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Is Human T-Lymphotropic Virus Type 1 Infection Associated With Hearing Loss?

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Objectives/Hypothesis: Human T-lymphotropic virus type 1 (HTLV-1) infection is endemic in the northeast area of Iran. Although various neurological disturbances have been reported in HTLV-1 infection, possible audiovestibular involvement during this infection has not yet been studied.

Study Design: Case control study.

Methods: Sixty-eight cases in three groups including 24 HTLV-1–infected patients with HTLV-1– associated myelopathy/tropical spastic paraparesis (HAM/TSP) (group 1), 23 HTLV-1–infected cases without clinical presentation (group 2), and 21 normal individuals (group 3) entered our study. A complete history of hearing-related disorders and a profile of audiologic tests, including pure-tone audiometry (PTA) with high frequencies, speech reception threshold (SRT), and auditory brainstem response (ABR) were taken.

Results: Subjective audiovestibular complaints of participants showed a significant difference among HAM/TSP patients and the two other groups regarding hearing loss and tinnitus, but not vertigo or aural fullness. Hearing evaluation by SRT and PTA in all frequencies showed a significant difference between HAM/TSP patients (group 1) and the controls (group 3). The difference was also significant between asymptomatic cases (group 2) and the controls only in PTA frequencies above 4 kHz. Auditory brainstem-evoked potential did not show any significant differences among the groups regarding latency of I, III, and V waves and interwave differences.

Conclusions: HTLV-1 infection, particularly in those with a clinical presentation, appears to accompany hearing loss. Based on the results of PTA and ABR tests, this study may suggest a cochlear source of hearing impairment rather than neural problems.

Key Words: Human T-lymphotropic virus type 1, HTLV-1–associated myelopathy and tropical spastic paraparesis, hearing, tinnitus, vertigo.

Level of Evidence: 3b.

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INTRODUCTION

Northeastern Iran (Khorasan Province) is among the areas with endemic human T-lymphotropic virus type-1 (HTLV-1). South America, Central Africa, the Caribbean, Southern Japan, and the Middle East are also endemic distributors of this infection. Ten to 20 million people around the world are estimated to be infected with HTLV-1.[1,2] Of the general population in Mashhad, Iran, the biggest central city of Khorasan Province, 2% to 3% are believed to be involved.[3–5] Less than 1% to 2% of seropositive individuals develop neurologic disorders; the rest remain asymptomatic. The most common clinical presentation is HTLV-1–associated myelopathy and tropical spastic paraparesis (HAM/TSP).[6] Another well-known HTLV-1–associated disorder is adult T-cell leukemia/lymphoma (ATLL). Both viral and host factors are important in the pathogenesis of neurologic disorders associated with this infection. HTLV-1 subgroup, proviral load, and human leukocyte antigen are the most important factors determining development of neurologic disorders.[1,7]

HTLV-1 infection may cause diverse neurological presentations such as myelopathy, cerebellar ataxia, dementia, myositis, vertigo, nystagmus, cranial neuropathy, polyneuropathy, optic neuritis, and an amyotrophic lateral sclerosis–like syndrome.[1,7–10] Various mechanisms have been proposed regarding the pathogenesis of central nervous system involvement. Direct attack of the virus to the neurons is not confirmed; however, indirect damage of the nervous system by lymphocytes and autoimmune mechanisms (both humeral and cellular) is a more acceptable hypothesis. Some cytokines, such as tumor necrosis factor, platelet activating factor, and interleukins have been found in the serum of HAM/TSP patients, and these appear to be responsible for

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TABLE I.
Age, Sex, and Duration of the Symptomatic Phase Among Groups.

	Groups	Mean Age, yr (±SD)	Difference	Duration of Symptoms, yr	Sex (Male/Female)	Difference
1	HAM/TSP patients	45.5 ± 8.5		5.1 ± 0.6	15/13	
2	HTLV-1 infected	43.9 ± 7.5	NS	NA	11/10	NS
3	Normal individuals	38.9 ± 12.3		NA	10/9	
Total		43.2 ± 9.6		NA	36/32	

HAM/TSP = HTLV-1 associated myelopathy/tropical spastic paraparesis; HTLV-1 = human T-lymphotropic virus type 1; NA = not applicable; NS = not significant; SD = standard deviation.

demyelination in the nervous system. The ratio of CD4-positive to CD8-positive T cells is increased in these patients, and the function of natural killer cells is altered in ATLL and HAM/TSP patients.[1,10–13]

To the best of our knowledge through searches of the literature using MEDLINE and other online databases, no studies have been published on a possible audiovestibular involvement of this infection; however, there is one case report of hearing loss in an HTLV-1–infected patient with ATLL[14] and another report on multimodality-evoked potentials including brainstem auditory evoked potentials in HTLV-1–associated myelopathy.[15] The aim of this study was to evaluate audiovestibular abnormalities that might be associated with HTLV-1 infection.

MATERIALS AND METHODS

In a case control study in 2010 to 2011, 68 participants in three groups including 24 HTLV-1– infected patients with HAM/TSP (group 1), 23 HTLV-1 infected cases without clinical presentation (i.e., without HAM/TSP) (group 2), and 21 normal individuals (group 3) entered into our study. All cases were referred by a neurologist from the HTLV-1 clinic of our hospital, a referral center for all HTLV-1–infected cases and HAM/TSP patients in northeast Iran. All HTLV-1–infected cases had high levels of serum antibody against HTLV-1, based on an enzyme-linked immunosorbent assay test, and their infection was also confirmed by either serum Western blot analysis or a serum polymerase chain reaction test. HAM/TSP was diagnosed according to World Health Organization criteria.[16] The control group was selected from healthy individuals with no known neurologic or otologic disease.

In the ear, nose, and throat clinic, a comprehensive history regarding previous hearing loss and other otologic disorders, such as tinnitus and vertigo, was taken for all three groups. Known cases of hearing loss, such as ear trauma, congenital ear problems, ototoxic drugs, meningitis, posterior fossa tumors, multiple sclerosis, hypothyroidism, mumps, chronic otitis media, cholesteatoma, diabetes, noise-induced hearing loss, and systemic autoimmune diseases, were excluded. Next, a physical examination and microscopic ear exam were performed, followed by audiometric evaluation including measurements of speech reception threshold (SRT), speech discrimination score, pure-tone audiometry (PTA), including high frequencies (10, 12, 14, and 16 kHz) evaluation (MA53; MAICO, Berlin, Germany), and impedance tests including tympanogram, and acoustic reflex (MI44, MAICO). An evoked auditory brainstem responses (ABR) test was performed (Eclips, EP 25; Interacoustics, Assens, Denmark). The latency of I, III, and V waves, interpeak latency between I–III, III–V, and I–V, and also the difference between the V latency of the two sides (interaural difference) (IT V) were taken into consideration. Hearing loss was defined as a decrease >10 dB at each tested frequency compared with normal thresholds (<25 dB); abnormal ABR was considered to be a delay of more than 0.2 ms in wave latencies. The results were compared among the three groups.

SPSS software (SPSS Inc., Chicago, IL) was used to describe and analyze the study results. Statistical significance was ascertained using analysis of variance (ANOVA) (Tukey test) to compare results between each of the groups. A P value of $<.05$ was considered statistically significant.

The hearing tests used caused no harm to any patients; however, each of the study participants signed written informed consent, and the study protocol was approved by the local ethics committee at Mashhad University of Medical Sciences.

RESULTS

The mean age of all participants was 43.2 ± 9.6, and the male/female ratio was 36/32. Although the control group was slightly younger, this was not statistically significant (Table I). Clinical presentations of the HAM/TSP patients (including audiovestibular complaints) are listed in Table II. The otoscopic exam, air-bone gaps on PTA, and tympanograms showed no significant differences among the groups, suggesting that there were no middle ear or eustachian tube changes due to HTLV-1 infection.

TABLE II.
Neurologic and Otologic Signs and Symptoms of the HAM/TSP Patients (Group 1).

Symptoms and Signs	Frequency	%
Paraparesis	24	100%
Paresthesia	18	75%
Radicular pain	16	66%
Cerebellum involvement	6	25%
Urinary incontinence	5	21%
Nystagmus	5	21%
Ataxia	4	17%
Quadriparesis	3	13%
Cognitive disorders	1	4%
Hearing loss	12	50%
Tinnitus	5	21%
Ear fullness	4	17%
Vertigo	0	0

HAM/TSP = human T-lymphotropic virus type 1–associated myelopathy/tropical spastic paraparesis.

TABLE III.
Audiometry Results in the Three Groups and the Statistical Comparisons (Tukey Analysis).

	Group 1 (Symptomatic)	Group 2 (Infected Nonsymptomatic)	Group 3 (Normal)	*P* Value 1, 2	*P* Value 1, 3	*P* Value 2, 3
SRT						
Right	11.52 ± 7.2	9.57 ± 4.2	7.37 ± 3.4	.428	.032*	.365
Left	12.61 ± 9.3	10.00 ± 5.4	7.89 ± 3.8	.389	.043*	.471
250 Hz						
Right	7.39 ± 7.6	7.08 ± 2.9	3.95 ± 2.0	.988	.051	.072
Left	9.82 ± 9.4	6.88 ± 3.2	4.21 ± 3.8	.454	.201	.844
500 Hz						
Right	8.26 ± 8.0	6.46 ± 2.7	4.21 ± 2.5	.497	.025*	.264
Left	10.54 ± 10.3	6.88 ± 3.5	3.95 ± 3.9	.226	.002*	.126
1,000 Hz						
Right	8.26 ± 6.6	6.46 ± 4.9	3.68 ± 3.6	.519	.021*	.224
Left	13.04 ± 13.8	6.88 ± 5.6	3.95 ± 4.5	.100	.001*	.220
2,000 Hz						
Right	9.87 ± 8.4	7.29 ± 5.8	5.26 ± 5.1	.434	.005*	.107
Left	13.93 ± 14.2	7.92 ± 7.5	3.42 ± 4.1	.299	.012*	.302
4,000 Hz						
Right	16.43 ± 11.6	14.37 ± 10.3	3.42 ± 3.3	.997	<.001*	<.001*
Left	21.25 ± 17.3	13.33 ± 12.2	5.79 ± 4.4	.342	.001*	.053
8,000 Hz						
Right	25.54 ± 17.0	23.96 ± 17.0	6.58 ± 5.7	.925	<.001*	<.001*
Left	32.86 ± 19.3	25.21 ± 17.5	6.32 ± 3.6	.735	<.001*	<.001*
10,000 Hz						
Right	35.04 ± 15.7	32.71 ± 23.0	8.68 ± 5.4	.990	<.001*	<.001*
Left	43.21 ± 18.9	27.71 ± 20.5	10.79 ± 7.1	.101	<.001*	.001*
12,500 Hz						
Right	46.36 ± 15.2	36.67 ± 24.0	10.53 ± 6.2	.993	<.001*	<.001*
Left	50.00 ± 19.3	34.58 ± 23.4	11.32 ± 7.6	.302	<.001*	<.001*
14,000 Hz						
Right	59.82 ± 18.3	51.46 ± 24.6	12.63 ± 4.5	.690	<.001*	<.001*
Left	62.50 ± 18.0	52.29 ± 26.7	13.16 ± 5.5	.721	<.001*	<.001*
16,000 Hz						
Right	58.39 ± 13.5	49.38 ± 17.0	13.42 ± 16.0	.131	<.001*	<.001*
Left	60.71 ± 12.9	50.42 ± 16.2	13.95 ± 3.9	.118	<.001*	<.001*

*Significant difference.
SRT = speech reception threshold.

Hearing evaluation according to SRT and PTA across almost all frequencies showed a significant difference between HAM/TSP patients (group 1) and the control group (group 3). However, the SRT and the PTA values for frequencies lower than 8 kHz in group 1 were within the normal range (Table III). Comparing the results of group 2 (infected nonsymptomatic patients) and group 3 (controls) revealed significant differences in PTA values in frequencies above 4 kHz (Table III). Also, the results show poorer hearing thresholds in group 1 compared with group 2, but this difference was not statistically significant.

The ABR potentials did not show any significant differences among the groups regarding latency of I, III, or V waves, or in IT V latency comparisons (Table IV).

DISCUSSION

Sensorineural hearing loss (SNHL) occurs when there is damage to the inner ear (cochlea) or to the neural pathways from the inner ear to the brain. In general, SNHL cannot be medically or surgically corrected and represents the most common type of permanent hearing loss. There are many causes of SNHL, including ototoxic drugs, aging, head trauma, ear malformations, noise-induced hearing loss, genetically predisposed conditions, and systemic diseases such as autoimmune disorders.

HTLV was the first human retrovirus discovered. HTLV belongs to the retroviridae family in the genus deltaretrovirus. Retroviruses are RNA viruses that use an enzyme called reverse transcriptase to produce DNA from RNA. The DNA is subsequently incorporated into

TABLE IV.
Auditory Brainstem Response Wave Latencies in the Three Groups.

	Group 1 (Symptomatic), Mean ± SD, ms	Group 2 (Infected Nonsymptomatic), Mean ± SD, ms	Group 3 (Normal), Mean ± SD, ms	*P* Value
I				
Right	1.50 ± 0.15	1.54 ± 0.20	1.40 ± 0.27	.329
Left	1.50 ± 0.12	1.51 ± 0.18	1.51 ± 0.23	.703
III				
Right	3.52 ± 0.24	3.59 ± 0.22	3.40 ± 0.30	.394
Left	3.65 ± 0.30	2.10 ± 0.16	3.81 ± 0.40	.830
V				
Right	5.42 ± 0.25	5.47 ± 0.24	5.50 ± 0.50	.504
Left	5.48 ± 0.31	5.51 ± 0.24	5.50 ± 0.40	.547
IPL (I–III)				
Right	2.05 ± 0.20	2.03 ± 0.14	2.10 ± 0.12	.961
Left	1.88 ± 0.11	2.10 ± 0.16	2.01 ± 0.12	.729
IPL (III–V)				
Right	1.88 ± 0.11	1.88 ± 0.09	1.90 ± 0.11	.750
Left	1.84 ± 0.17	1.98 ± 0.42	1.80 ± 0.12	.178
IPL (I–V)				
Right	3.92 ± 0.22	3.92 ± 0.16	4.10 ± 0.16	.922
Left	3.90 ± 0.20	3.91 ± 0.51	4.01 ± 0.19	.962
IT (V)	0.15 ± 0.21	0.10 ± 0.08	0.15 ± 0.08	.347

IPL = interpeak latency; IT = interaural V latency; SD = standard deviation.

the host's genome. HTLV predominantly affects the T lymphocytes specifically, with HTLV-1 predominantly affecting the CD4 lymphocytes. In 1979, T-cell lymphotropic virus was isolated in a patient with cutaneous T-cell lymphoma,[17] a condition that can cause diseases of the nervous system or leukemia.

The vast majority of individuals infected with HTLV-1 do not develop symptoms, and the virus appears to remain in the body throughout life without causing any harm. However, approximately one in 20 people who become infected by HTLV-1 will become symptomatic with an HTLV-1–associated illness at some point in their lifetime, usually several decades after the initial infection. ATLL and HTLV-1–associated myelopathy are the two diseases most commonly caused by HTLV-1. HAM/TSP develops in 1% to 2% of individuals with an HTLV-1 infection.[18]

The pathophysiology of HAM/TSP remains unclear, but can be defined clinically as a slowly progressive degenerative disease that primarily affects the corticospinal tracts of the thoracic cord. Major pathologic findings of HAM/TSP may include inflammatory perivascular and parenchymal infiltration by T-lymphocyte cells, leading to degeneration and fibrosis in the spinal cord. Immunologic mechanisms may be involved in the development of HAM/TSP. This is likely mediated through autoimmune processes or cytotoxic attack on HTLV-1–infected cells.

HTLV-1 may also be associated with a broader spectrum of neurologic abnormalities that are not as severe as HAM/TSP. It is not clearly established whether individuals with other neurologic abnormalities will eventually develop HAM/TSP or whether they will remain stable.[19] It is known that HTLV-1 virus can cause inflammation not only in the spinal cord but in almost any organ. Inflammatory conditions seen in those infected with HTLV-1 include inflammation of the eye (uveitis),[20] muscles (polymyositis), lung (alveolitis), joints (arthritis),[21] and skin (infective dermatitis).[22] These conditions are even less common than ATLL and HAM, and the skin disease is usually only seen in tropical climates. However, other disorders such as peripheral neuropathy, polyradiculoneuropathy, myopathy, and peripheral facial paresis have also been reported. Audiovestibular involvement has not been studied yet, except for a few case reports of hearing loss.[14] On the other hand, there are several reports on otologic manifestations of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, the other more prevalent member of the retroviridae family. HIV infection may cause both middle ear and ABR changes.[23] Middle ear involvement is more common in children, whereas ABR more commonly changes in HIV-infected adults.[24] Hearing loss in HIV possibly results from the direct action of the virus, the ototoxic effects of antiretroviral treatments, and opportunistic infections.[25] Moreover, vestibular evaluations have shown a reduction in the labyrinthine function of HIV-infected individuals, which means inner ear pathology in addition to central nervous system involvement.[26]

Our study shows that the hearing system is affected in HTLV-1 infection, both subjectively and objectively. A marked decrease in hearing thresholds in both low and high frequencies and also SRT values may show an association between this infection and auditory involvement;

however, normal brain stem auditory evoked potential signifies cochlear involvement versus neural pathway damage. Subjective vertigo was not reported by any patients or controls; however, subclinical vestibular involvement needs to be uncovered by more sensitive paraclinical tests such as electronystagmography and videonystagmography. To the best of our knowledge, there are no studies on audiovestibular involvement for comparison.

The hearing loss associated with cochlear disorders is usually SNHL,[27] and high-frequency audiometry is a sensitive method with which to detect the threshold changes at earlier stages.[28] With the cochlea being tonotopic,[29] the results of this study suggest hair cell damage in all parts of the cochlear turns. However, as the threshold changes are more notable in the frequencies above 8 kHz, with the lower frequency results remaining within the normal range (<25 dB), the damage appears to be more dramatic in the basal turn, which is associated with high-frequency hearing. Moreover, the difference between the infected nonsymptomatic and normal group was noted only in frequencies above 4 kHz, and this may also verify the concept that the damage begins in the basal turn of the cochlea. High-frequency PTA may be helpful in assessing progression to the symptomatic phases; this presumption needs to be more thoroughly evaluated in a time-course follow-up of all symptoms. Whether this is a lymphocytic infiltration or a direct neuroepithelial (cochlear hair cell) involvement should be investigated in a histopathologic study. At present, cochlear involvement during HTLV-1 infection is only a hypothesis that awaits further investigation. Otoacoustic emissions and cochlear microphonics are helpful as complementary assessment tools to confirm cochlear damages in future studies.

Normal ABR-wave generation depends on the structural integrity and temporal synchrony of neuronal activities in the brainstem.[30] Considering the ABR results, it seems that although HTLV-1 affects the nervous system, the auditory brainstem pathway is functionally spared.

Another important point to mention is that the symptomatic group were all taking baclofen and gabapentin, neither of which have proven to be ototoxic. Interferon-a, a newly recommended treatment for symptomatic HTLV-1 patients, which may have adverse otologic effects,[31] was not used in these patients.

CONCLUSION

Hearing loss appears to be associated with HTLV-1 infection, particularly in those with other clinical presentations. Based on the results of PTA and ABR tests, the results of this study may suggest a cochlear origin of hearing impairment rather than neural problems.

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