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Original

Hyperacusis and plasma levels of cytokines in migraine

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Introduction
Migraine is a chronic pain that represents a public health problem and compromises quality of life, with an inflammatory factor involved in its pathophysiology.

Objective
To verify whether there is an increase in serum cytokines in patients with migraine associated with hyperacusis.

Methods
The sample consisted of 80 participants in the episodic and/or chronic migraine group, with/without aura, and 80 healthy individuals; aged 18 to 60 years of both sexes. Instruments used: ID-migraine, Migraine Disability Assessment (MIDAS); Short-Form Headache Impact Test (HIT-6), State Trait Anxiety Inventory (STAI) Y1 Y2, Beck Inventory, Allodynia and Hyperacusis Questionnaire; interleukin dosage by flow cytometry.

Results
The sample was homogeneous for sex, age and race ($p>0.05$). There was an association between hyperacusis and migraine ($p<0.001$). 41.2% of patients with migraine had hyperacusis. The majority of the population with migraine had phonophobia (87.8%); photophobia (93.7%); osmophobia (61.5%); episodic migraine (65.4%); prodrome and postdrome in 80% of them; half of them did not have aura (52%) or allodynia (53.2%). Regarding serum cytokine levels, they had higher levels of IL-2 and TNF-α (Mann-Whitney, $p<0.001$). INF-γ, IL-4, IL-6, IL-10 in plasma did not differ statistically between the control and migraine groups (Mann-Whitney, $p>0.05$). The association of hyperacusis with cytokines IL-2, IL-4 and TNFA (Mann-Whitney, $p>0.05$) in migraine patients was observed.

Conclusion
It was possible to verify that there was a significant difference in plasma cytokine levels between the groups. The increase in inflammatory markers indicates the possibility of complementary treatment, allowing the intervention of other professionals from multi and interdisciplinary teams.

Keywords:
Hyperacusis
Migraine
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Introduction

Migraine is a disease that affects more than 1 billion people worldwide, representing 14.4% of the world's population, with women being the most affected, accounting for 2/3 of cases. The main symptom of migraine is headache, characterized by moderate to severe intensity, typically pulsatile, unilateral accompanied by phonophobia, photophobia and nausea; it can be chronic with or without aura (1–5).

There is strong supporting evidence for an interaction between the nervous system and the immune system, but there are still a few gaps to be clarified regarding the exact mechanism. Some clinical studies have already shown an increase in pro-inflammatory cytokines in migraineurs, especially during the pain phase, as well as a reduction in the levels of anti-inflammatory cytokines. It cannot be excluded that genetic factors may also be involved in this process (4,6–8).

Cytokines are protein molecules, glycosylated or not, which send stimulatory, modulatory or even inhibitory signals to the different cells of the immune system. They have an autocrine function acting on the producing cell itself, a paracrine function acting on nearby cells and an endocrine function when their action is remote acting on concentrations (9). They regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation and/or differentiation of various cells and by regulating the secretion of antibodies or other cytokines (10). Some of the characteristics inherent to cytokines are: pleiotropy: a single cytokine exerts different biological effects on different cell types; redundancy: two or more cytokines that perform the same functions; 3) synergism: the combined effect of two or more cytokines is greater than the combined actions of the individual cytokines; 4) antagonism: the effects of one cytokine inhibit or compensate for the effects of another cytokine; 5) cascade induction: the actions of a given cytokine on its target cells are responsible for stimulating the production of other cytokines. These characteristics allow cytokines to regulate cellular activity and immune response in a coordinated and interactive manner, binding to specific receptors on the membranes of target cells, triggering signal transduction pathways that induce gene expression (10).

Hyperacusis is known as an audiological factor which causes various other conditions for the individual who is hypersensitive to any type of sound and intensity, generating unexpected discomfort which is sometimes even unbearable. There are several possible causes, and it occurs in various age groups and pathologies and in normal-hearing patients (11). As for pathophysiology, it is also important to note that there is an association between the altered limbic system, cortex and auditory pathways (12). There are differences between hyperacusis, autophony and misophonia, where hyperacusis is discomfort with any type of sound, regardless of the intensity and type of noise presented, autophony is discomfort generated by human voices that are perceived as high intensity; misophonia is discomfort with sounds and patterns and specific meanings for the individual, with the physical characteristics of the individual being secondary. The reaction is related to the individual's previous history and subjective factors such as individual interpretation or the belief that the sound carries a certain danger or harm (13,14).

Regarding the epidemiology of hyperacusis, as there is no universal understanding of the various concepts mentioned, the prevalence and incidence of this pathology are difficult to determine, and it is not possible to determine the prevalence and incidence in adults and children (13). Hyperacusis can be present in a number of conditions, including tinnitus, migraines, Meniere's disease, autism, multiple sclerosis and others (11,15,16).

Although the presence of hyperacusis as part of migraine complaints is significant (2,15,17,18) there are not enough studies to indicate whether there is an increase in cytokines in patients who complain of migraine associated with hyperacusis. The aim of this study is therefore to analyze plasma cytokine levels in migraine patients and their relationship with hyperacusis.

Methods

Ethical considerations

The Research Ethics Committee approved the project, according to the approval opinion of the Brazil Platform CAAE: 98316718.7.0000.0020, following the responsibilities and rules defined. It is worth remembering that all participants signed an Informed Consent Form, after a detailed explanation of its development, in accordance with Resolution 466/2012 of the National Health Council.

Study design

Prospective observational case-control study with participants matched for age, sex, BMI and waist circumference.

Study population

160 participants, 80 with episodic and/or chronic migraine, with or without aura, according to the International Classification of Headache Disorders, and 80 in the control group, i.e. people without migraine. To take part in this study, participants had to be aged

between 18 and 60 of both sexes. Individuals with severe, uncontrolled neurological, psychiatric or inflammatory diseases were excluded. All the participants were treated at the Academic Headache Outpatient Clinic of the PUCPR Campus Londrina-PR, which is run by a neurologist -Dr. Aline Vitali da Silva- from the Unified Health System (SUS).

Clinical profile

First, the participants underwent a clinical assessment and answered the self-administered ID-migraine questionnaire (9).

A structured interview via Google Forms®, developed by the Headache Research Group at PUCPR, Londrina Campus, contained demographic data (name, age, sex, self-declared race); it also covered the presence or absence of signs and symptoms of current infection; anthropometric data (height, weight, abdominal circumference); as well as information related to migraine, such as the presence or absence of aura. In addition, the Allodynia questionnaire was also used to measure sensitivity to non-painful stimuli, which is a predictor of negative impact on migraine patients' quality of life. Finally, the hyperacusis questionnaire (adapted) was used to estimate the importance of patients' phonophobia.

Cytokine levels in the plasma of the study participants were measured by the Cytometric Bead Array (CBA) method, using the Th1/Th2 kit (IL-2, IL-4, IL-10, INF-γ and TNF-α BD Pharmingen, CA, USA). The protocol described by Mitelman et al. (15), six populations of beads with different fluorescence intensities are conjugated with a specific capture antibody for each cytokine, mixed to form the CBA and read on the FL3 channel of the BD Accuri C6® flow cytometer (BD Biosciences, San Jose, CA). The bead populations were visualized according to their respective fluorescence intensities: from the least bright to the brightest. In the CBA, the cytokine capture beads are mixed with the detection antibody conjugated to the fluorochrome PE, and then incubated with the samples. The acquisition tubes were prepared with: 50 μL of sample, 50 μL of the bead mixture and 50 μL of the Th1/Th2 PE detection reagent (Human Th1/Th2 PE Detection Reagent/1 vial, 4 mL). The same procedure was carried out to obtain the standard curve. The tubes were homogenized and incubated for three hours at room temperature in the dark. The results were generated in graphs and tables using cytokine levels in quantitative formats were generated by FCAP Array v.3 software (Soft Flow Hungary Ltd, Pécs, Hungary). Limits of detection: CBA Th1/Th2: IL-2 (2.6 pg/mL), IL-4 (2.6 pg/mL), IL-10 (2.8 pg/mL), TNF-α (2.8 pg/mL), INF-γ (7.1 pg/mL), IL-6 (2.6 pg/mL).

Statistical Analysis

Categorical data was equated using the Mann-Whitney test. The migraine and hyperocclusion and control groups were compared using Student's parametric t-test. A significant difference was considered when $p<0.05$. The analyses were carried out using the statistical program SPSS version 26.0.

Results

The sample was homogeneous in terms of gender, age, BMI, race, hypertension and diabetes mellitus ($p>0.05$). Hyperacusis was associated with migraine ($p<0.001$). A larger proportion (89.9%) of the participants in the control group did not have hyperacusis and 41.2% of the patients with migraine had hyperacusis.

Table 1. Association between demographic-clinical variables and migraine in the study population (n= 160)

	Migraine		
	Case	**Control**	**P value**
Sex n (%)			
Male	18 (22.5)	20 (25)	0.426
Female	62 (77.5)	60 (75)	
Race n (%)			
White	57 (71.2)	63 (79.7)	0.144
Nonwhite	23 (28.8)	16 (20.3)	
Arterial hypertension Sistemic n (%)			
Yes	8 (10.0)	4 (11.3)	0.514
No	71(63.0)	63 (88.9)	
Diabetes Mellitus n (%)			
Yes	3 (3.8)	4 (5.6)	0.441
No	76 (96.2)	63 (94.4)	
Hyperacusis n (%)			
Yes	47 (58.8)	71 (89.9)	0.001
No	33 (41.2)	8 (10.1)	
Age Mean±SD	33.1±13.5)	33.4±14.9	0.655
BMI Mean±SD	26.7±5.2	25.1±6.1	0.433

Table 2. Clinical data and symptoms related to the migraineurs 'condition

Exploratory Variables	Migraine
Phonophobia n (%)	
Yes	67 (85.8)
No	11 (14.2)
Photophobia n (%)	
Yes	72 (93.7)
No	6 (07.7)
Osmophobia n (%)	
Yes	48 (61.5)
No	30 (38.5)
Type of headache n (%)	
Episodic	51 (65.4)
Chronic	27 (34.6)
Aura n (%)	
Yes	37 (46.8)
No	42 (53.2)
Visual Aura n (%)	
Yes	39 (67.2)
No	19 (32.8)
Sensitive aura n (%)	
Yes	18 (31.6)
No	39 (68.4)
Prodrome n (%)	
Yes	64 (81.0)
No	15 (19.0)
Allodynia (%)	
Yes	37 (46.8)
No	42 (53.2)
Postdrome n (%)	
Yes	64 (80.0)
No	15 (20.0)

It was found that the majority of migraineurs had phonophobia/hyperacusis (85.8%); photophobia (93.7%); osmophobia (61.5%); a large proportion had episodic migraines (65.4%); 80% had prodrome and postdrome migraines (84.5%); the majority had no aura (52%) or allodynia (53.2%) (Table 2).

Considering serum cytokine levels, it was observed that patients with migraine had higher levels of IL-2 and TNF-α (Mann-Whitney test, $p<0.001$, Figure 1). The quantification of INF-γ, IL-4, IL-6 and IL-10 in plasma did not differ statistically between the control and migraine groups (Mann-Whitney test, $p>0.05$).

Table 3 shows the comparison between the means of the cytokines and hyperacusis. The TNFA, IL-2 and IL-4 cytokines had higher means among patients with hyperacusis compared to the control group ($p<0.05$). For the other cytokines IL-6, IL-10 and INFY, the means did not differ statistically between the control group and the hyperacusis group ($p>0.05$, Mann-Whitney test).

Table 3. Comparison between plasma levels of cytokines and hyperacusis in patients with migraine

Interleukin	Hyperacusis	N	Mean	p-value
TNFA	Without	109	3.96	**0.001**
	With	31	11.58	
IL-10	Without	112	3.12	**0.746**
	With	33	3.70	
IL-6	Without	113	3.38	**0.390**
	With	34	4.65	
IL-4	Without	108	1.54	**0.044**
	With	26	2.54	
IL-2	Without	106	2.65	**0.007**
	With	26	4.88	
INFY	Without	107	8.77	**0.919**
	With	31	9.06	

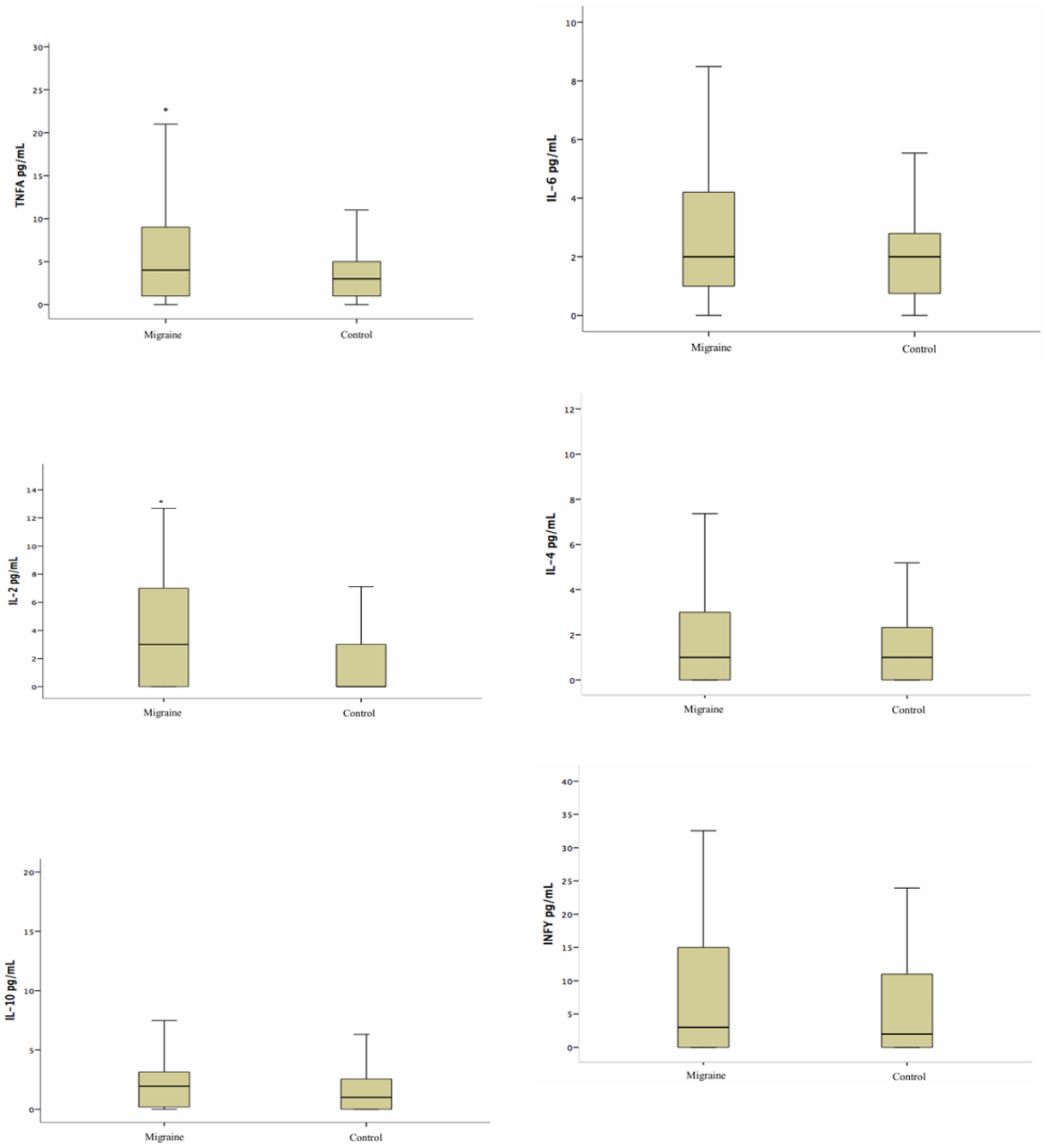

Figure 1. Comparison of TNFA, IL-2, IL-10, IL-6, IL-4 and INFY serum levels (pg/mL) in patients with migraine and control group. *Statistically significant difference determined by the Mann-Whitney test ($p < 0.05$).

Discussion

There was an association between hyperacusis and migraine. There are limited studies on the causal relationship between hyperacusis and migraine, but many studies have shown that hyperacusis is present in migraine, as suggested by Silva-Néto (19), although components associated with hearing loss or retrocochlear pathologies have not yet been associated as a causal or predictive factor for hyperacusis in migraine.

Maistro et al. (15) conducted a prospective case-control study with 276 patients, in which they found that osmophobia, the chronic form and greater disability were predictors of hyperacusis in individuals with migraine. There are no further reports or studies mentioning causal factors relating to hyperacusis.

It is interesting to note that in the results obtained in this study, both osmophobia and photophobia are associated with hyperacusis and migraine. Studies such as Maistro et al. (15) and Silva-Néto (19) reported that osmophobia was associated with photophobia and phonophobia with primary migraine of the tension-type headache type in 33% of participants. There are literature reviews that correlate these cytokines with pain, where it is suggested that increased serum levels of IL-2, IL-4 and TNF-α in patients with migraine and associated hyperacusis intensify pain, since these interleukins and tumor necrosis factor alpha participate in the increase of inflammation (9,10,15,20,21)

Thus, future studies could consider a population exclusively complaining of hyperacusis and migraine to better explore the symptom and find more accurate results, as well as the biological mechanisms involved in this pathology. A noteworthy fact is that identifying the distribution of inflammatory markers can help professionals in multidisciplinary healthcare teams treating migrant patients to track the effects or effectiveness of therapeutic responses, including proposals for therapeutic intervention for hyperacusis in patients with associated complaints. Thus, it becomes possible to recognize vulnerable groups for early intervention and rehabilitation.

Conclusion

There was an association between hyperacusis and migraine; and that migraine and hyperacusis patients had high serum levels of TNFA, IL-2 and IL-4 compared to the control group.

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