

## Article

# Interictal Photophobia and Phonophobia Are Related to the Presence of Aura and High Frequency of Attacks in Patients with Migraine

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**Abstract:** Background: Despite that photophobia and phonophobia are well-known symptoms related to migraine, it is unclear whether they affect daily life activities during the headache-free period. Objective: To evaluate the interictal photophobia/phonophobia intensity during daily activities in migraineurs and non-headache individuals. Methods: Women with migraine without aura (MoA, n = 30), migraine with aura (MA, n = 30), chronic migraine (CM, n = 30) and without headache (CG, n = 30) reported the photophobia and phonophobia intensity during daily activities using a Likert scale ranging from 0 (no discomfort) to 10 (maximum discomfort). Results: The migraine groups reported higher intensity of interictal photophobia and phonophobia than CG during “driving” and “social situations”, respectively ( $p < 0.05$ ). MA and CM groups presented higher intensity of phonophobia than CG, hearing sounds in everyday situations and listening to conversations in noisy places ( $p < 0.05$ ). Also, the MA group presented higher interictal phonophobia than the CG to keep concentration in noisy places ( $p < 0.05$ ). Weak positive correlations were observed between the intensity of both photophobia and phonophobia with migraine intensity, frequency of migraine and frequency of aura ( $p < 0.05$ ). Conclusion: Interictally, the intensity of photophobia and phonophobia reported during daily activities is higher in patients with migraine, especially those with aura and chronic migraine, than in non-headache subjects.

**Keywords:** hypersensitivity; visual discomfort; auditory discomfort; headache



**Citation:** Pinheiro, C.F.; Moreira, J.R.; Carvalho, G.F.; Zorzin, L.; Dach, F.; Bevilaqua-Grossi, D. Interictal Photophobia and Phonophobia Are Related to the Presence of Aura and High Frequency of Attacks in Patients with Migraine. *Appl. Sci.* **2021**, *11*, 2474. <https://doi.org/10.3390/app11062474>

Academic Editor:  
Wojciech Kolanowski

Received: 9 February 2021

Accepted: 5 March 2021

Published: 10 March 2021

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## 1. Introduction

Phonophobia and photophobia are symptoms often associated with migraine [1], affecting over 80% of the patients [2,3]. Although the pathophysiology related to these symptoms in migraine is unclear, it is well-known that there is overall increased responsiveness to auditory and visual stimuli during the attacks [4,5]. Overall, a functional change of the hypothalamo-thalamo-brainstem networks is suggested as a source of photophobia and phonophobia in migraineurs [4]. Also, these symptoms remain at a lower level during the headache-free period [6–9].

Photophobia and phonophobia have been studied through questionnaires ascertaining the presence of these symptoms during the headache attack, with a focus on the diagnostic improvement of the migraine-related photophobia and phonophobia [10–12]. Previous studies have also investigated the level of these symptoms, especially photophobia, in different subtypes of migraine, but with conflicting findings [3,13–16]. Based on neuroimaging studies showing higher visual network connectivity and visual cortex activation in migraineurs with aura in contrast to those without aura [13,14], as well a visual-nociceptive

integration at the brainstem level in chronic migraineurs [17], it is expected that there will be higher photophobia in patients with aura and chronic migraine. Cucchiara et al. [13] and Pearl et al. [16] confirmed this hypothesis, in contrast to other studies [14,15], but they did not differentiate these symptoms in the ictal and interictal period. Regarding phonophobia, it has been suggested to be associated with migraine frequency [3,16] but seems not related to the presence of aura [16].

Visual and auditory discomfort may lead to behavioral consequences and a negative impact on migraineurs' quality of life, affecting basic tasks and social activities. Patients with interictal photophobia are more likely to manifest symptoms of depression and anxiety compared to migraine patients without interictal photophobia [18]. Phonophobia, besides also being associated with anxiety, is associated with stress that may induce emotional and cognitive reactions, such as difficulties in concentration [19]. Furthermore, both visual and auditory stimuli are likely to trigger a migraine attack [5,20]. Therefore, the knowledge of the photo- and phono-phobia perception in different migraine subtypes can contribute to understanding how the sensory stimuli can affect the daily routine of migraine sufferers even on a headache-free day.

Accordingly, this study aimed to evaluate the self-perception of photophobia and phonophobia intensity of migraineurs with and without aura, chronic migraineurs, and control individuals during daily activities. We hypothesize that during the pain-free period, patients with migraine with aura and chronic migraine would be more sensitive than migraineurs without aura and the controls.

## 2. Materials and Methods

### 2.1. Study Design and Sample

This cross-sectional study was performed between January 2018 and February 2019. Consecutive patients of the female sex, aged between 18 and 55 years, were selected from a University-based outpatient headache clinic, diagnosed according to the International Headache Classification [1] by neurology experts in headache. To be included, patients should have reported at least three headache-days per month during the last three months. According to the frequency of attacks and to the presence of aura, they were subclassified into three migraine groups: migraine without aura (MoA), migraine with aura (MA), and chronic migraine (CM). To avoid an overlap between groups regarding the migraine frequency, patients with 15 or more headache-days per month were classified as chronic, and migraineurs with 3 to 12 headache-days monthly composed the groups with and without aura. A control group (CG) was selected from the community and comprised of age-matched women with no report of headache during the last five years and no previous diagnosis of any primary headaches.

Individuals with the following conditions were excluded: presence of cerebrovascular diseases risk, such as diabetes mellitus, hypertension, and dyslipidemia, degenerative brain diseases, history of neurosurgery and head trauma, uncorrected visual/auditory impairment or visual/auditory loss (partial and total), and pregnancy. Furthermore, we also excluded patients with migraine who had a concomitant headache diagnosis and with migraine attack in the moment of assessment.

### 2.2. Procedures

An examiner collected data regarding age and headache features such as migraine onset, frequency and intensity, and frequency of aura. To evaluate the photophobia intensity, the volunteers were asked about the intensity of visual discomfort during the following activities: (i) Driving, (ii) looking at a bright screen, (iii) social activities, and (iv) walking during a sunny day. They used a Likert scale ranging from 0 (no discomfort) to 10 (maximum discomfort). To investigate the phonophobia levels, the same scale was used to quantify the auditory discomfort in the following conditions: (i) Social situations, (ii) hearing sounds in everyday situations, (iii) listening to conversations in noisy places, and (iv) concentration in noisy surroundings. The questions were adapted from validated pho-

tophobia and hyperacusis questionnaires [18,19,21]. Patients with migraine were instructed to answer questions based on a headache-free day.

### 2.3. Statistical Analysis

An a priori sample size was calculated using the G. Power 3.1.9.7. A minimum of 120 subjects (30 in each group) was required based on detecting significant medium effect size ( $\rho = 0.35$ ) with an  $\alpha$  of 0.05 and a desired power of 0.90. The normality of residuals was verified using the Shapiro–Wilk’s test. Normal data were expressed by mean and standard deviation (SD), and non-normal data were presented by the median and interquartile interval. The groups were contrasted for age and photo- and phono-phobia intensity using a one-way analysis of variance (ANOVA) with Least Significant Difference post-hoc test, and Cohen’s *d* was used to verify the effect size (ES) of the significant pairwise comparisons. According to Cohen’s *d* classification, 0.2 is considered a small effect size, 0.5 represents a medium effect size, and 0.8 a large effect size [22]. Migraine features were compared using the Kruskal–Wallis test with the Mann–Whitney test as a post-hoc for pairwise comparisons. The presence of interictal photophobia and phonophobia for each activity assessed was contrasted through groups using the Chi-square test. Cramer’s *V* was used to measure the effect size for the Chi-square test. Regarding this analysis having 3 degrees of freedom (df), the Cramer’s *V* equal to 0.06 is considered a small effect size, 0.17 is a medium effect size, and 0.29 is a large effect size [23]. Spearman’s rho correlation encompassed only migraine participants to verify the association between photo- and phono-phobia intensity and migraine frequency, migraine intensity, and the frequency of aura. For correlation analysis, photophobia intensity was obtained from the sum of values obtained from visual discomfort questions, and for phonophobia intensity, we consider the sum of values related to auditory discomfort. Correlation values less than 0.40 mean a weak correlation, 0.40 to 0.69 mean a moderate correlation, and more than 0.70 means a strong correlation [24]. The analysis was performed using the SPSS® software (IBM, New York, NY, USA, version 20.0), a two-tailed hypothesis was tested, and the significance level was set at 0.05.

### 3. Results

Among 152 patients, 32 were excluded due to the following reasons: presence of concomitant headache diagnosis ( $n = 6$ ), history of head or neck trauma ( $n = 4$ ), headache frequency lesser than three days/month ( $n = 6$ ), and failure to attend the scheduled assessment ( $n = 16$ ). Therefore, 120 participants (30 in each group) were included and completed the assessment. No differences were verified between groups regarding age, migraine onset, and migraine intensity ( $p > 0.05$ , Table 1). The use of prophylactic medication was similar between migraine groups ( $\chi^2 = 4.46$ ,  $p = 0.107$ , Table 1). As expected, the headache frequency of the chronic migraine group was higher than the other migraine groups ( $p < 0.05$ , Table 1).

**Table 1.** Sample demographics and headache characteristics.

	Control (n = 30)	Migraine without Aura (n = 30)	Migraine with Aura (n = 30)	Chronic Migraine (n = 30)	<i>p</i> -Value
Age, years: mean (SD)	31.30 (9.27)	32.46 (8.66)	32.16 (8.33)	34.56 (10.00)	0.556
Migraine onset, years: median (Q3–Q1)	-	16.50 (12.25)	15.50 (11.25)	15.00 (16.25)	0.670
Migraine frequency, monthly: median (Q3–Q1)	-	7.00 (6.00) <sup>a</sup>	8.00 (5.00) <sup>a</sup>	20.00 (10.00)	<0.001
Migraine intensity, NPRS: median (Q3–Q1)	-	8.00 (1.00)	8.00 (2.00)	8.00 (3.00)	0.168
Use of prophylactic medication: n (%)	-	9 (30)	12 (40)	17 (56.7)	0.107

<sup>a</sup>  $p < 0.05$  vs. chronic migraine group. NPRS: numeric rating pain scale, SD: standard deviation.

### Interictal Photophobia and Phonophobia

Four participants of each group reported not to drive ( $n = 16$ ), so they were not able to quantify the photophobia during this activity. Regarding the prevalence of interictal visual discomfort, the three migraine groups presented a higher prevalence than the control group for driving ( $\chi^2 = 8.99$ ,  $df = 3$ ,  $p = 0.031$ ,  $ES = 0.29$ ), looking at a bright screen ( $\chi^2 = 14.37$ ,  $df = 3$ ,  $p = 0.002$ ,  $ES = 0.34$ ), and performing social activities ( $\chi^2 = 16.83$ ,  $df = 3$ ,  $p = 0.001$ ,  $ES = 0.37$ , Table 2). No difference was observed between the four groups on the prevalence of interictal photophobia for walking during a sunny day ( $\chi^2 = 6.00$ ,  $df = 3$ ,  $p = 0.13$ , Table 2). For the prevalence of interictal auditory discomfort, the three migraine groups presented a higher prevalence than the control group during social situations ( $\chi^2 = 24.30$ ,  $df = 3$ ,  $ES = 0.45$ ,  $p < 0.001$ ) and for hearing sounds in everyday situations ( $\chi^2 = 9.47$ ,  $df = 3$ ,  $ES = 0.28$ ,  $p = 0.027$ , Table 2). A similar prevalence of interictal phonophobia was observed between the four groups for listening to conversations in noisy places ( $\chi^2 = 1.63$ ,  $df = 3$ ,  $p = 0.735$ ) and for concentrating in noisy surroundings ( $\chi^2 = 2.67$ ,  $df = 3$ ,  $p = 0.542$ , Table 2).

**Table 2.** Prevalence (% , n) of interictal photophobia and phonophobia during daily activities.

	Control (n = 30)	Migraine without Aura (n = 30)	Migraine with Aura (n = 30)	Chronic Migraine (n = 30)	p-Value
Photophobia					
Driving <sup>*,a</sup>	57.7 (15)	65.4 (17)	76.9 (20)	92.3 (24)	0.031
Looking at a bright screen <sup>a</sup>	36.7 (11)	76.7 (23)	76.7 (23)	53.3 (16)	0.002
Social activities <sup>a</sup>	16.7 (5)	60.0 (18)	63.3 (19)	40.0 (12)	0.001
Walking during a sunny day	50.0 (15)	73.3 (22)	76.7 (23)	60.0 (18)	0.136
Phonophobia					
Social situations <sup>a</sup>	33.3 (10)	83.3 (25)	86.7 (26)	63.3 (19)	<0.001
Hearing sounds in everyday situations <sup>a</sup>	43.3 (13)	70.0 (21)	80.0 (24)	60.0 (18)	0.027
Listening to conversations in noisy places	83.3 (25)	90.0 (27)	93.3 (28)	90.0 (27)	0.735
Concentrating in noisy surroundings	86.7 (26)	93.3 (28)	96.7 (29)	86.7 (26)	0.542

\* N = 26 in each group; <sup>a</sup>  $p < 0.05$ .

The data from the Likert scale showed differences between groups in the intensity of photophobia only for “driving” ( $F(3,75) = 2.92$ ,  $p = 0.040$ , Table 3). In contrast to the control group, the three groups of migraine-sufferers reported higher intensity of interictal photophobia during that activity (MoA vs CG:  $p = 0.017$ ,  $ES = 0.94$ ; MA vs CG:  $p = 0.014$ ,  $ES = 0.77$ ; CM vs CG:  $p = 0.013$ ,  $ES = 0.86$ ; Table 3). Differences in the remaining between-group comparison were not verified ( $p < 0.05$ , Table 3). No differences between groups were observed for interictal photophobia for the following activities: “looking at a bright screen” ( $F(3,72) = 2.44$ ,  $p = 0.072$ ), “social activities” ( $F(3,53) = 1.52$ ,  $p = 0.219$ ), and “walking during a sunny day” ( $F(3,77) = 2.60$ ,  $p = 0.058$ , Table 3).

We observed differences between groups in the intensity of interictal phonophobia in all the activities assessed: “socials activities” ( $F(3,85) = 4.70$ ,  $p = 0.004$ ), “hearing sounds in everyday situations” ( $F(3,75) = 6.08$ ,  $p = 0.001$ ), “listening to conversations in noisy places” ( $F(3,106) = 7.26$ ,  $p < 0.001$ ), and “concentrating in noisy surroundings” ( $F(3,108) = 3.62$ ,  $p = 0.015$ , Table 3). Both groups, migraine with aura and chronic migraine groups, exhibited higher intensity of interictal phonophobia than the control group for performing social activities (MA vs. CG:  $p = 0.012$ ,  $ES = 0.96$ ; CM vs. CG:  $p = 0.002$ ,  $ES = 1.11$ ), hearing sounds in everyday situations (MA vs. CG:  $p < 0.0001$ ,  $ES = 1.37$ ; CM vs. CG:  $p = 0.002$ ,  $ES = 1.24$ ), and listening to conversations in noisy places (MA vs. CG:  $p = 0.001$ ,  $ES = 0.94$ ; CM vs. CG:  $p < 0.0001$ ,  $ES = 1.19$ ). The migraine with aura group also presented higher interictal phonophobia than the control group for concentrating in noisy surroundings ( $p = 0.001$ ,  $ES = 0.91$ ). In addition, higher phonophobia intensity was observed in the chronic migraine

group than the migraine without aura group for performing social activities ( $p = 0.010$ ,  $ES = 0.73$ ) and listening to conversations in noisy places ( $p = 0.010$ ,  $ES = 0.71$ ), and in the migraine with aura group in comparison to the migraine without aura group for hearing sounds in everyday situations ( $p = 0.010$ ,  $ES = 0.82$ ; Table 3). Differences in the remaining between-group comparison were not verified ( $p < 0.05$ , Table 3).

**Table 3.** Interictal photophobia and phonophobia during daily activities (mean and 95% confidence interval).

	Control	Migraine without Aura	Migraine with Aura	Chronic Migraine	<i>p</i> -Value
<b>Photophobia</b>					
Driving	3.4 (2.0 to 4.7)	5.5 (4.5 to 6.6) <sup>a</sup>	5.5 (4.1 to 6.8) <sup>a</sup>	5.4 (4.5 to 6.4) <sup>a</sup>	0.040
Looking at a bright screen	3.1 (2.2 to 4.0)	5.2 (4.1 to 6.2)	4.6 (3.6 to 5.7)	4.3 (3.4 to 5.1)	0.072
Social activities	2.4 (1.3 to 5.1)	4.6 (3.0 to 6.2)	4.3 (3.4 to 5.3)	4.6 (3.5 to 5.7)	0.219
Walking during a sunny day	3.2 (2.2 to 4.3)	4.4 (3.4 to 5.5)	5.2 (4.3 to 6.2)	4.8 (3.8 to 5.9)	0.058
<b>Phonophobia</b>					
Social situations	3.2 (1.6 to 4.9)	4.1 (2.9 to 5.3) <sup>a</sup>	5.5 (4.6 to 6.4) <sup>a</sup>	6.0 (5.0 to 6.9) <sup>a,b</sup>	0.004
Hearing sounds in everyday situations	3.1 (2.2 to 3.9)	4.0 (3.2 to 5.0)	5.7 (4.7 to 6.7) <sup>a,b</sup>	5.2 (4.3 to 6.1) <sup>a</sup>	0.001
Listening to conversations in noisy places	3.9 (2.9 to 4.9)	5.1 (4.2 to 6.1)	6.3 (5.3 to 7.3) <sup>a</sup>	6.9 (5.9 to 7.9) <sup>a,b</sup>	0.001
Concentrating in noisy surroundings	5.3 (4.3 to 6.4)	6.4 (5.4 to 7.4)	7.7 (6.7 to 8.7) <sup>a</sup>	6.6 (5.6 to 7.7)	0.015

<sup>a</sup>  $p < 0.05$  vs. controls; <sup>b</sup>  $p < 0.05$  vs. migraine without aura.

Correlation analysis revealed weak positive associations between photophobia and phonophobia intensities with migraine features (migraine intensity, frequency of attacks, and frequency of aura) ( $p < 0.05$ , Table 4).

**Table 4.** Correlation ( $r$ , 95%confidence interval (CI)) between photo- and phono-phobia intensity and migraine features ( $n = 90$  \*).

	Photophobia Intensity (0–40)	Phonophobia Intensity (0–40)
Intensity of migraine attacks (0–10)	0.24 (0.05 to 0.41) <sup>a</sup>	0.32 (0.14 to 0.47) <sup>b</sup>
Frequency of migraine attacks (days/month)	0.32 (−0.13 to 0.48) <sup>b</sup>	0.33 (0.16 to 0.47) <sup>b</sup>
Frequency of aura (days/month)	0.30 (0.14 to 0.46) <sup>a</sup>	0.25 (0.08 to 0.41) <sup>a</sup>

<sup>a</sup>  $p < 0.01$ , <sup>b</sup>  $p < 0.001$ . \* Analysis performed considering only the individuals with migraine.

#### 4. Discussion

Our findings were in agreement with our initial hypothesis since the intensity of photophobia and photophobia reported during daily activities were greater in migraine individuals, especially those with aura and chronic migraine, than controls. Also, for some activities, migraineurs with aura and chronic migraine were more affected than migraineurs without aura, and both photophobia and phonophobia were correlated to migraine intensity, migraine frequency, and frequency of aura.

Interictal photophobia and phonophobia have been studied previously [3,6,18,25], but our study was the first one to investigate the presence and intensity of these symptoms during daily activities in patients with different subtypes of migraine, during the headache-free period. It adds new insights into sensory hypersensitivity maintained out of the headache phase, which may differ according to the migraine subtype. According to our findings, individuals with migraine exhibit moderate to intense levels of discomfort, while controls reported discomfort levels ranging from mild to moderate. In addition, as photo- and phono-phobia can act as triggers for migraine attacks [20], patients who have greater interictal sensitivity to visual and auditory stimuli may be more susceptible to new attacks.

Although photo- and phono-phobia were reported by most of the patients with migraine, individuals with aura and high frequency of attacks were more affected interictally.



A recent study explored photophobia and phonophobia in migraine subtypes [16], but the questionnaires used did not assess the symptoms in daily activities, and also did not specifically refer to the ictal period or the interictal period, making it difficult to assign the results to the interictal period. In the referred study [16], the authors observed an association between photophobia and migraine aura and chronic migraine, but the phonophobia was associated with chronic migraine only. Our results observed higher photo- and phono-phobia intensity in both groups, migraine with aura and chronic migraine, compared to controls. With our methodological design, we have addressed efforts to emphasize that our questions referred to the headache-free period.

The interictal higher sensitivity to innocuous visual and auditory stimuli exhibited by patients with aura and chronic migraine can indicate altered sensorial processing in these groups. Interictal hypersensitization has also been described for other sensory stimuli. Cutaneous allodynia, the perception of pain or discomfort in response to innocuous thermal and/or mechanical stimuli applied to the skin, is a common phenomenon among migraineurs [26]. Although cutaneous allodynia is commonly remarkable during the ictal period, migraineurs also exhibit lower mechanical pain threshold and thermal pain threshold interictally [4]. Also, interictal cutaneous allodynia is associated with the frequency of migraine attacks [16]. Similarly, patients with chronic migraine present more interictal photophobia [16,27] and phonophobia [3,16], and our results reinforce it. It has been speculated that increased sensory sensitivities in chronic migraine might reflect a chronic central sensitization similar to the mechanism proposed for cutaneous allodynia [27]. Gathering these findings together suggested that chronic migraine is linked to a multimodal sensory hypersensitivity.

Regarding the presence of aura, Datta et al. [14] and Cucchiara et al. [13] reported that patients with aura have increased activation in the primary visual cortex in response to a visual stimulus, compared to migraineurs without aura and controls. Indeed, the cortical spreading depression, the physiological basis of aura, can activate brainstem regions involved in the processing of nociceptive information via trigeminovascular mechanisms, reducing the threshold of nociceptive neurons at the thalamus [26]. Therefore, despite the similar prevalence of photo- and phono-phobia in migraine groups, the presence of aura may facilitate the occurrence of the hyperresponsiveness to visual and auditory stimuli.

For the clinicians, it is important to know the subgroups of patients who are likely to present higher sensory sensitivity, since visual and auditory stimuli can trigger a migraine attack [5]. Due to the effect sizes observed, we can attribute a high clinical significance to the differences observed, especially for differences between migraine groups, indicating the effect of migraine sub-diagnosis on the interictal phonophobia. Additionally, interictal photophobia and phonophobia are associated with attentional difficulties in patients with migraine [28], and the activities with highest discomfort intensities observed in our sample are related to attentional demands (driving and concentrating in noise surroundings). Thus, health professionals should consider educational approaches on photophobia and phonophobia for migraine patients, with orientations about the perception of these symptoms and their role on migraine inside and outside attacks, as well as strategies to reduce the discomfort in everyday situations and workplaces, for example, use of sunglasses, lower screen brightness, and use of earplugs in noisy places.

However, we assume some limitations. First, since women present higher prevalence and severity of photophobia and phonophobia [29], our findings might not represent the general population. Also, when the study was designed, there were no photophobia and phonophobia questionnaires specific for migraine or any headache. Previous studies have used general photophobia and hyperacusis questionnaires in patients with migraine [8,16], but the authors assume the difficulty of discriminating between the ictal and interictal periods. For this reason, we rely on these tools for selecting queries about daily activities of social and attentional fields, which are usually common in our population to ensure the pragmatism of the study. Recently, Cortez et al. [12] developed and validated a photophobia symptom impact scale with an excellent reliability in migraine sufferers

(Cronbach's alpha = 0.95), and future studies can use this tool in patients with different types of migraine and other headaches. Another limitation is related to the chronic migraine group since it was composed of patients with few headache-free periods. These individuals may have overestimated the photophobia and phonophobia intensity, considering the difficulty of differentiating between pain and pain-free periods.

Despite the limitations, our study was the first to analyze the self-perception of interictal photophobia and phonophobia intensity in migraine subtypes. Therefore, the results from our study reinforce the necessity of educational, clinical approaches focused on clarifying the symptoms of photophobia and phonophobia and how they may affect daily activities, and orientating strategies to minimize it.

## 5. Conclusions

Greater photophobia and phonophobia levels in the interictal period are reported during daily activities by patients with migraine, especially those with aura and chronic migraine, in contrast to non-headache individuals. These results contribute to improving the clinical education approaches to the effects of photophobia and phonophobia in specific sub-diagnoses of migraine.

**Author Contributions:** Conceptualization, C.F.P., J.R.M., G.F.C., F.D. and D.B.-G.; methodology, C.F.P., G.F.C. and D.B.-G.; formal analysis, C.F.P. and J.R.M.; investigation, C.F.P., J.R.M., G.F.C., L.Z., F.D. and D.B.-G.; data curation, G.F.C., J.R.M. and L.Z.; writing—original draft preparation, C.F.P. and J.R.M.; writing—review and editing, C.F.P., J.R.M., G.F.C., L.Z., F.D. and D.B.-G.; supervision, D.B.-G.; project administration, C.F.P. and D.B.-G.; funding acquisition, D.B.-G. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo, grant numbers 2015/18031-5 and 2018/23832-5.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Ribeirão Preto Medical School of University of São Paulo (protocol code 15572/2016, approved 08-Mar-2017).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to containing information that could compromise the privacy of research participants.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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