The Journal of Laryngology & Otology (2014), ***128***, *772–779*.

doi:10.1017/S0022215114001996

MAIN ARTICLE

Does the human immunodeficiency virus influence the vestibulocollic reflex pathways? A comparative study

B M HEINZE[1], B M VINCK[1], D W SWANEPOEL[1,2,3]

[1]*Department of Speech-Language Pathology and Audiology, University of Pretoria, South Africa,* [2]*Ear Sciences Centre, School of Surgery, University of Western Australia, Nedlands, and* [3]*Ear Science Institute Australia, Subiaco, Australia*

Abstract

Background: This study compared vestibulocollic reflex and vestibulo-ocular reflex functioning in subjects with and without human immunodeficiency virus. It also described test results throughout progression of the disease and compared the results of human immunodeficiency virus positive subjects who were receiving antiretroviral therapies with those not receiving this treatment.

Methods: Subjects comprised 53 adults with human immunodeficiency virus (mean age 38.5 ± 4.4 years) and 38 without human immunodeficiency virus (mean age 36.9 ± 8.2 years). Clinical examinations included cervical vestibular-evoked myogenic potential and bithermal caloric testing.

Results: Abnormal cervical vestibular-evoked myogenic potential and caloric results were significantly higher in the human immunodeficiency virus positive group ($p = 0.001$), with an odds ratio of 10.2. Vestibulocollic reflex and vestibulo-ocular reflex involvement increased with progression of the disease. There were more abnormal test results in subjects receiving antiretroviral therapies (66.7 per cent) than in those not receiving antiretroviral therapies (63.6 per cent), but this difference was insignificant.

Conclusion: Human immunodeficiency virus seems to influence vestibulocollic reflex pathways. Combining cervical vestibular-evoked myogenic potential and caloric testing may be useful to detect early neurological involvement in human immunodeficiency virus positive subjects.

Key words: Human Immunodeficiency Virus; Vestibulocollic Reflex; Vestibulo-Ocular Reflex; Vestibular Evoked Myogenic Potentials; Caloric Testing

Introduction

The vestibular system senses movement, and sends this information to the cerebellum and vestibular nuclei in the brainstem. Motion and other sensory information are processed and integrated: gaze is stabilised during head movement by means of the vestibulo-ocular reflex, and body and head stability is maintained via the vestibulospinal reflex and vestibulocollic reflex respectively.[1,2] A pathway that includes the saccule, inferior vestibular nerve and vestibulospinal tract mediates and actives the vestibulocollic reflex.[3,4] Cervical or collic vestibular-evoked myogenic potentials are a manifestation arising from the vestibulocollic reflex of the vestibulospinal tract[5] which is mediated ipsilaterally by a three neuron arc. Uchino and colleagues described the anatomical pathway of the vestibulocollic reflex, also known as the sacculocollic reflex.[6] Primary vestibular neurons that travel from the saccule via the inferior vestibular nerve, project into second order vestibular neurons in the lateral vestibular nucleus in the brainstem. From there, neurons descend in the medial vestibulospinal tracts and connect to the motor nuclei of the accessory nerve. Third order vestibular neurons descend to the flexor and extensor neck muscles via the medial vestibulospinal tract.[6]

Cervical vestibular-evoked myogenic potentials are ipsilaterally evoked short latency responses, which can be measured with an active electrode over a contracted sternocleidomastoid muscle,[7] capable of evoking the vestibulocollic reflex.[8] This is perhaps the most direct way of testing vestibulocollic reflex functioning.[9] Cervical vestibular-evoked myogenic potential abnormalities may indicate a lesion at any point along the vestibulocollic reflex pathway. Testing of the vestibulo-ocular reflex pathways, which include the horizontal semicircular canal, superior vestibular nerve and ascending neural path to the extra-ocular muscles,[10] is well characterised and the

Accepted for publication 16 January 2014 First published online 28 August 2014

basis of many commonly used vestibular tests.[2] These include, but are not limited to the caloric test[11] and rotational tests.[12] Testing of the vestibulospinal reflex pathways may include posturography.[11]

The vestibulo-ocular reflex and vestibulospinal reflex pathways have been examined and described in individuals with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). A recent systematic literature review summarised all vestibular tests and findings in subjects with HIV and/or AIDS, and demonstrated that tests of vestibular function concentrated on the vestibulo-ocular reflex and vestibulospinal reflex pathways only.[13] To date, no studies have investigated the vestibulocollic reflex pathways, as examined using cervical vestibular-evoked myogenic potential testing, in subjects with HIV and/or AIDS. This may in part be attributable to that fact that cervical vestibular-evoked myogenic potential testing has only recently been included in clinical test batteries of vestibular function, having proved useful in identifying vestibular disorders.[9]

This study aimed to: (1) describe and compare the functioning of the vestibulocollic reflex and the well characterised vestibulo-ocular reflex in subjects with and without HIV; (2) describe the vestibulocollic reflex and vestibulo-ocular reflex throughout progression of the disease; and (3) compare the vestibulocollic reflex and vestibulo-ocular reflex in HIV-positive subjects receiving antiretroviral therapies with those who were not receiving antiretroviral therapies.

Materials and methods

The Research and Ethics Review Committee of the University of Pretoria and a tertiary referral hospital approved the current study. A cross-sectional comparative research design was employed and convenience sampling was used to recruit subjects. Each subject provided written informed consent to participate in the study.

Subjects

The experimental group comprised subjects with HIV, who were drafted from the infectious disease clinic of a tertiary referral hospital in South Africa. The subjects' HIV status was confirmed by blood serological testing. The researchers obtained written informed consent to access these individuals' medical records, which contained this data. The control group consisted of subjects confirmed to be HIV-negative. These were employees of the tertiary referral hospital and acquaintances of the researchers, all of whom agreed to undergo a blood serological test for HIV.

A total of 91 subjects, 53 adults with HIV and 38 without HIV, were evaluated for participation in the study. Table I summarises the characteristics of participating subjects. There were no statistically significant differences in mean ages between the groups ($p = 0.26$; *t*-test). Previous research indicates that age affects the vestibular system after 55 to 65 years;[14] in order to minimise the likelihood of age affecting the results, only subjects below the age of 50 years were allowed to participate in the study.

TABLE I
DESCRIPTION OF SUBJECTS

Factor	HIV-positive group	HIV-negative group
Number of subjects	53	38
Mean age ± SD (y)	38.5 ± 4.4	36.9 ± 8.2
Age range (y)	23–49	20–50
Gender (% males (M:F))	55 (29:24)	47.4 (18:20)
CDC category (*n*)		
– 1	15	n/a
– 2	20	n/a
– 3	18	n/a
ARV therapy users (*n*)	42	n/a
Non-ARV therapy users (*n*)	11	n/a

HIV = human immunodeficiency virus; SD = standard deviation; y = years; M:F = male to female ratio; CDC = Centers for Disease Control and Prevention Classification System for HIV Infection; n/a = not applicable; ARV = antiretroviral

The subjects with HIV were divided into categories according to their cluster of differentiation 4 cell count, as documented in their medical files (cell count was determined at the infectious disease clinic, at the start of the study). Subjects with counts higher than 500 cells/μl were assigned to category 1 of the Centers for Disease Control and Prevention Classification System for HIV Infection, while those with counts of 200–499 cells/μl and less than 200 cells/μl were assigned to categories 2 and 3 respectively.[15] The HIV-positive subjects were evenly distributed between the three categories. Fifteen subjects were in category 1 (8 male, 7 female), 20 were in category 2 (8 male, 12 female) and 18 were in category 3 (8 male, 10 female).

The HIV subjects were further divided into two subgroups, one comprising those who were receiving antiretroviral therapies ($n = 42$) and another comprising those not receiving antiretroviral therapies ($n = 11$). Those undergoing antiretroviral therapy received a combination of at least three of the following drugs: tenofovir, lamivudine, efavirenz, emtricitabine, nevirapine, stavudine, zidovudine and lopinavir/ritonavir.

Otological and audiological examinations

An otoscopic examination was performed to inspect the external auditory canal for any debris or foreign objects that might cause occlusion of the ear canal, and to identify any possible perforation of the tympanic membrane. Subjects with obstructed ear canals were referred to a clinician for extraction prior to participation in the study.

Tympanometry was performed using a diagnostic 226 Hz probe tone (GSI TympStar™). The following criteria were used for normal adult acoustic admittance profiling: ear canal volume, 0.8 to 2.0 ml; compliance, 0.3 to 1.8 ml; and middle-ear pressure, −100 to +50

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

daPa.[16] Type A tympanograms were revealed for 49 subjects with HIV and for 38 subjects without HIV.

Pure tone audiometry (air and bone conduction) was performed to determine the presence of air–bone gaps (GSI 61™). Air–bone gaps larger than 10 dB were found in the four HIV-positive subjects with abnormal compliance and middle-ear pressure, suggesting a conductive component. No air–bone gaps were found for the 49 HIV-positive and 38 HIV-negative subjects with type A tympanograms.

Vestibulo-ocular reflex test

Caloric tests were used to describe the vestibulo-ocular reflex. Rotational testing was not available to the researchers. Tests of spontaneous nystagmus, with and without fixation, preceded caloric stimulation. Video nystagmography (performed with a Visual Eyes infrared video-based system from Micromedical Technologies, Chatham, Illinois, USA) was used to record any spontaneous nystagmus and caloric-induced nystagmus.

Bithermal (cool 24°C, warm 47°C) air caloric testing (AirFX; Micromedical Technologies) was used to irrigate the external auditory canal. Air caloric irrigation was chosen over water irrigation because water irrigation of the external ear canal may result in damage to the delicate skin lining of the outer ear, which in turn places it at risk of invasive external otitis due to bacterial invasion.[17] This frequently occurs in those who are immunocompromised, such as persons with HIV. Subjects were placed in a supine position with the head tilted forward at an angle of 30° from the horizontal plane for correct positioning of the horizontal semicircular canals. Air was irrigated for 60 seconds, with 5-minute intervals between stimuli.

The peak of the slow phase eye velocity of caloric nystagmus post-irrigation was used as a parameter of superior vestibular nerve and horizontal canal function. The formula reported by Jongkees *et al*. was used to calculate unilateral weakness or asymmetry and directional preponderance.[18] A unilateral weakness or asymmetry of 20 per cent or more,[11,19] directional preponderance of 30 per cent or more,[11] bilateral weakness, or hyperreflexia was considered abnormal. Bilateral weakness or hypoactive responses were regarded as the total warm responses from both sides of less than 11 degrees per second, and the total cool responses from both sides of less than 6 degrees per second.[20] Hyperreflexia or hyperactive responses were regarded as the total responses from both sides of more than 221 degrees per second.[19]

Vestibulocollic reflex test

Cervical vestibular-evoked myogenic potential testing was performed using an auditory-evoked potential system (Bio-logic Navigator Pro; Natus Medical, San Carlos, California, USA). Insert-type earphones (ER-3; Etymotic Research, Elk Grove Village, Illinois, USA) with disposable foam tips were used.

Subjects were comfortably seated with their head rotated approximately 45° to the opposite side of the ear being tested. A blood pressure manometer, with the rolled up inflatable cuff positioned between the subject's hand and jaw, was used to provide feedback of the contracted sternocleidomastoid muscle during the recording of the cervical vestibular-evoked myogenic potentials. The subjects pushed with their heads against the rolled up inflatable cuff and were asked to sustain a pressure of 40 mmHg. This allowed control of the sternocleidomastoid muscle contractions and ensured comparable muscle contractions between the left and right side.[21] Both the subjects and the investigator monitored this sustained pressure.

Every measurement, even those indicating absent responses, was repeated twice to test for wave reproducibility and to eliminate potential artefacts. The average of the two recordings was used for analysis. The first peak on the waveforms was marked as P1, while the second (occurring within a period of 30 ms) was marked as N1.

The researchers recorded and measured P1 and N1 latencies (in milliseconds), inter-peak amplitude (in microvolts), and amplitude asymmetry (in percentages). The asymmetry ratio was determined by calculating the interaural amplitude difference according to the following formula: ((left ear amplitude – right ear amplitude)/(left ear amplitude + right ear amplitude)) × 100. Responses were interpreted as follows: (1) the absence of unilateral or bilateral waveforms was considered abnormal (absence of an identifiable P1 and N1 peak); (2) latencies above the upper limits for P1 and N1 latencies (17.0 ms and 26.3 ms respectively – calculated from two standard deviations above the mean of the HIV-negative group) were regarded as present yet delayed, and considered abnormal; and (3) the presence of an amplitude asymmetry ratio of 40 per cent or more was considered abnormal, as it indicated side-to-side differences in amplitude.[22]

Results

All analyses of data were performed using the statistical software package SPSS® for Windows, version 21. Means, standard deviations and percentages were used to describe the data. A one-way analysis of variance was used to compare the distribution of HIV-positive subjects between the three categories of the Classification System for HIV Infection.[15] The one-sample Kolmogorov–Smirnov test was used to demonstrate normality of the data. The independent samples *t*-test was used to compare the mean values between the experimental and control groups. *P*-values of less than 0.05 were accepted as statistically significant. Odds ratios were calculated. The chi-square non-parametric test was used to compare the findings between the two study groups and the three Classification System categories.

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

TABLE II
DISTRIBUTION OF ABNORMAL FINDINGS BY GROUP

Parameter	HIV-positive group (*n* (%))	HIV-negative group (*n* (%))
Abnormal cervical VEMP	12 (22.6)	2 (5.3)
Abnormal caloric	8 (15.1)	2 (5.3)
Abnormal cervical VEMP with abnormal caloric	11 (20.8)	2 (5.3)
Abnormal cervical VEMP due to middle-ear pathology*	4 (7.5)	0 (0)
Total abnormalities†	35 (66)	6 (15.8)

*As demonstrated by abnormal middle-ear compliance and pressure, and air–bone gaps. †$p = 0.001$ (between-group difference). HIV = human immunodeficiency virus; VEMP = vestibular-evoked myogenic potential

TABLE III
DESCRIPTION OF ABNORMAL FINDINGS

Parameter	HIV-positive group (*n* (%))	HIV-negative group (*n* (%))
Cervical VEMP		
– Absent unilateral*	3 (5.7)	1 (2.6)
– Absent bilateral	5 (9.4)	1 (2.6)
– Delayed unilateral	1 (1.9)	–
– Delayed bilateral	5 (9.4)	–
– Absent unilateral* with delayed unilateral	3 (5.7)	–
– Asymmetry ratio ≥40%	10 (18.9)	3 (7.9)
Caloric		
– Unilateral weakness	15 (28.3)	3 (7.9)
– Bilateral weakness	1 (1.9)	1 (2.6)
– Hyperreflexia	2 (3.8)	–
– Directional preponderance	3 (5.7)	–

*Data of the four subjects with middle-ear pathology excluded here. HIV = human immunodeficiency virus; VEMP = vestibular-evoked myogenic potential

Abnormalities

Abnormal cervical vestibular-evoked myogenic potential and caloric test results were found in 66 per cent ($n = 35$) of the subjects with HIV, compared with only 15.8 per cent ($n = 6$) of the subjects without HIV, indicating a significantly higher occurrence of pathology in subjects with HIV ($p = 0.001$; chi-square). The recordings indicated absent cervical vestibular-evoked myogenic potentials for the four HIV-positive subjects with abnormal tympanograms and air–bone gaps. This association between vestibular signs and HIV was further confirmed by the odds ratio, calculated as 10.2. This indicated a 10.2 times higher risk of abnormal cervical vestibular-evoked myogenic potential and caloric responses in persons who were HIV-positive.

Table II shows the distribution of abnormal cervical vestibular-evoked myogenic potential and caloric test results in the HIV-positive and HIV-negative groups. Abnormal cervical vestibular-evoked myogenic potential results were found in 43.4 per cent ($n = 23$) and abnormal caloric results in 35.8 per cent ($n = 19$) of subjects with HIV. Abnormal cervical vestibular-evoked myogenic potential results due to middle-ear pathology were found in 7.5 per cent ($n = 4$) of subjects with HIV. The cervical vestibular-evoked myogenic potential results were abnormal in 10.5 per cent ($n = 4$) and the caloric results were abnormal in 10.5 per cent ($n = 4$) of the subjects without HIV.

Table III shows the occurrence of abnormal cervical vestibular-evoked myogenic potential results according to absent waveforms, delayed P1 and/or N1 latencies, and amplitude asymmetry of 40 per cent or more. In the HIV-positive group, the recordings for 20.8 per cent ($n = 11$) of subjects indicated absent cervical vestibular-evoked myogenic potentials, not including the four subjects with middle-ear pathology. Of the six subjects with unilaterally absent cervical vestibular-evoked myogenic potentials, the left side was affected in five subjects and the right side affected in one subject. Only one subject in the HIV-negative group had absent cervical vestibular-evoked myogenic potentials bilaterally. There was a significantly higher occurrence of absent cervical vestibular-evoked myogenic potentials among the subjects with HIV than for subjects without HIV ($p = 0.003$; chi-square). Table III further indicates that in the HIV-positive group 17 per cent ($n = 9$) of subjects presented with delayed latencies. Four subjects showed delayed latencies unilaterally and five bilaterally.

There were no significant differences observed regarding the mean latencies of P1 and N1 to the left or right side in either of the study groups ($p > 0.05$; *t*-test). Table IV indicates the distribution of the mean P1 and N1 latencies, as well as the inter-peak amplitude differences in both the HIV-positive and HIV-negative groups as revealed by cervical vestibular-evoked myogenic potential testing. P1 latencies were statistically (but not clinically) significantly delayed in the HIV-positive group. N1 latencies showed no difference between the two groups.

TABLE IV
MEAN LATENCY AND INTER-PEAK AMPLITUDE RESULTS*

Group	Ears (*n*)†	P1 latency (ms)	N1 latency (ms)	Inter-peak amplitude (μV)
HIV-positive (mean ± SD)	84	15.2 ± 2.2	21.7 ± 2.4	201.2 ± 51.1
HIV-negative (mean ± SD)	73	13.9 ± 1.6	21.7 ± 4.1	172.7 ± 63.4
p (*t*-test)		0.001	0.89	0.003

*From cervical vestibular-evoked myogenic potential recordings. †Data for ears with absent cervical vestibular-evoked myogenic potentials not used. HIV = human immunodeficiency virus; SD = standard deviation

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

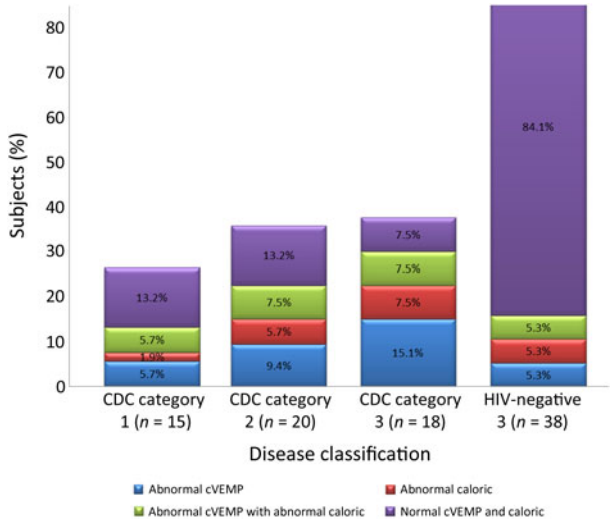

FIG. 1

Cervical vestibular-evoked myogenic potential (cVEMP) and caloric test results throughout disease progression. CDC = Centers for Disease Control and Prevention Classification System for HIV Infection; HIV = human immunodeficiency virus

Disease progression

Figure 1 illustrates the cervical vestibular-evoked myogenic potential and caloric test results throughout the progression of the disease. The HIV-positive subjects were divided into the three categories of the Classification System for HIV Infection based upon their cluster of differentiation 4 cell counts at the time of participation.[15] Normal cervical vestibular-evoked myogenic potential and caloric test results were recorded in 34 per cent of subjects with HIV. The occurrence of abnormal test results increased from 13.3 per cent for those in category 1, to 22.6 per cent in category 2 and 30.1 per cent in category 3 of disease progression (Figure 1).

Antiretroviral therapy

Table V shows the distribution of abnormal cervical vestibular-evoked myogenic potential and caloric results of the HIV-positive subjects receiving antiretroviral therapies compared with those not receiving antiretroviral therapies. Of the 42 antiretroviral therapy users, 66.7 per cent ($n = 28$) showed abnormal cervical vestibular-evoked myogenic potential and caloric test results. Of the 11 non-antiretroviral therapy users, 63.6 per cent ($n = 7$) showed abnormal cervical vestibular-evoked myogenic potential and caloric test results. Although the occurrence of abnormal test results was higher among the antiretroviral therapy users, this difference was not statistically significant ($p = 0.91$; chi-square).

TABLE V

DISTRIBUTION OF ABNORMAL FINDINGS FOR HIV-POSITIVE ANTIRETROVIRAL THERAPY USERS VERSUS NON-USERS

Parameter	ARV therapy users (n (%))*	Non-ARV therapy users (n (%))†
Abnormal cervical VEMP	13 (30.9)	3 (27.3)
Abnormal caloric	4 (9.5)	4 (36.4)
Abnormal cervical VEMP with abnormal caloric	11 (26.2)	0 (0)
Total abnormalities‡	28 (66.7)	7 (63.6)

*$n = 42$; †$n = 11$. ‡$p = 0.91$ (between-group difference). HIV = human immunodeficiency virus; ARV = antiretroviral; VEMP = vestibular-evoked myogenic potential

Discussion

In this study, subjects with HIV presented with significantly more abnormal cervical vestibular-evoked myogenic potential and caloric test findings than those without HIV. Two-thirds of the subjects with HIV (66 per cent) presented with at least one abnormality on the cervical vestibular-evoked myogenic potential and caloric test parameters, compared with only 15.8 per cent of subjects without HIV. The calculated odds ratio suggested that subjects with HIV had a 10.2 higher risk of having abnormal cervical vestibular-evoked myogenic potential and caloric test results than subjects without HIV.

Regarding the reliable recording of cervical vestibular-evoked myogenic potential responses, the use of a correction algorithm remains the favoured method, as well as monitoring the electromyographic (EMG) activity of the sternocleidomastoid muscle.[21] The current study did not have access to these algorithms or EMG systems, which is a limitation of the study. However, the results of a recent study concluded that the use of the blood pressure manometer may be a useful alternative for reliable recordings of these responses.[21]

The caloric findings in the current study can be compared with those of four previous research reports that employed a group study design of adult subjects with HIV.[23–26] Abnormal caloric test findings demonstrate the presence of abnormal functioning of the vestibulo-ocular reflex pathway. Three of the four studies showed abnormal caloric test findings in subjects with HIV that were similar to those in the current study (in which 35.8 per cent of HIV subjects ($n = 19$) were affected). The two most recent studies found abnormal caloric test results in 43.3 and 50 per cent respectively in their sample of HIV subjects.[23,24] Their subjects were all symptomatic as they suffered from chronic dizziness. An earlier study found slightly fewer cases of abnormal caloric test results compared with the current study; specifically, 11.6 per cent of their sample of HIV subjects were affected.[26] In contrast, only one study reported no abnormal caloric test findings in HIV subjects.[25] No noticeable differences were found between the caloric test protocols employed in these reports, but the subjects in the study by Castello and colleagues were all asymptomatic without any vestibular symptoms (e.g. vertigo,

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

dizziness or disequilibrium),[25] which could explain the absence of abnormal caloric responses. It is interesting to note that 66.4 per cent ($n = 29$) of HIV-positive subjects in the study by Hausler and colleagues were asymptomatic, yet the authors reported abnormal caloric test findings among those subjects too.[26] However, these authors did not indicate whether their subjects used antiretroviral therapies or any medication for secondary infections that could contribute to the abnormal caloric test findings.

To our knowledge, no other published research has utilised cervical vestibular-evoked myogenic potential testing to describe the functioning of the vestibulocollic reflex pathways in subjects with HIV. The current study demonstrated a significantly higher number of abnormal cervical vestibular-evoked myogenic potential results in HIV subjects than in non-HIV subjects. The mean P1 latencies were statistically significantly delayed in the HIV-positive group. The abnormal cervical vestibular-evoked myogenic potential test results suggest a high occurrence of abnormal functioning of the vestibulocollic reflex pathways in subjects with HIV. The abnormal caloric test results also suggest a higher occurrence of abnormal functioning of the vestibulo-ocular reflex pathways in subjects with HIV compared with those without the disease. The caloric test is a very low frequency test, namely 0.003 Hz;[27] the mid-range and higher frequencies were therefore not assessed, meaning that the occurrence of vestibulo-ocular reflex abnormality as assessed with the caloric test may be even higher.

Possible mechanisms for the increased vestibulocollic reflex and vestibulo-ocular reflex abnormalities include opportunistic infections, ototoxic treatments and direct effects of HIV.[13] Opportunistic infections may affect the functioning and integrity of both branches of the vestibular nerve (and the structures that they innervate). Young reported five patients with the herpes zoster virus, a common HIV-related opportunistic infection, suffering from vertigo.[28] Unfortunately, the author did not indicate in the report whether these subjects were HIV-positive. Nonetheless, recordings revealed absent cervical vestibular-evoked myogenic potentials for all five subjects (100 per cent). In addition, recordings revealed absent caloric responses for four subjects (80 per cent). In another study, 10 subjects with Ramsay Hunt syndrome, another common HIV-related opportunistic infection, underwent cervical vestibular-evoked myogenic potential and caloric testing.[29] Once again, the authors did not indicate the subjects' HIV status. Similar to Young,[28] the study revealed abnormal cervical vestibular-evoked myogenic potentials in 7 subjects (70 per cent) and abnormal caloric results in all 10 subjects (100 per cent). Another study of subjects infected with cytomegalovirus demonstrated abnormal cervical vestibular-evoked myogenic potential and caloric test results (23.1 per cent and 30.8 per cent respectively).[30] Cytomegalovirus is another common HIV-related opportunistic infection that has been reported to cause sensorineural hearing loss, and peripheral and central neurological manifestations, in subjects infected with HIV (the HIV status of subjects in the aforementioned study was not indicated).[31,32] These findings suggest that opportunistic infections like herpes zoster virus and Ramsay Hunt syndrome may result in involvement of both the vestibulocollic reflex and vestibulo-ocular reflex pathways.

The use of antiretroviral therapies could also contribute to the higher occurrence of abnormal cervical vestibular-evoked myogenic potential and caloric test findings in subjects with HIV. Those exposed to antiretroviral therapies presented with slightly more cervical vestibular-evoked myogenic potential and caloric testing abnormalities (66.7 per cent) than those not receiving antiretroviral therapies (63.6 per cent); these differences, however, were not statistically significant. Recent studies found similar results with auditory brainstem response (ABR) testing, demonstrating a higher occurrence of abnormal ABR findings in subjects receiving antiretroviral therapies (62.5 per cent) compared with those not receiving antiretroviral therapies (50 per cent), although the difference was not statistically significant.[33] Such findings suggest that the auditory and vestibular nerves, and the structures that they innervate, are at risk as a result of the possible ototoxic effects of some antiretroviral therapies.

Antiretroviral regimes may consist of three or more classes of drugs, and one or more of these are nucleoside or nucleotide analogue reverse transcriptase inhibitors.[34] One adverse effect of these inhibitors is mitochondrial toxicity, which is responsible for, among other things, myopathy and neuropathy.[35] Neuropathy is a dysfunction of the nervous system, and may therefore involve the vestibular branches of the VIIIth cranial nerve. Additionally, there are case reports of ototoxic sensorineural hearing loss associated with the use of nucleoside or nucleotide analogue reverse transcriptase inhibitors which may have been induced by a reduction in the mitochondrial DNA content, although ageing and the virus itself could have contributed to mitochondrial DNA mutations.[36] If these drugs can cause sensorineural hearing loss and affect the auditory brainstem pathways, it is also likely that they can affect the vestibular nerves and/or end organs in subjects receiving antiretroviral therapies.

A recent study compared the vestibular function of HIV-positive subjects receiving highly active antiretroviral therapy with that of age- and gender-matched HIV-negative subjects.[37] They performed vestibular screening tests, which consisted of head thrust tests, Dix–Hallpike manoeuvres and Romberg balance tests, and found no significant difference between the two groups. The subjects were excluded if they had vestibular complaints, as this could suggest that they were centrally compensated. Therefore, the vestibular screening tests employed may have been underpowered

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

for the detection of subclinical vestibular involvement in subjects who were centrally compensated.

The occurrence of abnormal cervical vestibular-evoked myogenic potential and caloric test findings increased with progression of the disease, rising from 13.3 per cent in the early stages (Classification System for HIV Infection[15] category 1) to 30.1 per cent in the advanced stages (category 3). Three previous studies that also used a cross-sectional research design also demonstrated an increase in vestibular involvement from early to advanced disease stages.[23,24,26] A detailed summary of those findings has been reviewed elsewhere.[13] There is a higher occurrence of abnormal cervical vestibular-evoked myogenic potential and caloric test findings in the advanced stages of HIV due to the reduction in cluster of differentiation 4 cell counts, which places the infected individual at risk of various opportunistic infections. This necessitates the use of antiretroviral therapies to strengthen immunity in order to combat opportunistic infections; however, the vestibular nerves and structures of the vestibular end organs may be susceptible to ototoxicity and to the infections themselves, resulting in abnormal cervical vestibular-evoked myogenic potential and caloric test results.

- **The vestibulocollic reflex stabilises the head during active movements**
- **Testing of the vestibulo-ocular reflex is the basis of many vestibular tests**
- **The occurrence of abnormal vestibular function is high in adults infected with human immunodeficiency virus (HIV)**
- **Previous reports focused on vestibulo-ocular reflex tests; it was not known whether HIV affected vestibulocollic reflex pathways**
- **Cervical or collic vestibular-evoked myogenic potentials allow direct testing of vestibulocollic reflex pathways**
- **The study results indicated a high occurrence of vestibulocollic reflex pathway abnormalities in adults with HIV**

The VIIIth cranial nerve and brainstem pathways may undergo neuropathological changes such as subcortical demyelination because of the HIV infection itself.[38,39] This may explain the ABR abnormalities observed in HIV-positive individuals with and without clinical features of the disease, irrespective of normal hearing thresholds.[38] As ABRs may indicate subclinical pathological changes in the peripheral auditory nervous system, cervical vestibular-evoked myogenic potential and caloric testing may indicate pathological changes in the vestibulo-ocular reflex and vestibulocollic reflex pathways respectively in adults infected with HIV. Posturography may be useful too in detecting pathological changes in the vestibulospinal reflex pathways;[40] however, this test procedure was unavailable to the researchers.

Conclusion

There was a significantly higher occurrence of abnormal cervical vestibular-evoked myogenic potential responses and caloric test results in the adults with HIV than in those without HIV. The abnormalities shown by the cervical vestibular-evoked myogenic potential and caloric tests were probably due to pathology of the vestibulocollic reflex and vestibulo-ocular reflex pathways respectively. A combination of cervical vestibular-evoked myogenic potential and caloric tests in the vestibular test battery for adults infected with HIV may offer a tool for detecting early neurological involvement, irrespective of disease progression and clinical manifestations.

References

1 Goebel JA. Practical anatomy and physiology. In: Goebel JA, ed. *Practical Management of the Dizzy Patient*, 2nd edn. Philadelphia: Wolters Kluwer, 2008;1–13
2 Fife TD. Overview of anatomy and physiology of the vestibular system. In: Eggers SDZ, Zee DS, eds. Vertigo and Imbalance: Clinical Neurophysiology of the Vestibular System. *Handbook of Clinical Neurophysiology*. Amsterdam: Elsevier, 2010;**9**(2): 5–17
3 Ito K, Ishimoto S, Murofushi T. Narrow internal auditory meatus: an idiopathic case confirming the origin and pathway of vestibular evoked myogenic potentials in humans. *Arch Otolaryngol Head Neck Surg* 2001;**127**:275–8
4 Wilson VJ, Boyle R, Fukushima K, Rose PK, Shinoda Y, Suqiuchi Y *et al*. The vestibulocollic reflex. *J Vestib Res* 1995;**5**:147–70
5 Rosengren SM, Welgampola MS, Colebatch JG. Vestibular evoked myogenic potentials: past, present and future. *Clin Neurophysiol* 2010;**121**:636–51
6 Uchino Y, Sato H, Sasaki M, Imaqawa M, Ikeqami H, Isu N *et al*. Sacculocollic reflex arcs in cats. *J Neurophysiol* 1997; **77**:3003–12
7 Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiatry* 1994;**57**:190–7
8 Colebatch JG, Rothwell JC. Motor unit excitability changes mediating vestibulocollic reflexes in the sternocleidomastoid muscle. *Clin Neurophysiol* 2004;**115**:2567–73
9 Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. *Neurology* 2005;**64**:1682–8
10 Wester M. Vestibular evoked myogenic potentials. In: Atcherson SR, Stoody TM, eds. *Auditory Electrophysiology: A Clinical Guide*. New York: Thieme Medical Publishers, 2012;289–306
11 Baloh RW, Kerber KA. *Clinical Neurophysiology of the Vestibular System*, 4th edn. Oxford: University Press, 2011
12 Brandt T, Strupp M. General vestibular testing. *Clin Neurophysiol* 2005;**116**:406–26
13 Heinze BM, Swanepoel DW, Hofmeyr LM. Systematic review of vestibular disorders related to human immunodeficiency virus and acquired immunodeficiency syndrome. *J Laryngol Otol* 2011;**125**:881–90
14 Maes L, Dhooge I, D'haenens W, Bockstael A, Keppler H, Philips B *et al*. The effect of age on the sinusoidal harmonic acceleration test, pseudorandom rotation test, velocity step test, caloric test, and vestibular evoked myogenic potential test. *Ear Hear* 2010;**31**:84–94
15 CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;**41**(RR-17):1–19
16 Jerger J. Clinical experience with impedance audiometry. *Arch Otolaryngol* 1970;**92**:311–24

https://doi.org/10.1017/S0022215114001996 Published online by Cambridge University Press

17 Zikk D, Rapoport Y, Himelfarb MZ. Invasive external otitis after removal of impacted cerumen by irrigation. *N Engl J Med* 1991;**325**:969–70
18 Jongkees LB, Maas J, Philipszoon A. Clinical nystagmography: a detailed study of electro-nystagmography in 341 patients with vertigo. *Pract Otorhinolaryngol (Basel)* 1962;**24**:65–93
19 Jacobson GP, Newman CW, Peterson EL. Interpretation and usefulness of caloric testing. In: Jacobson GP, Newman CW, Kartush JM, eds. *Handbook of Balance Function Testing*. San Diego: Singular Publishing Group, 1997;193–234
20 Barber HO, Stockwell CW. *Manual of Electronystagmography*, 2nd edn. St Louis: CV Mosby, 1980
21 Maes L, Vinck BM, De Vel E, D'Haenens W, Bockstael A, Keppler H *et al*. The vestibular evoked myogenic potential: a test-retest reliability study. *Clin Neurophysiol* 2009;**120**:594–600
22 Akin FW, Murnane OD. Vestibular evoked myogenic potentials. In: Jacobson GP, Shepard NT, eds. *Balance Function Assessment and Management*. San Diego: Plural Publishing, 2008;405–34
23 Castello E, Baroni N, Pallestrini E. Neurotological and auditory brain stem response findings in human immunodeficiency virus positive patients without neurologic manifestations. *Ann Otol Rhinol Laryngol* 1998;**107**:1054–60
24 Hausler R, Vibert D, Koralnik IJ, Hirschel B. Neuro-otological manifestations in different stages of HIV infection. *Acta Otolaryngol Suppl* 1991;**481**:515–21
25 Teggi R, Giordano L, Pistorio V, Bussi M. Vestibular function in HIV patients: preliminary report. *Acta Otolaryngol* 2006;**26**: 140–6
26 Teggi R, Ceserani N, Luce FL, Lazzarin A, Bussi M. Otoneurological findings in human immunodeficiency virus positive patients. *J Laryngol Otol* 2008;**122**:1289–94
27 White JA. Laboratory tests of vestibular and balance functioning. In: Hughes GB, Pensak ML, eds. *Clinical Otology*, 3rd edn. New York: Thieme, 2007;132–49
28 Young YH. Vestibular evoked myogenic potentials: a clinical tool for testing the inferior vestibular nerve integrity [in Chinese]. *Acta Neurologica Taiwanica* 2002;**11**:120–7
29 Ozeki H, Iwasaki S, Ushio M, Takeuchi N, Murofushi T. The lesion site of vestibular dysfunction in Ramsay Hunt syndrome: a study by click and galvanic VEMP. *J Vestib Res* 2006;**16**: 217–22
30 Zagólski O. Vestibular-evoked myogenic potentials and caloric stimulation in infants with congenital cytomegalovirus infection. *J Laryngol Otol* 2008;**122**:574–9
31 Meynard JL, El Amrani M, Meyohas MC, Fligny I, Gozlan J, Rozenbaum W *et al*. Two cases of cytomegalovirus infection revealed by hearing loss in HIV-infected patients. *Biomed Pharmacother* 1997;**51**:461–3
32 Vancíková Z, Dvorák P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals–a review. *Curr Drug Targets Immune Endocr Metabol Disord* 2001;**1**: 179–87
33 Matas CG, Silva SM, de Almeida Marcon B, Gonçalves IC. Electrophysiological manifestations in adults with HIV/AIDS submitted and not submitted to antiretroviral therapy. *Pro Fono* 2010;**22**:107–12
34 Moyle G. Clinical manifestations and management of antiretroviral nucleoside analog-related mitochondrial toxicity. *Clin Ther* 2000;**22**:911–36
35 Warnke D, Barreto J, Temesgen Z. Therapeutic review: antiretroviral drugs. *J Clin Pharmacol* 2007;**47**:1570–9
36 Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. *Clin Infect Dis* 2001;**32**:1623–7
37 Cohen HS, Cox C, Springer G, Hoffman HJ, Young MA, Margolick JB *et al*. Prevalence of abnormalities in vestibular function and balance among HIV-seropositive and HIV-seronegative women and men. *PLoS One* 2012;**7**:1–7
38 Bankaitis AE, Keith RW. Audiological changes associated with HIV infection. *Ear Nose Throat J* 1995;**74**:353–9
39 Reyes-Contreras L, Silva-Rojas A, Ysunza-Rivera A, Jiménez-Ruíz G, Berruecos-Villalobos P, Romo-Gutiérrez G. Brainstem auditory evoked response in HIV-infected patients with and without AIDS. *Arch Med Res* 2002;**33**:25–8
40 Dellepiane M, Medicina MC, Mora R, Salami A. Static and dynamic posturography in patients with asymptomatic HIV-1 infection and AIDS. *Acta Otorhinolaryngol Ital* 2005; **25**:353–8

Address for correspondence:
Dr Barbara M Heinze,
Department of Speech-Language Pathology and Audiology,
Private Bag X20, Hatfield,
Pretoria 0028, South Africa

Fax: +27 12 4203517
E-mail: barbara.heinze@up.ac.za

Dr B M Heinze takes responsibility for the integrity of the content of the paper
Competing interests: None declared