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Research article

Migraine is associated with altered levels of neurotrophins

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HIGHLIGHTS

- Patients with episodic and chronic migraine showed higher NT4/5 levels than control individuals.
- Chronic migraine was associated with lower levels of BDNF.
- Our findings suggest that NT4/5 and BDNF are involved in migraine pathogenesis.

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ABSTRACT

Neurotrophic factors have been implicated in hyperalgesia and peripheral levels of these molecules were altered in behavioral and neurological disorders. The objectives of this study were to assess neurotrophic factors levels in migraine patients in comparison with controls, and to investigate whether there was any association between them and clinical parameters. This was a cross-sectional study. We measured serum levels of neurotrophin family members – nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 and 4/5 (NT3 and NT4/5) – and glial cell line-derived factor (GDNF) in patients suffering from migraine and matched controls. One hundred forty-one people were enrolled in this study, seventy-one were migraine patients and seventy were controls. Migraine patients showed more depressive and anxiety symptoms than control individuals as assessed, respectively, by the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory. Chronic and episodic migraine patients showed higher NT4/5 levels than control individuals ($P = 0.001$). Patients with chronic migraine had lower levels of BDNF that were not influenced by the presence of depressive symptoms ($P = 0.02$). This is the first report to evaluate NT3 and NT-4/5 levels in migraine patients. Our findings suggest a possible role of neurotrophic factors in migraine pathophysiology.

1. Introduction

Migraine is a high prevalent primary headache [1]. The pathophysiological mechanisms of migraine are complex and not fully clarified yet. It has been proposed that during migraine attacks there is activation of the trigeminovascular system and the subsequent release of vasoactive neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P [2]. The transient receptor potential vanilloid receptor-1 (TRPV1) is a pain receptor channel. The activation of TRVP1 induces the release of CGRP and substance P leading to pain; however, the sensitivity of TRPV1 to painful stimuli is not static and can be enhanced. Several chemical stimuli, including neurotrophic factors, can act on TRVP1 increasing its sensitivity to painful stimuli and therefore predisposing to hyperalgesia and allodynia [3].

Abbreviations: CGRP, calcitonin gene-related peptide; TRP1, transient receptor potential vanilloid receptor-1; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT3, neurotrophin 3; NT4/5, neurotrophin 4/5; GDNF, glial cell line-derived factor; HIT-6, headache impact test; ASC, allodynia symptom checklist; BAI, Beck anxiety inventory; BDI, Beck depression inventory.

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Neurotrophic factors play an important role in central nervous system functioning and development [4]. Previous studies demonstrated the involvement of neurotrophic factors in behavioral and neurological disorders, including Alzheimer's disease [5], bipolar disorder [6] and depression [7]. Akin to what was shown in neuropsychiatric disorders, levels of neurotrophic factors are also altered in diseases related to chronic pain, such as fibromyalgia [8]. Members of two neurotrophic factors families have been implicated in nociceptive process, including the neurotrophin family, composed of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT4/5), and a member of the transforming growth factor beta superfamily, glial cell line-derived factor (GDNF) [4]. It has been shown that such molecules – especially NGF, BDNF and GDNF – act on pain process through the regulation of TRPV1 expression and release of CGRP and substance P [9]. However, only few studies to date have been performed to establish the relationship between neurotrophic factors and migraine pathophysiology.

The aim of the current study was to compare peripheral neurotrophic factor levels between migraine patients and controls, and to evaluate whether there is any association between these molecules and clinical parameters in migraine. We hypothesized that: (i) there are changes in the serum levels of neurotrophic factors in patients with chronic or episodic migraine, and (ii) the serum levels of neurotrophic factors are associated with determined clinical parameters like allodynia and psychiatric comorbidity.

2. Methods

This was a cross-sectional study conducted from June to December 2011. This study was approved by the Ethics Committee on research of the "Escola Superior de Ciências of Santa Casa de Vitória", Vitória, Brazil. Migraine patients were recruited from outpatient headache clinic of the Santa Casa de Misericórdia Hospital, Vitória, Brazil during their first attendance. The diagnosis of migraine was done by a neurologist based on the International Classification on Headache Disorders–2nd edition [1]. According to this classification migraine was defined as headache attacks lasting 4–72 h with at least two of the following characteristics (unilateral location, pulsating quality, moderate or severe pain intensity, aggravation with routine physical activity), with nausea and/or vomiting or phonophobia and photophobia, and not attributed to another disorder. Episodic migraine was defined as migraine headache less than 15 days per month and chronic migraine was defined as migraine headache on 15 or more days per month in the absence of medication overuse. Control subjects were recruited through active search among healthy volunteers without history of primary headaches that were accompanying patients. Only adults were included in this study. People diagnosed with inflammatory, infectious, allergic, autoimmune, hepatic, neurodegenerative, and tumor diseases, as well as pregnant women and people in use of drugs action on the immune system were excluded from the study.

Demographic data (age, ethnicity, and marital status), headache characteristics (length of disease, frequency of attacks in the last month) were recorded. Headache impact test (HIT-6) [10] and allodynia symptom checklist (ASC) [11] were recorded from patients. Anxiety symptoms were evaluated with the Beck Anxiety Inventory (BAI) [12] and depressive symptoms with the Beck Depression Inventory (BDI) [13].

Blood sample was collected (8 ml) and serum obtained after centrifugation. The serum samples were kept at −80 °C until analysis. We measured the serum levels of BDNF, NGF, GDNF, NT3, and NT4/5 using a commercially available immunoassay enzyme-linked immunosorbent assay kit (R&D systems) according to the procedures provided by the manufacturer. All samples were assayed in duplicate, and analyses were blinded to clinical diagnosis. The detection limits were 5 pg/mL for BDNF and 10 pg/mL for NGF, GDNF, NT3, and NT4/5.

Table 1
Demographic and clinical characteristics in individuals with migraine and controls.

	Control ($n = 70$)	Migraine patients ($n = 71$)	P-value
Age (years)	44.5 ± 15.1	40.4 ± 14.6	N.S.[a]
Gender			
Female (%)	88.6	93.0	N.S.[b]
Male (%)	11.4	7.0	
Race			
White (%)	44.3	46.5	N.S.[b]
Black (%)	37.1	43.1	
Brown (%)	18.6	9.9	
Marital Status			
Married (%)	42.9	50.7	N.S.[b]
Single or widowed (%)	57.1	49.3	
BDI score	4.0 (4.2–.7.2)	13.0 (12.7–18.5)	<0.001[c]
BAI score	4.6 ± 4.3	15.4 ± 12.8	<0.001[a]

BAI = Beck Anxiety Inventory; BDI =Beck Depression Inventory; N.S. = non significant.
[a] T test.
[b] Chi-square test.
[c] Mann–Whitney.

Statistical analyzes were performed with SPSS, version 19.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to test normality. Mann–Whitney and Kruskal–Wallis tests were used for the median comparisons of continuous data. Demographic characteristics were compared using chi-square analyses. Pearson and Spearman coefficients were calculated for the variables relating to neurotrophic factors levels and others continuous variables. The analysis of covariance was performed through ANCOVA test. $P \leq 0.05$ was considered statistically significant.

3. Results

One hundred forty-one people were enrolled in this study, seventy-one were migraine patients and seventy were controls. Patients and controls did not differ in age, sex, ethnicity, BMI and marital status. Migraine patients showed more depressive and anxiety symptoms than control subjects as assessed by BDI and BAI, respectively (Table 1). Among patients with migraine forty-eight (67.6%) were classified as having episodic migraine, twenty-three (34.2%) as having chronic migraine, fifty-nine (83.1%) as migraine without and twelve (16.9%) as migraine with aura. The mean disease duration was 20.1 ± 13.6 years and HIT-6 score was 62.2 ± 8.2, indicating significant disease impact. The mean disease duration among patients with episodic migraine was 19.35 ± 12.76 years while in chronic migraine it was 21.7 ± 15.33 years ($P = 0.56$). Cutaneous allodynia (defined as ASC score ≥ 3) was present in 59.4% of individuals with migraine, and the mean score of allodynia obtained was 4 ± 3.6, indicating mild cutaneous allodynia.

When patients were stratified according to the frequency of migraine attacks, it was noticed that BDI scores were higher in patients with chronic migraine than in patients with episodic migraine (mean ± SD, 22.9 ± 10.1 and 12.1 ± 11.9, respectively; $P < 0.001$). Allodynia symptom measured by ASC and headache impact measured by HIT-6 did not show any difference between chronic and episodic migraine patients.

Fig. 1 shows the serum levels of neurotrophic factors in control individuals and patients with episodic or chronic migraine. No differences were found in serum levels of NGF, NT3 and GDNF among groups (Fig. 1a–c). Chronic and episodic migraine patients showed higher NT4/5 levels than control individuals (Fig. 1d). Chronic migraine patients showed lower serum levels of BDNF than patients