

Serum levels of adiponectin, CCL3/MIP-1 α , and CCL5/RANTES discriminate migraine from tension-type headache patients

Níveis séricos de adiponectina, CCL3/MIP-1 α e CCL5/RANTES discriminam pacientes com migrânea e cefaleia do tipo tensional

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ABSTRACT

Objectives: Inflammatory molecules and neurotrophic factors are implicated in pain modulation; however, their role in primary headaches is not yet clear. The aim of this study was to compare the levels of serum biomarkers in migraine and tension-type headache. **Methods:** This was a cross-sectional study. We measured serum levels of adiponectin, chemokines, and neurotrophic factors in patients with migraine and tension-type headache. Depression and anxiety symptoms, headache impact and frequency, and allodynia were recorded. **Results:** We included sixty-eight patients with migraine and forty-eight with tension-type headache. Cutaneous allodynia ($p = 0.035$), CCL3/MIP-1 α ($p = 0.041$), CCL5/RANTES ($p = 0.013$), and ADP ($p = 0.017$) were significantly higher in migraine than in tension-type headache. The differences occurred independently of anxiety and depressive symptoms, frequency and impact of headache, and the presence of pain. **Conclusions:** This study showed higher CCL3/MIP-1 α , CCL5/RANTES, and ADP levels in migraine in comparison with tension-type headache. Our findings suggest distinctive roles of these molecules in the pathophysiology of these primary headaches.

Keywords: migraine disorders; tension-type headache; adiponectin; chemokines; neurotrophic factors.

RESUMO

Objetivos: Moléculas inflamatórias e fatores neurotróficos estão implicados na modulação dolorosa, contudo, seu papel nas cefaleias primárias não é claro. O objetivo do presente estudo foi comparar níveis de biomarcadores séricos na migrânea e cefaleia do tipo tensional. **Métodos:** Este foi um estudo transversal, no qual foram avaliados níveis de adiponectina, quimiocinas e fatores neurotróficos em pacientes com migrânea e cefaleia do tipo tensional. Sintomas depressivos e ansiosos, o impacto e a frequência da cefaleia e alodínea foram registrados. **Resultados:** Foram incluídos 68 pacientes com migrânea e 48 pacientes com cefaleia do tipo tensional. A alodínea cutânea ($p = 0.035$), CCL3/MIP-1 α ($p = 0.041$), CCL5/RANTES ($p = 0.013$), e adiponectina ($p = 0.017$) foram maiores na migrânea, independentemente de sintomas depressivos e ansiosos, frequência e impacto da cefaleia. **Conclusões:** Níveis de CCL3/MIP-1 α , CCL5/RANTES e adiponectina foram maiores na migrânea do que na cefaleia do tipo tensional, sugerindo papéis distintos destas moléculas na fisiopatologia destas duas cefaleias primárias.

Palavras-chave: transtornos de enxaqueca; cefaleia do tipo tensional; adiponectina; quimiocinas; fatores neurotróficos.

Migraine and tension-type headache (TTH) are the most frequent primary headaches and their differentiation is based on strict clinical diagnostic criteria¹. Though different theories have been formulated to explain these disorders, their pathophysiology remains largely unknown.

Migraine is considered a neurovascular disorder with complex genetic background. Trigeminovascular system

activation with subsequent release of vasoactive neuropeptides has been proposed to explain migraine attacks², while central sensitization possibly plays a role in migraine chronification³. Conversely, TTH pathophysiology has been thought to be associated with both peripheral (increased myofascial pain sensitivity and peripheral sensitization of myofascial nociceptors) and central

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Conflict of interest: There is no conflict of interest to declare.

Support: This work was funded by CNPq and Fapemig, Brazil.

Received 16 September 2015 ; Accepted 25 May 2016.

(sensitization of second-order neurons and somatosensory cortex) mechanisms⁴.

Adiponectin (ADP) is a cytokine exclusively secreted by adipocytes that participates in the regulation of glucose and lipids metabolism, and also displays anti-inflammatory properties. Its plasmatic levels are reduced in obesity, insulin resistance, and metabolic syndrome; while its levels were shown to be raised in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease⁵. Chemokines (*i.e.* chemoattractant cytokine) are a family of small proteins that mediate the migration of leukocytes into inflammatory sites. The family is composed of about 50 related molecules divided into four subfamilies according to the number and spacing of cysteine residues⁶. Neurotrophic factors are polypeptides responsible for neuron survival, axon growth, and the expression of essential proteins for neuronal functioning. Neurotrophic factors are classified in different families, such as the glial cell line-derived neurotrophic factor (GDNF) family and the neurotrophin super-family that includes the brain-derived neurotrophic factor (BDNF), the nerve-growth factor (NGF), the neurotrophin-3 (NT-3), and the neurotrophin-4/5 (NT-4/5)⁷.

Some studies have proposed that pro- and anti-inflammatory molecules may play a role in the pathophysiology of migraine^{8,9,10} and TTH^{11,12,13}. The association between neurotrophic factors and migraine^{14,15,16}, and neurotrophic factors and TTH^{17,18} has also been investigated. As different pathophysiological mechanisms have been proposed for migraine and TTH, it is possible that the profile of these molecules may be distinct in these two disorders. No previous study has compared these molecules levels in patients with migraine and TTH.

The aim of the current study was to compare ADP, chemokines, and neurotrophic factors serum levels between migraine and TTH patients.

METHOD

We have recently compared ADP, chemokines, and neurotrophic factors between patients with migraine and controls^{9,10,14,16}, and between patients with TTH and controls^{12,13,18}. In the current study we aimed to compare these molecules levels between a group of patients with migraine and a group of patients with TTH.

This was a cross section study including sixty-eight patients with migraine and forty-eight patients with TTH prospectively enrolled from the headache outpatient clinic of the Santa Casa de Misericórdia Hospital, Vitória, Brazil at their first visit to the clinic. All diagnoses were in accordance with the International Classification on Headache Disorders – 2nd edition¹⁹. The minimal age for the inclusion of patients was 18 years-old. Patients with inflammatory, infectious, autoimmune, and neoplastic

diseases were not included in the study, as well as pregnant women and people in use of corticosteroids or immunosuppressant drugs. Demographic (age, ethnicity, and marital status) and headache (time of disease, frequency of attacks in the last month) data were recorded. The Beck Anxiety Inventory (BAI) was used to evaluate the severity of anxiety symptoms, while the Beck Depression Inventory (BDI) the severity of depressive symptoms. Body mass index (BMI), Headache impact test (HIT-6)²⁰ and allodynia symptom checklist (ASC), with cutaneous allodynia defined as ASC score ≥ 3 ²¹, were recorded from all subjects. This study received full approval by the Ethics Committee on Research of the “Escola Superior de Ciências da Santa Casa de Vitória”, Vitória, Brazil, and informed consent was obtained from each patient.

Whole blood was collected from all the participants, and serum was obtained after centrifugation and kept at -80C until analysis. For analysis we used the same procedures previously described^{9,10,12,13,14,16,18}. The assay conditions were controlled, standardized and pre-optimized to ensure repeatability and reproducibility. Analyses were blinded to clinical diagnosis.

Statistical analysis

The data were analyzed with the SPSS, version 15.0 for Windows. The confidence interval was of 95% and the significance level was set at $P < 0.05$. Verification of normal distribution of data was performed using the Kolmogorov-Smirnov test. Mann-Whitney was used for the medians comparisons of continuous data. Categorical characteristics were compared using chi-square analyses. Binary logistic regression analysis with elimination of nonsignificant covariates was performed with the diagnosis of migraine and TTH as the dependent variables.

RESULTS

Migraine and TTH patients did not differ in age, sex, ethnicity, BMI, marital status, time of disease, and age at headache onset (Table 1). Migraine patients showed more depressive and anxiety symptoms than TTH patients as assessed by BDI and BAI, respectively (Table 1). Patients with migraine had higher number of headache days per month, percentage of chronic headache (> 15 headache days per month), headache impact, and percentage of cutaneous allodynia (Table 1). The percentages of migraine and TTH patients with headache at the time of the assessment were not significantly different.

In univariate analysis, a significant difference in CCL11 (chemokine ligand 11)/eotaxin ($P=0.043$), CCL24 (chemokine ligand 24)/Eotaxin2 ($p = 0.003$), CXCL10/IP-10 (chemokine ligand 10/interferon gamma inducible protein-10) ($p < 0.001$), CCL2/MCP-1 (chemokine ligand 2/ monocyte

chemoattractant protein-1) ($p = 0.034$), CCL3/MIP-1 α (chemokine ligand 3/ macrophage inflammatory protein-1 alpha) ($p = 0.001$), CCL5/RANTES (chemokine ligand 5/regulated on activation, normal T cell expressed and secreted) ($p = 0.002$), and ADP ($p < 0.001$) serum levels were found between migraine and TTH (Table 2). No significant differences were found in neurotrophic factors levels between migraine and TTH. After adjusted analysis including ASC score, depression and anxiety scores, ADP, chemokines, and neurotrophic factors levels as covariates and migraine and TTH as dependent variables we found

that the only variables independently associated with the diagnosis (headache x TTH) were cutaneous allodynia ($P = 0.035$), CCL3/MIP 1 α ($p = 0.041$), CCL5/RANTES ($p = 0.013$), and ADP ($p = 0.017$) (Figure).

DISCUSSION

The current study showed that higher serum levels of CCL3/MIP-1 α , CCL5/RANTES, and ADP discriminate migraine patients from TTH patients.

Table 1. Demographic and clinical characteristics in patients with migraine and tension-type headache.

Variable	Migraine	Tension-Type Headache	p
Age (years)	44 (18-64)	43.5 (19-76)	0.730
Gender			
Male (%)	5 (4.3)	5 (4.3)	
Female (%)	63 (54.3)	43 (37.1)	0.563
Marital status			
Married (%)	34 (29.3)	15 (12.9)	
Single (%)	34 (29.3)	33 (28.5)	0.440
Ethnic distribution			
White	32 (27.6)	20 (17.2)	
Brown	30 (25.9)	23 (19.8)	0.841
Black	6 (5.2)	5 (4.3)	
BMI: body mass index	25.07 (19.4-32)	25.6 (18.75-45.72)	0.518
Time of disease (years)	20 (3-45)	13 (1-51)	0.055
Age of onset (years)	16 (7-58)	17 (7-58)	0.780
BDI: beck depression inventory	11 (0-41)	8 (0-54)	0.010*
BAI: beck anxiety inventory	9 (1-54)	7.5 (0-22)	0.022*
HIT-6: headache impact test	63 (36-76)	51.5 (36-70)	< 0.001*
Number of headache days per moth	7 (1-15)	3 (1-30)	< 0.001*
Chronic headache (%)	23 (33.8)	5 (10.4)	0.004**
Headache at the time of clinical assessment (%)	19 (27.9)	14 (29.2)	0.885
Cutaneous allodynia (%)	36 (52.9)	7 (14.6)	< 0.001**

* Mann-Whitney test; **Chi-square analyses.

Table 2. Adiponectin, chemokines, amd neurotrophic factors levels in patients with migraine and tension-type headache.

Variable	Migraine	Tension-Type Headache	p
CCL11/eotaxin (pg/mL)	777.7 (300.5-11663.3)	819.05 (163.84-12460)	0.043*
CCL24/Eotaxin2 (pg/mL)	2507.7 (461.2-8192.5)	2340.7 (501.6-8360.5)	0.003*
CXCL8/IL-8 (pg/mL)	457.7 (276.25-653.7)	412.78 (123.4-1756.3)	0.660
CXCL10/IP-10 (pg/mL)	295.7 (198-2180.2)	2674 (133-5037.6)	< 0.001*
CCL2/MCP-1 (pg/mL)	2479.1 (976.1-8202.2)	1812.4 (669.3-31056.8)	0.034*
CCL3/MIP-1 α (pg/mL)	341.8 (13.5-15719.4)	183.1 (13.5-15592.8)	0.001*
CCL5/RANTES (pg/mL)	21643.4 (1765.1-28790.7)	20052.4 (0-40027.6)	0.002*
GDNF (pg/mL)	68.2 (6.5-4730.9)	80.4 (5.1-7311.8)	0.850
NGF (pg/mL)	64.4 (15.8-217.2)	77.82 (0-4737.4)	0.730
NT-3 (pg/mL)	45.7 (8.4-4835.3)	82.3 (7.9-6141.6)	0.346
NT-4/5 (pg/mL)	34.7 (15.3-3078.5)	32.2 (0-15194.1)	0.187
BDNF (pg/mL)	6476.9 (3854.5-9305.9)	6532.9 (4083.4-11584.6)	0.850
Adiponectin (pg/mL)	42075.9 (24915.3-48045.9)	31150 (20421.2-69227.6)	< 0.001*

CCL2/MCP-1: chemokine ligand 2/ monocyte chemoattractant protein-1; CCL3/MIP-1 α : chemokine ligand 3/ macrophage inflammatory protein-1 alpha; CCL5/RANTES: chemokine ligand 5/regulated on activation, normal T cell expressed and secreted; CXCL8/IL-8: chemokine ligand 8/interleukin-8; CXCL10/IP-10: chemokine ligand 10/interferon gamma inducible protein-10; GDNF: Glial cell line-derived neurotrophic factor; NGF: Nerve-growth factor; NT: neurotrophin-3 and neurotrophin-4/5.

*Mann-Whitney test.

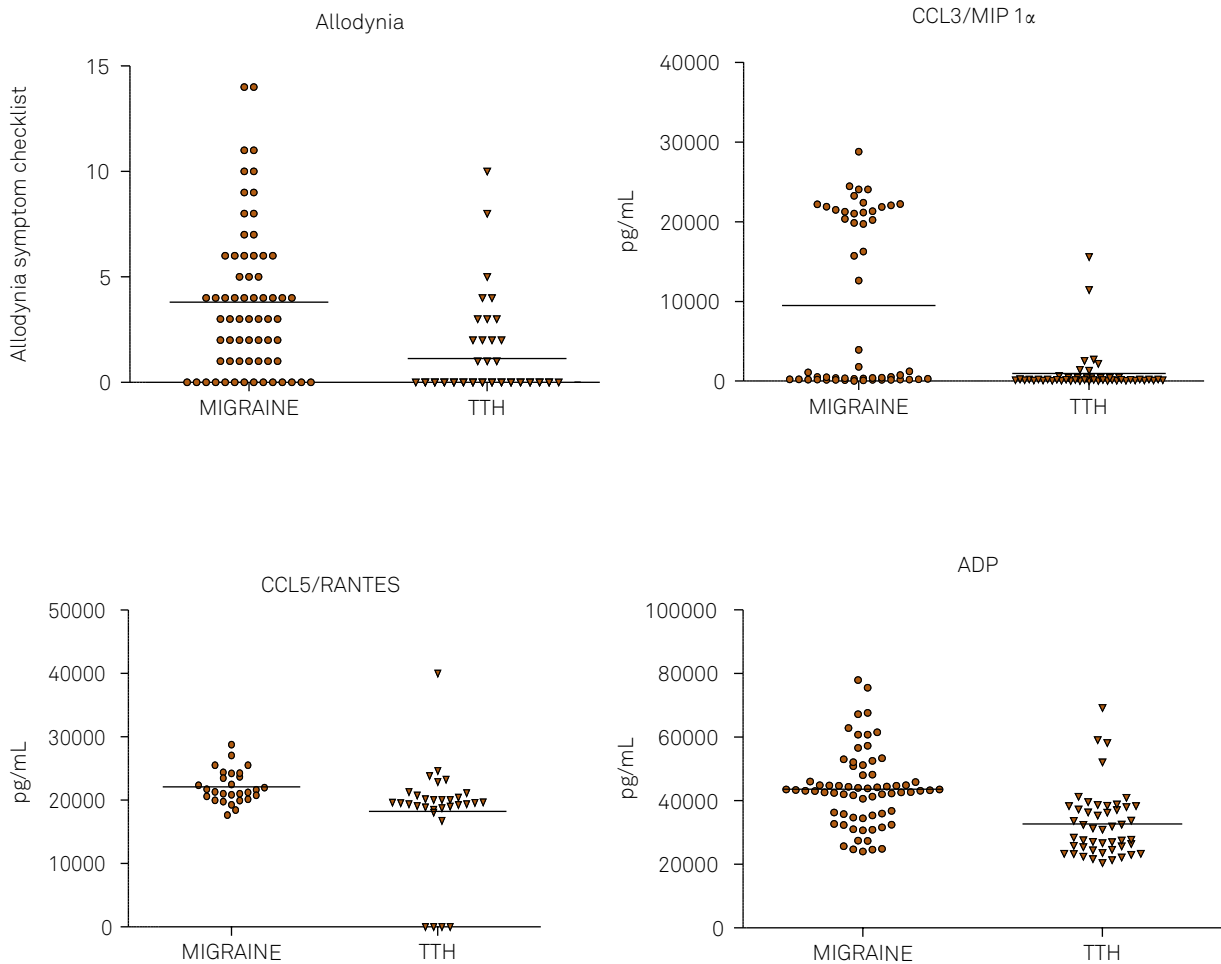


Figure. Allodynia, CCL3/MIP-1 α (chemokine ligand 3/ macrophage inflammatory protein-1 alpha), CCL5/RANTES (chemokine ligand 5/regulated on activation, normal T cell expressed and secreted), and adiponectin in migraine and tension-type headache patients. Differences in allodynia symptom checklist (A) and in plasma levels of CCL3/MIP-1 α (B), CCL5/RANTES (C), and adiponectin (D) between patients with migraine and tension-type headache (TTH).

CCL-3/MIP-1 α is a pro-inflammatory chemokine that participates in acute and chronic inflammatory responses by recruiting T-cells, monocytes, dendritic, and NK cells, playing an important role in the pathogenesis of many inflammatory conditions²². CCL-3/MIP-1 α also acts as a mediator of chronic pain²³. We have previously shown that CCL-3/MIP-1 α levels were higher in migraine patients than in subjects without any type of headache disorder¹⁰, but CCL-3/MIP-1 α levels in migraine have not been compared with other headache disorders yet.

CCL5/RANTES is a protein that is chemotactic for T-cells and eosinophils, among other leukocytes²⁴. This molecule is also involved in sensory regulation and neuropathic pain²³. CCL5/RANTES has been previously shown to be higher during migraine attacks²⁵, but in the present study this molecule was higher in migraine regardless of presence of pain.

The higher ADP levels in migraine found in the present study are in agreement with some previous studies^{9,10}, although discrepant findings have also been reported²⁶.

The fact that these three molecules were increased in migraine compared with TTH strengthens the hypothesis that

inflammatory mechanisms are involved in the pathophysiology of migraine. This finding also supports that different pathophysiological processes underlie these two disorders. It is tempting to speculate that inflammatory molecules may exert a stimulatory effect on the trigeminal vascular system thus enhancing the susceptibility to migraine attacks²⁷. Alternatively, these molecules played a role in sensory regulation and sensitization. Our findings are compatible with the latter hypothesis since migraine patients had significantly more cutaneous allodynia, a marker of central sensitization, than patients with TTH²⁶. It is possible that the increased production of these molecules affects sensory regulation promoting central sensitization that occurs to a greater extent in migraine than in TTH.

Patients with anxiety and depressive symptoms have higher levels of chemokines^{28,29} and ADP³⁰. Considering that migraine patients had more depressive and anxiety symptoms than patients with TTH, this could potentially explain the observed elevated levels of CCL-3/MIP-1, CCL5/RANTES, and ADP in migraine. Nevertheless this hypothesis seems

unlikely since the results persisted after adjusted analysis with anxiety and depression scores as covariates, suggesting that the higher levels of CCL-3/MIP-1, CCL5/RANTES, and ADP in migraine were not due to the presence of psychiatric comorbidities. It is also unlikely that the found difference was the result of increased frequency and impact of headache in patients with migraine in comparison with TTH.

The limitations of the present study include its cross-sectional design, precluding the establishment of causal relationships. Also, we found only a modest difference between ADP and chemokine levels between migraine and TTH with a considerable overlap between these two populations. This undermines the potential role of these molecules as biomarkers of migraine diagnosis. Therefore, larger and prospective studies are still needed to investigate their role

as biomarkers. As strengthens of the study it must be mentioned the number of subjects enrolled and the several serum biomarkers measured.

In conclusion, our results suggest that the inflammatory process is involved in the pathophysiology of migraine. The different profile of inflammatory markers can contribute to a better understanding of the pathophysiological boundaries between migraine and TTH. A better knowledge on the molecules involved in primary headache pathogenesis may tailor the development of new and more effective pharmacological strategies for the treatment of these disorders.

Acknowledgments

We gratefully acknowledge the contribution of Cassio Lacerda and Tarnara Camprostrini in data collection.

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