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ALLODYNIA AND CLINICAL FEATURES IN WOMEN WITH PERSISTENT HEADACHE ATTRIBUTED TO MILD TRAUMATIC INJURY TO THE HEAD IN COMPARISON WITH WOMEN WITH MIGRAINE

Neurology

Hugo André de Lima Martins Physician (UFPE), Doctor in Neuropsychiatry and Behavioral Sciences, UFPE

Valdenilson Ribeiro Ribas* Psychologist (UFPE), Doctor in Neuropsychiatry and Behavioral Sciences, UFPE*Corresponding Author

Daniella Araújo de Oliveira Physiotherapist (UFPE), Doctor in Neuropsychiatry and Behavioral Sciences, UFPE

Marcelo MoraesValença Physician (UFPE), Doctor in General Physiology from Ribeirão Preto Medical School, University of São Paulo (USP, 1989).

ABSTRACT

Introduction: Post-traumatic headache is the most common symptom found in the post-traumatic syndrome. Objective: The aim of this study was to evaluate the presence of tactile or thermal allodynia in women with persistent headache. **Method:** The women were divided into three groups: (a) Individuals without headache (b) persistent post-traumatic headache and (c) migraine (n=29). The allodynia was evaluated by the quantitative method using the Semmens-Weinstein esthesiometer to determine the pressure thresholds, and glass test tubes filled with warm or cold water for the thermal sensitivity evaluation. For the cutaneous allodynia qualitative evaluation, a questionnaire was used. **Results:** Patients with persistent headache attributed to traumatic injury to the head presented mechanical and thermal sensitivity thresholds lower than the control group ($p<0.05$) and a quantity of cephalic and extra-cephalic allodynic symptoms greater than that found in the controls ($p<0.05$). **Conclusion:** Cephalic and extracephalic allodynia is a common phenomenon in patients with posttraumatic headache.

KEYWORDS

Headache, Allodynia, Brain injury, Migraine, Pain, Post-traumatic headache. Disclosure: The authors report no conflicts of interest.

INTRODUCTION

According to the International Classification of Headache Disorders (ICHD-3 beta) , the persistent post-traumatic headache (pPTH) occurs after traumatic brain injury (TBI) in individuals with no previous history of headache or in those who harbor primary headaches when they seem to worse in close relationship to a head trauma, with the persistence of the pain for more than three months after the traumatic brain injury (TBI) .

Up to now, the clinical features of pPTH have not been clearly determined. When a new headache occurs for the first time in close temporal relationship with the TBI, it is classified as a secondary headache attributable to trauma, even if the headache presents similar characteristics to migraine, tension-type headache or cluster headache .

Martins and colleagues evaluated 41 patients (men and women) suffering from post-traumatic headache after mild TBI (i.e. a temporary loss of brain function) and reported that the most prevalent type of headache fulfilling the diagnostic IHS criteria was migraine without aura (39%), followed by chronic tension-type headache (34%) .

Similar results were described by Souza and coworkers , with the most prevalent clinical form being migraine-like headache (70.3%), followed by headache resembling tension-type headache (51.8%) in a group of patients with pPTH following mild TBI.

Furthermore, cutaneous allodynia occurs in a high proportion of patients with various types of primary headache, both during attack and in the intercritical period . Bigal and collaborators reported that cutaneous allodynia prevalence was particularly high in transformed migraine (68.3%) and in episodic migraine (63.2%). Cutaneous allodynia was also present in other subtypes of headache, such as probable migraine (42.6%), severe episodic tension-type headache (36.7%) and other chronic headaches (36.8%). The main question is whether post-traumatic headache, a secondary headache, also presents cutaneous allodynia during the disease progression, since the characteristic headache expression is very similar to that found in migraine or tension-type headaches .

Cutaneous allodynia is characterized by the painful response to non-noxious stimuli on the skin, such as thermal and mechanical stimuli . The underlying mechanism of cutaneous allodynia seems to be the sensitization of second-order neurons in the central nervous system that receive converged sensory impulses from the skin and intracranial structures .

In fact, the symptomatological features of pPTH may resemble those of virtually any subtype of primary headache. To date, there is no universal agreement on the way that pPTH should be diagnosed and classified. Thus, the objective of this study was to verify the occurrence of cutaneous allodynia and other clinical features in pPTH attributed to mild TBI in women, in comparison with migraineurs and healthy women.

METHODS

In this study the women were allocated to three groups: (I) volunteers with no previous history of headache (control group, n=25, aged 14-84; 35 ± 17), (II) pPTH after mild TBI and no previous history of primary headache (n=19, aged 11-68; 34 ± 16), and (III) migraine group (n=29, aged 13-59; 36 ± 10). The groups with migraine and pPTH were established based on the ICHD-3 beta . All volunteers and patients were assessed in the outpatient unit of Getúlio Vargas hospital, in Recife, Brazil.

Sensory Testing

The patients were asked about their history of headache, its characteristics (i.e. duration, intensity of pain, unilaterality, pulsatility) and associated symptoms (i.e. nausea, vomiting, photophobia and photophobia). The patients were evaluated in the intercritical period, at least 24 hours after the resolution of the last attack. The assessment of allodynia was made at a single point in time and was carried out by a single investigator (HALM).

The presence of allodynia was assessed first by asking the patients to give written yes/no responses to written question as follows: Has the patient experienced abnormal scalp sensitivity or discomfort outside headache attacks? If yes, does this abnormal sensitivity or discomfort arise from: (a) combing your hair; (b) making a ponytail; (c) wearing glasses; (d) wearing earrings; (e) wearing a necklace; (f) wearing a hat; (g) washing the face; (h) placing your head on the pillow; (i) exposure to heat; (j) exposure to cold; (k) wearing tight clothes; (l) using objects on the wrist; (m) covering with a heavy blanket; (n) taking a shower; or

(0) wearing rings .

For pain threshold testing, calibrated Semmes-Weinstein Von Frey Aesthesiometer for touch assessment of five different target forces, 0.4 g, 2 g, 8 g, 15 g and 60 g, were applied sequentially in 12 skin areas: both facial areas (first, second and third divisions of the trigeminal nerve); skin over the cervical muscles; ventral forearms and over the lower part of the thighs. The filaments were applied sequentially and repeated three times, a single positive response being sufficient to indicate that such a strand/force represented the sensitivity threshold of the patient.

The thermal sensitivity threshold was evaluated using glass test tubes, with surface contact on the patient's skin measuring 2x2 cm. The temperature was verified by a thermometer (incoterm) and the areas of application in the patients were the same as the ones used in tests with the von Frey filaments. The cold stimulus was made with water at a temperature of 25°C and the hot stimulus at a temperature of 40°C, based on a study carried out by Sand and coworkers . Each thermal stimulus was applied three times for 3 seconds at each point.

No preventive drug was used to treat the headache disorder until the evaluation of the patients.

Statistical Analysis.

The statistical analysis was performed by obtaining the arithmetic mean as a statistical measure. For the comparison between groups, the chi-square or Fisher's exact test was used for the qualitative or categorical variables when appropriate, and F (Anova), Mann-Whitney and Kruskal-Wallis for the numerical variables. In the case of a significant difference using the Kruskal-Wallis test, comparisons were made using Dunn's test. The choice of the nonparametric tests was due to the non-Gaussian distribution of the data. The data are shown as mean ± standard deviation.

This study was approved by the Ethics Committee of the Federal University of Pernambuco, Recife, Brazil (N.044/07).

RESULTS

The time interval between the TBI and the evaluation of the patient in the pPTH group was 27 ± 4 months. There was no difference in age between the groups ($p>0.05$, Anova). The clinical characteristics encountered in the patients with pPTH were similar to those observed in the migraine group (Table 1).

In the mechanical sensorial evaluation, the stimulus required to trigger the allodynic or painful response was lower in patients with pPTH or with migraine than in the group without headache in all skin areas evaluated (Table 2).

In the thermal sensorial evaluation by heat and cold (Table 3) patients with either pPTH or migraine presented a higher number of patients with allodynic response to each stimulus when compared to individuals without headache ($p<0.05$). On the other hand, no significant differences were observed in either heat or cold allodynia between the migraine group and the pPTH group (Table 3).

Table 4 shows that cephalic and extra-cephalic allodynic symptoms are more frequent in patients with pPTH, as well as in those individuals with migraine when compared with the control group without headache. No statistical differences were observed between the pPTH and migraine groups of patients.

DISCUSSION

In this study, we demonstrated that the features of pPTH after mild TBI in women with no previous history of primary headache are very similar to those encountered in female migraineurs. In addition, the tactile and thermal types of allodynia are a common finding in both pPTH and migraine, with a similar frequency.

The evaluation and management of the patient with pPTH resulting from mild TBI continue to represent a challenge for specialists in headache disorders. Although the majority of the cases are solved by the end of the first year following the TBI, a number of patients still complain of headache after this period. Up to the 85% of our cases reported pPTH lasting more than one year. Due to the absence of objective findings, there is always controversy as to whether the symptoms are real, psychogenic or "produced .

The data found in the literature on the occurrence of cutaneous allodynia in post-traumatic headache are scanty. Defrin and colleagues recently reported that individuals who suffered traumatic head injuries and developed pPTH had higher thermal thresholds, which might indicate nervous system damage to the pain and temperature neuron control systems. A lower pressure-pain threshold in the head in comparison to healthy controls was also observed . Unlike the present study, the above-mentioned authors evaluated subjects with pPTH following mild TBI resulting from moderate and severe and used only the quantitative sensory test. The low threshold of sensitivity observed in patients with pPTH, for both the mechanical and thermal (heat and cold) stimulus demonstrates that in these patients there is a dysfunction in the neural pathways involved in the cutaneous interpretation of different types of stimuli, from a light touch to a painful form of stimulus.

A number of authors have demonstrated the presence of cutaneous allodynia in patients with primary forms of headache, in both the critical and intercritical periods. The central sensitization mediated by the axonal injury affecting the brainstem structures that inhibit the pain may be one of the determinants of chronicity of the post-traumatic headache .

For many years it was thought that victims of mild TBI presented subjective complaints of a psychiatric/neurological nature, rather than a real major nervous system disorder, for the purpose of obtaining legal compensation through the judicial system. Interestingly, after the resolution of such issues, patients with pPTH did not feel any pain relief, as would have been expected . The post-traumatic headache was also related to as a premorbid profile, suggesting that only susceptible individuals would develop such symptoms .

One of the greatest challenges in the management of patients with pPTH, due to mild TBI, is the absence of any objective physical changes in the neurological examination, or in the evaluation by routine radiological examinations such as computed tomography or magnetic resonance imaging, which leads most professionals to regard patients as individuals simulating a morbid condition or with a symptomatology with no organic cause, such as a minor psychological disorder .

These subjects evaluated in the present study also participated in other study in order to determine the association of pPTH with depression, anxiety and quality of life. And indeed, the individuals with pPTH had high levels of anxiety and depression symptoms and reduced quality of life, in a similar way to what was found in migraineurs .

The results of this study demonstrate that pPTH probably has an organic substrate, subsuming all the data collected by several authors in an attempt to prove the existence of a cerebral biochemical change as the cause of the syndrome.

Indeed, Sarmento and colleagues found a reduction in the N-acetylaspartate (a marker of neuronal vitality) levels and an increase of the choline (a marker of membrane turnover) levels in different cerebral regions using spectroscopy magnetic resonance imaging of subjects with post-traumatic headache (9 acute and 8 persistent), indicating that these patients suffered a significant brain tissue damage.

It is estimated that more than 6 individuals/1,000 suffer from mild TBI annually . In addition, a retrospective survey reported that 88.6% of those who experienced a concussion did not recognize that they really had suffered a concussion, suggesting that mild TBI is underestimated and, thereby, may be a daily life relatively frequent event.

Taking the facts into consideration, we may wonder: Are those patients with PTH genetically susceptible to migraine and, in these cases, the mild brain trauma was an initial trigger of the migraine onset? Or migraine may be in some subjects an acquired event? Both questions remain to be answered.

In conclusion, cephalic and extracephalic allodynia is a common phenomenon in patients with pPTH after mild TBI, as was also observed in migraineurs . The characteristic features of pPTH after mild TBI in individuals with no previous history of primary headache (at least in women) are very similar to those of migraine, which suggests a common physiopathogenic mechanism.

Clinical implications

Bullet Points

1. In this study, the allodynia was evaluated by the quantitative method using the Semmens-Weinstein esthesiometer and quantitative evaluation (simplified questionnaire). This is the first study, which searched allodynia in patients with post-traumatic headache using both methods;

2. The allodynia in all patients were evaluated in the intercritical period, at least 24 hours after the resolution of the last attack;

3. All patients with post-traumatic headache had no prior history of any type of headache.

Table 1 – Comparison between the group with persistent post-traumatic headache without previous history of primary headache (pPTH, n=19) after mild head injury and the group with migraine (n=29) in relation to the diagnostic criteria of migraine according the ICHD-3 beta (2013)

Diagnostic criterium	pPTH		Migraine	
	n	%	n	%
Duration of crises from 4 to 72 hours	14/19	73.7	29/29	100
Unilaterality	11/19	57.8	22/29	75.8
Pulsatility	10/19	52.6	20/29	68.9
Moderate or severe intensity	13/19	68.4	25/29	86.2
Exacerbated by physical activity	11/19	57.8	19/29	65.5
Nausea and/or vomiting	5/19	26.3	20/29	68.9
Photophobia and phonophobia	9/19	47.3	15/29	51.7

*There was no statistical difference between groups using Fisher's exact test regarding the migraine features analyzed.

Table 2. Evaluation of the static mechanical allodynia by the stimulation with von Frey hair filaments in the three groups of individuals: (I) individuals without headache, (II) patients with migraine and (III) patients with persistent posttraumatic headache (pPTH) after mild traumatic brain injury

Areas of stimulation	Control	Migraine	pPTH
Right V1	6.4 ± 0.7(A)	4.5±1.2(B) **	4.7±1.3(B) **
Left V1	5.1±1.4(A)	4.1±1.1(B) *	3.9±0.9(B) *
Right V2	6.0±1.0(A)	4.5±1.1(B) **	4.5±1.2(B) **
Left V2	5.0±1.4(A)	4.0±1.1(B) *	3.9±0.9(B) *
Right V3	5.8±1,211(A)	4.330±1,081(B) **	4.301±1,193(B) **
Left V3	5.2±1.4(A)	3.998±1,073(B) **	3.949±0,9475(B)**
Right C3	5.4±1.6(A)	4.225±1,666(B) **	4.091±1,058(B) **
Left C3	5.5±1.3(A)	4.117±1,031(B) **	3.962±0,9545(B) **
Right C8	5.2±1.4(A)	4.225±1,166(B) *	4.091±1,058(B) *
Left C8	5.4±1.4(A)	4.040±0,9111(B) *	3.871±0,9766(B) *
Right L3	5.0±1.4(A)	4.120±1.073(B) *	3.981±0.869(B) *
Left L3	5.333±1.357(A)	4.105±0.9120(B) *	4.053±0.9225(B) *

(A) and (B) represent the equality or the statistical difference among each group. If the letters in parentheses are different, the significant difference among the groups exists. V1; first division of trigeminal nerve, V2; second division of trigeminal nerve, V3; third division of trigeminal nerve; C3, posterior cervical area; C8, distal part of the forearms; L3, lower part of the thighs. The Kruskal-Wallis test was used with p<0.05* or p<0.001** and expresses data in (mean± standard deviation).

Table 3. Evaluation of the thermal allodynia to heat or cold stimuli in the three groups of individuals: (I) control, (II) patients with migraine and (III) patients with persistent posttraumatic headache (pPTH) after mild traumatic brain headache

Areas of stimulation	Control n	%	Migraine n	%	pPTH n	%		Control n	%	Migraine n	%	pPTH n	%
	to heat stimulus							to cold stimulus					
Right V1	2/25	8	10/29 *	34%	8/19*	42		1/25	4	8/29*	27	9/19 *	47
Left V1	2/25	8	13/29 *	44%	4/19*	21		1/25	4	8/29*	27	6/19 *	31
Right V2	1/25	4	12/29 *	41%	8/19*	42		0/25	0	7/29*	24	9/19 *	47
Left V2	1/25	4	12/29 *	41%	4/19*	21		0/25	0	9/29*	31	5/19 *	26
Right V3	1/25	4	10/29 *	34%	8/19*	42		0/25	0	6/29*	20	9/19 *	47
Left V3	1/25	4	13/29 *	44%	6/19*	31		0/25	0	8/29*	27	6/19 *	31
Right C3	1/25	4	10/29 *	34%	7/19*	36		0/25	0	5/29*	17	4/19 *	21
Left C3	1/25	4	9/29*	31%	3/19*	16		0/25	0	4/29	13	2/19	10
Right C8	1/25	4	8/29*	27%	5/19*	26		0/25	0	3/29*	10	5/19 *	26
Left C8	1/25	4	10/29 *	34%	3/19*	16		0/25	0	4/29	13	3/19	16
Right L3	1/25	4	9/29*	31%	5/19*	26		0/25	0	4/29*	13	5/19 *	26
Left L3	1/25	4	10/29 *	34%	3/19*	16		0/25	0	5/29	17	3/19	16

V1; first division of trigeminal nerve, V2; second division of trigeminal nerve, V3; third division of trigeminal nerve, C3; posterior cervical area, C8; distal part of the forearms, L3; lower part of the thighs.

Chi-square test was used with p<0.05.

Table 4. Evaluation of allodynia using the questionnaire reported by Guy et al. (2010).

Places of stimulation	Control		Migraine		pPTH	
	n	%	n	%	n	%
Earrings	1/25	4	10/29*	34	6/19 *	31
Combing the hair	2/25	8	21/29**	72	17/19 **	89
Ponytail	3/25	12	21/29**	72	8/19 **	42
Wearing glasses	1/25	4	15/29**	51	6/19 **	31
Necklace	1/25	4	16/29**	56	6/19 **	31
Wearing a hat	1/25	4	23/29**	79	10/19 **	52
Washing the face	1/25	4	8/29*	27	7/19 *	36
Put the head on the pillow	1/25	4	18/29**	62	12/19 **	63
Heat exposure	3/25	12	17/29**	58	13/19 **	68
Cold exposure	0/25	0	4/29*	13	7/19 *	36
Covering with a blanket	1/25	4	6/29*	20	6/19 *	31
Wearing a ring	1/25	4	11/29*	37	5/19 *	26
Taking a shower	1/25	4	6/29*	20	6/19 *	31
Wearing tight clothes	1/25	4	23/29**	79	12/19 **	63
Objects in the wrist	1/25	4	17/29**	58	8/19 **	42

Fisher's exact test was used with p<0.05* or p<0.001** and expresses data in frequency and percentage). It was compared the without headache group with migraine or pPTH groups.

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