Critical Review: What is the Existing Evidence of the Impact of Antiretroviral Drugs and Human Immunodeficiency Virus on the Auditory System?

Mrema, Y.
M.Cl.Sc. (Aud) Candidate
School of Communication Sciences and Disorders, U.W.O

This critical review examines the current research on the impact of circulating antiretroviral agents and HIV on the auditory system. Each of the studies adopted group comparison and descriptive case-control studies. Overall, research findings indicate that HIV and/or antiretroviral agents evoke changes in the auditory system and upper and lower brainstem of HIV infected adults; however, less consideration has been directed at examining the impact of antiretroviral drugs and HIV on the auditory system in the pediatric population.

Introduction

Human Immunodeficiency Virus (HIV) has a dramatic impact on the practice of medicine, including audiology. More than thirty percent of patients diagnosed with the HIV virus have clinical findings in the audiological region. Numerous studies such as those by Polich et al. (2002) and Linnville et al. (1997) have shown that HIV, which is caused by retrovirus, has a neurological impact on the central nervous system (CNS) as well as reported cognitive impairment in a percentage of HIV infected subjects. Clinical presentation of HIV involves opportunistic infections such as cancer and tuberculosis.

Marra and her colleagues indicated that hearing loss caused by antiretroviral drugs could be a result of compromised mitochondrial energy production in the inner ear. Nucleoside antiretroviral agents damage mitochondrial DNA by acting as mitochondrial DNA chain terminator. Other mutations seen in HIV patients with hearing loss are mitochondrial DNA point mutation and deletion. Mitochondrial DNA abnormality is known to accumulate with age; so older individuals may be more susceptible to mitochondrial DNA damage induced by antiretroviral agents.

HIV has a growing mortality rate and reduced quality of life of those infected. Although antiretroviral therapy has shown prolonged life expectancy within this population, the therapy itself is toxic. As future audiologists, we need to be familiar with ways in which the virus and its treatment options can affect the auditory system and possible recommendations to give to persons with HIV.

To date, almost all of the research conducted has concentrated on the adult population. For this critical review, the studies discussed will analyse the impact HIV and/or antiretroviral agents have on the auditory system of adult participants. Research has been unable to isolate definitely the effects of HIV on the auditory system from that of antiretroviral agents.

Objective

The primary objective of this paper was to critically evaluate the existing literature pertaining to the impact of antiretroviral drugs and HIV on the auditory system of adults. The secondary objective was to enlighten audiologists on current findings regarding this subject and propose recommendations on how to proceed with HIV patients in clinical audiological settings.

Methods

Search Strategy

Computerized databases, including CINAHL, Medline and PubMed, were searched using the following search strategy:

((HIV) OR (antiretroviral agents) OR (zidovudine) OR (antiretroviral therapy) AND (hearing loss) OR (hearing) OR (brainstem)).

This strategy was unsuccessful; therefore, other articles were discovered through article referencing.

The search was limited to articles written in English.

Selection Criteria

Research studies selected for inclusion in this critical review paper were required to investigate the effect of HIV and antiretroviral drugs on the auditory system of adult subjects. The original focus was strictly the pediatric population, but due to the

limited research with this population, studies involving any children were excluded. The limited amount of research can be explained by possible ethical considerations on conducting studies on human children. No limits were set regarding the methodological design or outcome measures.

Data Collection

Results of the literature search yielded four articles congruent with the aforementioned selection criteria that were descriptive group comparison designs.

Results

Impact of HIV on the auditory system

Birchall et al. (1992) conducted a case controlled study with HIV subjects from the Centre for Disease Control (CDC). The study evaluated the impact of HIV on the auditory function of adults. This was achieved by objectively measuring their pure tone thresholds and brainstem auditory evoked responses (BSERs) and comparing them to age and sex-matched normative data obtained from National Physical Laboratory Data. Pure tone audiometry was performed using TDH headphones. Air conduction and bone conduction thresholds were obtained from 250 Hz to 8 kHz and 500 Hz and 4 kHz respectively. Air conduction threshold levels at 1, 2, 4 and 2, 4, 8 kHz were then averaged. BSERs and I-V, I-III and III-V interwave intervals were recorded using alternative clicks administered at 70 dB above hearing threshold. White noise was presented to the opposite ear at 40 dB below stimulus.

The researchers recruited 18 male patients from CDC. All were HIV antibody positive with no clinical or serological evidence of syphilis. Patients were previously classified using the CDC groupings into group II, III and IV disease on the basis of clinical findings. Group II consisted of patients with asymptomatic infections. Group III patients had persistent glandular lymphadenopathy and group IV was comprised of patients with Acquired Immunodeficiency Syndrome (AIDS), symptomatic infections and especially neurological abnormalities and cancers. The study applied inclusion criteria such as normal middle ear function. Strict exclusion criteria such as prior use of antiretroviral drug, history of industrial noise exposure were also included because of the potential effect on the central nervous system and evoked potential responses.

Appropriate statistics were used to analyze the data. The outcome of this study indicated that 56% of the subjects complained of otological symptoms since being diagnosed with HIV. These symptoms included tinnitus, deafness, feeling of "pressure" in the ear and vertigo. Abnormal pure tone results were found in 39% of the subjects and, of these, 22% had bilateral abnormalities. There was an increase in latencies in all of the waves when compared to norms in 28% of the subjects. Wave III delay was observed in 39% of the subjects. No significant difference was observed between the three HIV groups in pure tone average results and BSER interpeak latencies I-V, I-III and III-V.

Pagano et al. (1992) examined the effect of HIV on the auditory system. The researchers compared the BSERs of HIV positive subjects from CDC groups III and IV with control groups: HIV negative drug abusers and normal healthy controls. Researchers recruited 35 male and female HIV positive subjects, some of whom were drug abusers. The drug abusers control group consumed the same drugs as the HIV positive group. All subjects had normal hearing at the time of BSER measurement. Pure tone audiometry and BSERs results were obtained and compared to normative control groups. Electrode placement was the same as the study carried out by Birchall and his colleagues. However, a square-wave compression click stimulus of 0.1 ms duration was presented at 60 dB normal hearing level during this study. A strict inclusion and exclusion criteria were applied; however the use of antiretroviral drugs with HIV positive patients was not indicated in this study.

After application of statistical measures, it was found that interwave latencies I-V and III-V were higher in HIV positive subjects and significantly higher in subjects with a more severe HIV condition. There was no significant difference in interwave latencies between the HIV positive groups. There was also no significant difference between the interwave latencies of the normal healthy group and HIV negative subjects.

Impact of HIV and antiretroviral agents on the auditory system

Marra et al. (1997) studied the association between hearing loss and antiretroviral therapy in HIV infected subjects. The case-control study involved 99 middle-aged male and female subjects recruited from a university-based HIV clinic. A standardized interview was conducted focusing on risk factors associated with hearing loss. Hearing thresholds were measured at 1, 2 and 4 kHz using a portable audiometer. Hearing loss was defined as

threshold higher than 25 dB Hearing Level at 4 kHz in one or both ears.

The outcome of this study indicated that 32% of the subjects had hearing loss with 59% of these having bilateral loss. Hearing loss was common to subjects who were taking antiretroviral agents. There was a significant association between hearing loss and antiretroviral therapy for subjects aged 35 years and older and not for those younger than 35 years. Another common otological complaint was tinnitus in 30% of the subjects.

Chandrasekhar et al. (2000) quantified the incidence of ear disease in patients infected with HIV. The study achieved this by carrying out a descriptive data collection using an otologic examination and questionnaire and an audiological evaluation. Pure tone audiometry, speech discrimination scores, immittance and otoacoustic emissions (OAE) were evaluated on each patient.

A sample of 50 male and female HIV positive subjects were recruited exclusively based on their HIV positive status and not based on their otological history or complaint. The collected data were compared to established norms, though the specificity of the normative data was not specified. Subjects were divided according to CDC categories based on the opportunistic diseases they possessed and the severity of their HIV condition.

The results demonstrated a significant degree of high frequency sensorineural hearing loss. An interesting finding revealed subjects in their 30s had significantly better hearing thresholds than older and younger subjects. Patients in their 20s had average hearing thresholds closer to those patients in their 40s and 50s. Thirty-four percent of the subjects reported aural fullness, 32% complaint of dizziness, 29% reported some degree of hearing loss, 23% reported otalgia and 5% reported otorrhea. Patients with severe cases of HIV had a greater degree of hearing loss. Those with diagnosed hearing loss had poor OAE results. Frequent otologic diagnoses encountered in the HIV subjects included otitis externa, acute otitis media and otitis media with effusion.

Discussion

The aforementioned research indicates that HIV and/or antiretroviral therapy have an effect on the auditory function. However, the inadequate sample size makes the interpretation of the results questionable. Birchall et al. (1992) was the only study found that examined the effect of HIV in the absence of antiretroviral therapy on the auditory system. This study did not include female participants, which is not representing the full spectrum of the population affected by HIV. This study also did not analyse the integrity of outer hair cell function prior to the participants' involvement in the study and so may be affected by peripheral hearing loss.

Another concern was the study by Pagano et al., which expanded the HIV population to include HIV drug abusers. The researchers also included two control groups: normal healthy controls and HIV negative drug abusers. However, the researchers did not indicate whether the HIV positive participants were receiving any antiretroviral therapy during the time of the study.

A final concern was that only high frequencies were being evaluated in all reviewed studies and thresholds at interoctaves were not obtained. Marra et al. only tested threshold at three decibel levels: 25, 40 and 60 dB HL. The reliability of the data is weak as a portable audiometer was used during data collection. The researchers did not state whether a sound booth was used during the study. The fail criterion for this study was greater than 25 dB HL at 4 kHz, which further decreased the reliability of the findings.

In the studies that required the HIV positive subjects to take an antiretroviral drug, there was no indication of whether a strict compliance to take the drug was reinforced. In all the studies, it is difficult to isolate the effect of HIV alone from that of HIV and/or antiretroviral therapy. It is challenging to find HIV positive subjects who have not undergone the antiretroviral therapy. It is also difficult to really know if the effects on the auditory function are due to HIV alone or possibly one of the numerous opportunistic diseases that accompany HIV.

Conclusion

Upon evaluating and analyzing the existing research on the impact of HIV and antiretroviral drugs on the auditory system, it is clear that HIV and/or antiretroviral drugs have an effect on the auditory function. HIV and antiretroviral drugs have shown changes in the auditory and both lower and upper brainstem function as demonstrated by increased latencies of waves III and V. However, it is evident that appropriate audiological tests need to be done for HIV patients and they need to be monitored on a consistent basis.

Recommendations

There is a need for future research in this area to better understand the effect of the HIV disease and antiretroviral agents on the auditory system in both the pediatric and geriatric population. Further studies should be conducted focusing on the suprathreshold hearing in HIV positive subjects and larger sample sizes need to be used. New research should aim at conducting more broad vigorous tests rather than just high frequency pure tone audiometry to represent other otological abnormalities that are beyond the peripheral system.

Audiologists need to consistently monitor the HIV positive patients in their clinics. Antiretroviral therapy has been shown to dramatically decrease the death rates, frequency and severity of opportunistic infections among HIV positive patients. Hearing aids, tinnitus maskers and assistive listening devices are possible options for this population as with the available drugs, HIV infected patients are living much longer than a decade ago. As audiologists, we need to improve their quality of life to ensure they continue to participate in the activities they once were a part of prior to their audiological abnormalities.

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