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INFLAMMATORY MARKERS AND SERUM MAGNESIUM IN PATIENTS WITH MIGRAINE - A CASE-CONTROL STUDY

MARCADORES INFLAMATÓRIOS E MAGNÉSIO SÉRICOS EM PACIENTES COM MIGRÂNEA - UM ESTUDO CASO-CONTROLE

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ABSTRACT: **Introduction**: Migraine is a ubiquitous condition. A higher inflammatory level agents trigger trigeminal nerves activation and neuropeptides release and cause neuroinflammation. Magnesium deficiency plays a role stimulating spreading cortical depression. This study aims to determine the correlation among inflammatory-markers, magnesium and migraine. **Methods**: Prospective, case-control, quantitative. Divided into 2 groups: Case and Control. Included healthy people between 18 to 60 years. A form with anthropometric, socioeconomic and clinical data and Magnesium and inflammatory-markers serum were filled. Analyzed using SPSS. **Results**: Groups were significantly different in migraine family history and insomnia. Magnesium [Control:1.97±0.16, Case:2.06±0.40; p:0.379], C-Reactive Protein [Control:4.40±3.66, case:3.17±4.61, p:0.088], ESR [Control:7.34±6.71, Case:16.16±13,50, p:<0.00001], LDL-c [Control:98.49±31.33, Case:116.65±38,55, p:0,035], HDL-c [Control:61.45±19,11, Case:50.36±19,04, p:0,005], Ferritin [Control:63.37±64.93, Case:105.34±213,11, p:0,315], Fibrinogen [Control:279.79±93,12, Case:378.32±131.82, p:0,017]. **Conclusion**: There was a significant correlation among migraine, insomnia and family inheritance. The ratio between migraine and inflammatory-markers was significant for LDL-c, ESR, fibrinogen and HDL-c. In magnesium, no significant differences.

KEYWORDS: Neurogenic Inflammation. Magnesium. Migraine.

RESUMO: **Introdução**: Migrânea é uma condição ubíqua. Agentes inflamatórios em níveis mais elevados desencadeiam a ativação dos nervos trigêmeos e a liberação de neuropeptídeos e causam neuroinflamação. Deficiência de magnésio desempenha papel estimulando a propagação da depressão cortical. Este estudo tem como objetivo determinar a correlação entre marcadores inflamatórios, magnésio e migrânea. **Métodos**: Estudo Prospectivo, caso-controle, quantitativo. Dividido em 2 grupos: Caso e Controle. Incluiu pessoas saudáveis entre 18 e 60 anos. Preencheu-se um formulário com dados antropométricos, socioeconômicos e clínicos e níveis de magnésio e marcadores inflamatórios. Analisado usando SPSS. **Resultados**: Grupos foram significativamente diferentes na história familiar e insônia. Magnésio[Controle:1,97±0,16,Caso:2,06±0,40;p:0,379], Proteína-C Reativa [Controle:4,40±3,66,caso:3,17±4,61,p:0,088], VHS[Controle:7,34±6,71, Caso:16,16±13,50, p:<0,00001], LDL-c [Controle:98,49±31,33, Caso:116,65±38,55, p:0,035], HDL-c[Controle:61,45±19,11, Caso:50,36±19,04, p:0,005], Ferritina[Controle:63,37±64,93, Caso:105,34±213,11, p:0,315], Fibrinogênio[Controle:279,79±93,12, Caso:378,32±131,82, p:0,017]. **Conclusão**: Houve correlação significativa entre migrânea, insônia e herança familiar. A relação entre migrânea e marcadores inflamatórios foi significativa para LDL-c, VHS, fibrinogênio e HDL-c. No magnésio, não houve diferenças.

PALAVRAS-CHAVE: Inflamação Neurogênica. Magnésio. Migrânea.

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INTRODUCTION

Migraine is a ubiquitous neurological condition and affect approximately 1 billion people worldwide, mainly females. It is the second leading cause of absenteeism and it´s responsible for more absenteeism than all others neurological disorders. Diagnosis is based on clinical criteria provided by the International Classification of Headache Disorders 3rd edition (ICHD-3).[1]

Recurrent headache attacks of moderate to severe intensity lasting 4 to 72 hours are the clinical characteristics suggestive of migraine. The diagnosis should be considered if a typical headache attack is unilateral, pulsatile and aggravated by physical activity, symptoms commonly accompanied by nausea, vomiting, photophobia and phonophobia. Some people report that migraine is preceded by an aura, which is characterized by reversible focal neurological symptoms, most commonly visual or sensory disturbances.[1]

Migraine is a complex disorder. Multiple theories and precipitating factors have been implicated in its genesis, such as obesity, vascular factors, neurogenic factors and trigeminal activity. Recent findings have focused on the neurogenic inflammation theory, which emphasizes the effect of the release of inflammatory factors on the activation and sensitization of peripheral nociceptors. It is also proposed that a higher level of these inflammatory agents could provoke the activation of trigeminal nerves and the release of vasoactive neuropeptides and, consequently, contribute to inflammation.[2]

Neurogenic inflammation around trigeminal dural afferents plays an important role in migraine attacks generation, while plasma protein extravasation and vasodilation play potent roles in neurogenic inflammation as well as in its generation. It has been suggested that activation of trigeminal sensory fibres leads to neurogenic inflammation within the meningeal vasculature mediated by the release of neuropeptides from trigeminal sensory fibres and is characterized by plasma protein extravasation, vasodilation and mast cell degranulation and is directly implicated in the pathogenesis of migraine. However, studies on post-capillary leak blockade have shown that receptor-mediated leak inhibition has failed to treat migraine attacks.[3]

Magnesium deficiency also plays an essential role in the pathogenesis of migraine attacks by altering the secretion of neurotransmitters, stimulating spreading cortical depression and increasing platelet aggregation. Spreading depression is specified by the breakdown of ionic homeostasis and it´s related to a temporary arrest of neuronal function and is understood to play a central role in the pathogenesis of migraine and requires the release of glutamate. N-methyl-D-aspartate (NMDA) receptors play a critical role in its propagation. Previous investigations have reported that, by magnetic resonance spectroscopy (MRS) confirmation in the brain, decreased levels of Magnesium in the serum, saliva and cerebrospinal fluid (CSF) of migraine patients are obvious during and between migraine attacks.[4]

Magnesium deficiency influences neuroinflammation, serotonin receptor affinity, NMDA receptor blockade, calcium channel and glutamate and nitric oxide activity. Magnesium thus neutralizes the vascular and neurogenic mechanisms of migraine. Magnesium has also been suggested as a treatment choice for migraine due to its property of blocking the NMDA receptor, a receptor identified as an important contributor to pain transmission. Furthermore, magnesium supports calcium homeostasis by binding the NMDA receptor, moderating the release of substance P and controlling the production of nitric oxide. The decrease in the serum level of ionized magnesium (IMg2+) and the increase in the serum ratio of ionized calcium (Ca2+) to Mg2+ will possibly increase the affinity of serotonin for serotonin receptors in the cerebral vascular muscle, inducing cerebral vasoconstriction.[4]

This study aim stablishes the relationship between inflammatory markers, serum magnesium and migraine. Also, to determine the causal relationship between inflammatory markers and electrolytes and migraine and to demonstrate other associated factors such as weight, sex, lifestyle, sleep quality and family inheritance.

METHODOLOGY

This is a prospective longitudinal case-control with prospective data collection study, quantitative, sampled by convenience. Patients treated at the Neurology outpatient clinic with a diagnosis of migraine according to the ICHD-3 criteria from October 1, 2022 to December 8, 2023, were selected for this study. The patients were divided into 2 groups: Migraine (Case) and Control Group. The group control was composed of healthy individuals without migratory headaches, post-traumatic headaches or other trigemino-autonomic headaches or other chronic pain.

Eligible individuals were considered to be aged between 18 and 60 years of both sexes, without a medical history of allergic, inflammatory, infectious or immunological diseases, and other chronic disorders, including cardiovascular disorders, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, irritable bowel and lung and infectious diseases. In addition, others neurological diseases (including epilepsy, Parkinson's disease, multiple sclerosis, Alzheimer's disease, other subtypes of headaches, etc.). Furthermore, the diagnosis of episodic or chronic migraine was confirmed by the attending neurologist at the outpatient clinic following the criteria of the International Headache Society (ICHD-3). Those who reported any of these related diseases and those who refused to sign the informed consent form were excluded.

All patients with migraine who filled out the inclusion criteria was underwent a neurological examination and received a headache diary, in order to record the characteristics of their attacks during the subsequent two months and return them at the second assessment. This was carried out in person or via telemedicine, and during this period the laboratory tests were collected.

The headache diary helps patients record the frequency of attacks, the intensity of each headache (ranging from 0 to 10), and the amount of analgesics used. The visual analogue scale (VAS) scoring system was applied as a valuable instrument to assess pain intensity as follows: from 0 (approximately no pain) to 10 (the worst possible pain experienced by the patient).

A form was filled out by the person responsible for the research and/or by resident doctors at the Hospital with the help of the patient. It contained anthropometric, socioeconomic, diagnostic, sex, age, among other data. Serum levels of Magnesium (mg/dL), C-Reactive Protein (CRP) (mg/dL), Ferritin (ng/dL), HDL-c (mg/dL) and LDL-c (mg/dL), ESR (mm /h), fibrinogen according to specific methods. The patients were instructed to get a good night's sleep and fast for 12 hours before the blood collection. HDL Cholesterol was determined by the colorimeric Trinder method by dry chemistry and LDL by calculation in Martin's Formula, Magnesium by the colorimetric method, Ferritin by in vitro immunometric automation, ESR by capillary photometry (X Microtest), C-Reactive Protein by the Monoclonal Anti-CRP antibody method with Horseradish peroxidase by dry chemistry, Fibrinogen by the Coagulometric method.

The control group filled out the same form with anthropometric, socioeconomic, diagnostic, sex, age, among other data and performed the same laboratory tests. This group was made up of companions of patients treated at the Neurology outpatient clinic, hospital and university employees, undergraduate and postgraduate students and other volunteers. The data obtained were organized in the Microsoft

Office Excel version 2016 program and analyzed using the Statistical Package for the Social Sciences® (SPSS), version 26.0 software.

Descriptive analysis was applied to qualitative variables and relative and absolute frequency was applied to quantitative variables. The position measurement (mean and median) and dispersion (standard deviation) were also applied in the description. To compare groups in relation to social and clinical profile, the chi-square test was applied, and for those that were significant, logistic regression was performed to calculate the odds ratio. For quantitative variables, the Mann-Whitney U test was applied. For all tests, a significance level of 5% and a confidence level of 95% were applied.

To carry out this research, authorization was requested from the Research Ethics Committee (CEP) of the University Hospital of the Federal University of Piauí (UFPI), in compliance with the ethical precepts and regulations of Resolution 466/2012 of the National Health Council (CNS) which deals with and regulates the guidelines and standards involving research with human beings (BRASIL, 2012). The work was approved under assent number 5630306 on September 8, 2022 and CAAE 61401822.1.0000.8050.

RESULTS

The study initially included 118 patients, 40 in the Control group and 78 in the Case group (Patient with Migraine). Of these, 8 in the control group were excluded due to loss to follow-up. In the case group, 19 were excluded due to loss to follow-up, 12 due to failure to complete the headache diary and 11 due to failure to perform laboratory tests. In the end, there were 36 patients in the Case group (52.9% of the sample) and 32 in the control group (47.1% of the sample).

Table 01 demonstrates the sample social profile. 38.2% of patients aged between 30 and 39 years old and 32.4% between 18 and 29 years old. 22.1%, between 40 and 49 years old and 7.4% between 50 and 59 years old. 50% were single and 38.2% married, 7.4% were divorced, 2.9% lived in common-lam marriage and 1.5% were widowed. 86.8% were female and 13.2% male. 57.4% had university education, 33.8% high school, 5.9% elementary school and 2.9% had no education. 42.6% had a monthly income of 3 to 5 minimum wages, 22.15% less than 1 minimum wage, 22.1% more than 5 minimum wages and 13.2% 1 to 2 minimum wages.

Table 01- Characterization of the social profile of patients treated at the Neurology outpatient clinic with a diagnosis of migraine according to the ICHD-3 criteria by Neurologists from the University Hospital of the Federal University of Piauí (HU-UFPI) and the control group. Teresina-PI-2023.

	N(%)	CI-95%	Avarage (CI-95%)	Sd
Age group			35,44(33,16-37,73)	9,44
18-29 years	22(32,4)	(22,1-44,0)		
30-39 years	26(38,2)	(27,4-50,1)		
40-49 years	15(22,1)	(13,5-32,9)		
50-59 years	5(7,4)	(2,9-15,4)		
Sex				
Male	9(13,2)	(6,8-22,8)		
Female	59(86,8)	(77,2-93,2)		
Marital status				
Married	26(38,2)	(27,4-50,1)		
Divorced or Separated	5(7,4)	(2,9-15,4)		
Single	34(50,0)	(38,3-61,7)		
Common-law marriage	2(2,9)	(0,6-9,1)		
Widower	1(1,5)	(0,2-6,7)		
Education				
Elementary school	4(5,9)	(2,0-13,4)		
High school	23(33,8)	(23,4-45,6)		
University education	39(57,4)	(45,5-68,6)		
No education	2(2,9)	(0,6-9,1)		
Monthly income				
< 1 Minimum Wage	15(22,1)	(13,5-32,9)		
1 - 2 Minimum Wages	9(13,2)	(6,8-22,8)		
3 - 5 Minimum Wages	29(42,6)	(31,4-54,5)		
> 5 Minimum Wages	15(22,1)	(13,5-32,9)		

Source: Author (2023).
[1]CI-95% -Confidence interval for the proportion.
[2]CI-95% -Confidence interval for the mean.
Sd: Standard Deviation

The Table 02 shows the sample clinical profile. The average weight was 65.09 kilos and the average height was 160.47cm. The average body mass index (BMI) is 24.6; 55.9% had a BMI between 18.5 and 24.9, 38.2% had a BMI between 25 and 29.9, 4.4% had a BMI ≥ 30 and 1.5% had a BMI less than 18.5. The average age at onset of symptoms was 22.14 years. 38.9% started symptoms before the age of 17, 33.3 between 18 and 29 years old, 25% between 30 and 39 years old and 2.8% between 40 and 49 years old and no one started symptoms after the age of 50. 58.8% of individuals practiced physical activity and 41.2% did not practice.

Table 02- Clinical profile of patients treated at the Neurology outpatient clinic with a diagnosis of migraine according to the ICHD-3 criteria by Neurologists from the HU-UFPI and control group. Teresina-PI-2023.

	N(%)	CI-95%	Avarage (CI-95%)	Sd
Weight (Kg)			65,09(61,13-69,05)	16,37
Height (cm)			160,47(158,11-162,83)	9,77
BMI			24,61(23,67-25,55)	3,88
< 18,5 (Low Weight)	1(1,5)	(0,2-6,7)		
18,5-24,9 (Normal Weight)	38(55,9)	(44,0-67,2)		
25-29,9 (Overweight)	26(38,2)	(27,4-50,1)		
≥30 (Obesity)	3(4,4)	(1,3-11,3)		
Sympton onset age			22,14(18,35-25,92)	11,18
Sympton onset age Groups				
0 a 17 years	14(38,9)	(24,3-55,2)		
18 a 29 years	12(33,3)	(19,7-49,5)		
30 a 39 years	9(25,0)	(13,2-40,7)		
40 a 49 years	1(2,8)	(0,3-12,3)		
50 a 59 years	0(0,0)			
60 years or more	0(0,0)			
Prior Prophylactic Treatment				
No	22(32,4)	(22,1-44,0)		
Yes	17(25,0)	(15,9-36,2)		
No apply	29(42,6)	(31,4-54,5)		
Migraine Family history				
No	41(60,3)	(48,4-71,3)		
Yes	27(39,7)	(28,7-51,6)		
Insomnia				
No	38(55,9)	(44,0-67,2)		
Yes	30(44,1)	(32,8-56,0)		
Physical Activity Practice				
No	28(41,2)	(30,0-53,0)		
Yes	40(58,8)	(47,0-70,0)		
Physical Activity per week frequency				
2	4(10,5)	(3,7-23,1)		
3	12(31,6)	(18,6-47,3)		
4	6(15,8)	(6,9-29,7)		
5	10(26,3)	(14,4-41,7)		
6	6(15,8)	(6,9-29,7)		
Aura Presence				
No	16(23,5)	(14,7-34,6)		
Yes	20(29,4)	(19,6-40,9)		
No apply	32(47,1)	(35,5-58,8)		
Contraceptive use				
No	46(67,6)	(56,0-77,9)		
Yes	16(23,5)	(14,7-34,6)		
No apply	6(8,8)	(3,8-17,3)		
VAS (Avarage)			4,61(3,76-5,46)	1,92
Number of Days per Month			10,95(7,94-13,97)	8,50
Cronic Migraine	10(14,7)	(7,8-24,5)		
Episodic Migraine	26(38,2)	(27,4-50,1)		
Control group	32(47,1)	(35,5-58,8)		
Painkillers per Week (Average)			2,10(1,35-2,85)	2,05

Source: Author (2023).
[1]CI-95% -Confidence interval for the proportion.
[2]CI-95% -Confidence interval for the mean.
Sd: Standard Deviation

The majority had migraines with aura (29.4%) and the majority did not use contraceptives (67.6%). The average score on the Pain Assessment Scale (VAS) was 4.61, the average number of days of pain was 10.95 and the average number of analgesics per week was 2.10. 47.1% of the sample were in the control group, 38.2% were classified as episodic migraine and 14.7% as chronic migraine.

Table 03- Association between the groups and the social profile of patients treated at the Neurology outpatient clinic with a diagnosis of migraine according to the ICHD-3 criteria by Neurologists at the University Hospital of the Federal University of Piauí (HU-UFPI). Teresina-PI-2023.

	Group			
	Control	Case		
	N(%)	N(%)	P-value	OR-95%
	Social Profile			
Age Range			0,058	
18-29 years	10(31,3)	12(33,3)		
30-39 years	17(53,1)	9(25,0)		
40-49 years	4(12,5)	11(30,6)		
50-59 years	1(3,1)	4(11,1)		
Sex			0,376	
Male	3(9,4)	6(16,7)		
Female	29(90,6)	30(83,3)		
Marital Status			0,790	
Married	11(34,4)	15(41,7)		
Divorced or Separated	2(6,3)	3(8,3)		
Single	18(56,3)	16(44,4)		
Common-law marriage	1(3,1)	1(2,8)		
Widower	0(0,0)	1(2,8)		
Education			**<0,001**	
Elementary school	0(0,0)	4(11,1)		-
High school	4(12,5)	19(52,8)		-
Universitary education	28(87,5)	11(30,6)		-
No educational	0(0,0)	2(5,6)		B
Monthly income			**<0,001**	
< 1 Minimum Wage	0(0,0)	15(41,7)		-
1 - 2 Minimum Wages	8(25,0)	1(2,8)		-
3 - 5 Minimum Wages	10(31,3)	19(52,8)		26,600(3,042-232,610)
> 5 Minimum Wages	14(43,8)	1(2,8)		B

Source: Author (2023).
[1]Chi-square test, with yates correction, at the 5% level.
[2]Odds ratio, at 5% level

Table 03 demonstrates the association between groups and social profile. There was no significant difference in the mean age between the groups (p: 0.056). Between the sexes there were also no significant differences (p 0.376). There were significant differences in monthly income with p< 0.001. There were no significant differences in relation to marital status (p 0.790). There was a significant difference in relation to educational level (p< 0.001).

Table 04 - Association between the groups and the clinical profile of patients treated at the Neurology outpatient clinic with a diagnosis of migraine according to the ICHD-3 criteria by Neurologists at the University Hospital of the Federal University of Piauí (HU-UFPI). Teresina-PI-2023.

	Group			
	Control	Case		
	N(%)	N(%)	P-value	OR-95%
Clinical Profile				
BMI			0,226	
< 18,5 (Low Weight)	1(3,1)	0(0,0)		
18,5-24,9 (Normal Weight)	17(53,1)	21(58,3)		
25-29,9 (Overweight)	14(43,8)	12(33,3)		
≥30 (Obesity)	0(0,0)	3(8,3)		
Sympton onset age groups			-	
0 a 17 years	0(0,0)	14(38,9)		
18 a 29 years	0(0,0)	12(33,3)		
30 a 39 years	0(0,0)	9(25,0)		
40 a 49 years	0(0,0)	1(2,8)		
50 a 59 years	0(0,0)	0(0,0)		
60 years or more	0(0,0)	0(0,0)		
Migraine Family history			**<0,001**	**-**
No	28(87,5)	13(36,1)		B
Yes	4(12,5)	23(63,9)		
Insomnia			**<0,001**	
No	26(81,3)	12(33,3)		B
Yes	6(18,8)	24(66,7)		8,667(2,810-26,725)
Physical Activity Practice			0,117	
No	10(31,3)	18(50,0)		
Yes	22(68,8)	18(50,0)		
Physical Activity per week frequency in days			0,082	
2	1(4,3)	3(20,0)		
3	7(30,4)	5(33,3)		
4	2(8,7)	4(26,7)		
5	7(30,4)	3(20,0)		
6	6(26,1)	0(0,0)		
Aura Presence			-	
No	0(0,0)	16(44,4)		
Yes	0(0,0)	20(55,6)		
Contraceptive use			0,106	
No	18(64,3)	28(82,4)		
Yes	10(35,7)	6(17,6)		

Source: Author (2023).
[1]Chi-square test, with yates correction, at the 5% level.
[2]Odds ratio, at 5% level.

Table 04 shows the relationship between the groups and the clinical profile. There were no significant differences in BMI between groups (p 0.226). There were significant differences in family history of migraine between the groups, 87.5% of people in the control group had no family history of migraine and 63.9% of people in the case group had a family history of migraine (p<0.001).

There were also significant differences in insomnia between the two groups, 81.3% of individuals in the control group did not report insomnia and 66.7% in the case group reported insomnia (p<0.001). There were no significant differences between the practice of physical activity (p 0.117). Regarding the

use of contraceptives, there were no differences (p 0.106). 55.6% of people with migraine reported an aura and 44.4% did not report it.

The Table 5 demonstrates the relationship between the groups and inflammatory markers and magnesium. The inflammatory markers ESR, LDL-c, and Fibrinogen were significantly higher in the case group with p <0.001, 0.035 and 0.017 respectively. HDL-c was significantly lower in the case group (p 0.005). There were no significant differences in magnesium, C-reactive protein and Ferritin between the groups with p of 0.379, 0.088 and 0.315 respectively.

Table 05- Association between groups and Inflammatory Markers and Magnesium. Teresina-PI-2023.

	Control	Case	
	Avarage ± Sd	Avarage ± Sd	P-value
Magnesium	1,97±0,16	2,06±0,40	0,379
C-Reactiv protein	4,40±3,66	3,17±4,61	0,088
ESR	7,34±6,71	16,16±13,50	**<0,0001**
LDL-c	98,49±31,33	116,65±38,55	**0,035**
HDL-c	61,45±19,11	50,36±19,04	**0,005**
Ferritin	63,37±64,93	105,34±213,11	0,315
Fibrinogen	279,79±93,12	378,32±131,82	**0,017**

Source: Author (2023).

[1] Mann-Whitney U test, at the 5% level.

DISCUSSION

The sample highlights an important disparity between sexes. In the case group, 83% are female. In general, Migraine, with or without aura, begins earlier in men than women and the Migraine with aura incidence peaks occurs at 5 years, with an estimated incidence rate of 6.6 per 1000 people/ year and the migraine without Aura peaks between 10 and 11 years, with an estimate of 10 per 1,000 person/years. New cases are uncommon in men in their 20s. In women, the Migraine with Aura peak incidence rate is 14.1 per 1,000 person/years between 12 and 13 years and 18.9 per 1,000 person/years between 14 and 17 years. Surveys carried out in the United States revealed that 17.6% of women and 5.7% of men had one or more migraine attacks per year. The prevalence of migraine varied considerably according to age and was higher in men and women between 35 and 45 years.[5]

Chronic migraine among participants in this study was 27.7%. At population levels, around 8% of patients with Migraine develop the chronic form and in reference health services these numbers tend to be higher. It is associated with greater use of health care resources, including more frequent visits to primary care physicians, specialists, and emergency than the episodic form. Individuals with chronic migraine are also admitted and treated more frequently in hospitals and undergo more diagnostic tests than those with the episodic form, in addition to being more susceptible to medication abuse.[6]

When comparing the groups, there were no significant differences in relation to age (p 0.058), sex (p 0.376), weight (p 0.226) and physical activity (p 0.226), therefore the groups were balanced in the main biological variables.

The study also demonstrated the relationship between migraine and positive family history with p < 0.001. Several genes have been associated with migraine and a polygenic trait with multiple genetic variants, each with a small effect on many genetic loci accumulating to lead to the disease[7]. This genetic basis is complicated. According to family and twin studies, the expected family inheritance of migraine

is 30 to 60%. However, at least one monogenic inheritance has been described in a form of migraine caused by mutations in the CACNA1A, ATP1A2 and SCN1A genes and is associated with hemiplegic migraine[8]. Susceptibility to other diseases is the result of the interaction of these genetic variations with each other and environmental and lifestyle factors; linking the polymorphism to a variant that causes a certain effect, or even to the affected gene, is often a challenge.[9]

The risk for insomnia in this study was approximately 8 times higher in the case group with $p < 0.001$. A significantly higher prevalence of insomnia and complaints of insomnia has been documented in patients with migraine compared to those without headache and a higher prevalence of migraine has been reported in individuals with insomnia compared to those without insomnia. The association between migraine and insomnia appears to be bidirectional. The presence of insomnia is associated with increased pain intensity, impact, frequency of attacks and risk of chronicity. The association observed between insomnia and migraine was considered not only attributable to anxiety and depression.[10]

Among the inflammatory markers included in this study, LDL-c, HDL-c, ESR and Fibrinogen stood out, which showed a statistically significant difference between the groups of 0.035, 0.005, < 0.000001 and 0.017 respectively. HDL-c reduces inflammation in several cell types, including endothelial cells and macrophages, and exerts this effect through several mechanisms. Reduces inflammation in monocytes and attenuates binding of monocytes to adhesion molecules on the surface of activated endothelial cells. This highlights several potential targets to improve the anti-inflammatory properties of HDL-c in endothelial cells.[11]

Several biological activities result from the action of HDL-c including reverse cholesterol transport, as well as antioxidant, anti-inflammatory, antiapoptotic, antithrombotic and antiatherosclerotic effects. In coronary artery disease (CAD), for example, serum levels of HDL-c correlated inversely with circulating pro-inflammatory levels of monocytes, thus suggesting inflammatory properties in this condition[12]. Large population-based studies have shown a decrease in HDL-c levels and its association with migraine. However, results have not been replicated consistently due to methodological variability.[13]

Low-density lipoproteins (LDL) represent the most significant biochemical variable associated with atheroma and their reduction has been associated with a reduced incidence of major cardiovascular (CV) events. The CV risk associated with increased inflammatory markers was well established after the detection of elevated levels of high-sensitivity C-reactive protein. LDL undergoes oxidation by the combined action of lipoxygenases, reactive oxygen species, peroxynitrite and/or myeloperoxidase and thus LDL and its oxidized phospholipids further stimulate the inflammatory activation of macrophages and vascular smooth muscle cells, stimulate endothelial cells by inducing expression molecules of surface adhesion on endothelial cells that mediate the rolling and adhesion of blood leukocytes (monocytes and T cells) and are also immunogenic because they present different structures derived from lipid peroxidation, such as phospholipids and malondialdehyde that are recognized as antigens by the immune system and act as targets of innate immunity and as critical modulators of inflammatory responses.[14]

In a 2021 Meta-Analysis, the results were compatible with higher LDL-c levels in patients with migraine and the sensitivity analysis generated attenuated values, but consistently and significantly higher values for patients with migraine even with corrections made for weight, fasting collection and comorbidities.[15]

The lipid profile found in this study, low HDL-c and high LDL-c, may raise signs of higher mortality in this population group. A 2022 meta-analysis demonstrated that migraine was associated with an increased risk of myocardial infarction, unspecified stroke, ischemic stroke, and hemorrhagic stroke.

Migraine with aura showed an even higher risk of cardiovascular mortality. The exact mechanisms underlying the association between migraine and cardiovascular and cerebrovascular events are not yet well understood. Previous studies have demonstrated reduced numbers and functions of circulating endothelial progenitor cells, along with increased platelet activity in affected patients.[16]

In this study, Fibrinogen had a mean of 378.32±131.82 and was statistically significantly higher than the control group (p 0.017). Several binding sites have been recognized on fibrinogen molecules that are responsible for its possible interaction with different receptors or adhesion molecules expressed on different cells of the hematopoietic, immune and nervous systems. Like CRP, it is an acute phase protein and is increased in pathological conditions. Higher concentrations are associated with human diseases with an inflammatory component, including CAD.[17]

It has been speculated that fibrinogen could serve as a therapeutic target for neurological diseases, and several animal experiments have confirmed the protective and therapeutic effects of fibrinogen depletion in neurogenic inflammation. A chronic migraine model was used in a study on defibinogenation and pain improvement, but the results were inconclusive[18]. Previous studies have reported different findings related to the levels of fibrinogen or fibrin degradation products in patients with migraine. These findings may indicate and help characterize neurogenic inflammation.[19]

ESR was also significantly higher than the control group with p< 0.000001. ESR measures the rate at which erythrocytes precipitate or settle in the plasma of anticoagulated blood in a random sample over a specified period of time (usually 60 minutes) in millimeters (mm)/hour. In general, they stabilized more quickly in the presence of increased levels of fibrinogen[20]. Increased ESR has long been considered an indicator of inflammation, in addition, numerous studies have identified fibrinogen as the main protein that increases ESR.[21]

In this study, there were no significant differences between the case and control groups related to C-reactive Protein. However, it has been shown in several studies to be an important inflammatory marker. CRP concentration was significantly higher in patients with migraine than in controls in several studies.[22]

Ferritin in the control group had a mean of 63.37 and sd ±64.93 in the case group of 105.34 sd ±213.11 but this difference was not significantly significant (p: 0.315). Serum ferritin is a well-known acute phase protein and can be used as a marker for various inflammatory pathologies, such as systemic lupus erythematosus or rheumatoid arthritis and is not only regulated by inflammatory stimuli, but can also function as an intensifier of the inflammatory response[23]. A 2004 study also found no significant differences between the control group and the group with migraines and other headaches.[24]

There were also no significant differences in serum magnesium concentration in the two groups. Magnesium is the second most common intracellular cation found in all tissues, influencing a series of neurochemical processes. Mg deficiency plays an essential role in the pathogenesis of migraine by altering the secretion of neurotransmitters, stimulating cortical spreading depression (ACD) and increasing platelet aggregation. APD is specified by the breakdown of ionic homeostasis and is related to a temporary arrest of neuronal function and plays a fundamental role in the pathogenesis of migraine. Magnesium deficiency influences neuroinflammation, serotonin receptor affinity, NMDA receptor blockade, calcium channel and glutamate and nitric oxide activity and neutralizes the vascular and neurogenic mechanisms of migraine.[4]

A 2016 study demonstrated the relationship between magnesium deficiency and seizure frequency. In this study, the control group had an average of 1.95mg/dl and the case group had an average of 1.3mg/dl in the interictal phase and 1.09mg/dl during the migraine attack with p<0.0001.[25]

Limitations of the study include the lack of serial measurements of serum levels and the sample selected by convenience. The important difference between the groups is also mentioned, mainly related to educational and social level.

CONCLUSION

The study demonstrated an important predominance of women in the sample. There was also an important relationship between migraine and sleep disorders and family inheritance.

Important relationships between migraine and inflammation were also identified, with statistical significance for LDL-c and fibrinogen as high pro-inflammatory markers and low HDL-c as an anti-inflammatory marker consumed. This raises important aspects related to the systemic nature of the disease. All of this enhance the importance of a holistic look at individuals with migraine, understanding them not only as a person with a headache, but also as an individual whose life is impacted globally. There were no significant differences in serum magnesium levels between the case and control groups in this study.

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