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Changes in measures of vestibular and balance function and hippocampus volume in Alzheimer's disease and mild cognitive impairment

Helen S Cohen, EdD, OTR[1,*], **Christie M Lincoln, MD**[2], **Valory N Pavlik, PhD**[3], **Haleh Sangi-Haghpeykar, PhD**[4]

[1]Department of Otolaryngology – Head and Neck Surgery, Baylor College of Medicine

[2]Department of Radiology, Baylor College of Medicine

[3]Department of Neurology, Baylor College of Medicine

[4]Department of Obstetrics and Gynecology, Baylor College of Medicine

Abstract

Objective.—To test the hypotheses that people with Alzheimer's disease and mild cognitive impairment have increased frequency of vestibular impairments and decreased hippocampal volume compared to healthy age-matched controls.

Study design: Retrospective, with some historical controls

Setting: Out-patient, tertiary care center

Subjects: People with mild to moderate dementia diagnosed with Alzheimer's disease and with mild cognitive impairment.

Main outcome measures: A standard clinical battery of objective tests of the vestibular system, and screening for balance; available clinical diagnostic MRIs were reviewed and post-processed to quantify the left and right hippocampal volumes utilizing both manual segmentation and computer automated segmentation.

Results.—Study subjects (N=26) had significantly more vestibular impairments, especially on Dix-Hallpike maneuvers and cervical vestibular evoked myogenic potentials (cVEMP), than historical controls. No differences were found between mild and moderate dementia subjects. Independence on instrumental activities of daily living in subjects with age-normal balance approached statistical differences from subjects with age-abnormal balance. MRI data were available for 11 subjects. Subjects with abnormal cVEMP had significantly reduced left hippocampal MRI's using manual segmentation compared to subjects with normal cVEMP.

Conclusion.—The data from this small sample support and extend previous evidence for vestibular impairments in this population. The small MRI sample set should be considered

[*]To whom correspondence should be addressed: Helen S Cohen, EdD, Dept of Otolaryngology – Head and Neck Surgery, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, hcohen@bcm.edu, Telephone: 713-798-5900, FAX: 713-798-8658.

preliminary evidence, and suggests the need for further research, with a more robust sample and high-resolution MRIs performed for the purpose of hippocampal analysis.

Keywords

Dementia; vestibular disorders; MRI; hippocampus; VEMP

Introduction

Several studies suggest that vestibular impairment may be related to Alzheimer's Disease (AD), although the results are mixed. Harun et al. reported that AD patients who were tested on cervical vestibular evoked myogenic potentials (cVEMP) and head impulse tests had impaired spatial skills, and spatial skills were worse among subjects who appeared to have vestibular disorders (1, 2). This finding is significant because AD patients have reduced hippocampal volume (3), and the hippocampus is involved in spatial orientation. By contrast, a small sample of AD patients were shown to have balance deficits and impaired scores on the Fukuda stepping test, but they had no deficits on bi-thermal caloric tests of the vestibulo-ocular reflex (VOR) (4). AD subjects have been shown to have deficits on static posturography (5). These studies are problematic because the Fukuda stepping test has been discredited (6–8) and static posturography has limited uses.

Direct and indirect evidence indicates the presence of vestibular input on hippocampal place cells and head direction cells, reviewed elsewhere (9, 10). Vestibular input probably has an anatomical distribution that is greater in the dorsal hippocampus and dorsal dentate gyrus than the ventral hippocampus or in CA1 (11). Rats with chemically induced bilateral peripheral vestibular loss show increased long term potentiation in the dentate gyrus and upregulation of NMDA receptor expression in the dentate gyrus and in CA1 (12). These studies suggest that vestibular input may have a direct or indirect influence on spatial memory functions mediated by the hippocampus. Those functions are often impaired in AD (12, 13). By comparison, however, patients with surgical unilateral vestibular loss showed no changed in hippocampal volume (14). Therefore, the extent that vestibular projections contribute to hippocampal volume is unclear.

Previc suggested that vestibular loss contributes to AD via degeneration of medial-temporal regions and related pathways in the caudate nucleus and hippocampus (15). Vestibular input may project to the caudate nucleus (16), and vestibularly-mediated path integration – a type of spatial orientation skill -- has been shown to be impaired after vestibular and caudate nucleus lesions (17). Also, two studies of vestibular nuclei show changes that are characteristic of changes in the hippocampus of AD patients. Neurofibrillary tangles have been found in the lateral vestibular nuclei of AD patients but only minimally in control subjects (18). Also, plaques, decreased dendritic spines, impairments of the Golgi apparatus, and decreased neuronal vesicles have been found in the medial vestibular nuclei of AD patients (19).

These studies suggest that deficits in vestibular function may contribute to deficits in spatial orientation functions mediated by the vestibular system and the hippocampus and may contribute to decreased input to the hippocampus, resulting in decreased hippocampal

volume. The findings are not clear-cut, however. In the present study we tested two hypotheses: that individuals with AD and with mild cognitive impairment (MCI) would have decreased performance on standard, clinical objective tests of the vestibular system and well-normed balance screening tests; and that individuals with decreased vestibular test results would have decreased hippocampal volumes.

Methods

Subjects

Subjects were adults diagnosed with either AD (n=16) or MCI (n=10). They were all recruited from among the caseload of the Alzheimer's Disease and Memory Disorder Center at Baylor College of Medicine. Patients who present to the Center with memory complaints undergo an evaluation by a neurologist specializing in dementia and they complete a standardized workup that includes a detailed history and interview with the patient and informant, neurological and physical examinations, an MRI of the brain, neuropsychological testing, APOE genotyping, and screening laboratory studies. They or their care givers completed the Physical Self-Maintenance Scale (PSMS) and Independent Activities of Daily Living scale (IADL) to rate the patient's ability to function independently (20). Therefore, data from those scales were already available for this study.

Due to cost, amyloid status is only determined in patients who screen for clinical trials so that information was not available. Diagnoses are made by a panel of physicians and neuropsychologists who met weekly at a consensus conference. Consensus diagnoses for AD and MCI are determined using well-established criteria (21–23). We used their most current diagnoses.

Subjects were recruited between October 2019 and January 2021. The final sample included 26 people, mean age 76.1, range 64.6 to 91.0 years, with 14 males and 12 females. The mean Mini Mental Status Exam score on the most recent test was 21.0, SD 3.8. Subjects were all ambulatory and able to stand unsupported on the floor for at least 60 seconds, had cervical range of motion within functional limits, and had no significant musculoskeletal impairments. Although an MRI was part of the standard diagnostic work-up, some people had had their MRI's outside of the institution and the raw data were not available. Some others had incomplete data. Therefore, MRI data were available for only 11 subjects.

To participate in this study, subjects had to have a Mini Mental State Score > 10 (mild-moderate AD or MCI) and be capable of following the instructions during testing. All subjects were accompanied by their legal representatives, who gave written informed consent if the subject was unable to do so.

We wanted to be able to compare subjects in this study to individuals of the same age who did not have MCI or AD, and who had been tested in the same laboratory with the same equipment. Therefore, we compared the vestibular test findings from the new subjects to data from subjects who were previously tested in this lab (24). Details are provided in the Results.

MRI description

In patients with symptoms related to Alzheimer's, an anatomical brain MRI is performed to assess atrophy of the medial temporal lobe structures. This atrophy is highly associated with the presence of neurofibrillary tangles and neuronal loss (25–27). A retrospective review of the clinical anatomic MRIs was performed on all subjects with specific inclusion criteria: a high resolution T1 sequence with oblique coronal orientation that is perpendicular to the long axis of the hippocampus; and date of the MRIs after January 1, 2017 to ensure common availability of high resolution imaging. Data from any subject was excluded primarily if the images had motion or if the quality of imaging had inadequate resolution as deemed by the neuroradiologist (CML). The routine clinical practice MRI parameters used for the T1 weighted sequence done for patients with memory loss or cognitive impairment included: Sagittal 3D T1W TFE scan with field of view 256mm (frequency) x 244mm (phase) x 190, repetition time of 7.1msec, echo time of 3.2msec, resolution voxel 1 × 1 × 1mm, total number of slice sections at 190, matrix 256 × 232 and NEX of 1. These parameters satisfy the need for clinical qualitative assessment that is usually subject to ambiguity and interobserver inconsistency.

Once a subject's MRI met the inclusion criteria, post processing of the imaging data set was performed with quantitative analysis that utilized both computer automated and manually segmented techniques. The computer-automated technique employed a free, online MRI brain volumetry, VolBrain (http://volbrain.upv.es) (28). Manual segmentation was performed with MIPAV (Medical Image Processing, Analysis, and Visualization; version 10.0.0), a free medical imaging processing software package from the National Institutes of Health. Each technique allowed for quantifying the individual hippocampi, i.e. right and left and in total. The computer-automated segmentation technique required uploading the T1 MRI images into VolBrain and, after several hours, the software extracted the volumes and emailed a report of the individual volume of each hippocampus and in total in cubic centimeters. By comparison, for the manual segmentation method, T1 imaging was loaded into MIPAV software, the entire hippocampus was identified, and was manually traced on contiguous slices by the neuroradiologist (CML). The contiguous voxel information was used to calculate volume in cubic centimeters. Reference data for hippocampal volumes were taken from the paper by Sanchez-Benavides et al (29).

Balance testing

All subjects were tested on standard, normed screening tests of walking and standing balance using Tandem Walking with eyes closed (TW) (30) and the modified Romberg test, also known as the modified Clinical Test of Sensory Integration on Balance (CTSIB) (31). To standardize footwear and to ensure good hygiene, all subjects were tested without shoes but wearing socks, per standard practice with these tests. Per standard procedure, to perform TW subjects practiced 5 heel-to-toe steps with eyes open and then with eyes closed. Then they were asked to perform 10 steps with eyes closed and arms crossed. The dependent measure was the number of steps performed without stepping out of line, taking an extra step, moving the arms, or opening the eyes.

To perform the modified CTSIB subjects stood on 10 cm thick, medium density, continuously compliant foam (Sunmate, Dynamic Systems, Leicester, NC) with feet together and arms crossed, looking straight ahead (31). All trials were performed with eyes closed. Trial 1 was performed without additional head movements (head still). Trial 2 was performed with head moving in yaw (shaking left/right about the vertical axis) in time to an oscillating sound played at 0.3 Hz. Trial 3 was performed with head moving in pitch (nodding up/ down about the intra-aural axis) in time to the 0.3 Hz sound. The dependent measure for each trial was the amount of time the subject could stand without opening the eyes, moving the arms, or taking a step.

Objective vestibular testing.

Subjects were tested on a standard clinical battery. For cervical vestibular evoked myogenic potentials (cVEMP), surface Ag/AgCl electrodes were placed over the bulk of the sternocleidomastoid, with the reference electrode over the sternum and the ground electrode on the forehead. Testing was performed at 500 Hz, maximum 100 dB nHL, 200 msec interval testing. Responses were considered abnormal if thresholds were < 70 dB or showed marked asymmetry ≥ 100%, and were unmeasurable if no response could be detected.

For all other tests, eye movements were recorded with infra-red video-oculography. They were tested on spontaneous nystagmus in the dark with eyes open and then with Dix-Hallpike maneuvers, supine roll tests and bi-thermal caloric tests with water at 30° C and 43°C. The cut-point for bi-thermal caloric testing was set at ≥20% unilateral weakness. Results of Dix-Hallpike maneuvers and supine roll tests were considered abnormal if three or more beats of nystagmus were recorded.

For Dix-Hallpike maneuvers, responses were categorized as either normal (no nystagmus), classical nystagmus, or non-classical nystagmus. Classical nystagmus included components that were vertical up-beating, horizontal ipsilaterally-beating, and torsional ipsilaterally beating, which began after a delay of a few seconds (32, 33). All other nystagmus in response to Dix-Hallpike testing was classified as non-classical.

Statistical methods

To compare the entire sample to previously published data on healthy control subjects (historical controls), only the 22 study subjects ages ≥ 70 years were used, to make the mean ages of the groups comparable. For the subgroup analyses comparing AD to MCI study subjects on balance and vestibular function tests, all study subjects were used. MRI data were available for only 11 study subjects, so all of those subjects were used. Study subjects and historical controls were compared by Chi-square/Fisher exact tests for grouped data, t-tests or ANOVA for continuous normally distributed data, and Wilcoxon rank sum test for non-normal data. $P < 0.05$ was considered significant. Statistical analyses were performed using SAS statistical software (version 9.4; Cary, NC).

Results

Comparison to historical healthy controls

When vestibular test results from subjects in this study were compared to historical controls (24), to make the groups most comparable we used only the 22 study subjects aged ≥ 70, mean age 77.8 years (SD 5.7), and 62 controls also aged ≥ 70 years, mean age 75.8 years (SD4.2), including 41 (65%) females, 21 (35%) males. The ages of the groups did not differ significantly.

Several differences were found. 1) Study subjects had significantly more spontaneous nystagmus than historical controls. 2) Study subjects had significantly more tests on cVEMP with responses that were too small to be detectable. 3) Study subjects had fewer normal and nonclassical responses than the historical controls but the differences were not statistically significant; study subjects had significantly more classical positive responses to Dix-Hallpike testing than historical controls. 4) Study subjects showed significantly more abnormalities on the summary scores indicating abnormal responses on any vestibular subtests, compared to historical controls. No significant differences were found between the two groups on bi-thermal caloric testing, TW, or any CTSIB trials. See Table 1 for details.

Association between degree of cognitive impairment and test results

We performed analyses of the vestibular and balance tests from the entire cohort of 26 study subjects. For statistical analyses we divided the group into MCI or early AD, i.e., MMSE score < 22 (range 10–21), and moderate AD, MMSE score ≥ 22 (range 22–30) (34). Because we excluded patients with severe impairment, we chose an MMSE cut-point of 22, rather than 20, to maximize the contrast between those with relatively mild cognitive impairment and those with more advanced impairment. No significant differences were found between groups on any tests. See Table 2 for details.

Comparison to ADL scores

Data from the PSMS and IADL scales were tested separately against the VNG summary scores and balance summary scores. These scales use ordinal scoring with lower scores closer to normal or independence. PSMS scores did not differ significantly by normal and abnormal balancer groups. IADL scores approached significance, $p < 0.08$, however: subjects with normal balance (N=3), mean IADL score = 10.3 (SD, 4.6); subjects with abnormal balance scores (N=23), mean IADL score = 17.6 (SD, 6.7). If the sample had been larger, the IADL scores in normal- and abnormal-balance groups would probably have differed significantly. PSMS and IADL scores did not differ significantly by normal- and abnormal-VNG summary score groups.

MRI results

All 11 study subjects for whom MRI data were available had decreased right-side hippocampus volumes. Some, but not all, had decreased left-side hippocampal volumes. Therefore, we used data only for the left sides. Because radiologic data can be analyzed by hand, i.e. manual segmentation, and by computer program, i.e. computer automated segmentation, we analyzed data using both types of analyses. As shown in Table 3,

significant differences between subgroups with normal and reduced left hippocampus values were found only for cVEMP calculated with manual segmentation by the neuroradiologist. The values from computer automated segmentation for cVEMP approached significance.

Discussion

Between groups findings

The results from the comparison between study subjects and historical controls suggest that study subjects had more vestibular pathology than healthy controls. The presence of significantly more spontaneous nystagmus in the study subjects indicates the occurrence of central pathology in people without vertigo, because spontaneous nystagmus is never normal. Classical Dix-Hallpike responses may indicate benign paroxysmal positional vertigo of the posterior semicircular canal (BPPV), although we cannot be sure from test results, alone. That canal is innervated by the inferior branch of the vestibular nerve, which projects to at least the medial and lateral vestibular nuclei (35, 36) and possibly other parts of the vestibular nuclear complex. The significant differences between study subjects and historical controls is a new finding, and might represent some susceptibility in these patients to the underlying causes of BPPV or some retrograde impairment in responses due to pathological changes in the vestibular nuclei.

The reason for the relatively large percentage of study subjects who had unmeasurable responses to cVEMP might mean one of two things. Either many subjects had conductive hearing loss or, as previous evidence suggests, these patients have impaired vestibulosaccular function. The saccule is innervated by part of the inferior branch of the vestibular nerve and is known to project to parts of the vestibular nuclei (37–39) although the exact pathways remain poorly understood. Thus, these responses might represent retrograde changes in the vestibular nerve due to AD-related changes in the vestibular nuclei. Alternatively, these changes may indicate some susceptibility to local vascular changes or to viral damage, an exploration of which is beyond the scope of this research.

An alternative possibility, i.e. a high prevalence of conductive hearing loss, is unlikely. No evidence indicates the occurrence of an unusual level of conductive hearing loss in this population. All subjects had otoscopy before testing and they had their ears cleaned by an otolaryngologist if cerumen occluded the tympanic membranes. Subjects who used hearing aids were able to hear adequately with them. All subjects had cervical range of motion within functional limits. No subjects had difficulty following instructions to lift their heads from the treatment for the few seconds of each test run.

Therefore, the cVEMP results probably indicate the absence of responses or responses so small that they were beyond the capability of the equipment to detect them without using unsafe levels of sound stimuli. This finding supports previous evidence of decreased cVEMP responses in this population (2). This finding is of more than just academic interest. Previous investigators have shown a relationship between decreased cVEMP responses in AD patients and decreased driving performance (40). Therefore, this finding has implications for public safety.

The lack of difference in bi-thermal caloric responses but the finding of differences in cVEMP is interesting. Responses to bi-thermal caloric testing are thought to come primarily from the lateral semicircular canal/ superior portion of the vestibular nerve, although saccular input does affect the response (41, 42). Responses from cVEMP are thought to be primarily saccular, and thus primarily through the inferior portion of the vestibular nerve. This finding may resolve the differences in the literature. Differences between AD patients and healthy controls have been reported on bi-thermal caloric tests (4) but other research has shown significant decrements on cVEMP compared to healthy controls (2).

We have confirmed the finding of differences in cVEMP between dementia and controls subjects but not the finding of bi-thermal caloric differences. A possible explanation is that the differences lie in the blood supply to the regions of the vestibular nuclei that receive projections from those parts of the vestibular nerve, such as the descending vestibular nucleus or the Y nucleus, or to the presence of other AD-related changes such as Beta-amyloid or the presence of neurofibrillary plaques and tangles. Looking into that question is beyond the scope of this study.

The finding of no differences between study subjects and historical controls on screening tests of balance, i.e. TW and CTSIB, is not surprising. All subjects were ambulatory. The literature does not strongly support the idea of balance problems in this population and does not indicate the occurrence of particular problems with peripheral neuropathy or musculoskeletal problems.

Between subgroup findings

We found no statistically significant differences between the AD and MCI subjects. Some differences may exist but the small sample size precluded finding them. On some tests, however, the differences may not exist. We have no reason to believe that we should have found differences on bi-thermal caloric testing, for example.

The finding that IADL scores approached differing between subjects with normal and abnormal balance is not surprising. Many instrumental skills require good balance and weight-shifting ability of the type that was tested in this study. Vestibular and balance impairments are known to cause ADL deficits in personal care skills that require mobility and balance skill, on specific mobility skills and on many IADL skills (43–46). Quite likely had the sample size been larger a significant difference would have been found. These data are important because they suggest the functional implications of vestibular impairments in the Alzheimer's population.

MRI findings

In this study, most MRI findings were not statistically significant, probably due to the small sample size. The significant finding of MRI results for cVEMP with manual segmentation is new, however, and supports the behavioral finding of reduced cVEMP scores in this population. The finding with computer automated segmentation approached significance. The difference may be due to the greater clinical sensitivity of the neuroradiologist's clinical judgement. This finding for cVEMP evidence supports previous findings in the literature

and suggests that this relationship between vestibular input and hippocampal volume may underlie the spatial orientation deficits that have been found in AD patients (1).

Potential functional implications

The finding of vestibular impairments in some subjects has some functional implications. Patients with vestibular disorders have decreased independence in activities of daily living (ADLs), in self-care, mobility, and instrumental ADLs (43, 44, 47–53). These problems are caused by the spatial disorientation, balance problems, and blurred vision that are characteristic of vestibular disorders. Also, vestibular disorders have been reported to be associated with some executive function problems (54), although not to the same level as AD and MCI. AD and MCI are well-known to cause ADL deficits (55). Furthermore, patients with AD have increased problems with sleep. The finding of increased positive responses to Dix-Hallpike testing might indicate an increase in benign paroxysmal positional vertigo, which is known to affect sleep. Thus, the functional limitations caused by vestibular impairments may add to the ADL deficits that this population already has, decreasing their functional skills further.

Limitations of the study.

Due to difficulty recruiting participants during the COVID-19 pandemic, our sample size was relatively small for this highly variable population. We had planned on a larger sample but were unable to recruit more subjects for a study that did not include medically necessary tests. Therefore, this work should be considered a pilot study. A larger sample might have provided more statistically significant findings.

Because patients in the Alzheimer's Disease Center are not required to have their MRI's performed at our institution results were unavailable for more than half the cohort, thus yielding a very small sample. A larger sample may have yielded more significant results. Nevertheless, the finding with cVEMP is interesting, and would bear following up with larger samples. The quality of some MRI's was adequate for clinical care but not for research. Some evidence suggests that vestibular input is greater to the dorsal hippocampus and dorsal dentate gyrus than to the ventral hippocampus and to CA1 (11). Therefore, we would have expected decreased hippocampal volumes in the dorsal hippocampus in subjects with abnormal cVEMP scores, but the reduced quality of the images did not allow for that level of refinement in the analyses.

Finally, the vestibular and balance tests were not performed at the same time as the MMSE and MRI. Those results might have changed over time. We used the most current test results available and were unable to obtain more current MMSE and MRI results.

Conclusion.

This study shows that patients with AD have increased frequency of positive findings on Dix-Hallpike testing but not on bi-thermal caloric testing, compared to age-matched controls. This study also suggests that they have reduced hippocampal volume, in the area that receives vestibular input.

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Table 1.

Comparisons to historical controls. Percent (n/ sample size)

Test	Study subjects	Healthy controls	p-values
Bi-thermal caloric weakness, abnormal responses	31.8 (N=7)	16.1 (N=10)	0.21
Dix-Hallpike responses			0.005
a) normal	a) 59.1 (N=13)	a) 65.0 (N=39)	
b) classical	b) 22.7 (N=5)	b) 1.7 (N=1)	
c) nonclassical	c) 18.2 (N=4)	c) 33.3 (N=20)	
cVEMP responses			0.03
a) normal	a) 53.9 (N=14)	a) 76.7 (N=46)	
b) abnormal but measurable	b) 0	b) 0	
c) unmeasurable	c) 46.2 (N=12)	c) 23.3 (N=14)	
Summary VNG score, abnormal	95.5 (N=21)	59.7 (N=37)	0.002
Spontaneous nystagmus present	90.91 (N=20)	16.1 (N=1)	<0.001
TW eyes closed, abnormal	47.6 (N=10)	48.4 (N=30)	0.99
CTSIB head still, abnormal	72.7 (N=16)	67.7 (N=42)	0.70
CTSIB head yaw, abnormal	86.4 (N=19)	66.1 (41)	0.10
CTSIB head pitch, abnormal	45.4 (N=10)	87.1 (N=54)	0.52

Table 2.

Results on vestibular tests compared within the study subjects. Percent of subgroup (N). p-values are from Fisher exact and Chi square tests.

Test	Mild MMSE score (N=15)	Moderate MMSE score (N=11)	P-values
Bi-thermal caloric test			P=0.99
a) Normal	60.0% (9)	63.6% (7)	
b) Abnormal	40.0% (6)	36.4% (4)	
Dix-Hallpike responses			P=0.65
a) normal	13.3% (2)	27.3% (3)	
b) classical	26.7% (4)	18.2% (2)	
c) nonclassical	60.0% (9)	54.6% (6)	
cVEMP responses			P=0.95
a) Normal	53.3% (8)	54.6% (6)	
b) Abnormal	46.7% (7)	45.5% (5)	
Spontaneous nystagmus			P=0.99
a) Normal	6.7% (1)	9.1% (1)	
b) Abnormal	93.3% (14)	90.9% (10)	
TW eyes closed			P=0.46
a) Normal	40.0% (6)	54.6% (6)	
b) Abnormal	60.0% (9)	45.4% (5)	
CTSIB head still			P=0.99
a) Normal	26.7% (N=4)	18.2% (2)	
b) Abnormal	73.3% (N=11)	81.8% (9)	
CTSIB head yaw			P=0.99
a) Normal	20.0% (3)	18.2% (2)	
b) Abnormal	80.0% (12)	81.8% (9)	
CTSIB head pitch			P=0.99
a) Normal	20.0% (3)	18.2% (2)	
b) Abnormal	73.3% (12)	81.8% (9)	

Table 3.

Mean (SD) hippocampal volumes by manual segmentation (MS) and by computer automated segmentation (CAS) methodologies, by test results. P-values represent t-tests or Wilcoxon rank sum test or ANOVA.

Test (N for normal and abnormal test results)	Mean (SD) hippocampal values	Mean Hippocampal volume MS P-values	Mean Hippocampal volume CAS P=values
Bi-thermal caloric tests		P=0.67	P=0.66
(Normal N=8, abnormal N=3)			
Normal MS	1.22 (0.68)		
Abnormal MS	1.43 (0.82)		
Normal CAS	1.27 (0.47)		
	1.14 (0.13)		
Dix-Hallpike maneuvers		P=0.028	P=0.097
(Normal N=3, abnormal classical N=4, abnormal nonclassical N=4)			
Normal MS	1.35 (1.04)		
Abnormal classical MS	1.12 (0.50)		
Abnormal nonclassical MS	1.39 (0.73)		
Normal CAS	1.16 (0.36)		
Abnormal classical CAS	1.31 (0.42)		
	1.21 (0.52)		
Abnormal nonclassical segmented			
cVEMP		P=0.86	P=0.90
(Normal N=4, abnormal N=7)			
Normal MS	1.85 (0.67)		
Abnormal MS	0.95 (0.47)		
Normal CAS	0.96 (0.22)		
Abnormal CAS	1.39 (0.42)		
Spontaneous nystagmus		P=0.78	P=0.81
(Normal scores, N=2; abnormal scores, N=9)			
Normal MS	1.15 (0.62)		
Abnormal MS	1.31 (0.73)		
Normal CAS	1.17 (0.01)		
Abnormal CAS	1.25 (0.45)		
Tandem walking		P=0.98	P=0.55
(Normal scores, N=7; abnormal scores, N=4)			
Normal MS	1.29 (0.64)		
Abnormal MS	1.27 (0.87)		
Normal CAS	1.29 (0.47)		
Abnormal CAS	1.13 (0.30)		

Test (N for normal and abnormal test results)	Mean (SD) hippocampal values	Mean Hippocampal volume MS P-values	Mean Hippocampal volume CAS P=values
CTSIB, head still		P=0.98	P=0.93
(Normal scores, N=4; abnormal scores, N=7)			
Normal CSTIB MS	1.27 (0.42)		
Abnormal CTSIB MS	1.28 (0.66)		
Normal CTSIB CAS	1.25 (0.52)		
Abnormal CTSIB CAS	1.22 (0.37)		
CTSIB head yaw		P=0.62	P=0.84
(Normal scores, N=3; abnormal scores, N=8)			
Normal MS	1.46 (0.91)		
Abnormal MS	1.21 (0.64)		
Normal CAS	1.28 (0.64)		
Abnormal CAS	1.22 (0.34)		
CTSIB head pitch		P=0.62	P=0.84
Normal scores, N=3; abnormal scores, N=8)			
Normal MS	1.46 (0.91)		
Abnormal MS	1.21 (0.64)		
Normal CAS	1.28 (0.64)		
Abnormal CAS	1.22 (0.34)		