THE CAUSES OF HEARING LOSS IN HIV INFECTION

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HIV Infection

Infection with human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS), is a major health problem worldwide, with approximately 38 million adults and 2.3 million children (under 15 years of age) currently living with HIV infection. In 2005, there were approximately 4.9 million new HIV infections and 3.1 million AIDS related deaths. Sub-Saharan Africa has the largest burden of infection worldwide (UNAIDS 2005; http://www.unaids.org/Epi2005/doc/EPIupdate2005_pdf_en/epi-update2005_en.pdf).

HIV can be isolated from several body fluids including semen, cervical secretions, blood and breast milk. The commonest route of transmission of HIV infection is by sexual intercourse. Other routes include receiving contaminated blood products or the use of contaminated needles. Mother to child infection, termed vertical transmission, is the commonest route of HIV infection in children, with the majority of infections occurring perinatally. Vertical transmission can be reduced by the use of antiretroviral drugs (used in the treatment of HIV infection), the avoidance of breast feeding and delivery by Caesarian section.

The HIV virus infects cells of the immune system and in particular CD4+ T cells which play an important role in the immune response to both HIV infection and many other infectious organisms. Defects in CD4+ T cell function are observed in HIV infection and their numbers in peripheral blood decline with advancing disease. When the CD4+ T cell number falls below 200 x 10^6/l an individual with HIV infection is particularly prone to certain types of infections, termed opportunistic infections.

The World Health Organization (WHO) describes four stages of HIV infection in adults and adolescents and three stages in children.[1] (http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf). Antiretroviral therapy is recommended in resource-limited settings for adults and adolescents with advanced HIV infection (WHO Stage IV disease and individuals with WHO Stage III disease with a CD4+ T cell count < 350 x10^6/l) - and those with WHO Stage I and II disease with a CD4+ T cell counts ≥ 200 x10^6/l. Treatment is recommended in children with advanced disease (WHO Stage III) and those with WHO Stage I or II disease with a low CD4+ T cell percentage (the CD4+ T cell percentage threshold varies depending upon the age of the child). Currently, less than 5% of individuals in resource-limited settings who need antiretroviral therapy have access to it. The WHO '3 by 5' initiative aims to treat 3 million individuals in resource limited settings by the end of 2005 (http://www.who.int/3by5/about/initiative/en/index.html).

Four classes of antiretroviral drugs are currently available. These include:

1. Nucleoside reverse transcriptase inhibitors (NRTIs).
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs).
3. Protease inhibitors (PIs).
4. Fusion inhibitors (used to salvage therapy when treatment options are limited).

Standard treatment regimens, termed highly active antiretroviral therapy (HAART), use triple combinations of drugs usually from two different drug classes. Adherence to HAART is important to reduce the risk of developing drug resistance that would limit future treatment options. Treatment response is determined both clinically and by the measurement of surrogate markers (CD4+ T cell count and the HIV viral load in plasma). HAART is associated with a reduction in both morbidity and mortality. Information regarding the costs of antiretroviral agents in resource limited settings are provided at the following websites:

http://www.who.int/3by5/amds/untanglingtheweb07.pdf

http://www.who.int/3by5/amds/en/AFROarvindicator.pdf

http://www.who.int/3by5/amds/sourcesAug05.pdf

Table 1: Causes of Hearing Loss in HIV Infection

Aetiology	Type of hearing loss described	Ref.
Otitis externa	CHL	2
Polyps in the external ear canal	CHL	2
Acute /recurrent otitis media	SNHL/CHL	2, 3
Otosyphilis	SNHL	3, 4
Ramsay Hunt Syndrome	SNHL	5
Medications *(see Table 2)*	SNHL	6
Direct effects of HIV on 8th cranial nerve	SNHL	7, 8, 9
Opportunistic infections		
a. Cytomegalovirus	SNHL	10
b. Extrapulmonary *Pneumocystis jiroveci*	CHL	2
c. Cryptococcal meningitis	Not stated	11
d. Invasive aspergillosis (temporal bone)	SNHL	3
HIV related malignancy	CHL	
a. Kaposi's sarcoma	Not stated	2
b. Lymphoma (tympanic membrane)		12

Footnote:
SNHL = sensorineural hearing loss
CHL = conductive hearing loss

Causes of Hearing Loss: HIV

Hearing Loss in HIV Infection

Several causes of hearing loss are described in HIV infection and these are listed in Table 1, along with the type of hearing loss described, if known. Some causes of hearing loss are common to both HIV negative and HIV positive individuals, although in HIV infection the individual may present with more severe disease. Other causes are a consequence of HIV infection itself or as a result of an opportunistic infection. The main causes of hearing loss in HIV infection are described in the following sections.

Recurrent Otitis Media

Recurrent episodes of acute otitis media (AOM) are common in children, both in HIV negative and positive individuals, and can result in hearing loss. However, AOM may be the first presentation of HIV infection in children and should always be considered in children presenting with severe disease, particularly if they fail to respond to conventional therapies, have frequent relapses or have otitis media secondary to an unusual organism(s).

The number of episodes of AOM per year in children born to HIV infected mothers, who either acquired HIV infection vertically or were subsequently found to be HIV negative (by 18 months of age), were studied by Barnett et al.[13] In the HIV negative group, the mean number of episodes of AOM per year decreased during the first three years of life whilst it increased in the HIV positive group. By three years of age, all HIV positive children had experienced at least one episode of AOM, compared to 75% in the HIV negative group - and 80% of the HIV positive children had experienced 6 or more episodes of AOM compared to 0% in the HIV negative group. The frequency of AOM episodes in the HIV positive children was associated with their CD4+ T cell counts; children with lower CD4+ T cell numbers had more episodes of AOM compared to those with normal CD4+ T cell counts.

Otosyphilis

Syphilis, is caused by the spirochaete, *Treponema pallidum*, and should always be considered in any HIV positive individual presenting with a unilateral or bilateral sensorineural hearing loss that often rapidly progresses. The hearing loss may fluctuate in severity and be relatively sudden in onset. The majority of HIV positive individuals described presenting with hearing loss secondary to syphilis infection had latent syphilis at the time of diagnosis.[4] It has been hypothesised that co-infection with HIV may accelerate the development of otosyphilis. Little information is available regarding the treatment of otosyphilis in HIV infection and, in particular, whether steroids should be used in addition to penicillin therapy.

Ramsay Hunt Syndrome

Herpes zoster virus infections occur more frequently in HIV positive individuals and are often associated with more severe disease, such as the involvement of multiple dermatomes in shingles or the presence of disseminated disease. Ramsay Hunt syndrome is well described in HIV negative individuals and it remains unclear whether HIV positive individuals have a more severe form of the condition. It usually presents with unilateral ear pain, a vesicular rash and a facial palsy on the side of the ear lesions.[5] Unilateral hearing loss and impairment of balance mechanisms are described. The facial weakness often fails to completely recover.

Medications

Several medications are used in the treatment HIV infection. Complications are potentially ototoxic and may result in a sensorineural hearing loss; see Table 2. Damage to the auditory pathways may be a consequence of direct effects on the hair cells within the inner ear or as a result of toxic metabolic effects on the stria vascularis in the inner ear.[6] The reversibility of the hearing loss observed is usually drug dependent and dose related.

A few individuals receiving antiretroviral therapy containing at least one or two of the NRTIs listed in Table 2 have subsequently developed a hearing loss.[17,18] It is unclear whether certain NRTIs or combinations of NRTIs are more likely to cause otoxicity and whether the damage is potentially reversible, if detected early. The proposed mechanism of the ototoxicity is direct damage to mitochondrial DNA. Mitochondrial toxicity has been associated with other side effects related to NRTIs including peripheral neuropathy, pancreatitis and the development of lactic acidosis. It is possible that mitochrondrial DNA damage could be responsible for the development of hearing loss, as several hereditary conditions with known mutations in mitochondrial DNA have hearing loss as a clinical feature.

There is only one report of hearing loss in a HIV positive individual receiving

Table 2: Drugs used in the Treatment of HIV Infection and its Complications that may be Associated with Hearing Loss

Drug Class	Examples	Organism	Reference
Antibiotics			
Aminoglycosides	e.g., amikacin	*Mycobacterium tuberculosis*	6, 14
	streptomycin	*Mycobacterium tuberculosis*	6, 14
Macrolides	e.g., azithromycin	MAI	6
	clarithromycin	MAI	6
		Toxoplasmosis gondii	
Co-trimoxazole (Trimethoprim - (sulphamethoxazole)		*Pneumocystis jiroveci*	15
Antifungal agents	e.g., amphotericin	*Cryptococcus*	16
Antiretroviral agents			
NRTIs	e.g., zidovudine	HIV	17, 18
	didanosine	HIV	17, 19
	stavudine	HIV	18
	lamivudine	HIV	18
Antiviral agents Nucelotide analogue	cidofovir	Cytomegalovirus infection	20

Footnote:
MAI = *Mycobacterium avium-intracellulare*
For information on the treatment of these infections in HIV infection see reference 21.

antiretroviral therapy with a protease inhibitor based regimen, namely lopinavir-ritonavir.[22] The patient was also taking azithromycin, a known ototoxic drug.[6] A potential drug interaction between ritonavir and azithromycin may have been responsible for the hearing loss observed, as ritonavir is a potent inhibitor of cytochrome P450, a liver enzyme that is involved in the metabolism of many drugs. Inhibition of this enzyme may have resulted in increased blood levels of azithromycin.

HIV

HIV can infect the central nervous system and may potentially affect the eighth cranial nerve directly causing a sensorineural hearing loss. In one case series, 4 out of 18 HIV positive patients described a hearing loss that could not be attributed to another cause.[7] Seven of these individuals had abnormal pure tone audiometry (PTA) findings, of which four had bilateral changes.

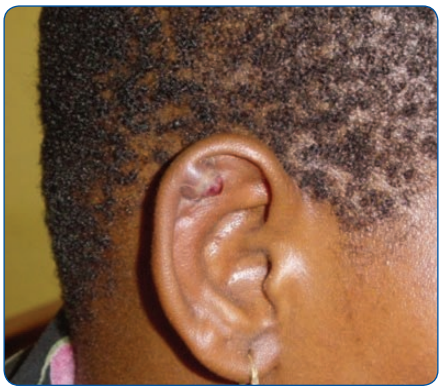
Sudden bilateral sensorineural hearing loss has been described in one patient who presented with symptoms compatible with primary HIV infection but at the time of testing had a fully positive HIV antibody response (no IgM detected).[8] Examination of the cerebrospinal fluid revealed oligoclonal bands directed against HIV-1 p24 antigen, consistent with HIV infection within the central nervous system.

Opportunistic Infections

Hearing loss has been described in several opportunistic infections associated with HIV infection (see Table 1).

Cytomegalovirus (CMV) infection usually occurs in individuals with advanced HIV infection, with a persistent CD4+ T cell count less than 50 x10^6/l. Common presentations include a retinitis (may result in blindness), colitis, pneumonitis or an encephalitis. Hearing loss associated with CMV infection has been described in a few cases and improvements in hearing have been described following antiviral therapy.[10]

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) often presents subacutely with a potentially life-threatening pulmonary infection. It usually occurs in HIV positive individuals with a CD4+ T cell count less than 200 x 106/l. Manifestations outside the respiratory system are rare and include otitis media and mastoiditis.[3]



Kaposi's sarcoma of the pinna
Photo: Piet van Hasselt

Cryptococcal meningitis, caused by the fungus *Cryptococcus neoformans*, usually presents with a headache and a fever in HIV positive individuals with a CD4+ T cell count of less than 100 x10^6/l. It can present with confusion and seizures and may be insidious in onset. Involvement of cranial nerves has been described and hearing loss documented in a few instances.[11] It is unclear whether the hearing loss observed is a direct result of infection of the eighth cranial nerve or a consequence of the raised intracranial pressure frequently seen in this condition.

Chronic osteomyelitis of the temporal bone, due to *Aspergillus* infection, has been described in at least one HIV positive individual presenting with a unilateral hearing loss.[3] The diagnosis was confirmed histologically and by culture.

HIV Related Malignancies

There are only a handful of case reports of HIV positive patients developing a hearing loss as a consequence of a HIV related malignancy such as Kaposi's sarcoma (KS) or a lymphoma. Both these malignancies are AIDS defining illnesses.

KS is a tumour arising from vascular and lymphatic endothelium (cell layer lining the vascular and lymphatic vessels). It is characterised by palpable, firm, purple/brownish plaques or nodules on the skin (Figure 1) and may be a result of infection with Kaposi's sarcoma herpes virus type 8 (KSHV8). Three clinical presentations of KS are recognised: a) a sporadic/classic form, originally described in Jews b) an endemic form, described predominantly in males from central Africa, and c) the immunosuppressed form seen in HIV infection.

HIV related KS is commonly seen in homosexual men and often presents with widespread skin and mucous membrane involvement (especially in the mouth on the hard palate). Lesions affecting the skin of the outer ear may potentially obstruct the external auditory canal resulting in a conductive hearing loss. KS may also affect other organs including the gastrointestinal tract, the lungs and the lymph nodes. Specific treatment is often not required as the lesions usually regress once the patient commences HAART. For localised disease radiotherapy, or intralesional chemotherapy (injection directly into the lesion) is sometimes indicated.

Lymphoma of the tympanic membrane has been described in one HIV positive patient presenting with left sided ear pain, hearing loss and facial weakness.[12] Examination of the ear revealed a mass behind the tympanic membrane which histologically was confirmed as a high grade, B-cell lymphoma.

Discussion

Hearing loss is an important and often overlooked clinical manifestation of HIV infection and may represent the first sign of an individual's HIV disease. A high level of suspicion is, therefore, required to consider HIV infection in the differential diagnosis of an individual presenting with a hearing loss. The severity of the clinical presentation, the frequency of relapses (if relevant) and the identification of unusual causative organisms (e.g., opportunistic infections) should alert the health worker to the possibility that the patient is immunosuppressed.

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MALARIA AND DEAFNESS

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An estimated 2.7 million people die from malaria annually, the majority of whom are children and, in fact, account for 11% of childhood deaths in developing countries. Like all serious infections, for example, meningitis and encephalitis, malaria has been implicated as a cause of deafness and, according to Sowumni (1997)[1] is a recognised complication of cerebral malaria. Several studies in West Africa have confirmed the link between malaria and deafness.[2] Many factors, among them age, type of fever, low immunity, and type of malarial parasite may be responsible for auditory changes. Problems of balance after malaria are not often reported.

The mechanism is not clear but the hearing loss is usually sensori-neural suggesting damage to the cochlea itself or somewhere along the eighth nerve pathway.

Anti-malarials and Otoxicity

It has been known for many years that most anti-malarials are ototoxic and, in fact, the most commonly used anti-malarial, quinine, has developed very many side effects, known as cinchonism which include deafness and tinnitus. The mechanism of action of quinine has not been determined but it appears to interfere with the function of plasmodial DNA. It can also be used for night cramps and is found as a 'filler' for narcotic drugs. Much of the information available about toxicity is in relation to oculotoxicity and cardiotoxicity.[3] There have been no longitudinal studies on children with cerebral malaria and, mainly because of its high mortality, the hidden disability is not recognised.

Ototoxicity and neurotoxicity have been implicated with other anti-malarials, mefloquine and chloroquine.[4] It has been suggested that the ototoxicity of the anti-malarials may have a common pathway, involving the exposure of the auditory neurones to harm. Studies of the hearing loss attributed to quinine drug treatment show that it is usually reversible, pointing to drug rather than disease as a cause of deafness.

More recent clinical experience with artemisinins has shown them to be the most rapidly acting anti-malarial available.[5] They tend to be used in those areas where there is widespread resistance by *Plasmodium falciparum*. The artemisinins have been viewed favourably as a critical intervention. They have a short half life and should be used in combination with lumefantrine. This combination is known as a co-artemether and its ototoxic effect has been shown in a study by Toovey and Jamieson in South Africa.[6] The disease and treatment of malaria can give rise to loss of hearing and/or tinnitus. Fortunately, many of the effects are reversible but when managing malaria in the ideal situation, pre-treatment auditory assessment should be made - and the possibility of residual tinnitus or deafness should be kept in mind when treating a patient for malaria.