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Hyperventilation Induced Nystagmus in Dizzy Patients

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Abstract

Hyperventilation Induced Nystagmus (HVIN) is associated with chronic peripheral vestibular disease.

Objectives: 1) Study the correlation of HVIN with patient's co-morbid diseases and otological diagnosis.

2) Study the association between HVIN and the result of the caloric test.

Materials and Methods: Patients were evaluated in the dizziness clinic during the years 2010-2011. HVIN was assessed after hyperventilating for 60 sec, during the Videonystagmography (VNG) exam. Patients were summarized as having unilateral peripheral vestibular diseases, central diseases or unknown.

Results: One hundred and fifty patients were examined. Comorbidities included cardiovascular disease (N=24), cardiovascular risk factors (N=66), respiratory diseases (N=12), neurological diseases (N=23) and psychiatric disorders (N=9). HVIN was observed in 32/150 (21.3%) patients and ranged from 8.3% (respiratory disease) to 33.3% (in the psychiatric patient group). Among patients with unilateral canal paresis, 9/40 (22.5%) exhibited HVIN, compared to 23/110 (20.9%) patients with a negative caloric test (p-value 0.833). Six out of 39 patients (15.3%) with central diseases exhibited HVIN, compared to 16/66 (24.2%) among patients with peripheral diseases (p-value 0.555). Among patients with a normal caloric exam and positive HVIN 12/23 (52%) had peripheral disease.

Conclusion: We did not find an association between HVIN and patients characteristics or co-morbid disease. Our study also did not find association between HVIN and the final diagnosis.

Keywords: Hyperventilation; Nystagmus; Dizziness; Vertigo

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Introduction

The association between hyperventilation and dizziness was reported as early as 1939 [1]. Initially, hyperventilation was thought to be associated with psychogenic and stress related causes. Later on, it was observed that hyperventilation may trigger nystagmus (hyperventilation-induced nystagmus, i.e., HVIN) among certain individuals, which raised the hypothesis that HVIN may unmask vestibular asymmetry. The pathophysiology of HVIN is unclear. Hyperventilation may cause cerebral vasoconstriction and reduction in blood flow in as much as 50% of the patients [2]. This may cause cortical suppression, which in turn may affect vestibular compensatory mechanisms [3]. Hyperventilation also lowers pCO2 levels in cerebral circulation, altering pH and ionized calcium levels, which increase neuronal excitability and may affect vestibular conduction [4,5]. Among patients with unilateral peripheral vestibulopathy the prevalence of HVIN may reach as high as 34% [3]. Among patients with vestibular neuronitis HVIN was shown to be more prevalent during the acute attack, compared to the follow-up stage (51% compared to 21%) [6]. The presence of HVIN among patients with acoustic neuroma was reported to be 58% to 82% among pre-surgery patients and 100% following surgery [5,7].

The prevalence of HVIN among chronic peripheral or central diseases has not been reported and its association with the caloric test is still not fully clear. Since HVIN presumably affects vestibular organs through acid-base levels and electrolyte changes it one may question its' relation with specific systemic diseases [5,7]. Such data would enable us to better understand the pathophysiology of HVIN and its' role in the evaluation of the dizzy patient.

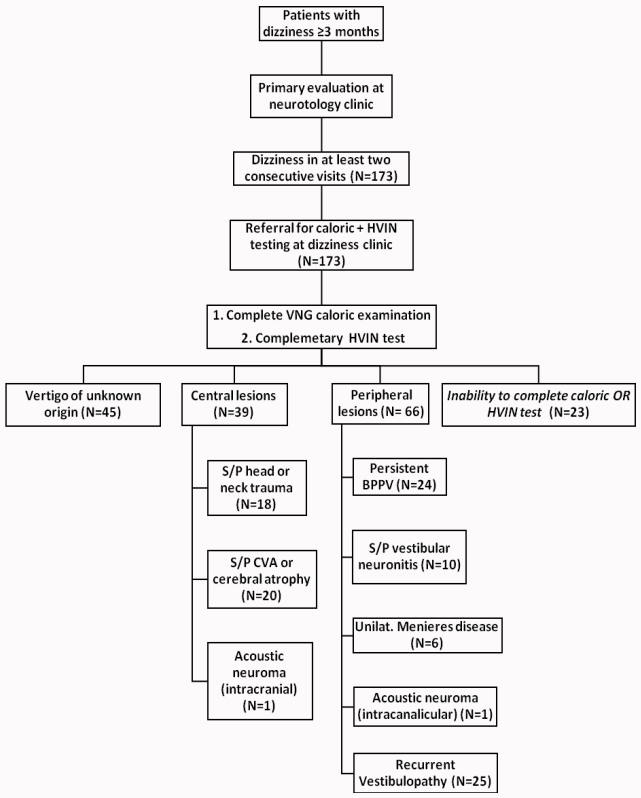

Figure 1: Patient evaluation protocol.
HVIN: Hyperventilation Induced Nystagmus; VNG: Videonystagmography; BPPV: Benign Paroxysmal Positional Vertigo; CVA: Cerebrovascular Accident

The objective of this study was: 1. To assess the relation between HVIN with patient characteristics, co-morbid diseases the caloric test, and final diagnosis. 2. Conclude on whether HVIN may have a role in the diagnosis of dizzy patient.

Patients and Methods

Included in the study were patients referred to our tertiary dizziness clinic during 2010-2011. All patients underwent a complete dizziness evaluation, including medical history, neurotological exam and Videonystagmography (VNG). VNG included a bi-thermal caloric test and HVIN test. Excitability differences ≥ 25 deg/sec were considered abnormal. Inclusion criteria included: 1) Adults with dizziness lasting three or more months, documented in at least two consecutive visits at our neurotology clinic. 2) Completion of VNG recordings, including caloric exam and HVIN test. Exclusion criteria included inability to fully complete VNG testing and/or one minute of hyperventilation.

Hyperventilation-induced nystagmus test protocol

During the VNG exam, following the complete recovery of the patient from the caloric excitation, patients were asked to hyperventilate while sitting in room air, for 60 sec. Eye movements were recorded and measured with VNG goggles in the supine position. Recordings were performed with eyes open and closed, measuring the peak velocity and the direction of nystagmus. Upon completion of the physician's evaluation and VNG recording, patients were summarized according to a final neurotological diagnosis.

Patients' diagnoses

Patients' final diagnoses were categorized into three main groups: 1) Peripheral diseases, including recurrent vestibulopathy, persistent BPPV, status after vestibular neuronitis, unilateral Meniere's disease, and intracanalicular acoustic neuroma. 2) Central cause, including status after head or neck trauma, status after CVA or cerebral atrophy, and extracanalicular acoustic neuroma. 3) Vertigo of unknown cause.

Table 1: Co-morbidities subgroups.

Cardiovascular disease (N=24)	Ischemic heart disease (N=7) Status post myocardial infarction (N=5) Status post coronary artery stenting (N=4) Aortic aneurysm (N=1) Peripheral vascular disease (N=3) Anatomical abnormalities (N=3) Status post valve replacement (N=1)
Cardiovascular disease risk factor (N=66)	Systemic Hypertension (N=22) Pulmonary hypertension (N=1) Orthostatic hypotension/ recurrent syncope (N=1) Dyslipidemia (N=11) Diabetes mellitus (N=12) Abnormal Electrocardiography results (N=3) Carotid artery stenosis (N=2) Obesity (N=14)
Respiratory disease (N=12)	Obstructive sleep apnea (N=6) Asthma (N=2) Chronic obstructive pulmonary disorder (N=3) Emphysema (N=1)
Neurological disease (N=23)	Alzheimer's disease (N=2) Status post CVA (N=7) Status post TIA (N=4) Complex regional pain syndrome (N= 1) Hypotonia(N=1) Cognitive disturbances (N=1) Traumatic brain injury (N=1) Peripheral neuropathy (N=2) Epilepsy (N=1) Meningioma (N=2) Spina bifida (N=1)
Psychiatric disorders (N=9)	Anxiety disorder (N=3) Depression (N=3) Post-traumatic stress disorder (N=1) Attention deficit hyperactivity syndrome (N=1) Somatization disorder (N=1)

Patients' co-morbid diseases

Co-morbid diseases were documented, based on updated computerized medical records from the family physician and all specialty clinics. The diseases were categorized into 5 main groups: 1) Cardiovascular diseases 2) cardiovascular risk factors 3) Respiratory diseases 4) Neurological diseases and 5) Psychiatric disorders. Details of each disease group are shown in Table 1.

Statistical analysis

Data were summarized using frequency tables, summary statistics, and p-values, as appropriate. The preferred method of analysis for continuous variables was parametric (variables presented as mean ± standard deviation). Non-parametric variables were presented as median with Interquartile Range (IQR) and shown graphically by box plot. Categorical variables were tested using Pearson's χ^2 test for contingency. All statistical tests were performed at α=0.05 (2-sided). P-values are presented after rounding to three decimal places. All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 18.0 for Windows; SPSS Inc., Chicago, IL, USA).

Research was conducted in compliance and approval of the requirements of the medical center's institutional review and ethical board; the Human Subjects Research Committee.

Results

One hundred and seventy-three patients were included in the

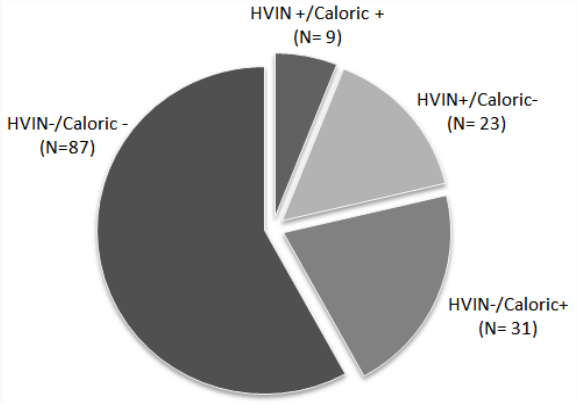

Figure 2: Prevalence of HVIN and caloric test.
*HVIN: Hyperventilation induced nystagmus; (+) positive test result; (-) negative test result

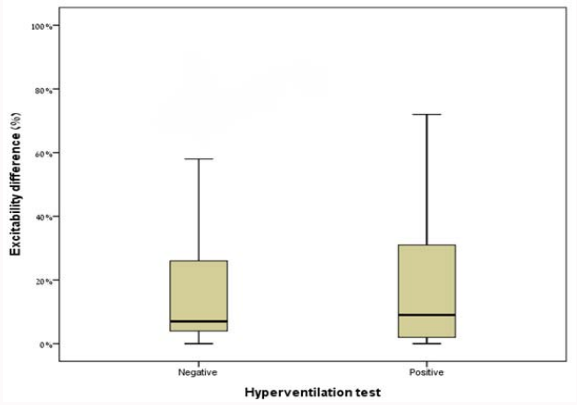

Figure 3: Association between HVIN and excitability difference of caloric test.

current study. Twenty-three patients were unable to fully complete the VNG (N=7) or HVIN test (N=16) and were excluded from the study, yielding a total of 150 patients (Figure 1). There were 49 males and 101 females, with a mean age of 55.9 years. Prevalence of specific co-morbid diseases is presented in Table 1. Seventy-six patients were diagnosed with at least one co-morbid disease. Based on the patients' history, neurotological exam, and VNG (and audiometry when indicated) the cause of dizziness was summarized as peripheral disease (N=66), central disease (N=39), or vertigo of unknown origin (N=45).

HVIN positive group

Thirty-two patients had a positive HVIN including 10 males and 22 females. Average age was 57.9 years. The incidence of a positive HVIN was 33.3% among patients with psychiatric disorders, 22.7% among patients with cardiovascular risk factors, and 16.6% among patients with cardiovascular disease. There was no statistically significant between a positive HVIN and co-morbid diseases (Table 2); 24.2% of the patients with peripheral disease exhibited a positive HVIN, compared to 22.2% and 15.3% in the unknown and central lesions groups, respectively Table 2.

In an attempt to examine the possible added contribution of the HVIN test, we focused on patients with positive HVIN test and negative caloric test. There were 23 patients with a positive HVIN and a normal VNG caloric test. The group comprised of 6 males and 17

Table 2: HVIN* test positivity among co-morbid disease and final diagnosis subgroups.

	HVIN+ (n=32)	HVIN- (n=118)	p-value
Co-morbidity			
Cardiovascular disease (N=24)	4 (16.6%)	20	0.543
Cardiovascular risk factors (N=66)	15 (22.7%)	51	0.712
Respiratory disease (N=12)	1 (8.3%)	11	0.252
Neurological disease (N=23)	3 (13.0%)	20	0.292
Psychiatric disorders (N=9)	3 (33.3%)	6	0.365
Neurotological Diagnosis			
Central (N=39)	6 (15.3%)	33	0.292
Peripheral (N=66)	16 (24.2%)	50	0.441
Origin unknown(N=45)	10 (22.2%)	35	0.862

*HVIN-Hyperventilation Induced Nystagmus

Table 3: HVIN* test positivity *vs.* caloric test positivity group stratification.

	HVIN + (n=32)	Caloric + (n=40)
Age (± SD)	57.9 (± 14.97)	58.63 (± 15.65)
Gender (%) Male	10 (31.3%)	16 (40%)
Co morbidities (%)		
Cardiovascular disease	4 (12.5%)	6 (15%)
Cardiovascular risk factors	15 (46.9%)	14 (35%)
Respiratory disease	1 (3.1%)	2 (5%)
Neurological disease	3 (9.3%)	1 (2.5%)
Psychiatric disorders	3 (9.3%)	1 (2.5%)
Neurotological diagnosis (%)		
Central lesions	6 (18.8%)	6 (15%)
Peripheral lesions	16 (50%)	24 (60%)
Origin Unknown	10 (31.3%)	10 (25.0%)

*HVIN- Hyperventilation Induced Nystagmus

females with a mean age of 56.7 years. Neurotological diagnosis within the group included 4 patients with central disease, 12 patients with peripheral lesions, and 7 patients with vertigo of unknown origin. There was no statistical difference between the groups (P=0.218).

HVIN and caloric test

Forty patients exhibited canal paresis compared to 32 patients who exhibited HVIN test positivity Table 3. Patients with HVIN positivity had a higher incidence of cardiovascular risk factors (46.9% *vs.* 35%), neurological disorders (9.3% *vs.* 2.5%), and psychiatric disorders (9.3% *vs.* 2.5%) however this was not statistically significant. 28.1% of patients with a positive HVIN test also had a positive caloric test, compared to 19.1% among patients with a negative HVIN test (Figure 2). Since caloric test positivity was chosen as >25% difference, we decided to further evaluate the association between the two by looking at caloric results as a continuous variable ranging from 0% to 100% (Figure 3). No correlation between the two tests was seen.

Direction of nystagmus in patients with a positive caloric and positive HVIN

A total of 9 patients exhibited both positive caloric and positive HVIN tests. Among them, 6 patients exhibited an ipsilateral nystagmus and 3 exhibited a contra-lateral nystagmus. Five of the six patients with ipsilateral nystagmus had a peripheral disease.

Discussion

While several studies have investigated certain clinical aspects of HVIN, there is limited data on its' relationship with chronic vestibular disease. In this study we examined the phenomenon of HVIN and its relationship to VNG caloric test results, co-morbid states, and neurotological diagnosis in consecutive patients from a tertiary dizziness clinic.

We consider three main limitations to our study:

1. The caloric result and neurotological diagnosis are not mutually exclusive, as the finding of canal paresis has a major contribution to the diagnosis of peripheral vestibular disease.

2. The central disease group refers to all central causes of dizziness, so comorbidities such as neurological diseases may contribute to labeling a patient with the diagnosis of central disease.

3. A comparatively large group of patients were categorized as dizziness of unknown origin. This group included patients in whom a clear diagnosis could not be made, following two or more visits. This represents our routine clinical practice, in which it may take several visits to make a clear diagnosis for the cause of dizziness. We felt it was important to include this group of patients in the study, rather than exclude them or alternatively attempt to establish a diagnosis, retrospectively. Their inclusion in the study was important for following the protocol of consecutive patients and this still enabled us to study a part of the parameters, such as comorbidities and the relationship of HVIN to the caloric test.

4. The study was retrospective and only VNG was performed as an additional vestibular test. Since, VHIT and VEMP have become routine exams for dizzy patients, but at the time of the study were not performed.

In our study the patients had to complete 60 sec of hyperventilation. When testing HVIN, previous studies have used 40 sec, 90 sec, and even 3 min [8-10]. We observed that our patients found it quite difficult to tolerate a longer period of hyperventilation (16 patients could not complete the test and had to be excluded). Robichaud [7] had patients hyperventilate for 90 sec and noted that some negative HVIN results may be attributed to the fact that patients were reluctant to fully complete the exam. Perhaps, if we insisted on continuing hyperventilation for 90 sec we would have found a higher incidence of HVIN; however, beyond the inconvenience to the patient, we may have ended up having to exclude a larger proportion of patients who could not complete the test.

The prevalence of HVIN among healthy volunteers was reported to be 3.5%, increasing to 8% and even 21.9% among patients with vestibular complaints [5,11,12]. The incidence of HVIN among patients with vestibular organ pathology was reported to range between 18% to 34% [3,7]. Our study found an overall incidence of 21.3% among consecutive dizzy patients, 24.2% among peripheral disease, and 15.3% among patients diagnosed with central lesions. There was no statistical significance in the presence of HVIN between peripheral and central diseases. This finding suggests that HVIN, on its own, is not useful in differentiating between the peripheral and central causes for dizziness.

The assumption that hyperventilation may lead to nystagmus through changes in blood flow and pH raised the question of whether HVIN may be caused by underlying diseases that affect systemic blood flow and acid base levels. If hyperventilation supposedly affects central compensatory mechanisms, what will be its effect on patients with underlying neurological diseases? Do patients with cardiovascular and respiratory system diseases experience more HVIN? Additionally, if dizziness is commonly experienced after hyperventilation among patients with anxiety, would HVIN have a higher incidence among patients with psychiatric disorders?

Our results indicate no association between HVIN test positivity and any of the groups of comorbid diseases. The most probable explanation of this result would be that these conditions vascular, respiratory, neurologic, and psychiatric exert similar systemic changes on central regions and vestibular organs and thus do not have any effect on the symmetry between the two vestibular organs which may be augmented by HVIN in certain individuals.

A central objective of this research was to study the relationship between HVIN and the VNG caloric test. Our study demonstrated a slightly higher rate of HVIN among patients with an excitability difference of more than 25% on caloric (22.5% positive compared to 20.9% negative caloric); however, the difference was not significant. This discrepancy may be explained by the fact that while caloric test measures the peripheral vestibular system alone (the horizontal semicircular canal in particular), hyperventilation also exerts its effect through transient ischemia in cerebral areas, probably affecting central compensatory mechanisms [7]. Robichoud [7] postulated that the finding of HVIN in patients with peripheral vestibular disease (defined as canal paresis on calories) may be caused by undiagnosed retrocochlear disease, thus necessitating head MRI. We cannot rule out this explanation, as MRI was not performed in our study.

HVIN in association with cerebellar disease has also been described. Minor and Zee [8] have reported an increase in the slow phase component of down beating nystagmus, among patients with cerebellar diseases following HVIN. Califano [12] reported that HVIN increased spontaneous down beating nystagmus in 7 out of 11 patients with cerebellar pathology and evoked a horizontal nystagmus in one patient. They also reported that among 152 patients with central diseases, 27 had positive HVIN, yielding an incidence of 17.8%. It is important to note that in their report, 19 out of the 27 had a purely horizontal nystagmus. Our study found HVIN in 18% of patients with central disease, all with horizontal nystagmus. Interestingly, 3 of the patients had dizziness related to head trauma.

In conclusion, our study did not find an association between HVIN and calories, diagnosis of dizziness, and comorbidities. Future prospects for investigation, except for repeating the study on a larger population, would be to exam the sensitivity and specificity of a positive HVIN with positive calorics for diagnosis of VS.

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