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Prevalence of Peripheral Vestibular Impairment in Adults with Human Immunodeficiency Virus

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Background and Objectives: Globally, the human immunodeficiency virus (HIV) is responsible for one of the most serious pandemics to date. The vulnerability of the vestibular system in individuals with HIV has been confirmed, and central vestibular impairments have been frequently reported. However, there are disagreements on the impact of HIV on peripheral vestibular function. Thus, the current study aimed to determine the prevalence of peripheral vestibular impairment, specifically related to the semi-circular canals (SCCs), in HIV-positive individuals receiving antiretroviral (ARV) treatment. **Subjects and Methods**: A total of 92 adults between the ages of 18 and 50 years (divided into two groups) participated in the study. The first group comprised HIV-positive individuals receiving ARV treatment (n_1=60), and the second group comprised HIV-negative participants (n_2=32). The video head impulse test was used to conduct the head impulse paradigm (HIMP). **Results**: Bilateral normal HIMP results were obtained in 95% of the HIV-positive participants and all HIV-negative participants. The gain of the left posterior SCCs was significantly lower in the HIV-positive group, while the gains of all other canals between the two groups were comparable. **Conclusions**: The prevalence of peripheral vestibular impairment in the HIV-positive group was not significantly different from that of the HIV-negative group. The reduced prevalence in the current study may be attributed to participant characteristics, the test battery employed, and the central compensation of the vestibular dysfunctions at the later stages of infection.

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KEY WORDS: Vestibular diseases · Head impulse test · Human immunodeficiency virus · Vestibular function tests.

Introduction

Human immunodeficiency virus (HIV) has been declared as a public health threat; 75.7 million people have been infected with it since the beginning of the epidemic [1]. At the end of 2018, 37.9 million people were living with HIV globally [1]. Most of these individuals (67.8% or 25.7 million) reside in Africa [2].

HIV targets the body's immune system by reducing the cluster of differentiation 4 cells (CD4+) or T-lymphocytes (T-cells), which assist the immune system in fighting off infections [3]. The stages of infection are classified according to the CD4+ count and the presence of co-morbid conditions. Although no effective cure exists, significant strides have been made in the treatment of HIV. With proper medical care and antiretroviral (ARV) therapy, the viral load can become undetectable. If left untreated, the immune function is suppressed, and the HIV-positive person is more vulnerable to certain cancers and opportunistic infections [3].

Opportunistic infections in HIV-positive individuals may present with various clinical manifestations, including otological complications [4]. HIV may affect the auditory and vestibular system directly, as suggested by post-mortem studies [5], or indirectly via secondary infections and various

ototoxic medications [6]. Auditory symptoms may include hearing loss, tinnitus, and otalgia [7], while vestibular symptoms may include vertigo, dizziness, and oscillopsia [8]. Any of these symptoms may have disabling effects on everyday function [9]; however, research investigating vestibular manifestations in HIV-positive individuals remains limited compared with information on auditory function [10].

Studies have suggested that all structures and tracts of the vestibular system may be vulnerable to the effects of HIV [5,11-13]. Although most studies concur that the prevalence and degree of central vestibular impairments are directly related to the progressive stage of HIV infection [12-15], a discrepancy concerning the impact of HIV on peripheral vestibular function exists. A recent study reported that peripheral vestibular impairment was the most prevalent finding in their sample [11], whilst earlier studies have suggested no peripheral vestibular involvement [14,16]. The different findings reported by these studies may be explained by methodological variances such as the participant selection process (e.g. progressive stage of infection) or the data collection procedures employed (e.g. specific test battery).

Most studies related to HIV and peripheral vestibular assessments have included caloric testing, which focuses on the horizontal semi-circular canal (SCC) [11,14,17,18]. Caloric irrigation is a useful clinical tool that can assess and quantify the functional status of the individual peripheral vestibular end organs. The test utilizes the mechanics of the vestibulo-ocular reflex (VOR) to specifically test the horizontal SCCs and their afferents [19].

The VOR consists of low frequencies, representing stationary head positions that are more vulnerable to peripheral vestibular impairment [20]. For this reason, the low-frequency caloric test (0.003 Hz) has been included in most research-driven test batteries. The VOR, however, also contains high-frequency information, which represents physiologic head movements used during real-life situations [20]. These high frequencies are not evaluated by the caloric test, and the total effect of a vestibular impairment on everyday function is not necessarily assessed [20,21]. Furthermore, the caloric test evaluates only one portion of the vestibular labyrinth, which includes the horizontal SSCs and superior vestibular nerve [22]. These structures as well as the anterior SCCs, posterior SCCs, and inferior vestibular nerve can be assessed using the head impulse paradigm (HIMP) [22]. The HIMP allows for the assessment of three distinct end organs (otolith organs are excluded), namely the SCCs, that are sensitive to angular accelerations (head rotations); it can be also used to evaluate the high frequencies of the VOR [20,23,24]. Therefore, the HIMP may be a valuable procedure to include to obtain additional insights (other than those obtained via caloric irrigation) on the effects on the function of the peripheral vestibular system.

Considering the significant impact of ARV treatment on extending life expectancy in HIV-positive individuals, the importance of maintaining and/or improving the quality of life should not be ignored [25]. In the past, the debilitating effect of vestibular symptoms had been underrated [12], which may have been due to the emphasis placed on treating more serious life-threatening symptoms of HIV [10]. However, optimizing the quality of life in HIV-positive individuals has become a greater priority and the disabling effects of vestibular symptoms are better understood; therefore, investigating the effects of HIV on the vestibular system remains critical. The current study aimed to determine the prevalence of peripheral vestibular impairment, specifically related to the SCCs, in HIV-positive individuals receiving ARV treatment.

Subjects and Methods

Participants

Potential participants were recruited from the clinic and pharmacy waiting areas at the research site. The nature and procedures of the study were explained (in verbal and written format). Only individuals who provided written informed consent were included in the study. Informed consent implied permission for the researcher to access participants' medical records. Two participant groups were included in the study. The first group comprised HIV-positive participants (n_1= 60), while the second group comprised HIV-negative participants (n_2=32) (Table 1). All participants were between 18 and 50 years old. In line with the contra-indications specified for the HIMP, individuals who presented with poor eyesight or severe neck injuries that restricted their range of head movement were excluded from the study [25]. Individuals in participant group 1 who had vestibular symptoms or dysfunction before their HIV diagnosis were excluded. These exclusion criteria ensured that if vestibular impairment was diagnosed, it could be attributed to the HIV infectious process rather than a pre-existing disorder. No participants in the HIV-negative group reported any vestibular symptoms, dysfunction, or any other serious ailments. However, some participants were using chronic medication for the management of hypertension (n_2=3) and cholesterol (n_2=1).

The progressive stages of infection of participants in the HIV-positive group were categorized using the 1992 revised Centres for Disease Control and Prevention (CDC) classification system [3] (Table 2 and Supplementary Table 1 in the online-only Data Supplement). There are three categories in

Table 1. Description of participants

	HIV-positive group				HIV-negative group
CDC category	A (n_1=3)	B (n_1=11)	C (n_1=14)	All (n_1=60)	N/A (n_2=32)
Age (in years)					
Mean	43.9	42.1	46.3	41.4	32.5
Range (SD)	25−52 (6.1)	36−47 (3.5)	40−53 (4.3)	23−50 (5.3)	18−50 (9.1)
Sex					
Male, n (%)	11 (30)	3 (30)	6 (40)	20 (33)	9 (28)
Female, n (%)	24 (70)	8 (70)	8 (60)	40 (67)	23 (72)

HIV: human immunodeficiency virus, CDC: Centres for Disease Control and Prevention, N/A: not applicable, D: standard deviation

Table 2. Centres for Disease Control and Prevention classification system for HIV infected adults and adolescents

CD4+ cell count	Clinical categories		
	A (asymptomatic acute HIV or PGL)	B (symptomatic conditions, not A or C)	C (AIDS-indicator conditions)
1) ≥500 cells/μL	A1	B1	C1
2) 200−499 cells/μL	A2	B2	C2
3) <200 cells/μL	A3	B3	C3

CD4+: cluster of differentiation 4 cells, HIV: human immunodeficiency virus, PGL: persistent generalized lymphadenopathy, AIDS: acquired immune deficiency syndrome

this classification. Categories A and B are assigned to asymptomatic and symptomatic HIV-positive individuals, respectively. The symptomatic conditions in category B may be attributed to a defect in cell-mediated immune function, and/or the management of these conditions may be complicated by the HIV infection. The final progressive stage of HIV is represented as category C, indicating that an individual has developed acquired immune deficiency syndrome (AIDS) [3].

More than half of the participants in the HIV-positive group (58%; n_1=35) were asymptomatic, and were allocated to category A; the remaining participants were allocated to categories B (18%; n_1=11) and C (23%; n_1=14). Participants followed several ARV protocols, with the majority receiving first-line ARV regimens (88%; n_1=53). The mean length of ARV use was 5.2 years (range: 1−13; ±3.6).

Methods

Data collection commenced after ethical clearance was obtained from the Medical Human Research Ethics Committee (protocol number: M160150) and permission was granted by the relevant government department. The study adhered to the World Medical Association's (WMA) Declaration of Helsinki Principles [26], specifically the ethical principles related to informed consent, autonomy, beneficence and non-maleficence, confidentiality, and anonymity.

Data collection involved the review of HIV-positive participant medical records, case history, and the performance of the HIMP. The Natus Otometrics (Denmark) ICS video head impulse test was used to conduct the HIMP. The system consists of a video Frenzel lightweight goggle and disposable face cushion. The HIMP was conducted in a dimly lit room, while participants were seated on a static chair facing a blank wall. The head was moved rapidly and unpredictably in different directions to assess the SCCs. Horizontal head rotations (jaw) were used to assess the horizontal SCCs. The pitching of the head from front to back was used to assess the right anterior-left posterior and left anterior-right posterior SCCs. The chair was moved 45° to the left for right anterior-left posterior and 45° to the right for left anterior-right posterior SCCs. Thereafter, the head was positioned at a 45° angle according to the software instructions. Head movements were conducted in the vertical plane in the direction of the canal being assessed [27]. Excellent test-retest reliability was established by conducting the HIMP on four HIV-negative participants twice at a one-week interval.

The parameters used during this test are outlined in Table 3 [23,27,28].

The criteria used to indicate abnormality included lowered gain in the presence of consistent covert (occurring during the head movement) or overt catch-up saccades (occurring after the head movement). These catch-up saccades had to occur within ~100 ms of the first head impulse or ~100 ms after the head had come to a stop. The raw HIMP data were analyzed to establish the true catch-up saccades and exclude artifacts. The data were also reviewed by an independent rater, and a 100% interrater agreement was established. A VOR deficit was defined as an average gain deficiency with the presence of a covert or overt saccade as indicated on the ICS soft-

ware [27]. The gain of the VOR was calculated as the ratio of the cumulative slow-phase eye velocity over the cumulative head velocity from the onset of the head impulse to the moment head velocity returned to zero [27, 28]. The raw data of the HIMP responses were reviewed by the researcher and an independent rater. A 100% inter-rater agreement was established.

Statistical analysis

All statistical analyses were performed using SAS Release 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to describe measures of variability [range and standard deviation and central tendencies (mean)]. The two-sample t-test and Fisher's exact test were used to determine the significance of mean values and percentages, respectively, of the two participant groups. A p-value of ≤0.05 was considered statistically significant for all probability tests.

Table 3. HIMP parameters

Description	Horizontal HIMP	Vertical HIMP
Impulses conducted	20	20
Velocity (degrees per second)	150–250	100–200
Amplitude (degrees)	10–15	10

HIMP: head impulse paradigm

Results

The presence of possible covert and/or overt saccades across various velocities tested were determined using the HIMP. Bilateral normal HIMP results were obtained in 100% (n_2=32) of the HIV-negative participants and 95% (n_1=57) of the HIV-positive participants. The remaining 5% of the HIV-positive participants presented with unilateral impairments of the horizontal (n_1=2) or the posterior SCCs (n_1=1) in the left ear. These three participants were older than 35 years (mean=39.9; ±0.58), and they had been receiving ARV treatment for less than three years on a current protocol comprising Efavirenz, Emtricitabine, and Tenofovir disoproxil fumarate.

The mean VOR gains and asymmetries of the HIMP are presented in Table 4 and 5. The mean VOR gain of the left posterior SCC was significantly lower in the HIV-positive group than the HIV-negative group (p<0.05; two-sample t-test). A statistically significant difference was also found between the mean VOR gains of the right posterior SCC in categories A and C and the HIV-negative group (p<0.05; two-sample t-test). The mean values of the other SCC did not differ significantly between the two groups (p>0.05; two-sample t-test).

The mean VOR asymmetries (%) of the HIMP of the horizontal and anterior SCCs did not differ significantly between the two groups. However, a statistically significant difference was found between the posterior SCCs for category A and the

Table 4. Mean VOR gains of the HIMP (n=92)

	HIV-positive group (n_1=60)								HIV-negative group (n_2=32)	
	Left ear				Right ear				Left ear	Right ear
CDC category	A (n_1=35)	B (n_1=11)	C (n_1=14)	All (n_1=60)	A (n_1=35)	B (n_1=11)	C (n_1=14)	All (n_1=60)	N/A (n_2=32)	N/A (n_2=32)
Lateral semi-circular canal										
Mean VOR gain	0.95	1.01	0.93	0.96	1.02	1.06	1.00	1.02	0.94	1.02
SD	0.09	0.12	0.04	0.08	0.12	0.12	0.09	0.11	±0.10	±0.10
Range	0.66–1.11	0.86–1.18	0.83–1.04	0.66–1.18	0.76–1.28	0.93–1.25	0.86–1.12	0.76–1.28	0.70–1.26	0.82–1.37
p-value	0.938	0.061	0.721	0.331	1.000	0.277	0.524	1.000		
Anterior semi-circular canal										
Mean VOR gain	0.91	0.82	0.87	0.86	0.90	0.85	0.91	0.89	0.87	0.91
SD	0.11	0.12	0.92	0.38	0.09	0.12	0.07	0.09	±0.10	±0.10
Range	0.65–1.16	0.74–1.10	0.73–1.01	0.65–1.16	0.67–1.05	0.71–1.04	0.72–1.04	0.67–1.05	0.71–1.16	0.78–1.08
p-value	0.119	0.176	1.000	0.848	0.670	0.129	1.000	0.274		
Posterior semi-circular canal										
Mean VOR gain	0.90	0.90	0.92	0.91	0.93	0.90	0.84	0.89	0.97	0.91
SD	0.09	0.12	0.05	0.09	0.32	0.06	0.08	0.15	±0.10	±0.10
Range	0.67–1.09	0.75–1.07	0.78–0.99	0.67–1.09	0.75–1.12	0.74–1.00	0.70–0.98	0.70–0.12	0.70–1.17	0.73–1.15
p-value	0.004*	0.026*	0.086	0.002*	0.020*	0.750	0.026*	0.465		

*statistically significant $p \leq 0.05$. VOR: vestibulo-ocular reflex, HIMP: head impulse paradigm, HIV: human immunodeficiency virus, CDC: Centres for Disease Control and Prevention, N/A: not applicable, SD: standard deviation

Table 5. Mean vestibulo-ocular reflex asymmetries of the head impulse paradigm (n=92)

	HIV-positive group				HIV-negative group
CDC category	A (n_1=35)	B (n_1=11)	C (n_1=14)	All (n_1=60)	N/A (n_2=32)
Lateral semi-circular canal					
Mean asymmetry (%)	7.88	6.56	7.01	7.15	8.80
SD	5.44	3.53	5.69	4.88	5.20
Range	0−21	2−13	0−14	0−21	0−23
p-value	0.482	0.193	0.302	0.135	
Anterior semi-circular canal					
Mean asymmetry (%)	7.73	7.52	7.86	7.70	8.60
SD	5.43	8.12	5.70	6.40	5.30
Range	0−27	0−21	1−16	0−27	1−18
p-value	0.509	0.616	0.672	0.498	
Posterior semi-circular canal					
Mean asymmetry (%)	8.10	8.65	8.91	8.50	12.30
SD	5.11	6.58	4.12	5.27	7.60
Range	0−19	2−27	0−20	0−27	0−31
p-value	0.009*	0.163	0.125	0.006*	

*statistically significant $p \leq 0.05$. HIV: human immunodeficiency virus, CDC: Centres for Disease Control and Prevention, N/A: not applicable, SD: standard deviation

entire HIV-positive group (p<0.05; two-sample t-test).

The 5% prevalence of peripheral vestibular impairment in the HIV-positive group was not statistically significant (p=0.54; Fisher's exact test).

Discussion

The VOR gains of the right horizontal- and anterior SSCs were higher than those of the left in both participant groups. These findings are consistent with a study that attributed this to the geometry of the test procedure [28]. As the response is measured from the right eye, an increased ocular rotation is required on this side to maintain fixation on the target, which may result in a smaller left-side VOR gain [28].

The mean VOR gain of the left posterior SCC was also significantly lower (p<0.05; two-sample t-test) in the HIV-positive group. Similar results were obtained in the right posterior SCC for participants in categories A and C. It has been suggested that increased age may result in VOR gain reduction of the posterior SCC but not in the anterior or horizontal SCCs [28]. This may be the case in the current study, as the mean age of the HIV-positive group (41.4 years; ±5.3) and the HIV-negative control group (32.5 years; ±9.1) was statistically significant (p<0.001; two-sample t-test). In addition, the results may have indicated damage to the inferior vestibular nerve in the HIV-positive group as the HIMP does not isolate the posterior canal from its efferent supply.

The current study reported an insignificant difference between the prevalence of peripheral vestibular impairment in the HIV-positive and HIV-negative groups. These findings can be attributed to three possible phenomena: the effect of ARVs on the immune system, the central compensation of the vestibular system, and the test battery used. Earlier studies ascribed the similarity between prevalence rates in HIV-positive and HIV-negative patients to the strengthening effect of ARV use on the immunity of HIV-positive individuals [16]. In the current study, all HIV-positive participants, irrespective of the CDC category, received ARVs. Similar conclusions were drawn by Heinze, et al. [11] who reported an insignificant difference between the vestibular results of HIV-positive participants receiving ARV treatment and treatment-naïve participants. In contrast to the participants in the current study, only a small percentage of their participants were using ARVs. Despite this, they reported that the prevalence of peripheral vestibular impairments increased from CDC category 1 to CDC category 2 but decreased from CDC category 2 to CDC category 3. A more recent study reported that there is evidence of vestibular symptoms in the HIV/AIDS population; however, the presentation appears to be acute, and they spontaneously resolve [15]. In this study, there was an increase (from 4% to 16%) in the number of participants receiving ARVs who reported vertigo at three months after starting treatment. Interestingly, after six months on ARVs no vestibular symptoms were reported by participants [15]. The premise for these findings is the potential occurrence of central compensation at the later stages of infection [15, 16].

However, the prevalence rate in the current study was significantly lower (p<0.01; Fisher's exact test) than that report-

ed by Heinze, et al. (45.3%; n=24) [11]. This difference in prevalence can, among others, be attributed to the vestibular assessment test battery. In contrast to the current study, a comprehensive test battery, which included bedside and diagnostic assessments such as the cervical vestibular evoked myogenic potential (cVEMP) and caloric tests, was used to assess all five end organs [11]. They attributed the high prevalence of peripheral vestibular impairment to the inclusion of the cVEMP test, among others [11]. They postulated that this test may have been more sensitive to the identification of sub-clinical impairments. However, diagnostic reference standards for cVEMPs are lacking, and research on the use of this procedure to identify vestibular disorders is limited. It is strongly recommended that the test results of this procedure should only be used and interpreted as a part of a holistic test battery [29].

The caloric test was also included in the test batteries of two previous studies [11,12]. A significantly higher prevalence of unilateral vestibular impairment was reported across the various progressive stages of HIV infection [11,12]. This higher prevalence may be attributed to the natural progression of HIV in the absence of treatment or the limited evaluation when using the caloric test; the caloric test is a low-frequency test, and it only evaluates a portion of the labyrinth.

In conclusion, the current study reported comparable peripheral vestibular function in the HIV-positive group receiving ARVs and the HIV-negative group as measured by the HIMP. Although the HIMP is a clinically effective test procedure, it should not be used in isolation to assess vestibular impairment. The current study is in agreement with previous research that suggested that a comprehensive vestibular test battery should be used to assess the vestibular system in its entirety [21,24]. Additional vestibular research using a comprehensive test battery is required in HIV-positive individuals, especially in light of the new ARV treatment guidelines, which recommend earlier treatment initiation and the use of less toxic drugs. Longitudinal studies to determine a causal relationship between HIV, treatment regimen, and treatment adherence and auditory and vestibular function is essential. Vestibular research in the field of HIV remains crucial, as a better understanding of HIV effects may contribute to more effective management strategies and, ultimately, improve quality of life.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.7874/jao.2020.00164.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: all authors. Data curation: Alison Millar. Formal analysis: Karin Joubert and Alison Millar. Funding acquisition: all authors. Investigation: Alison Millar. Methodology: all authors. Project administration: Alison Millar. Resources: Alison Millar. Software: Alison Millar. Supervision: Karin Joubert and Alida Naude. Validation: all authors. Visualization: all authors. Writing—original draft: Alison Millar. Writing—review & editing: Karin Joubert. Approval of final manuscript: all authors.

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