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Audiologic and vestibular findings in a sample of Human Immunodeficiency Virus type-1-infected Mexican children under Highly Active Antiretroviral Therapy

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Summary

Objective: There is little information about audiologic and vestibular disorders in pediatric patients infected with the Human Immunodeficiency Virus type-1 (HIV-1). The aim of this study was to evaluate audiologic and vestibular disorders in a sample of HIV-1-infected children receiving Highly Active Antiretroviral Therapy.
Methods: Patients underwent pure tone audiometry, speech discrimination testing, auditory brainstem responses, electronystagmography, and rotatory testing. HIV-1 viral load and absolute CD4+ cell counts were registered.
Results: Twenty-three patients were included, aged 4.5 years (median, range 5 months to 16 years). Pure tone audiometry was carried out in 12 children over 4 years of age: 4 (33%) showed hearing loss, 2 were conductive. Auditory brainstem responses were measured in all 23 patients, suggesting conductive hearing loss in 6 and sensorineural hearing loss in 2. Most patients with conductive hearing loss had the

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antecedent of acute or chronic suppurative otitis media but with dry ears at the time of evaluation ($p = 0.003$). Abnormal prolongations of interwave intervals in auditory brainstem responses were observed in 3 children (13%, 4 ears), an abnormal morphology in different components of auditory brainstem responses in 4 (17.4%, 7 ears), and abnormal amplitude patterns in 11 patients (48%, 17 ears). Vestibular tests were abnormal in all six patients tested, with asymmetries in caloric and rotatory tests. Although differences were not significant, in general, audiologic abnormalities were more frequent in patients with more prolonged HIV-1 infections, higher viral loads, or lower absolute CD4+ cell counts.

Conclusions: Conductive hearing loss associated with previous otitis media events, abnormalities in auditory brainstem responses suggesting disorders at different levels of the auditory pathways, and unilateral vestibular hyporeflexia were frequent findings in our sample of HIV-1-infected children under Highly Active Antiretroviral Therapy. These findings suggest that HIV-1-infected children should be submitted to audiologic and vestibular evaluation as early as possible in order to reduce their impact on the psychosocial development of these patients.

1. Introduction

In Mexico, about 2.4% of Human Immunodeficiency Virus (HIV-1)-infected patients are younger than 15 years old. During 2006, 5102 new cases of infection by HIV-1 were reported, and by November 2007, 2786 cases of pediatric HIV-1 infection had been reported [1]. Audiologic and vestibular symptoms occur in 5—34% of adult patients with a Human Immunodeficiency Virus (HIV-1) infection [2—7]. Audiologic symptoms include conductive hearing loss (HL), unilateral and bilateral sudden or progressive sensorineural HL, and tinnitus [3—7]. Vestibular symptoms include vertigo and ataxia with a number of oculomotor changes evident in electronystagmography (ENG), including hyporeflexia in caloric testing [2,7—9]. Several pathological changes in temporal bones have been found in HIV-1-infected adults, such as cytologic changes in hair cells in vestibular end organs that include inclusion bodies, viral-like particles, and hair bundle abnormalities. Furthermore, inclusions and viral-like particles have been observed in epithelial lining cells, supporting cells, and connective tissue cells [10,11]. Audiologic and vestibular symptoms may not be due to the direct effect of HIV infection alone, but rather to a combination of the effects of HIV infection coupled with those of opportunistic microorganisms or the ototoxic effects of treatment [3,7,12,13]. Additionally, although conductive HL has multiple causes, otitis media is one of the most frequent causes of conductive HL in both HIV-1-infected and non-infected children, and otitis media is also one of the most frequent opportunistic infections in children with AIDS [6—8,14]. Information concerning audiologic and vestibular findings in HIV-1-infected pediatric patients is scarce, and there are no studies evaluating the impact of HIV infection and antiretroviral treatment on the vestibulocochlear system in children [14]. The objective of the present study was to evaluate audiologic and vestibular disorders in a sample of HIV-1-infected children under Highly Active Antiretroviral Therapy (HAART).

2. Methods

2.1. Subjects

All HIV-1-infected patients under 17 years of age on HAART at the AIDS outpatient clinic of the Hospital de Pediatria, Centro Medico Nacional Siglo XXI, IMSS in Mexico City were eligible to be included in the study. A diagnosis of HIV-1 infection for infants less than 18 months of age was established with at least two positive HIV-1 RNA PCR assays [15,16], and for older children by detection of anti-HIV-1 antibodies by ELISA and Western blot tests [17,18]. Patients with a history of ear surgery or trauma, congenital hearing loss, or any central nervous system disease not related to HIV-1 infection were not eligible. Patients were categorized according to the 1994 CDC classification into the following groups: N = no signs/symptoms, A = mild signs/symptoms, B = moderate signs/symptoms, C = severe signs/symptoms; and 1 = no evidence of immunosuppression, 2 = moderate immunosuppression, 3 = severe immunosuppression [17]. Each patient was on HAART with either a three-drug regimen that included one protease inhibitor (PI) (Saquinavir in the form of hard gel capsules [SQVhgc]) and two nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine [ZDV] and didanosine [ddI]), or a four-drug regimen with two PIs (SQVhgc and ritonavir [RTV]) plus two NRTIs (ZDV and lamivudine [3TC]).

Drug dosages used were those recommended for pediatric patients [16,19—21]. Information about HIV disease and antiretroviral treatment was obtained by reviewing clinical charts. Written informed consent from parents or legal guardians, or from discharged patients, was obtained. The study protocol was approved by the Institutional Review Board of the Hospital de Pediatria.

2.2. Audiologic evaluation

On a prospective cross-sectional basis [22] and with a prior otoscopic examination, patients were submitted to audiologic evaluation: children younger than 4 years of age by auditory brainstem responses (ABR) (Viking III/IV P NT Nikolet Biomedical Inc., Madison, WI), and children older than 4 years of age by pure tone audiometry (PTA) (Amplaid 308, Milan, Italy) and ABR. ABR was carried out with active electrodes in A1 and A2 referred to Fpz by means of click-type alternate polarity stimuli with a frequency of 11.1 Hz for both audiologic and neurologic phases, with an analysis time of 10 ms for 1000 stimuli. Speech discrimination testing was carried out in nine patients who were able to perform the test. We considered children to have hearing loss if they demonstrated an auditory threshold elevation above 20 dB in either PTA or ABR. This variable was categorized for both PTA and ABR as follows: (a) mild HL, auditory threshold elevation of 21—40 dB; (b) moderate HL, auditory threshold 41—60 dB; (c) severe HL, auditory threshold 61—90 dB; and (d) profound HL, auditory threshold >90 dB [23]. Findings in speech discrimination testing were evaluated as previously described [24]. The ABR absolute and interpeak latencies, morphology, amplitude and ratio abnormalities for each patient were compared with published norms for infants and children [23,25—29].

2.3. Vestibular evaluation

Six children over 5 years of age who were able to cooperate were also submitted to vestibular evaluation with electronystagmography and rotatory tests (Electronystagmus Analysis and Stimulus Control V2.1, Toennies Gamblt, Erich JAEGER GmbH, Würzburg, Germany). The disequilibrium subjectively expressed by these children was evaluated by directly questioning the patient, parents, or guardian. We considered a child to have clinical disequilibrium if the patient, parent, or guardian mentioned any alteration in equilibrium manifested as vertigo (sensation of rotatory or spinning movement) or instability (sensation of falling or of floor moving). We considered a vestibular response to be abnormal if there was hyporeflexia in one or both ears, hyporeflexia in one ear if there was a 25% difference between the caloric tests, or hyporeflexia in both ears if the response was <20% [2,8]. ABR were performed by a licensed technician. PTA, speech discrimination testing, and vestibular tests were performed by an audiologist (MSM). All audiologic and vestibular tests were interpreted by a neurophysiologist (MIF).

2.4. HIV-1 infection and antiretroviral treatment

Information about HIV-1 disease included the age when HIV-related symptoms began, age at the beginning of HAART, age when audiologic and vestibular tests were carried out, the duration of the HIV disease at the beginning of HAART, clinical—immune category (according to 1994 CDC classification) [17], plasma RNA viral load (VL), and CD4+ cell counts at the beginning of HAART and when audiologic and vestibular tests were carried out. Information about past or current systemic, central nervous system (CNS) infections, otic opportunistic infections, and exposure to potential ototoxic therapeutic agents was obtained by questioning patients, parents, or guardians, and by clinical evaluation. If a middle ear effusion associated with a rapid onset of signs and symptoms of acute infection such as fever, ear pain, or a red and bulging tympanic membrane was present in a patient (or had been previously observed, as indicated in the clinical chart), then the patient was considered to have or have had acute otitis media. The presence or the antecedent of a middle ear effusion without signs of infection was considered as chronic otitis media with effusion, and the presence or antecedent of persisting suppurative otorrhea with perforation of the tympanic membrane was considered to be chronic suppurative otitis media [30,31]. Patients in this study were from a cohort being evaluated clinically once a month, and every 3 months by means of VL and CD4+/CD8+ cell counts [21,32]. Information concerning antiretroviral treatment, including antiretroviral drugs administered prior to HAART and time on HAART when audiologic and vestibular tests were carried out, as well as adherence to treatment, was obtained from Hospital de Pediatria AIDS outpatient clinic data, from the clinical charts, and by directly questioning parents or guardians, and the patients themselves when possible. VL was measured using Amplicor HIV-1 Monitor test version 1.5 (Roche Diagnostics, Branchburg, NJ), with a detection limit of 50 copies/mL. Genotyping of HIV-1 for detecting mutations related to resistance to antiretrovirals

was not done. Absolute CD4+/CD8+ cell-count analysis was performed with standard flow cytometric methods.

2.5. Statistical analysis

The nonparametric Mann—Whitney *U*-test was used to compare quantitative results between patients with and without HL. For comparing qualitative variables, the Fisher exact test was used. Statistical Analysis was performed using the Statistical Package for Social Sciences (SPSS) Version 12.0. A significance level of 0.05 was used for all tests [33].

3. Results

3.1. Patient sample

Twelve male and 11 female patients were studied between May and November 1999. Median (md) age was 4.5 years (range 5 months to 17 years). Nineteen patients (82.6%) were vertically infected and four (17.4%) acquired HIV infection by blood transfusion (three had hemophilia). The number of patients in the clinical categories at the time of enrollment was as follows: N = seven, A = three, B = seven, and C = six; the number in the immune categories was as follows: 1 = five, 2 = eight, and 3 = ten patients. The duration of HIV disease when patients began HAARTwas 20 months (median, range 1—89 months), and when audiologic and vestibular testing was carried out it was 25 months (1—96 months). Age at the beginning of HIV-1-related symptoms was 19 months (2—180 months). VL at the beginning of HAART was 5.27 $\log_{10}$ of the number of copies/mL (range 1.4—6.3) and at the time of audiologic and vestibular evaluation it was 1.6 $\log_{10}$ (0.4—5.7). CD4+ cell counts at the beginning of HAART were 329 cells/μL (97—2696) and 570 cells/μL (97—2696) at the time of audiologic and vestibular evaluation (Table 1).

One patient with the antecedent of suppurate chronic otitis media had tympanic perforation but with a dry ear when audiologic and vestibular evaluation was carried out (patient no. 23). Another five patients had the antecedent of acute (patients no. 8, 20, 22) or chronic (patients no. 15, 17) otitis media but were asymptomatic at enrollment. Eight patients had a history of exposure to aminoglycosides. Twenty children (87%) had received the four-drug regimen that included two PIs and two NRTIs during 5.5 months (range 3—19 months) prior to audiologic and vestibular evaluation. Seven of these children had previously received the three-drug regimen. The other three patients were receiving the three-drug regimen with one PI and two NRTIs. Thus, 10 patients either had received or were receiving the three-drug regimen during 15.5 months (range 3—26 months) before audiologic and vestibular evaluation. Four children had poor adherence at enrollment (patients 4, 9, 12, and 15) (Table 1).

3.2. Audiometry observations

PTA was performed on 12 patients over 4 years of age. HL was detected in four of these (33.3%): two had conductive, one sensorineural, and one mixed-type HL. The patient with sensorineural HL had a selective drop in sensitivity to high tone frequencies (patient no. 16). Speech discrimination testing was carried out in nine patients, and was abnormal in four, suggesting conductive involvement in two, cochlear involvement in one and a retrocochlear lesion in the other one. In this last patient, whose speech discrimination suggested a retrocochlear lesion, the PTA was normal (patient no. 4). Only three patients (13%) reported clinical HL when questioned (Table 2).

3.3. ABR results

ABR was performed on all the 23 patients, suggesting HL in 6 patients (23%, 8 ears), the majority suggestive of a peripheral-conductive type HL (6 out of 8 ears). In the other two ears, ABR suggested central lesion. With the exception of one patient, all children with conductive-type HL had the antecedent of one or more events of acute or chronic suppurative otitis media but with dry ears at the time of evaluation ($p = 0.003$). We detected low amplitude (wave V or for the entire waveform) in 11 patients (47.8%, 17 ears), inadequate definition of high-brainstem components in 3 patients (13%, 6 ears), an abnormal morphology in different ABR components in 4 patients (17.4%, 7 ears), reduction in amplitude ratio of wave V:I in 9 patients (39%, 13 ears), and immaturity data in 3 patients under 2 years old (13%). The immaturity data we found included reduced amplitude in the wave V in three patients and prolonged latencies in wave V in one. Abnormalities in ABR interwave intervals were detected in three children (13%, four ears): two of these had prolonged III—V and I—V interwave intervals, and one had prolonged I—III and I—V interwave intervals. The patient with prolonged I—III and I—V interwave intervals had previously received several antimicrobial regimens that included aminoglycosides. The other seven patients who had received aminoglycosides did not have any audiologic abnormality (Table 3).

Table 1 Demographic and HIV-1 infection-related data of 23 pediatric patients on Highly Active Antiretroviral Therapy (HAART)

Patient no.	Sex	Age[a]	CDC category	CD4+ cells[a]	CD4+ cells[b]	VL[a]	VL[b]	Age at beginning of symptoms	HAART regimen[c]	Previous HAART[c]	Time on HAART
1	M	4.7 y	A3	218	900	UDL	301,995 (5.48)	Unknown	A	—	5 m
2	F	10 m	C1	2309	2696	UDL	676,083 (5.83)	3 m	A	—	8 m
3	M	1.4 y	N3	142	285	UDL	251,189 (5.40)	—	A	—	7 m
4	M	13 y	C3	24	97	3162 (3.50)	5370 (3.73)	6.0 y	A	—	6 m
5	F	2.7 y	N1	—	1654	UDL	8913 (3.95)	—	A	—	4 m
6	M	1.1 y	B2	785	980	UDL	1,148,154 (6.06)	4 m	A	—	8 m
7	M	5 m	N2	910	570	501,188 (5.70)	501,188 (5.70)	—	A	—	4 m
8	F	8 y	B2	122	545	UDL	125,892 (5.10)	6 m	A	B	2.2 y
9	F	4.2 y	B2	527	1080	5012 (3.70)	50,119 (4.70)	—	A	B	2.1 y
10	F	4.2 y	N1	883	1389	126 (2.10)	25,119 (4.40)	—	B	—	2.2 y
11	M	16 y	C3	12	511	UDL	316,228 (5.50)	10.0 y	A	B	2.6 y
12	M	14.4 y	N3	59	114	10,965 (4.04)	7943 (3.90)	—	A	B	2.1 y
13	M	17.8 y	B3	88	566	UDL	15,849 (4.20)	15.0 y	A	B	2.2 y
14	F	12.6 y	C3	13	620	UDL	UDL	5.0 y	B	—	1.8 y
15	F	3.2 y	A2	1082	1080	125,892 (5.10)	3162 (3.50)	1.7 y	A	B	1.1 y
16	F	11.5 y	C3	451	209	UDL	1,995,262 (6.30)	2.7 y	A	B	1.1 y
17	F	1.8 y	B3	—	350	81 (1.91)	58,884 (4.77)	1.6 y	A	—	4 m
18	M	1.4 y	N2	920	1100	110 (2.04)	48,978 (4.69)	—	A	—	3 m
19	M	6.0 y	C3	18	110	186 (2.27)	186,209 (5.27)	6.0 y	A	—	5 m
20	M	4.5 y	N1	—	1762	UDL	1,288,250 (6.11)	—	A	—	8 m
21	F	11 y	B1	2553	2500	79 (1.90)	707,946 (5.85)	8 m	A	—	3 m
22	M	1.9 y	B2	320	528	UDL	213,796 (5.33)	1.0 y	A	—	3 m
23	F	6.0 y	A2	339	388	165,959 (5.22)	724,436 (5.86)	2 m	B	—	1.4 y

CDC: Centers for Disease Control and Prevention 1994 classification [17]; VL: number of copies of HIV-1 RNA/mL (log_{10}); M: male; F: female; y: years; m: months; UDL: under detection limit (<50 copies/mL).

[a] At enrollment.

[b] At beginning of HAART.

[c] Regimen A: ritonavir + saquinavir (SQV) + zidovudine (AZT) + lamivudine; Regimen B: SQV + AZT + didanosine.

Table 2 Audiologic findings in audiometry of 23 HIV-1-infected pediatric patients on Highly Active Antiretroviral Therapy

Patient no.	Clinical HL	PTA result	Type of HL	HL severity	Side of HL	Abnormal frequencies	SDT
1	No	Normal	—	—	—	—	ND
2	No	ND	—	—	—	—	ND
3	No	Normal	—	—	—	—	Normal
4	No	Normal	—	—	—	—	Retrocochlear lesion
5	No	ND	—	—	—	—	ND
6	No	ND	—	—	—	—	ND
7	No	ND	—	—	—	—	ND
8	No	ND	—	—	—	—	ND
9	No	Normal	—	—	—	—	ND
10	No	Normal	—	—	—	—	ND
11	Yes	HL	Mixed	Mild—moderate	Right	All	Cochlear lesion
12	No	HL	Conductive	Mild—moderate	Bilateral	All	Conductive lesion
13	No	Normal	—	—	—	—	Normal
14	No	Normal	—	—	—	—	Normal
15	No	ND	—	—	—	—	ND
16	No	HL	SN	Mild	Right	High	Normal
17	No	ND	—	—	—	—	ND
18	No	ND	—	—	—	—	ND
19	Yes	Normal	—	—	—	—	Normal
20	No	ND	—	—	—	—	ND
21	No	ND	—	—	—		ND
22	Yes	HL	Conductive	Mild—moderate	Left	All	Conductive lesion
23	No	ND	—	—	—	—	ND

HL: hearing loss; PTA: pure tone audiometry; SDT: speech discrimination testing; ND: not done; SN: sensorineural; Mixed: conductive and sensorineural.

3.4. Audiologic results and HIV disease

Although we did not find significant differences, in general patients with HL determined by audiometry as well as by ABR had HIV symptoms that manifested earlier (60 months vs. 104 months [md] with HL vs. without HL, respectively [$p = 0.08$]), higher VL at the time of audiologic evaluation (2239 copies of -viral RNA/mL vs. 1203 copies of viral RNA/mL [md] with HL vs. without HL [$p = 0.22$]), higher VL at the beginning of HAART (5.26 $\log_{10}$ vs. 4.18 $\log_{10}$ [$p = 0.17$]), and lower absolute CD4+ lymphocyte counts at the time of audiologic evaluation (209 cells/μL vs. 620 cells/μL [$p = 0.08$]) and at the beginning of HAART (59 cells/μL vs. 142 cells/μL [$p = 0.46$]). Also, no differences were found in the duration of HAART between patients with and without HL.

3.5. Vestibular results

Four children (17.4%), all over 5 years old, referred to disequilibrium disorders when questioned. ENG was carried out in 6 of 23 patients; alterations in smooth pursuit were detected in 1 patient of the 6 tested. Caloric tests were abnormal in the four patients tested, showing unilateral vestibular hyporeflexia. Rotatory tests were abnormal in the two patients for whom tests could be performed, with asymmetries in both vestibular and optovestibular tests. It must be pointed out that these tests were carried out only in those children who were able to cooperate, detecting at least one abnormality in some vestibular test in all the six patients evaluated (Table 4).

4. Discussion

Not much is known about the impact of the HIV disease or the toxicity of antiretroviral therapy on the cochlear and vestibular functions in children. Most information on the subject corresponds to adult patients [2—7,10,11]. Although the sample evaluated in the present study was small, most of the patients that were included acquired HIV infection perinatally, which is the most frequent way pediatric patients get HIV infection even in Mexico [1]. Also, our sample included patients from different clinical and immune categories, different evolution times for the HIV disease, VLs ranging from under detection limit to 5 $\log_{10}$, and CD4+ cell

Table 3 ABR findings in 23 HIV-1-infected pediatric patients on Highly Active Antiretroviral Therapy

Patient no.	Hearing loss severity	Localization	Absolute latencies	Conduction abnormalities	Morphology abnormalities	Amplitude	Wave V:I ratio reduced	High-brainstem components definition	Immaturity data
1	—	—	Normal	Absent	Normal	Normal	No	Normal	No
2	Moderate R	Peri Cond R	All waves prolonged R	Absent	Right	All reduced R	No	Normal	No
3	—	—	Normal	Absent	Normal	Normal	No	Normal	No
4	—	—	Normal	Absent	Normal	Normal	No	Normal	No
5	—	—	Normal	Absent	R & L	IV & V reduced R & L	R & L	Inadequate	No
6	—	—	Wave V prolonged R & L	Intervals III—V & I—V prolonged R & L	Normal	V reduced R & L	R & L	Normal	R & L
7	—	—	Normal	Absent	R & L	V reduced R & L	R & L	Inadequate	R & L
8	—	—	Normal	Absent	Normal	Normal	No	Normal	No
9	—	—	Normal	Absent	Normal	Normal	No	Normal	No
10	—	—	Normal	Absent	Normal	All reduced R	No	Normal	No
11	Moderate R	Central R	All waves prolonged R	Intervals I—III & I—V prolonged R	R & L	All reduced R & L	R	Inadequate	No
12	Moderate R mild L	Peri Cond R & L	All waves prolonged R & L	Absent	Normal	V reduced R	R	Normal	No
13	—	—	Normal	Absent	Normal	Normal	No	Normal	No
14	—	—	Normal	Absent	Normal	Normal	No	Normal	No
15	—	—	Normal	Absent	Normal	V reduced R & L	R & L	Normal	No
16	—	—	Normal	Absent	Normal	Normal	No	Normal	No
17	Moderate R	Central R	All waves prolonged R	Intervals III—V & I—V prolonged R	Normal	All reduced R	R	Normal	No
18	—	—	Normal	Absent	Normal	V reduced R & L	R & L	Normal	R & L
19	—	—	Normal	Absent	Normal	Normal	No	Normal	No
20	—	—	Normal	Absent	Normal	Normal	No	Normal	No
21	—	—	Normal	Absent	Normal	V reduced R	R	Normal	No
22	mild L	Peri Cond L	All waves prolonged L	Absent	Normal	Normal	No	Normal	No
23	Moderate R & L	Peri Cond R & L	All waves prolonged R & L	Absent	Normal	Normal	No	Normal	No

R: right; L: left; Peri: peripheral; Cond: conductive.

Table 4 Vestibular findings in 23 HIV-1-infected pediatric patients on Highly Active Antiretroviral Therapy

Patient no.	Clinical disequilibrium	ENG results	Smooth pursuit	Caloric tests	Rotatory tests
1	No	ND	—	—	ND
2	No	ND	—	—	ND
3	No	Normal	Normal	Unilateral weakness	ND
4	Unsteadiness	Abnormal	Saccadic	Unilateral weakness	ND
5	No	ND	—	—	ND
6	No	ND	—	—	ND
7	No	ND	—	—	ND
8	No	ND	—	—	ND
9	No	ND	—	—	ND
10	No	ND	—	—	ND
11	Unsteadiness	ND	—	—	Abnormal
12	No	Normal	Normal	—	ND
13	No	Abnormal	Normal	Unilateral weakness	ND
14	No	ND	—	—	ND
15	No	ND	—	—	ND
16	Unsteadiness	Abnormal	Normal	Unilateral weakness	ND
17	No	ND	—	—	ND
18	No	ND	—	—	ND
19	No	Normal	Normal	—	Abnormal
20	No	ND	—	—	ND
21	Unsteadiness	ND	—	—	ND
22	No	ND	—	—	ND
23	No	ND	—	—	ND

ENG: electronystagmography; ND: not done.

counts ranging from severe immunosuppression to normal counts. Therefore, this sample seems to be representative of the wide variety of HIV disease in pediatrics [15,16,18]. Even though standard therapy for pediatric patients is based on the combination of one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor plus two nucleoside analog reverse transcriptase inhibitors (NRTI) [16,20], most of our patients were receiving a regimen based on the combination of two PIs plus two NRTIs, because most of them came from a cohort being evaluated for comparison of two different antiretroviral regimens [21]. This is why poor adherence was only detected in four patients.

PTA and speech discrimination testing were only carried out in patients who were able to cooperate and who attended the testing. In the HIV-1-infected children in this study receiving HAART, we detected a similar frequency of abnormalities in audiometry (33%) and ABR (13—35%) to that reported in adult patients (4—34%) [2,6,7,34]. Cases of conductive-type HL predominated in both tests. Six of the eight children with HL had experienced acute or chronic otitis media events before enrollment. Although conductive HL has other etiologic factors, such as allergic and obstructive causes, otitis media is one of the most frequent causes of conductive HL in both HIV-1-infected and non-infected children, and otitis media is also one of the most frequent opportunistic infections in children with AIDS [18,30,31,35—37]. The only patient with sensorineural HL identified with pure tone testing (patient no. 16) had a selective drop in sensitivity to high tone frequencies, similar to the condition described in HIV-infected adults [2]. Speech discrimination testing corroborated PTA findings, with the exception of one patient. Although speech discrimination testing suggested a retrocochlear lesion in this patient (no. 4), ABR did not corroborate this finding. Nevertheless, he had alteration of oculomotor pathways demonstrated by the eye tracking test. This finding might also suggest central involvement that may be due to HIV [38]. HL was detected by verbal questioning in three patients only, but it was detected by PTA or ABR in eight. Although clinical HL can be difficult to detect in young children, this finding suggests that audiologic abnormalities may be present in asymptomatic HIV-1-infected children, even in the absence of other neurologic symptoms, as has been observed in adult patients [39,40]. Therefore, this finding also suggests that it is important to evaluate audiologic function in HIV-infected pediatric patients since a handicap in this area may affect the neurological and psychosocial development of these patients.

There was a wide range of abnormalities observed in different ABR parameters of our HIV-infected pediatric patients. The most frequent ABR

abnormality was low amplitude for the entire waveform. In spite of the fact that ABR amplitude is quite variable and susceptible to the effects of movement artefacts and fluctuations in background electroencephalographic activity, low amplitude was the most consistent finding among our patients. Additionally, the wave V:I ratio is a very reliable measurement for determining low amplitude, and it was also reduced in most of these patients [23]. The inadequate definition of high-brainstem components and the abnormalities in ABR morphology observed in some patients suggest that different levels in the auditory pathways may be affected; these abnormalities have been associated with the loss of the ability to localize sound sources spatially, but not with HL [41]. Only one of these patients had HL, and this was demonstrated only by pure tone testing. We detected a high frequency of alterations in the amplitude of different components of the auditory pathway responses, predominately amplitude ratio abnormalities in waves V:I such as those found by Reyes-Contreras et al. in HIV-1-infected adult patients [39]. These alterations might be due to fewer active fibers, or to desynchronization of the volley, secondary to the wide spectrum of conduction velocities. These results might suggest an incipient alteration in slow conduction fibers, perhaps caused by HIV [39,41]. The immaturity data found were predictable because we included several infants and young children in our sample. The three patients with this kind of data were under 2 years of age, and the data corresponds to that which has previously been related to an early age (23).

The abnormalities in ABR interwave intervals detected in three patients may suggest effects on central auditory pathways secondary to the HIV infection [23,39]. A prolonged I—III interwave interval in ABR has been associated with the administration of ototoxic drugs [23]. This interval was prolonged only in the case of one patient in this study, and this patient had also previously received aminoglycosides (patient no. 11). Although it is not known if this alteration is also caused by antiretroviral drugs, aminoglycosides and other ototoxic drugs have been associated with this abnormality [23,41,42].

Although this study was not intended to evaluate causality, our patients with HL detected by audiometry or ABR presented HIV-related symptoms at an earlier age than those without HL. A number of studies have demonstrated that children with perinatally acquired HIV-1 infections start to have symptoms earlier than adult patients [18,43,44], and usually have higher VLs [15,18,20,43]. The VL at the initiation of HAART and at the time of audiologic evaluation was higher in patients with HL. The high rate of HIV replication at an early age may facilitate an earlier and greater impact of the HIV on the auditory system. These patients also had lower CD4+ lymphocyte counts at the beginning of HAART and during audiologic evaluation. Impairment of the immune system due to the high rate of viral replication increases the risk of complications due to opportunistic microorganisms in different organs, including the ear [18,43,44]. These findings suggest that HIV-1-infected children might show early HL, and perhaps other audiologic abnormalities, which may be secondary to the direct effect of HIV or to other opportunistic infections on the auditory system. We did not detect differences in time of exposure to HAART between patients having and not having HL. The small size of our sample may explain the lack of differences. Although ototoxicity has been attributed to some antiretroviral drugs in adult patients, primarily associated with nucleoside analog reverse transcriptase inhibitors, results have been inconsistent from one study to another [45—47].

The equilibrium disorders referred to clinically by four patients were corroborated by vestibular tests. With ENG, we detected abnormalities in the peripheral vestibular organ and in the vestibular and oculomotor pathways. Although the number of patients tested was small, these findings may suggest a direct HIV effect on both peripheral and central components of the vestibular system [2,10,11]. The patient who showed alterations in the smooth pursuit also presented unilateral weakness in caloric tests (patient 4). This patient had prior exposure to aminoglycosides, which could explain the abnormalities in caloric tests but not those observed in the smooth pursuit. Even though this latter abnormality was found only in one patient, it may be due to a direct HIV effect on central oculomotor pathways. Nevertheless, it must be emphasized that it is difficult to distinguish whether HIV itself, related opportunistic infections, or drug effects are responsible for some of the findings. The asymmetry found in rotatory tests also suggests both peripheral and central involvement, since lesions of the peripheral vestibular system typically impair only the vestibular (vestibular ocular reflex, VOR) responses, whereas lesions of the central nervous system impair optovestibular (visual VOR) interactions [38].

We found a high frequency of audiologic and vestibular abnormalities in our sample of HIV-1-infected children on HAART. The most frequent abnormalities were lower amplitude of wave V and reduction of the entire ABR, conductive HL, inadequate definition of high-brainstem components, and unilateral vestibular hyporeflexia. Because current antiretroviral therapies have significantly increased survival of HIV-1-infected pediatric patients, it is important to

detect audiologic and vestibular disorders in these patients as early as possible in order to reduce the impact of these disorders on the psychosocial development of the patients [42,48]. However, evaluation of larger cohorts, including different antiretrovirals regimens and, above all, controlled clinical assays, are needed before definitive conclusions about the impact of HIV disease and treatment on the audiologic and vestibular system may be drawn.

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