

Ocular vestibular evoked myogenic potential (VEMP) reveals subcortical HTLV-1-associated neurological disease

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Competing Interests

The authors declare that there are no competing or conflicting interests.

Abstract

Introduction: Vestibular Myogenic Evoked Potential (VEMP) evaluates vestibulo-ocular and vestibulospinal reflexes associated with posture. **Purpose:** To compare cervical and ocular VEMP in individuals with HTLV-1 associated myelopathy (HAM) and with HTLV-1-asymptomatic infection. **Materials and Methods:** This cross-sectional study included 52 HTLV-1-infected individuals (26 HAM and 26 asymptomatic carriers) and 26 negative controls. The groups were similar regarding age and gender. Participants underwent ocular and cervical VEMP that were performed simultaneously. The stimulus used to generate VEMP was a sound, low-frequency toneburst, intensity of 120 decibels normalized hearing level (dB nHL), bandpass filter from 10 to 1,500 Hz, with 100 stimuli at 500 Hertz (Hz) and 50 milliseconds (ms) recording time. An alteration in the electrophysiological waves

P13 and N23 for cervical VEMP and N10 and P15 waves for ocular VEMP was compared between groups. **Results:** Cervical VEMP was different among the groups for P13 ($p=0.001$) and N23 ($p=0.003$). Ocular VEMP was similar for N10 ($p=0.375$) and different for P15 ($p=0.000$). In the HTLV-1-asymptomatic group, 1(3.8%) individual presented changes in both ocular and cervical VEMP, while in HAM group, 16(61.5%) presented changes in both tests. **Conclusion:** Neurological impairment in HAM was not restricted to the spinal cord. The mesencephalic and thalamic connections, tested by ocular VEMP, were also altered. Damage of the oculomotor system, responsible for eye stabilization during head and body movements, may explain why dizziness is such a frequent complaint in HAM.

Keywords: Vestibular nerve; Evoked potentials, motor; Vestibule, labyrinth; Human T-lymphotropic virus 1; Saccule and Utricle

Authors' summary

Human T-cell lymphotropic virus type 1 (HTLV-1) infection is endemic in Brazil and can cause HTLV-1-associated myelopathy (HAM). This neurological disease progresses slowly and, within ten years after its onset, can confine the patient to a wheelchair. Changes in HAM inflammatory characteristics can subsequently occur in the cortex, subcortical white matter, cerebellum, and brainstem. In the present study, we used the electrophysiological test Vestibular Myogenic Evoked Potential (VEMP) to evaluate the thalamic, brainstem, and spinal neural connections. This test evaluates the peripheral and the central vestibular pathway and has been used to test the postural reflexes involved in the control of one's balance. The VEMP from

the oculomotor muscles demonstrated that a subcortical impairment occurs in HAM and can also occur in the asymptomatic phase of HTLV-1 infection.

1 **Introduction**

2 The Human T-cell lymphotropic virus type 1 (HTLV-1) infection affects
3 approximately 5-10 million people worldwide [1]. The majority of the infected
4 individuals remain asymptomatic throughout their lives [2]. The host genetic and
5 immunological factors seem to be related to the development of HTLV-1-associated
6 diseases [1,2].

7 The range of neurological manifestations of HTLV-1-associated myelopathy
8 (HAM) includes not only the spine, with the classical motor limitations affecting
9 the lower limbs, but also the autonomic dysfunction [3]. In fact, inflammatory
10 alterations due to HAM can be detected in the cortex, subcortical white matter,
11 cerebellum, and brainstem, mainly in the advanced phases of this disease [4-7].

12 The complaint of dizziness has proven to be frequent HAM and can be one
13 of the first symptoms of HTLV-1-neurological impairment [11,12]. Therefore,
14 individuals infected with HTLV-1 may present vague complaints, with no motor,
15 sensitive, or autonomic abnormalities [4-6]. HAM diagnosis is based on clinical
16 criteria that reveals established neurological damage [13].

17 Vestibular Evoked Myogenic Potential (VEMP) evaluates the integration of
18 the vestibular nerves with the brainstem and the muscular system. It tests the
19 peripheral and central vestibular pathway and has been used to test brainstem
20 functions [14,15] and postural reflexes [12,16]. VEMP tests the vestibulospinal and

21 vestibulo-ocular reflexes involved in the control of the postural balance. Normal
22 VEMP depends on the functional integrity of the saccular and utricular maculae, the
23 inferior vestibular nerve, the superior vestibular nerve, the vestibular nuclei, the
24 central vestibular pathways, and the neuromuscular plaques involved in these
25 reflexes [17,18].

26 The subclinical spinal cord injury related to HAM has been already shown
27 through VEMP of cervical and of lower limbs muscles, exams that are used to test
28 the vestibulospinal reflex [11,12,16,19,20]. The present study proposes the use of
29 VEMP of the oculomotor system (ocular VEMP) to test the subcortical pathways
30 associated with body balance to verify the extension of the HTLV-1-neurological
31 damage.

32 **Methods**

33 **Study design**

34 The study was a comparative cross-sectional analysis. Cervical VEMP and
35 ocular VEMP were compared between individuals with definite HAM and HTLV-1-
36 asymptomatic carriers and healthy controls.

37 **Ethical aspects**

38 This research was conducted in accordance with the principles expressed in the
39 Declaration of Helsinki and was approved by the Research Ethics Committee from
40 Universidade Federal de Minas Gerais (COEP UFMG), logged under protocol number
41 CAAE 92928518.3.0000.5149. All participants provided voluntary written consent and
42 declared that they were aware of the study procedures and their choice to participate.

43 **Sample size**

44 The sample size was calculated using G* Power software 3.1.9.2 (Heinrich-
45 Heine Universität Düsseldorf, Düsseldorf, Germany, 2007) to achieve a power of 80%
46 and a significance level of 5% based on the mean and standard deviation of the P13-
47 N23 response of patients with HAM and healthy controls [11]. The final calculation
48 included 26 participants per group.

49 **Participants**

50 The groups of study were recruited from a cohort of former blood donors
51 infected with HTLV-1 who have received follow-up from the Interdisciplinary
52 HTLV Research Group (GIPH) since 1997, in Belo Horizonte, Brazil [21]. The
53 GIPH evaluates the natural history, clinical manifestations and epidemiological
54 aspects of HTLV infection.

55 Seventy-eight individuals, 32 to 60 years of age, were invited to participate in
56 this study. The participants consisted of 26 individuals with definite HAM, 26 with
57 HTLV-1-asymptomatic infection, and a control group of 26 individuals not infected by
58 HTLV-1.

59 The classification of the participants infected by HTLV-1 regarding neurological
60 impairment followed the Expanded Disability Status Scale (EDSS) [22] and the
61 OSAME scale [23]: asymptomatic individual, (EDSS and OSAME - 0 on both scales)
62 and definite diagnosis of HAM (EDSS and OSAME greater than 2 on both scales).

63 Individuals with positive serology for the Human Immunodeficiency Virus
64 (HIV), HTLV-2, or any other blood-tested disease were excluded, as well as an

65 undetermined serology for HTLV-1 and a positive *Venereal Disease Research*
66 *Laboratory* (VDRL) test.

67 The control group consisted of active blood donors followed by GIPH as the
68 negative controls. Concerning all the participants, individuals with neurological
69 diseases, otitis, tympanic membrane perforation, history of otologic surgery or
70 peripheral vestibular disease, as well as individuals unable to perform cervical
71 rotation and ocular movement were excluded.

72 **Vestibular Evoked Myogenic Potential (VEMP)**

73 VEMP was performed with Labat® equipment, using two channels. The stimuli
74 were presented through ER 3A insertion phones, with disposable foam eartips. Tone
75 burst stimuli at an intensity of 120 decibels normalized hearing level (dB nHL) were
76 used. In this study, a bandpass filter of 10 to 1,500 Hertz (Hz) was used. To obtain each
77 record, 100 stimuli were presented at a frequency of 500 Hz at a rate of four stimuli per
78 second. The scan window was 50 milliseconds (ms). Each subject underwent at least
79 two stimulations per side, to verify the replication of the potential. The impedance
80 values, which had to be below 5 kiloohm (KΩ), were checked before each record [14].

81 The recording of cervical VEMP and ocular VEMP was performed
82 simultaneously. Channel 1 electrodes were used to record ocular VEMP and channel 2
83 electrodes to record cervical VEMP [14].

84 The active electrode related to cervical VEMP was placed on the opposite side at
85 the anterior border of the sternocleidomastoid muscle in its upper third, and the
86 reference electrode was placed in the sternal notch region. For ocular VEMP recording,
87 the active electrode (negative electrode) in channel 1 was placed approximately 1
88 centimeter (cm) below the lower eyelid, and the reference electrode (positive electrode)

89 was placed at a distance of approximately 1 cm from the active electrode. The ground
90 electrode was placed on the forehead (Fpz) (Fig 1).

91 **Fig 1. Simultaneous cervical and ocular VEMP.** (a) ground electrode. (b) auditory stimulus. (c) active
92 electrode on channel 2 at the anterior border of the sternocleidomastoid muscle in its upper third. (d)
93 reference electrode on channel 2 at the sternal notch region. (e) active electrode on channel 1 below the
94 lower eyelid. (f) reference electrode on channel 1 below the active electrode.

95 Participants were instructed to sit on the chair and keep their heads rotated to the
96 opposite side of the stimulated ear, causing contraction of the sternocleidomastoid
97 muscle. At the same time, the participant was instructed to look at a stationary target
98 located on the wall in front of him and then immediately at a fixed point located above
99 the target, which formed a vertical viewing angle of approximately 30° above the
100 horizontal plane. The Simultaneous ocular and cervical VEMP protocol is available at
101 dx.doi.org/10.17504/protocols.io.zmzf476.

102 The ocular VEMP is composed of two sets of biphasic waveforms. The first
103 biphasic potential has a negative peak (N) with an average latency of 10 ms, followed
104 by a positive peak (P) with an average latency of 15 ms, which is known as N10–P15.
105 The cervical VEMP consists of two sets of biphasic waveforms. The first biphasic
106 potential has a positive peak (P) with an average latency of 13 milliseconds (ms),
107 followed by a negative peak (N) with an average latency of 23 ms, which it known as
108 P13–N23 (Fig 2).

109 **Fig 2. Examples of tracings obtained by the VEMP records.** a) normal ocular VEMP. b) normal
110 cervical VEMP. c) altered ocular VEMP (no response). d) altered cervical VEMP (no response).

111 The American Society of Encephalography and Evoked Potentials' criteria for
112 evoked potentials were considered for the analysis of the latency values of the cervical
113 VEMP and ocular VEMP waves. The definition of altered latency values includes those
114 that exceed 2.5 standard deviations (SD) [24]. In this study, for cervical VEMP, we
115 considered the normal latency of 13 ms (± 2.5 SD) for P13 and 23 ms (± 2.5 SD) for
116 N23, while for ocular VEMP, we considered the normal latency of 10ms (± 2.5 SD) for
117 N10 and 15ms (± 2.5 SD) for P15 [25,26]. The validation of the analyzed reference
118 values was guaranteed by comparing these with parameters already established in other
119 national and international peer reviews [14,27,28].

120 The parameters considered in the VEMP analysis are the latency and amplitude
121 of the waves. However, the amplitude may vary according to age, muscular strength
122 [27,29], and cochlear diseases [30,31]. Therefore, amplitude was not considered in the
123 analysis since this variable is not consistent to define neural conduction abnormalities.

124 **Statistical analysis of data**

125 VEMP results were classified as normal and altered. Latency prolongation and
126 no response were considered as the altered results. Ocular and cervical VEMP were
127 compared between the groups infected and not infected by HTLV-1.

128 Statistical analysis was performed using the *Statistical Package for Social
129 Sciences* (SPSS), version 20.0. The normality of the samples was assessed using the
130 Kolmogorov-Smirnov and Shapiro-Wilk tests. The comparison between groups was
131 performed using the Kruskal-Wallis test, Chi-square or Fisher's Exact test, and
132 Kruskal-Wallis with Bonferroni correction. The adopted level of significance was
133 5% (p≤0.05).

134 **Results**

135 The characteristics of the studied population and the classification in the
136 neurological scales are described in Table 1. The groups were similar regarding gender
137 and age.

138 **Table 1. General characteristics and disability scales (EDSS and OMDS) of the**
139 **participants (n=78)**

Variables	Control (n=26)	Asymptomatic (n=26)	HAM (n=26)	p-value
Age	53.27 (3.39)	53.73 (7.66)	55.69 (4.44)	0.073 ^a
EDSS	0 (0)	0 (0)	3 (2.08)	0.000 ^a
OMDS	0 (0)	0 (0)	2.30 (1.84)	0.000 ^a
Gender				
Female	18 [69.2]	16 [61.5]	19 [73.1]	0.662 ^b
Male	8 [30.8]	10 [38.5]	7 [26.9]	

140

141 EDSS, expanded disability status scale; OMDS, Osame motor disability scale; SD, standard deviation; n,
142 number of participants. Data are expressed as mean (standard deviation); absolute number [percentage].

143 ^aKruskal-Wallis Test (p≤0.05) / ^bChi-square Test (p≤0.05)

144 The VEMP latencies were different among the groups. Table 2 indicates the
145 comparative analysis and identifies the groups for which the difference was relevant.

146 **Table 2. Comparison of the groups with HTLV-1-associated myelopathy,**
147 **asymptomatic infection and healthy controls according to the latency (ms) of**
148 **cervical VEMP and ocular VEMP. N=78**

Variables	G1 (n=26)	G2 (n=26 ^a)	G3 (n=26 ^b)	p - value *	Comparison groups	p - value **
Lat P13	12.8 (0.91)	13.7 (1.03)	14.8 (3.22)	0.001	G1 X G2 G1 X G3 G2 X G3	0.007 0.002 1.000
Lat N23	22.3 (1.36)	23.0 (2.44)	25.7 (4.43)	0.003	G1 X G2 G1 X G3 G2 X G3	0.919 0.003 0.060
Lat N10	10.5 (0.65)	10.4 (0.92)	11.5 (2.80)	0.375	-	-
Lat P15	15.4 (0.66)	15.7 (1.35)	18.2 (3.30)	0.000	G1 X G2 G1 X G3 G2 X G3	1.000 0.000 0.002

149

150 G1, group control; G2, group of asymptomatic individuals; G3, group of individuals with HAM; SD,
151 standard deviation; Lat, latency; n, number of participants. Data are expressed as mean (standard
152 deviation).

153 ^aFor Lat N23 data analysis, one case in which the response was absent was excluded.

154 ^bFor Lat P13 and Lat N23 data analysis, 3 and 6 cases, respectively, in which the response was absent
155 were excluded. For Lat N10 and Lat P15 data analysis, 2 and 3 cases, respectively, in which the response
156 was absent were excluded.

157 * Kruskal-wallis Test (p≤0.05) / ** Bonferroni Test

158 Table 3 describes the frequency of normal and altered results for cervical and
159 ocular VEMP in each group.

160 **Table 3. Comparison of cervical and ocular VEMP in the groups HTLV-1-
161 associated myelopathy, asymptomatic infection and controls. N=78**

Electrophysiological evaluation (VEMP)	G1 (n=26)	G2 (n=26)	G3 (n=26)	p - value *	Comparison groups	p - value **
Normal (cVEMP + oVEMP)	26 [100]	16 [61.5]	0 [0]	0.000	G1 X G2 G1 X G3 G2 X G3	0.001 0.004 0.002
cVEMP altered	0 [0]	7 [27]	7 [27]	0.689	-	-
oVEMP altered	0 [0]	2 [7.7]	3 [11.5]	1.000	-	-
cVEMP + oVEMP altered	0 [0]	1 [3.8]	16 [61.5]	0.000	G1 X G2 G1 X G3 G2 X G3	0.060 0.003 0.004

162

163 G1, group control; G2, group of asymptomatic individuals; G3, group of individuals with HAM; cVEMP,
164 cervical VEMP; oVEMP, ocular VEMP; n, number of participants. Data are expressed as absolute
165 number [percentage].

166 * Chi-square test or Fisher's Exact (p≤0.05) / ** Bonferroni Test

167 The VEMP response was categorized as 1) latency delay of N10-P15 waves
168 (ocular) or of P13-N23 waves (cervical); 2) absence of wave; 3) normal wave. Fig 3
169 shows the comparative analysis for ocular VEMP and Fig 4 for cervical VEMP.

170 **Fig 3. Comparison of ocular VEMP responses in individuals with HTLV-1-associated myelopathy,
171 with asymptomatic infection and seronegative controls (n=78).** G1, group control; G2, group of
172 asymptomatic individuals; G3, group of individuals with HAM. Chi-square or Fisher's Exact test (p≤0.05)

173 **Fig 4. Comparison of cervical VEMP responses in individuals with HTLV-1-associated myelopathy,
174 with asymptomatic infection and seronegative controls (n=78).** G1, group control; G2, group of
175 asymptomatic individuals; G3, group of individuals with HAM. Chi-square or Fisher's Exact test (p≤0.05)

176 Discussion

177 The auditory stimulus that evokes VEMP follows through the vestibular
178 regions of the brain, especially the pre-motor cortex, the inferior and medial
179 temporal gyrus, the Brodmann area, as well as the typically auditory areas, such as
180 the primary auditory cortex [32].

181 The latency delay of cervical VEMP has been related to the demyelination of the
182 primary afferent axon of the vestibulospinal tract and/or involvement of the vestibular
183 nucleus [33-35]. The absence of electrophysiological response may be explained by a
184 severe impairment of the vestibular-spinal pathway [36].

185 When the evoked potential changes from a prolonged latency to no response,
186 it is understood that there is a worsening in the neuronal damage [14,27,28]. This
187 pattern of response was previously observed in a cohort study of individuals infected by
188 HTLV-1 with myelopathy and asymptomatic carriers that were tested by cervical
189 VEMP [11].

190 Regarding cervical VEMP in the present study, we found that the great
191 majority of the patients with definite HAM presented alteration in cervical VEMP
192 response (88,5%). This data confirms previous studies that disclosed a cervical
193 spinal cord damage in HAM, emphasizing that the medullary abnormalities in HAM
194 are not restricted to the thoracolumbar level [37,38].

195 Regarding ocular VEMP, 61.5% of the patients with definite HAM and
196 alteration in cervical VEMP, presented also alteration in ocular VEMP (Table 3). The
197 neural connections involved in ocular VEMP are assumed to be thalamic and
198 mesencephalic [22,39-41]. The presumed pathway includes the vestibular primary

199 afferent, the vestibular nuclear complex, the medial longitudinal fasciculus, the
200 oculomotor nucleus and the oculomotor nerves [39]. Thus, a latency delay or an
201 absence of response depends on the disorganization of the primary afferents involved in
202 the vestibulo-ocular reflex [39,40].

203 The higher frequency of simultaneous alteration in ocular and cervical
204 VEMP of HAM group confirms a greater neurological impairment in these
205 individuals with more advanced spinal cord injury when compared to the group
206 with asymptomatic infection, although some individuals labeled as asymptomatic
207 carriers were disclosed with altered VEMP. The meaning of this finding has to be
208 studied as a possible signal predictive of HAM.

209 VEMP is able to detect subclinical neurological changes in HTLV-1
210 infection [16,19,32]. When effective therapeutic options for the HTLV-1
211 neurological disease are available, the subclinical diagnosis of neuronal injury will
212 have implications in decision-making regarding the beginning of the treatment in
213 the stage of incipient damage. For example, recent studies have shown that low
214 doses of corticosteroid can be beneficial in slowing HAM progression if treatment
215 is implemented at the onset of the HTLV-1-neurological manifestation [42,43].

216 Conclusion

217 Ocular VEMP demonstrated that a subcortical impairment occurs in HAM
218 and may occur even in the asymptomatic phase of HTLV-1 infection. Thus,
219 neurological impairment in HAM is not restricted to the spinal cord. The vestibulo-
220 ocular tract is subject to injury, compromising the oculomotor system in eye

221 stabilization during head and body movements which can explain the high
222 frequency of dizziness in patients with HAM.

223 **Supporting information**

224 **S1 Table. Diagnostic criteria of human T-cell lymphotropic virus type 1**
225 **(HTLV-1)- associated myelopathy (HAM)^a.** ^aCastro-costa CMDE, Araújo AQC,
226 Barreto MM, Takayanagui OM, Sohler MP, Silva ELMDA, et al. Proposal for
227 diagnostic criteria of tropical spastic paraparesis/HTLV-1-associated myelopathy
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229 10.1089/aid.2006.22.931.

230 **S1 Fig. Questionnaire**

231 **Acknowledgments**

232 We wish to thank the Interdisciplinary HTLV Research Group (GIPH) for the
233 support.

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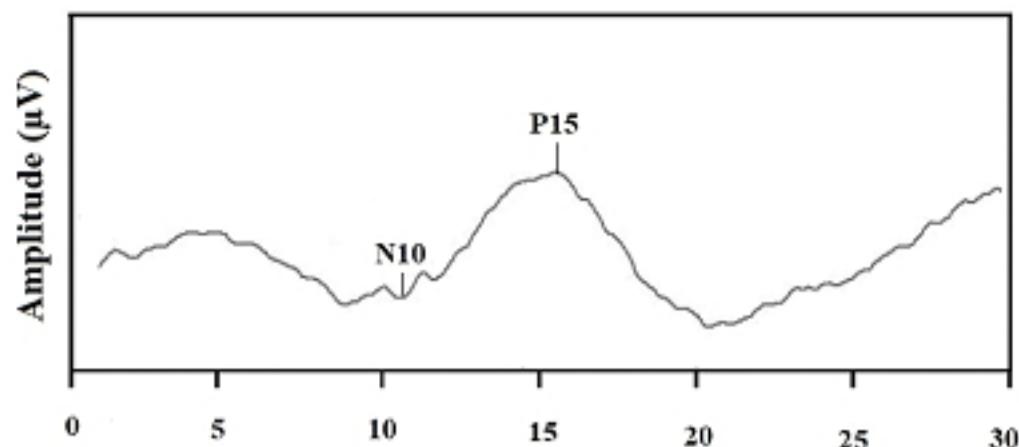
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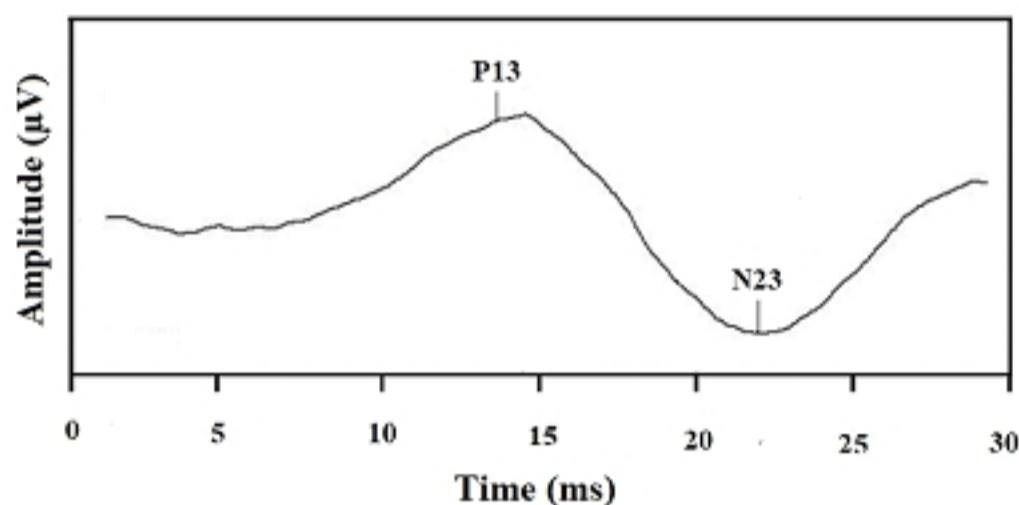
Figure

a)

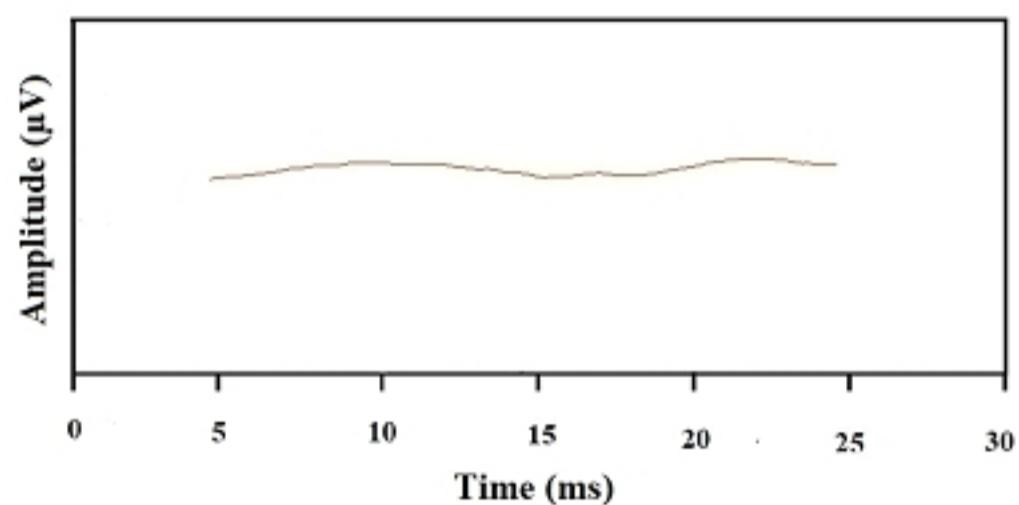


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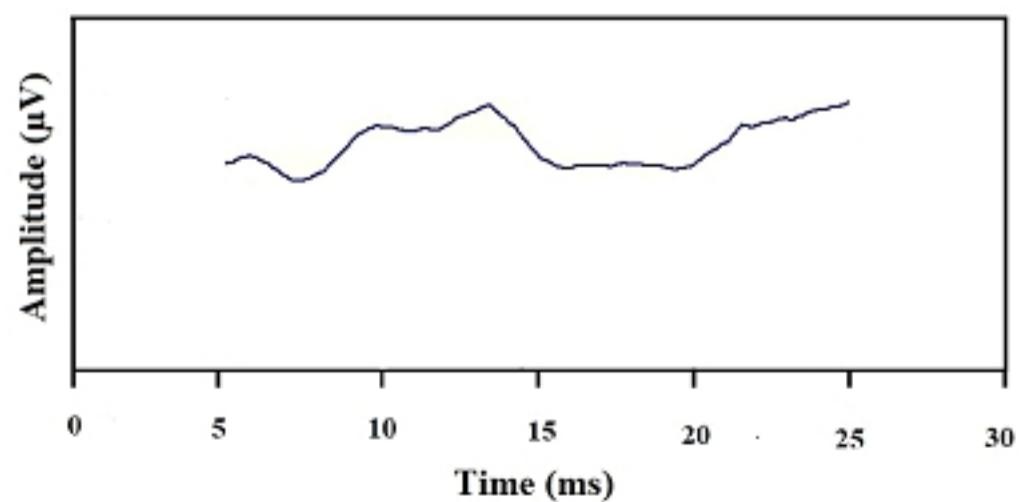
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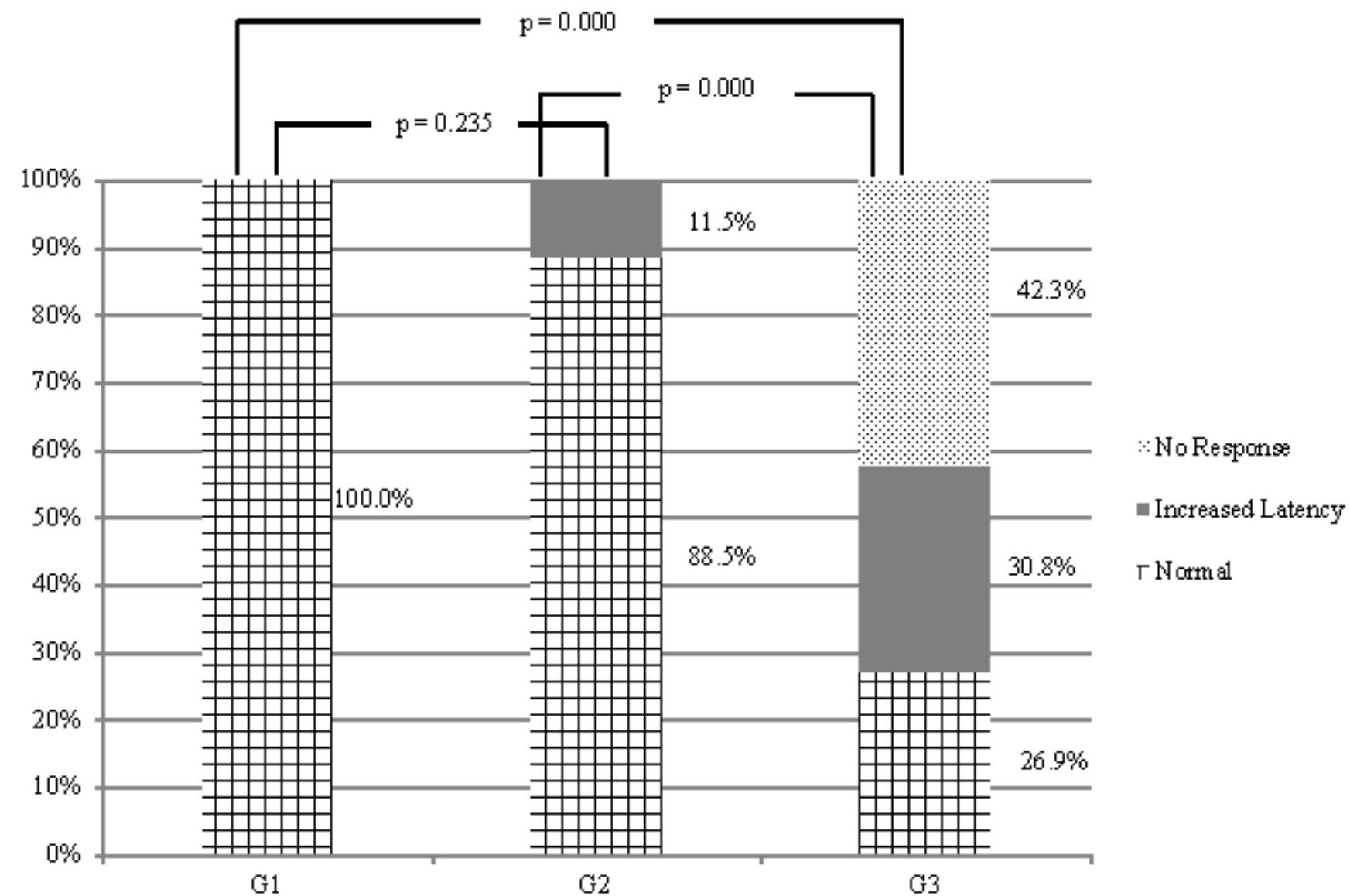
c)



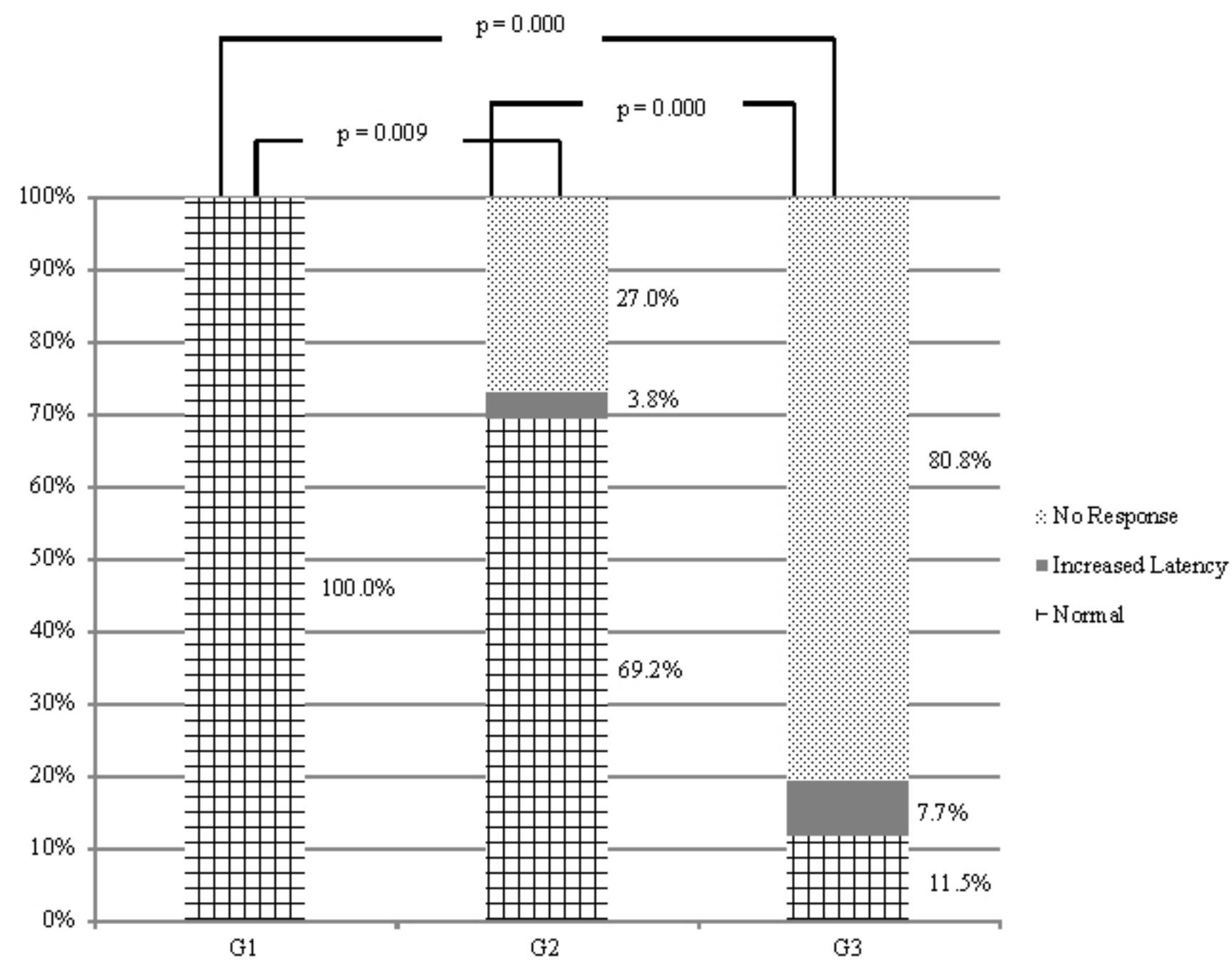
d)



Figure



Figure



Figure