Antiviral Therapy in a Child with Pediatric Human Immunodeficiency Virus (HIV): Case Study of Audiologic Findings

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Abstract

Over the past decade, much research has been conducted to determine the auditory consequences of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). This research, primarily using adult patients, has focused on the involvement of the central auditory nervous system (CANS). Measures of auditory evoked potentials, particularly the auditory brainstem response (ABR), can document changes in the CANS as the disease progresses and during treatment with antiviral therapies such as zidovudine (AZT) and didanosine (ddI). This case study presents the audiologic findings for a child with HIV infection. Evaluations were performed over a 2-year period prior to the initiation of antiviral therapy and following treatment. Audiologic measures included behavioral audiometry, tympanometry, otoacoustic emissions, and ABR latency/intensity functions and rate studies. Findings indicated a gradual shortening of all ABR component latencies following the initiation of antiviral therapy. In addition, a high-frequency hearing loss was detected during the final evaluation subsequent to 19 months of treatment with AZT and ddl.

Key Words: Auditory brainstem response, human immunodeficiency virus, ototoxicity, pediatric acquired immune deficiency syndrome, transient evoked otoacoustic emissions

Abbreviations: ABR = auditory brainstem response, AEP = auditory evoked potential, AIDS = acquired immune deficiency syndrome, AZT = zidovudine, CANS = central auditory nervous system, CMV = cytomegalovirus, ddI = didanosine, HIV = human immunodeficiency virus, IPI = interpeak interval, OAE = otoacoustic emissions, VRA = visual response audiometry

Pediatric human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) were initially described in 1982 (Centers for Disease Control [CDC], 1982; Oleske et al, 1983; Rubinstein et al, 1983). There are approximately 1500 new pediatric cases of HIV infection reported to the CDC each year and, at the end of June 1997, 7902 children had been diagnosed with pediatric AIDS in the U.S. (CDC, 1997). Approximately 90 percent of children with HIV infection contract the virus vertically from their mothers (CDC, 1997). The rate of transmission of HIV from a positive mother to her child varies from under 10 percent to up to 42 percent (European Collaborative Study, 1991; Dabis et al, 1993; Simonon et al, 1994). Administration of zidovudine (AZT) to already identified HIV-infected pregnant women and their newborns has reduced the vertical transmission of HIV in the U.S. from 22.6 percent to 7.6 percent (Connor et al, 1994). The mean survival time in the U.S. for a child infected vertically by HIV is 9.4 years (Kline, 1995). Due to the route of transmission and age when first infected, pediatric HIV differs from adult HIV infection. Specifically, HIV
attacks an immature immune system in a child. For this reason, the manifestations of the infection are not identical in children and adults.

Audiologic manifestations of HIV infection and AIDS are considered a direct consequence of the virus or secondary to pharmacologic treatment or viral complications (Bankaitis and Keith, 1995). Due to the involvement of the central nervous system in HIV infection, the most direct consequence to the auditory system is central auditory nervous system (CANS) abnormalities, some of which can be measured with auditory evoked potentials (AEPs). Auditory brainstem response (ABR) findings in adults with HIV and AIDS include prolonged absolute latencies of waves III and V and/or interpeak intervals (IPIs) of III–V and I–V (e.g., Lipton et al, 1988; Rosenhall et al, 1989). Less research with AEPs has been reported in children, and less agreement has been found among these studies. Findings in children include bilaterally prolonged I–V IPIs (Belman et al, 1985; Ultmann et al, 1985), unilateral I–V delays (Ultmann et al, 1985), unilateral delays of the I–III and III–V IPIs and delayed onset of wave I (Schmitt et al, 1991, 1992), and an abnormal response to increased rate of stimulus presentation (Belman et al, 1985; Frank et al, 1992; Frank and Pahwa, 1993).

Other audiologic findings in HIV and AIDS patients are secondary to complications and pharmacologic treatment. Many patients with AIDS complain of vertigo, tinnitus, and hearing loss. More specifically, audiologic complications include external otitis, otitis media, ototoxicity, and sensorineural hearing loss due to opportunistic infections. Opportunistic infections associated with otologic complications include herpes simplex virus, cytomegalovirus (CMV), and herpes zoster oticus (Rarey, 1990). In addition to these opportunistic infections, the treatment of HIV and AIDS patients relies on drug combinations that are potentially ototoxic to the patients (Bankaitis and Keith, 1995). However, antiviral drugs, while possibly ototoxic, have widespread important benefits, some of which may be measured using the ABR.

AZT and didanosine (ddI), two antiviral medications, have been shown to be effective in treating children with HIV (NIAID, 1997). Studies have shown that treatment with AZT can help a child grow and gain weight, as well as improve declining cognitive function and motor skills (NIAID, 1997). The ABR has shown promise in monitoring some central changes with antiviral therapy. Brivio et al (1991) reported on a 6.5-month-old boy with AIDS treated with AZT for 12 months. ABRs were recorded prior to and following initiation of therapy. Results indicated prolonged I–V IPIs at the initial test date. The I–V IPI gradually shortened over the 12 months of treatment with AZT and this shortening could not be attributed to maturation alone. Schmitt et al (1992) also reported on a child before and after treatment with AZT. Their study shows the return of a normal ABR after treatment with AZT. We report on the audiologic findings of one child before and after treatment with AZT and ddI.

CASE REPORT

History

This African-American female child was born December 13, 1993 at full term. The child's mother was HIV positive at the time of the child's birth; however, she reported that she was unaware of her HIV status. She was initially seen on January 19, 1994 at our HIV clinic. At that time, the child was classified as PO (indeterminate infection) by the 1987 CDC classification system for pediatric AIDS (CDC, 1987). Note that at the time this child was first evaluated, the true status of a child's HIV infection could not be determined for up to 15 months following birth due to the mother's antibodies present in the infant's blood. For this reason, children were classified as P0 (indeterminate infection) by the 1987 CDC classification system for pediatric AIDS (CDC, 1987). Note that at the time this child was first evaluated, the true status of a child's HIV infection could not be determined for up to 15 months following birth due to the mother's antibodies present in the infant's blood. For this reason, children were classified as P0 until AIDS symptoms appeared or the child began to test negative for HIV, termed seroreversion. Today, more sensitive tests exist and an infant's HIV status can be determined as early as 30 days after birth. Three serial audiologic studies were performed on this child at age 21 months, 34 months, and 43 months. At the time of all three test sessions, the child was classified as P113 (asymptomatic HIV infection with abnormal immune function). Thus, the child was known to be HIV positive with decreased immune system function; however, she presented with no symptoms of full-blown AIDS. In addition, the child did not have any significant otologic history, including otitis media.

Pharmacotherapy

The child was placed on prophylactic bactrim...
that the prescription was not consistently given by her parents. Prophylactic bactrim is routinely prescribed for all HIV-positive infants to prevent infection. On December 8, 1995, when the child was 24 months of age, she was placed on antiviral therapy consisting of AZT and ddI. These antiviral medications were also given sporadically until custody of the child was given to the maternal grandmother in the fall of 1996. The child has remained on AZT and ddI since that time.

**Evaluation 1**

The first audiologic evaluation took place on September 15, 1995 when the child was 21 months of age. At the time of this testing, bactrim was the only prescribed medication. As previously stated, the child was HIV positive and showing abnormalities of the immune system. Although the child was almost 2 years old, she would not tolerate earphones and could not be conditioned for play audiometry. For this reason, visual response audiometry (VRA) was used to measure behavioral thresholds. Results of behavioral VRA to warble tones and speech in the sound field can be seen in Table 1. These sound-field thresholds were within normal limits. Tympanometry was attempted during this visit; however, the child would not tolerate the probe in her ear. Transient evoked otoacoustic emissions (OAEs), measured while the child was sedated, can be seen in Figure 1 for this child's right and left ears, respectively. Emissions were present from 800 to 4000 Hz with an overall response of 18.8 dB for the left ear and 21.1 dB for the right ear. Figure 2 shows a wave V latency/intensity function for click stimuli at presentation levels of 20, 30, and 60 dB HL (10, 20, 50 dB nHL) re: 30 dB peSPL were used. The circles and the squares represent the right and left ears of the child, respectively. The lines represent ±1 standard deviation from the mean of normative data from Cevette (1984) from 50 children, 20+ months old. Thus, the normal latency values would fall within the area between the solid lines. Measurement parameters: click, 0.1 msec, 27.7/sec, ER-3A insert earphones; acquisition-filters, 100–3000 Hz, 6 dB/octave; sensitivity, 50 µV.

![Table 1](image)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
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<th>4000</th>
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*Thresholds measured in dB HL.

![Figure 1](image)

**Figure 1** Transient evoked otoacoustic emissions for the left and right ears from evaluation 1.

![Figure 2](image)

**Figure 2** Wave V latency/intensity functions from evaluation 1. Clicks were presented at 27.7 per second through ER-3A earphones. Presentation levels of 20, 30, and 60 dB HL (10, 20, 50 dB nHL) re: 30 dB peSPL were used. The circles and the squares represent the right and left ears of the child, respectively. The lines represent ±1 standard deviation from the mean of normative data from Cevette (1984) from 50 children, 20+ months old. Thus, the normal latency values would fall within the area between the solid lines. Measurement parameters: click, 0.1 msec, 27.7/sec, ER-3A insert earphones; acquisition-filters, 100–3000 Hz, 6 dB/octave; sensitivity, 50 µV.
Evaluation 2

Evaluation 2 was completed on October 31, 1996 when the child was 34 months old. At the time of this evaluation, the child was taking AZT, ddI, and bactrim. The child's grandmother reported consistent usage of all medications. Behavioral testing and OAEs were not completed at this evaluation because of time constraints. However, hearing sensitivity can be estimated from the click and tone burst ABR

30 dB HL. Although not plotted in this figure, similar prolongations were seen for waves I and III. Thus, the absolute latencies but not the IPIs were prolonged, as seen in cases of conductive hearing losses. However, the prolongations of waves I, III, and V in this child are in the absence of any conductive hearing loss as evidenced by the normal OAEs and VRA. In addition, both a 500-Hz and 8000-Hz tone burst ABR could be measured at normal levels (45 dB HL or 15 dB nHL [500 Hz] and 25 dB nHL [8000 Hz]). Figure 3 plots the absolute latencies of waves I, III, and V for the left and right ears of this child as represented by the squares and circles, respectively, at the three click presentation rates (7.7, 27.7, and 57.7 clicks/sec). All rate studies were performed at a level of 60 dB HL (50 dB nHL). Plotted next to the latencies for the child are the means (filled triangles) and ± 1 standard deviation error bars for six matched HIV-negative control subjects. There is a tendency for all components of this child's ABR to be slightly prolonged in relation to the HIV-negative controls. However, the IPIs of this child were not found to be prolonged in relation to the HIV-negative controls.

Evaluation 2

Evaluation 2 was completed on October 31, 1996 when the child was 34 months old. At the
findings. Figure 4 shows the wave V latency/intensity function for click stimuli at levels of 20, 30, and 60 dB HL (10, 20, and 50 dB nHL). As can be seen, wave V latencies have decreased significantly from evaluation 1 and now fall within the normative area. Note that the normative area between the solid lines does not vary from Figure 2 to Figure 4. ABRs to 500 Hz and 8000 Hz tone bursts were also obtained at normal levels bilaterally (45 dB HL or 15 dB nHL [500 Hz] and 25 dB nHL [8000 Hz]). From these ABR data, responses to click stimuli at 20 dB HL (10 dB nHL), and responses to 500 Hz and 8000 Hz tone bursts at 45 dB HL (15 dB nHL [500 Hz] and 25 dB nHL [8000 Hz]), normal hearing sensitivity can be inferred. Figure 5 plots the absolute latencies of waves I, III, and V for the left and right ears at the three click rates following evaluation 2. All rate studies were performed at a level of 60 dB HL (50 dB nHL). A comparison of this figure with Figure 3 again shows a decrease in the ABR component latencies since evaluation 1. Finally, the IPIs of this child’s ABR were not found to be prolonged in relation to the HIV-negative controls for this evaluation as well.

Evaluation 3

Evaluation 3 was completed July 24, 1997, when the child was 43 months old. At the time of this evaluation, the child was still classified as P1B according to the 1987 CDC classification system and was continuing to take AZT and ddI as antiviral therapy. However, viral load testing on May 7, 1997 and July 3, 1997 indicated possible viral progression. This test may indicate that the antiviral therapy is no longer effective. In addition to the antiviral agents, the child was still taking bactrim.

Again, although the child was over 3 years old, she would not tolerate earphones and could not be conditioned for play audiometry. Results of behavioral VRA testing in the sound field to warble tones and speech are found in Table 2. As can be seen, a hearing loss was detected at

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Thresholds measured in dB HL.
ABR Component Latencies for Evaluation 3

Figure 8 Absolute latencies from evaluation 3 of waves I, III, and V for the left and right ears of the child as represented by the squares and circles, respectively, at the three click rates (7.7, 27.7, and 57.7 clicks/sec). All rate studies were performed at a level of 60 dB HL (50 dB nHL). Plotted next to the latencies for the child are the means (filled triangles) and ± 1 standard deviation error bars for six matched HIV-negative control subjects.

pressure and membrane compliance. OAEs were not tested due to lack of cooperation from the child. Figure 6 again shows a wave V latency/intensity function for the results of evaluation 3. As can be seen, the wave V latencies are within the normal area or even shorter. When compared to the results of evaluation 2, this plot continues to show a decrease in wave V latency over time. ABRs were recorded for 500- and 8000-Hz tone bursts. Results indicated a response within normal limits (45 dB HL or 14 dB nHL) for 500 Hz; however, no response was obtained for the 8000-Hz tone burst at 45 dB HL (25 dB nHL). Figure 7 shows the ABR tracings for the 8000-Hz tone burst for the right and left ears of this child, respectively. The top tracings of each ear are the responses to 75 dB HL (55 dB nHL). The bottom tracings are the response to 45 dB HL (25 dB nHL). As can be seen, a robust response is measured at 75 dB HL. However, when the screening level is dropped to 45 dB HL, no response is seen. A response to 45 dB HL was seen bilaterally to the 8000-Hz tone burst in the previous two evaluations. Exact ABR tone burst threshold determination was not possible because the child awoke. These results are consistent with the behavioral findings of a sensorineural hearing loss in the high frequencies. Finally, Figure 8 shows the component latencies as a function of click rate for evaluation 3. These results are similar to evaluation 2 and to the mean results for the HIV-negative control subjects. Again, the IPIs were not found to be prolonged.

**DISCUSSION**

This paper reviews the results of three serial audiologic evaluations performed on an HIV-positive child at age 21 months, 34 months, and 43 months. The first evaluation, prior to the initiation of antiviral therapy (AZT and ddI), indicated normal hearing sensitivity measured behaviorally, with OAEs, and ABRs to click and tone burst stimuli. Developmental delays in the CANS were seen at evaluation 1 as evidenced by prolonged ABR component latencies of waves I, III, and V. At evaluations 2 and 3, a decrease in the absolute latencies of waves I, III, and V was seen. This decrease in the absolute latencies of waves I, III, and V cannot be attributed to maturation given that the child was born full term and was 21 months old at the date of the first evaluation. At the time of evaluations 2 and 3, the child was taking a combination of AZT and ddI for antiviral therapy. Behavioral VRA results and an absent 8000-Hz tone burst ABR at 45 dB HL at evaluation 3 indicated a change from this child’s normal hearing sensitivity (evaluations 1 and 2). Normal tympanograms were measured at this third evaluation, suggesting that the loss of hearing sensitivity is sensorineural in nature. The child had been on the antiviral therapies 19 months when this hearing loss was detected.

The prolongation of the absolute latencies of waves I, III, and V without a prolongation of any IPI has not been previously reported as a finding in pediatric HIV infection. This finding may represent a neurodevelopmental compromise of the auditory system that was improved with antiviral therapy. Previous research using children has reported prolonged IPIs more commonly than prolongations of absolute wave latencies. Further research is needed to determine the common ABR changes in HIV infection in children. In addition, more research is needed that uses the ABR to monitor CANS function during antiviral therapy. The finding of normal CANS function at evaluation 3 is interesting in light of two viral load tests indicating that the antiviral medications may no longer be effective. We plan to continue to monitor this child’s CANS involvement.

The finding of a sensorineural high-frequency hearing loss at the final evaluation documents the need to monitor children on antiviral therapy for possible ototoxicity, given the importance
of normal hearing for the development of speech and language. The lives of children with HIV infection are being prolonged with new antiviral therapies. Audiologists need to be aware of the possible ototoxic nature of antiviral therapies and intervene with habilitation strategies if hearing loss begins to interfere with development and communication.

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REFERENCES


