Association between migraine, constipation and lactose intolerance in adults patients

Associação entre enxaqueca, constipação intestinal e intolerância à lactose em pacientes adultos

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ABSTRACT

BACKGROUND AND OBJECTIVES: Considering the bidirectional connection between intestine and brain, the present study examined the association between migraine, lactose intolerance, and intestinal constipation in patients with status migrainosus.
METHODS: This is a cross-sectional retrospective study that included 97 patients aged 20 years or older. The impact of pain was assessed by the Migraine Disability Assessment and the Headache Impact Test-6 questionnaires. The pain intensity was measured by the visual analog scale. Chi-square and Student-t tests were used for the statistical analysis.
RESULTS: The sample consisted of 88.7% women, 56.8% overweight, 76.3% sedentary, 32% constipated and 23.7% lactose intolerant. Higher pain intensity (8.9±1.3) and impact pain mean was assessed by the Headache Impact Test-6 (67.6±5.3) and the Migraine Disability Assessment (36.7±26.3) in constipated patients compared to those without constipation. Lactose-intolerant patients presented higher migraine mean time (19.9±14.2) compared to lactose tolerant patients. Constipated and lactose intolerant patients presented higher prevalence of overweight (58.1 and 65.2%) and abdominal obesity (70.0 and 68.2%) compared to non-constipated and lactose tolerant patients, respectively.
CONCLUSION: Although were observed in the evaluated sample a considerable prevalence of constipation and lactose intolerance, higher mean scores in the questionnaires used for pain impact and intensity in constipated patients and longer migraine diagnosis time in those with lactose-intolerance, there was no statistical significance in the association between migraine and these two gastrointestinal disorders.

Keywords: Constipation, Dysbiosis, Headache, Lactose intolerance, Migraine disorders.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Ao considerar a conexão bidirecional entre intestino e cérebro, o presente estudo avaliou a associação entre enxaqueca, intolerância à lactose e constipação intestinal em pacientes em estado migranoso.
MÉTODOS: Trata-se de um estudo transversal e retrospectivo que incluiu 97 pacientes com idade igual ou superior a 20 anos. O impacto da dor foi avaliado pelos questionários: *Migraine Disability Assessment* e *Headache Impact Test*-6. A intensidade da dor foi avaliada pela escala analógica visual. Os testes Qui-quadrado e *Student-t* foram utilizados para análise estatística.
RESULTADOS: A amostra foi composta por 88,7% de mulheres, 56,8% com excesso de peso, 76,3% sedentários, 32% constipados e 23,7% intolerantes à lactose. Os constipados apresentaram maiores médias de impacto da dor pelo *Headache Impact Test*-6 (67,6±5,3) e pelo *Migraine Disability Assessment* (36,7±26,3) e intensidade da dor (8,9±1,3) do que os não constipados. Os pacientes intolerantes à lactose apresentaram maior média de tempo de enxaqueca (19,9±14,2) em relação aos tolerantes à lactose. Os pacientes constipados apresentaram maiores prevalências de excesso de peso (58,1 e 65,2%) e obesidade abdominal (70,0 e 68,2%) e intolerantes em relação aos sem constipação intestinal e aos tolerantes à lactose, respectivamente.
CONCLUSÃO: Embora identificadas prevalências consideráveis de constipação intestinal e intolerância à lactose na amostra avaliada, além de maiores médias de pontuação nos questionários utilizados para impacto e intensidade da dor nos pacientes constipados e de maior tempo de diagnóstico da migrânea nos intolerantes à lactose, não houve significância estatística na associação entre enxaqueca e esses distúrbios gastrointestinais.

Descritores: Cefaleia, Constipação intestinal, Disbiose, Intolerância à lactose, Transtornos de enxaqueca.

INTRODUCTION

Migraine headaches are a form of primary and neurovascular headache. When a migraine lasts more than 72 hours, the patient enters the status migrainosus[1]. Although the prevalence of migraine worldwide is approximately 11.5% and 15% in Brazil, its pathophysiology is not fully understood and it has several etiological factors, such as stress, foods with allergenic potential, neuroendocrine imbalances and nutritional deficiencies[2].

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It has been suggested that the gastrointestinal tract (GIT) is the main system responsible for the body's metabolic control, the largest supplier of nutrients and possible metabolic controller of more distant organs. During gestation, brain and intestinal cells develop almost simultaneously in the central nervous system and in the enteric nervous system and remain connected throughout life via the vagus nerve by bidirectional communication, intestinal-cerebral axis and by different neurological, immunological and endocrine mechanisms. Just as the brain can modulate the functioning of the intestine, the reverse also occurs. From what is ingested, the intestine can influence brain function[3].

When in balance, the intestinal microbiota prevents potentially pathogenic microorganisms present in it from exerting their effects. On the other hand, under certain circumstances, when there is intestinal dysbiosis, the proliferation of pathogens may occur, with consequent bacterial infection, inflammation and chronic disease, suggesting then that many human diseases have their origin in the composition of unbalanced intestinal microbiota[4]. Therefore, some GIT disorders related to intestinal microbiota imbalance, such as intestinal constipation and lactose intolerance, have gained prominence in the association with migraine[5,6].

It seems that intestinal dysbiosis is involved in the pathogenesis of chronic intestinal constipation. Intestinal constipation, in turn, is related to stress, dehydration, reduced water intake and decreased appetite. In addition to these conditions, the effort to evacuate can cause headache. Therefore, all these factors contribute to exacerbate migraine crisis[7]. Similarly, the imbalance of the intestinal microbiota can lead to lactose intolerance. Thus, lactose intolerant individuals, as a consequence of the absorption of toxins produced by non-digestion of lactose that generate inflammation in the intestinal mucosa may present other non-intestinal symptoms such as muscle and joint pain, allergies, headache, among others, identifying a close relationship with migraine[8].

There are few studies describing the simultaneous presence of headaches and intestinal constipation or headaches and lactose intolerance.

Thus, the present study aimed to evaluate the association between migraine, lactose intolerance and intestinal constipation in individuals with a clinical diagnosis of migraine.

METHODS

A cross-sectional quantitative retrospective study with a secondary database and an analytical-descriptive approach, developed at a Pharmacy school clinic, belonging to the Departamento de Ciências da Vida (DCV), Universidade do Estado da Bahia (UNEB), Campus I, Salvador, Bahia. Data collection was performed in August 2019 from medical records of patients seen in the first consultation, during the period of April 2018 to August 2019. Patients aged 20 years or more with clinical diagnosis of migraine were included. Children, adolescents, pregnant women, and nursing mothers were not included.

Trained interns and nutritionists collected weight, height and waist circumference (WC) according to the techniques recommended by the literature[9]. Body mass index (BMI=weight/height^2)[10] of patients was calculated according to the World Health Organization (WHO) criteria[11]. The measurement of WC was analyzed based on cutoff points suggested by the WHO[12]. BMI and WC were used to determine the anthropometric state. Information regarding the diagnosis of lactose intolerance was collected by blood test. As for migraine, the clinical diagnosis was made by a neurologist based on the guidelines of the International Headache Society[13]. The time of diagnosis of the disease in years was collected.

The impact of pain was evaluated using the Migraine Disability Assessment (MIDAS) and Headache Impact Test-6 (HIT-6) validated questionnaires. MIDAS quantifies, in number of days lost during a three-month period, the disability generated by headache in social, productive and labor activities.

The score is subdivided into grades: grade I (zero to 5), little or no disability; grade II (6 to 10), light disability; grade III (11 to 20), moderate disability; and grade IV (≥21), intense disability[14], and the *Headache Impact Test*-6 (HIT-6), composed by six questions that evaluate pain, work and social activities losses, as well as cognitive and humor alterations.

The score is subdivided into ranges: <50 points - little or no impact; 50 to 55 points - some impact; 56 to 59 points - substantial impact; ≥60 points - very intense impact[15].

Pain intensity was assessed by the also validated visual analog scale (VAS), in which the patient analyzes the intensity of their symptoms on a scale of zero to 10, being zero to 2 mild pain; 3 to 7 moderate pain; 8 to 10 intense pain[16].

According to the Rome III Criteria[17], individuals who in the last three months had two or more of the following indicators were considered constipated: 1- Effort to defecate at least 25% of the time; 2- Hard or irregular stools in at least 25% of defecations; 3- Feeling of incomplete defecation in at least 25% of the time; 4- Feeling of anorectal obstruction in at least 25% of defecations; 5- Manual maneuvers to facilitate defecation in at least 25% of the time; 6- ≤3 defecations per week.

The present study was approved by the Research Ethics Committee involving human beings at UNEB under opinion number 3.255.056, on April 10, 2019.

Statistical analysis

The data was entered into the Microsoft Office EXCEL 2013 software spreadsheet. For the categorical variables absolute (n) and relative (%) frequencies were used. For quantitative variables, the results were presented as means and standard deviations, considering the normal distribution of data. Pearson's Chi-square test for categorical variables and the T-Test for difference in means for continuous variables were used to detect statistically significant differences with a value of p≤0.05. The statistical software SPSS Statistic 20.0.0 was used for data analysis.

RESULTS

The demographic, anthropometric and lifestyle characteristics of the population studied are presented in table 1. The majority of patients were females (88,7%) and sedentary (76,3%). The mean age for both sexes was 40±12.32 years, with variation between 20 and 65 years old. According to the BMI, 56.8% of the individuals were

overweight, 40% had adequate weight and 3.2% were underweight. The amount of patients that presented inadequate WC was 67%.

Table 1. Patients profile

Variables	n	%
Gender		
Female	86	88.7
Male	11	11.3
BMI		
Underweight	3	3.2
Adequate weight	38	40.0
Overweight	54	56.8
WC		
Adequate	31	33.0
Inadequate	63	67.0
Physical exercise		
Yes	23	23.7
No	74	76.3

BMI = body mass index; WC = waist circumference.

According to table 2, despite the GIT disorders, a prevalence of 32 and 23.7% of constipated and lactose intolerant patients was identified, respectively. According to BMI and WC, constipated patients presented a higher prevalence of overweight (58.1%) and inadequate WC (70.0%), respectively. According to the same criteria, lactose intolerant patients also presented a higher prevalence of overweight (65.2%) and inappropriate WC (68.2%). P values did not indicate statistical significance.

The impact, according to the HIT-6 and MIDAS questionnaires, the intensity (EAV) and the time of diagnosis of migraine according to the presence or not of intestinal constipation or lactose intolerance are presented in table 3.

In patients in status migrainosus, the mean impact of ≥60 points on the HIT-6 questionnaire and ≥21 days lasting crisis on the MIDAS questionnaire, as well as the mean pain intensity, 8.6±1.6, were high. The duration of migraine, 14.9±10.9 years, was also high. There was no statistically significant difference between constipated and non-constipated individuals regarding pain intensity, pain impact and time of migraine diagnosis, however the mean scores of the impact questionnaires (HIT-6, MIDAS) and intensity of migraine were higher in constipated individuals when compared to those without intestinal constipation. A tendency in the HIT-6 questionnaire to identify an association between the impact of pain in constipated patients when compared to those without intestinal constipation is highlighted (p=0.06). There was also no statistically significant difference between lactose intolerant and lactose tolerant individuals regarding the factors analyzed in relation to migraine, although the time of diagnosis of migraine was longer (19.9±14.2 years) in patients with lactose intolerance compared to those with tolerance (13.9±10.0 years).

DISCUSSION

The sample was composed mostly of women, which can be explained by the fact that migraine is more present in women, since women are 2.5 to 4 times more affected than men[2,18]. In addition, 40 to 50% of women have migraine attacks before, during or shortly after menstruation[19]. In a population study, 20-60% of women reported an association between migraine and menstruation[20].

The results showed a predominance in adults, similar to other studies on the incidence and prevalence of migraine[18,21,22]. When compared to other chronic conditions, due to the difficulty of performing daily activities because of pain, migraine patients have significant limitations in the quality of life in relation to the healthy population. According to the Global Burden of Disease (GBD) 2015, migraine has been classified as the third biggest specific cause of disability in the world for both sexes and for individuals under the age of 50[23]. The longer the headache lasts, the greater the substantial decrease in quality of life and the increase in depression and anxiety, since a significant impact on mental and physical health[24] is generated, which can be linked to the large number of sedentary people in the studied sample.

Overweight and inadequate WC were present in more than half of the sample. Obesity was reported as a risk factor for headaches in general, as well as for chronic migraine specifically[25]. The increase in body fat directly produces the induction of adipoki-

Table 2. Total and according to anthropometric variables of intestinal constipation and lactose intolerance prevalence

	Total	BMI		P value*	WC		P value*
		Not overweight	Overweight		Adequate	Inadequate	
	% (n)	% (n)	% (n)		% (n)	% (n)	
Intestinal constipation	32,0 (31)	41,9 (13)	58,1 (18)	0,86	30,0 (09)	70,0 (21)	0,67
Lactose intolerance	23,7 (23)	34,8 (08)	65,2 (15)	0,35	31,8 (07)	68,2 (15)	0,89

BMI = body mass index; WC = waist circumference; *Pearson's Chi-square test.

Table 3. Association between impact, intensity and time of diagnosis of migraine and gastrointestinal disorders of constipation and lactose intolerance

Variables	Total	Constipation		P value*	Lactose intolerant		P value**
		Yes	No		Yes	No	
HIT-6 (points) (n=82)	65.7±6.7	67.6±5.3	64.9±7.1	0.06	65.5±5.9	65.8±7.0	0.84
MIDAS (days) (n=41)	31.5±25.1	36.7±26.3	29.5±24.9	0.44	28.0±22.5	32.2±25.9	0.67
VAS (n=79)	8.6±1.6	8.9±1.3	8.4±1.7	0.14	8.4±1.7	8.6±1.7	0.63
Migraine time (years) (n=41)	14.9±10.9	14.2±10.5	15.4±11.4	0.71	19.9±14.2	13.9±10.0	0.32

Values in mean±SD; HIT-6 = Headache Impact Test-6; MIDAS = Migraine Disability Assessment; VAS= visual analog scale; * p value compared values of means between constipated and non-constipated groups using the t-test for independent samples; ** p value compared values of means between lactose intolerant and lactose tolerant groups using the t-test for independent samples.

nes and several pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF)α. Authors investigated elevated plasma levels of pro-inflammatory cytokines in patients with migraine. Thus, a significant relationship was found between migraine and several inflammatory diseases, including obesity[26].
In the first study of the general population that assessed the association between migraine and obesity using BMI, 7601 participants in the National Health and Nutrition Examination Survey (NHANES), aged between 20 and 85, were assessed, identifying that those with obesity had a 37% increase in the chance of having migraine compared to those with normal weight[27]. To date, no longitudinal study has evaluated the effect of weight gain on the frequency of migraine. However, a cross-sectional study has shown that the risk of migraine in women of reproductive age has increased substantially with the increase in the severity of obesity[28].
The present study estimated the prevalence of two gastrointestinal diseases, intestinal constipation and lactose intolerance, in patients with migraine, observing a prevalence of 32% of constipated patients and 23.7% of patients with lactose intolerance. Gastrointestinal disorders seem to be more frequent in patients with migraine than in the general population[5]. Migraine attack is characterized by a complex series of symptoms that include gastrointestinal adverse effects such as nausea, vomiting, intestinal constipation and abdominal pain[29].
In addition, individuals diagnosed with intestinal constipation and lactose intolerance had considerable prevalence of overweight and abdominal obesity, although there was no statistical correlation. These prevalences were higher in lactose intolerant and constipated patients when compared to the prevalences of the anthropometric state in the general sample. Thus, it is possible that overweight and abdominal obesity, in addition to being risk factors for migraine[25], also make individuals more predisposed to gastrointestinal disorders due to the inflammatory mechanisms generated by the excess of adipose tissue[26].
Intestinal dysbiosis is a common feature of the three studied diseases: migraine, intestinal constipation and lactose intolerance. The GIT is colonized by trillions of microorganisms collectively called intestinal microbiota. Its composition is essential for the maintenance of important functions such as intestinal homeostasis, peristalsis, intestinal mucosal integrity, protection against pathogens and activation of immune responses[30,31]. The imbalance of intestinal microbiota can generate intolerances and intestinal constipation, in addition to migraine. On the other hand, both migraine and gastrointestinal diseases increase the intestine's permeability, and therefore increase systemic inflammatory activity, creating a vicious cycle[32].
One study showed that in 29 patients the number of days suffering from migraine and associated symptoms – assessed by two questionnaires, MIDAS and Henry Ford Hospital Headache Disability Inventory (HDI) - were significantly reduced after 12 weeks of treatment with the use of a probiotic specially developed for the study[33]. In another study, 1020 patients with migraine were treated for 8 weeks with the probiotic. During the period, the number of days of pain reduced from 2 to 1.4 days per week, while the intensity of migraine decreased from 5.1 to 2.1 points (zero = no pain to 6 = very intense pain)[21]. Therefore, it is plausible that improvement in dysbiosis results in less inflammatory activity and, possibly, a reduction in the activation of the trigeminovascular system[3].
Regardless of the questionnaire, it was verified that the mean impact of migraine was high, as well as the mean intensity of pain. The time of diagnosis of migraine was also high. One study showed that the majority of patients suffered from migraine for a considerable period: 64% for ≥10 years, 20% for 5 to 10 years and 16% for <5 years[22], similar to the mean of years assessed in the present study. As for the impact of pain, another study showed intense disability with the application of the MIDAS questionnaire (≥21 points) for 40.4% of the sample[34]. In another work, the mean score found in the application of HIT-6 was 53.4±8.7, assessing a moderate disability[35], differently from what was found in the present study. However, similarly to the present research, in a study from the United Kingdom, the HIT-6 score was 64.9 (range of 48 to 78 points), corresponding to a severe impact[22]. The mean of 7.1±1.9 was highlighted with the VAS in a population of 51 patients with migraine, identifying a mean lower than that found in the sample of the present study[36].
Higher means were identified for all the parameters of migraine evaluated, except for the time of diagnosis of the disease, in individuals with constipation compared to those without intestinal constipation, although the results were not statistically significant. There was also a greater tendency of the HIT-6 questionnaire to identify an association between the impact of pain and intestinal constipation. A cross-sectional study evaluated the association between gastrointestinal disorders, migraine and tension headaches. The sample consisted of overweight and obese individuals aged between 18 and 60. Of the total sample, 11.5% were diagnosed with migraine and of these, 11% were classified as constipated according to the Rome III criteria. The multivariable logistic regression applied in the study demonstrated a significant association between intestinal constipation and migraine[37].
A study involving 96 children and adolescents with migraine showed that 25% also had intestinal constipation and that all of these constipated patients, after receiving treatment for intestinal constipation with lactulose, magnesium hydroxide or macrogol, showed an improvement in their status migrainosus, assessed by questionnaire[7], suggesting that intestinal constipation can trigger migraine or that the two diseases share a common pathophysiological mechanism[38].
As for the relationship between assessed migraine parameters and lactose intolerance, this study did not present consistent results, observing only the trend towards a longer diagnosis of migraine in lactose intolerant patients compared to lactose tolerant patients. A prospective study investigated whether migraine patients had evidence of food intolerance - identified by the IgG test, and whether after the withdrawal of food causing intolerance there was an improvement in migraine. Sixty-one patients participated in the study and of these, 39 completed the 2 months investigation. Of the sample, 85.2% were lactose intolerant and almost all patients had multiple food intolerances. It has been demonstrated that migraine attacks can be related to IgG mediated food intolerances and that changing the diet by eliminating specific foods can be a potentially effective treatment for

migraine[22]. It is known that undigested food particles and bacterial metabolites can enter the bloodstream as a result of increased intestinal permeability, and these bacterial endotoxins can act on the trigeminovascular system to trigger migraine attacks[39].

In the present study, the sample of patients with migraine was constituted, in its majority, of sedentary, overweight and abdominally obese female individuals. Considerable prevalence of intestinal constipation and lactose intolerance were found, in addition to significant prevalence of overweight and abdominal obesity in individuals diagnosed with these two gastrointestinal disorders, highlighting that excess fat tissue, in addition to being a risk factor for migraine, also makes individuals more predisposed to GIT disorders. There was a prevalence of disabling impact, regardless of the indicator, intense pain and a large migraine diagnosis time.

Although higher averages were identified for the intensity and impact of migraine pain in constipated individuals compared to those without intestinal constipation, in addition to a longer diagnosis time in individuals with lactose intolerance when compared to those who are tolerant, there was no statistical association between migraine, intestinal constipation and lactose intolerance. This is a cross-sectional study, so there are limitations regarding the identification of cause and effect relationships, and it should also be considered that if the sample was larger, inferential analyses of statistical association would be possible. Furthermore, there are not enough studies in order to compare the association of migraine and the analyzed GIT disorders. However, these limitations do not compromise the quality of this study or the observations found. Further studies are needed to elucidate the relationship between migraine and GIT disorders, contributing with new therapeutics for migraine, as well as helping to prevent it.

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