is a common manifestation, and explore the relationship between clinical, radiological, and biological markers for disease and the auditory system.

Materials and Methods

Ethics Statement

All patients were seen at the National Institutes of Health Clinical Center, Bethesda, Maryland, and informed consent was obtained under an institutional review board-approved protocol (National Institute of Allergy and Infectious Diseases [NIAID] protocol 93-I-0106) for a prospective observational study examining the host genetics and immunology of cryptococcal disease in previously healthy, non-HIV infected adults. A diagnosis of CM was defined as a positive latex agglutination cryptococcal antigen or the isolation of *Cryptococcus* in one or more CSF cultures, or both.

Participants and patient clinical data

To characterize the type and severity of hearing loss in cryptococcal meningoencephalitis, 29 patients in the cohort (21 males, 8 females) aged 22–76 years, median 54 (interquartile range [IQR]: 46–60), most of whom developed auditory symptoms during the referral period (8/2009–9/2016), were examined. These patients came from a total cohort of 49 patients with CM enrolled over a seven-year period. Patients were initially referred to audiology with a bias toward those with auditory symptoms, but after April 2015, referrals were opened to all patients with sufficient mental status during their hospital stay. Initial auditory exams were conducted from 6 months to 3.5 years after diagnosis (median 1.5 y [IQR: 0.5–3.2]). Longitudinal data were collected on 21 with an average duration of follow-up of 20.3 months (1–64).

Comprehensive audiology examinations included, whenever possible, tympanometry, middle ear reflex measures, audiometry, otoacoustic emissions, and neurodiagnostic auditory brainstem response (ABR) studies. ABRs were graded from 0 to 4 with respect to waveform morphology, peak/interpeak latencies and amplitude ratios²¹. Grades 1 and 2 were considered normal; grades 3 and 4 were considered abnormal and consistent with involvement of the auditory nervous system; grade 0 was assigned when peripheral hearing loss precluded interpretation of the ABR. Hearing sensitivity was compared to age- and sex-matched normative data²². Each subject underwent comprehensive neurotologic evaluation including cranial nerve function.

All patients underwent a lumbar puncture for CSF analysis and magnetic resonance imaging (MRI) at the time of diagnosis, as well as upon referral to the NIH Clinical Center as previously described. MRI was conducted at the time of the initial audiology exam (all but two within 1 week) and evaluated in a blinded fashion to hearing loss status, focusing on the presence of internal auditory canal enhancement as well as gyral enhancement and ependymitis on post-gadolinium FLAIR as well as hydrocephalus.

Statistics

For comparing IAC enhancement with hearing, CSF glucose, and CSF antigen, the non-parametric Mann-Whitney test was utilized. Regression analyses between CSF glucose, total protein and hearing were conducted using a Spearman's rank order correlation, taking into account outliers identified with the Grubb's test. All analyses were performed using PRISM (version 6.0h, Graphpad Software, La Jolla, CA). Descriptive data are also provided.

Results

Study Subjects

As shown in Table 1, all 29 patients had normal CD4+ and CD8+ T lymphocyte counts and 2 had antibodies to GM-CSF, the latter reported previously in CM. The most common initial presenting symptoms at time of diagnosis (prior to referral to NIH) were headache and lethargy (21 and 15 patients, respectively) with low rates of fever ($> 38^{\circ}\text{C}$) (7 patients), all of which are typical of CM in this population^{25,26}. While most patients eventually developed hearing impairment, few reported subjective hearing deficits or tinnitus at the time of initial

presentation (2 and 3 patients, respectively), although these symptoms may have been obscured by the presence of headache or mental status change. In addition, all patients noted to have hearing impairment on admission or during the course of their stay had bilateral involvement. Laboratory findings during the initial treatment period prior to referral to NIH demonstrated abnormally low CSF glucose (median: 33 mg/dL; abnormal is below 40 mg/dL) with 18 (62%) below 40 mg/dL, as well as diagnostic CSF cryptococcal antigen titers (median 1:64), typical for CM. Patients were uniformly treated with at least 4 weeks of amphotericin B preparations, followed by oral fluconazole therapy for at least 1 year. All patients had negative CSF cultures at the time of auditory and MRI exams.

As shown in Figure 1A, most patients had varying degrees of what can be considered functionally significant hearing loss. Of 58 ears, only 16 (27%) had no hearing loss based on a .5/1/2/4 kHz pure-tone age-adjusted average. For males, who comprised nearly three-quarters of the cohort, forty-three percent of thresholds at 4 kHz, a critical frequency for speech understanding, were worse than what could be predicted based on age and sex alone (Figure 1B). Of ears with hearing loss, the most common (90%) type was sensorineural (Figure 2, top panel) and the majority of losses were either mild or moderate in degree (Figure 2, middle panel). In all cases with SNHL, distortion product otoacoustic emissions were appropriately absent (data not shown) suggesting a cochlear contribution to the loss. In addition, in ears for which the auditory brainstem response (ABR) study was performed and could be interpreted (38 ears), one-third (34%) with ABR Grade 3 and 4 demonstrated abnormalities that were not attributable to pure tone hearing sensitivity suggesting pathologic involvement of the 8th cranial nerve and/or auditory brainstem pathways (Figure 2, lower panel). When longitudinal changes in pure tone hearing were examined (Figure 3) the majority of clinically significant changes ($\pm >10$ dB) were an improvement in hearing which occurred across test frequencies; nine of 21 patients (43%) had improved hearing. In the total cohort, there was no correlation of improvement with corticosteroid treatment (Fisher exact test, $p = 0.67$); however, the study was not designed to assess the role of corticosteroids considering the first exam was typically six months after diagnosis, during which, presumably, most of the acute damage occurs. Eight (38%) patients with longitudinal data had no change in hearing, although one patient presented with no measurable hearing at baseline. Three patients' (14%) hearing became worse over the duration of follow up, and one patient (5%) had documented fluctuations in hearing (see clinical vignette), characterized by decline and recovery during the period of monitoring.

For the present cohort, initial CSF glucose and cryptococcal antigen (CrAg) at the time of presentation by latex agglutination at the time of CM diagnosis, available for 27 patients, were compared to the .5/1/2/4 kHz pure tone average for the worse hearing ear. A negative correlation was observed between CSF glucose reduction below 40 mg/dL and increased hearing loss, but was not statistically significant ($p = 0.06$). Unfortunately, we did not have access to initial serum glucose levels at the time of diagnosis to examine the ratio of CSF/serum glucose. Elevated CSF total protein, a measure of disease burden, showed a trend with elevated hearing threshold but was not statistically significant ($p = 0.18$). No correlation was evident between the initial CSF CrAg or CSF WBC and hearing ($p = 0.85, 0.37$, respectively).

As shown in Figure 4, group hearing loss was worse in ears with IAC enhancement on FLAIR MRI in the corresponding ear (left: $p = 0.02$; right: $p = 0.02$; Figure 4, A) which was highly significant when all ears were considered ($p < 0.001$). Lower CSF glucose levels were observed in the presence of IAC enhancement ($p = 0.02$; Figure 4, B), but CSF cryptococcal antigen levels ($p = 0.53$; Figure 4, C) were not different. In addition, neither gyrus enhancement nor the presence of ependymitis or ventromegaly ($p = 0.99, 0.81, \text{ and } 0.52$, respectively) on MRI was associated with hearing loss (data not shown). The clinical vignette (Fig. 5) shows a patient who was treated promptly with oral adjunctive steroid therapy while his antifungal remained constant (oral fluconazole) at the onset of an episode of acute hearing loss and demonstrated an apparent clinical response associated with a decrease in 8th cranial nerve inflammation on MRI and an improvement in hearing.

Discussion:

In the present study, we sought to investigate hearing loss in previously healthy, non-HIV patients with cryptococcal meningoencephalitis. In our cohort of 29 patients, mild or moderate SNHL occurred in over 64% of ears tested, with mild being the most common degree observed, suggesting necessary vigilance for hearing disability in CM. Hearing thresholds at 4 kHz, a critical frequency for speech understanding, were elevated in nearly half of patients beyond what would be predicted by age and sex, two common risk factors for hearing loss. This suggests disease-specific dysfunction, although occupational noise exposure history, with and without the use of hearing protection, was common in this group (71%). This is consistent with a number of clinical reports,^{27–32} as well as other reported case series documenting abnormal hearing in 14–33% of adults with CM^{17,33,34}, notably more than hearing loss in children with CM, reported to be less than 10%¹⁹. However, the rate is less than that observed in bacterial meningitis, which was recently shown to affect 44% of children with a preponderance of SNHL³⁵, but more than tuberculous meningitis which also causes a basilar meningitis similar to CM but has less than a 5% incidence of hearing loss³³. As shown here, cryptococcal-associated hearing loss may improve over time, possibly related to initiation of therapy, but may also persist in severity, which may be due either to the chronicity of the convalescence or the older age of the present cohort. Similar to the example in our clinical vignette, adjunctive dexamethasone in early stages of acute decline may improve hearing loss in bacterial meningitis, perhaps suggesting an analogous inflammatory mechanism that may play a role in cochleovestibular damage in CM³⁶.

The present study is one of the largest detailed otologic studies to date of non-HIV CM. Previously, Wang, *et al.* studied a group of 26 HIV-negative patients with cryptococcal meningitis, eight of whom had mild to severe SNHL after the infection¹⁸. The previous study identified several risk factors for associated SNHL, including a high cryptococcal antigen titer, concomitant visual impairment, and presence of meningeal enhancements on MRI. While comparison to concomitant visual impairment in our cohort was not possible, we did observe active CNS inflammation, suggested by increased internal auditory canal enhancement on post-contrast FLAIR MRI.

In this cohort, neither CSF glucose nor CSF cryptococcal antigen were significantly associated with elevated hearing thresholds. Low CSF glucose (CSF below 40 mg/dL) is a

readily available measure that correlates with elevated neurological damage in CM, measured by increased release into the CSF of the axonal damage marker, neurofilament light chain 1 (NFL-1)¹⁴. In addition, low CSF glucose, in the setting of negative CSF cultures is typical of PIIRS^{14,23} in which low CSF glucoses in the presence of negative CSF fungal cultures is common. Some patients have benefited from corticosteroid therapy in this syndrome^{37,38} as demonstrated after prompt intervention in the case reported in our clinical vignette. However, because the majority of patients in the present cohort were assessed after six months from the time of diagnosis (median time between diagnosis and exam = 1.5 y), any response from corticosteroid therapy in the 10 patients who received it during the acute setting (Table 1) would be difficult to assess. In addition, quantitative CSF fungal cultures were not available from the time of diagnosis; thus, the role of the initial fungal burden could not be rigorously examined. Interestingly, a previous study showed severe loss of spiral ganglion cells and cochlear nerve fibers in the internal auditory canal but only small numbers of *Cryptococci*, suggesting that inflammation could have been an important factor in hearing loss³⁹.

The present cohort also demonstrated neurological impairment in the auditory system with retrocochlear findings on ABR (grades 3 and 4) in one-third of ears, also demonstrated by increased FLAIR intensity on MRI for the 8th cranial nerve. The collective literature to date suggests the SNHL in *Cryptococcal* meningitis is often but not always bilateral, sudden in onset and then slowly progressive, fluctuating and possibly reversible, and can involve the vestibular system. The site of lesion can be cochlear or neural, which distinguishes it from bacterial meningitis, which tends to spare the retrocochlear pathway. We also observed in some cases that the SNHL can be sudden in onset (e.g., see clinical vignette) and may improve with corticosteroid therapy. Ultimately, we did not have sufficient data to determine whether corticosteroids may have an impact on progression or persistence of hearing loss, although the apparent inflammatory nature suggested between elevated IAC enhancement and hearing loss in this cohort suggests this could be entertained as therapy, similar to that utilized for CM arachnoiditis³⁸. In conclusion, sensorineural hearing deficits are common after CM, and may be sensory or neural in origin, or some combination of the two. These losses can be functionally significant, which in some cases can be severe or profound.

While this represents the largest detailed otologic study of CM in non-HIV patients, several limitations must be acknowledged. The overall referral cohort may be biased towards more severe cases that tend to seek tertiary medical referral, and hearing tests were sought primarily when patients were symptomatic. In addition, while the cohort is large for the reported literature, the sample size remains small and underpowered to determine the robustness of clinical associations reported, and may miss less common presentations or additional covariate associations. Furthermore, a delay in hearing examinations may miss early reversible symptoms, such as those that have been observed in strain-related differences in presentation or outcomes previously noted in non-HIV patients⁴⁰. We did not have sufficient numbers to identify these possible strain-related differences in hearing. Larger cohorts without symptomatic referral bias are necessary to confirm and expand on the findings reported here. Nevertheless, this study does show a strong propensity towards hearing loss in this population, regardless of fungal strain. Earlier vigilance and treatment with antifungal therapy may improve neurological outcomes, including hearing loss, and

further study is needed to assess the role of post-infectious inflammatory response syndromes and adjunctive immunotherapy.

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Figure 1:

A) Audiograms representing the worse hearing threshold in 29 patients with CM, assessed at the initial complete evaluation following hospital admission. Shaded gray denotes range of normal hearing sensitivity. B) Thresholds for males at 4 kHz plotted against age- and sex-matched norms. Top black line = 95th percentile; dashed line = 50th percentile; bottom light grey line = 5th percentile of ISO norms. Gray filled circles, right ear; black filled circles, left ear.

Figure 2:
Distribution of types and degree of hearing loss⁴¹ and ABR interpretation²¹ as indicated.

Figure 3:
Change in pure-tone hearing sensitivity by frequency from the initial to the most recent assessment in 21 patients with longitudinal hearing data. Median with interquartile range reported.

Figure 4:

Internal auditory canal (IAC) enhancement in relation to hearing (.5/1/2/4 kHz) is shown in panel A, where R positive vs. R negative $U=39.5$, L positive vs. L negative $U=40$, and Ears positive vs. Ears negative $U=162$. IAC enhancement with initial CSF glucose levels is shown in panel B, where IAC positive vs. IAC negative $U=36.5$. IAC enhancement and CSF cryptococcal antigen levels are shown in panel C, where IAC positive vs. IAC negative $U=60.5$. Bar indicates median with interquartile range. R, right; L, left; pos, positive; neg, negative.

Figure 5: Clinical vignette of acute hearing loss in CM

A 49-year-old male referred with clinical deterioration despite multiple courses of Amphotericin B + 5-Fluorocystine and negative cerebrospinal fluid (CSF) cultures. He presented for initial audiometric exam on **Day 1** of his admission at the NIH with c/o decreased hearing since his diagnosis of CM at an outside hospital 5 months prior (A). The following day he reported acute onset of tinnitus and vertigo. He returned to clinic on **Day 3** for ABR study and reported a sudden decline in hearing, roaring tinnitus, and aural fullness, in the left ear (B). ABR study was WNL to right ear stimulation, and abnormal (retrocochlear) to left ear stimulation. He was started on oral prednisone 1 mg/kg daily and returned 1 month post-steroids with improved symptoms and hearing (C). Contrast enhanced FLAIR (left panel) and T1 (right panel) MRIs on D) day 1 and E) 30 days after oral corticosteroids. White arrow points to the 8th cranial nerve on day 1; Blue arrow indicates the 8th cranial nerve 30 days after pulse corticosteroids.

Table 1.

Characteristics of 29 patients with central nervous system cryptococcosis

Variable	
Median age	54 [IQR:46.0–60.5]
Female	8
Race:	
White	21
African American	1
Hispanic	4
Asian	3
Cryptococcal species	
C. neoformans	19
C. gattii	6
Unknown	4
Median CD4 T cell count, cells/ml	694 [IQR: 343–1054]
Median CD8+ T cell count, cells/ml	351 [IQR: 180.5–646.5]
Anti-GMCSF antibody	2
Median CSF Cryptococcal antigen titer	1:128 [IQR: 1:8 – 1:832]
Median CSF glucose	33 [IQR: 20–45]
Median CSF WBC	98 [IQR: 9 – 234]
Presence of Shunt	3
Median time between diagnosis and exam, yr	1.5 [IQR: 0.5–3.25]
Antifungal treatment	
Lipid amphotericin B, wks	4 [Range: 2 – 16]
Fluconazole, yr	1 [Range: 1–3]
None	
Oral adjunctive corticosteroids	10
(1 mg/kg prednisone equivalent, then taper over 6–8 months)	
Signs and Symptoms at time of study	
Fever	7
Change in mental status	10
Headache	21
Visual changes	1
Subjective hearing loss	2
Tinnitus	3
Vertigo	8
Nausea/vomiting	9
Lethargy	15