▪ Headache Medicine 2021, 12(4):278-282 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2021.45

Review

Evaluation of the genetic variant -889 C>T of Il-1α in migraine - partial analysis

Maria Paula Bertoletti Juliani, Amanda Brant Rocha, Giovana Ortiz Zendrini, Valéria Aparecida Bello, Regina Célia Poli-Frederico, Aline Vitali da Silva

Universidade Católica do Paraná, Paraná, Brazil

Maria Paula Bertoletti Juliani
mariapaula_bertoletti@hotmail.com

Edited by:
Marcelo Moraes Valença

Abstract

Introduction

The pathophysiology of migraine integrates inflammatory and genetic aspects, with interleukin-1a being a component of this picture. This pro-inflammatory cytokine, responsible for inducing pyrogenic, hematological, and metabolic phenomena, is produced by macrophages and monocytes. Genetic variants, which can be found in the regulatory region of the gene for this substance, have clinical implications in different systems.

Objective

To evaluate the frequency of the -889C>T genetic variant of IL-1α and its association with clinical variables related to migraine.

Methods

Prospective case-control study composed of migraine patients and healthy controls aged between 18 and 60 years of age. Project approved by the Research Ethics Committee of PUCPR (No. 3,029,972). Demographic, clinical data on migraine classification and characteristics were collected using a structured form and validated questionnaires on anxiety (STAIY2), depression (BDI) and migraine-related disability (MIDAS). Genetic evaluation was performed with blood or saliva samples that were subjected to polymerase chain reaction (PCR), followed by electrophoresis in 1.5% agarose gel. Categorical data were analyzed by chi-square test or Fisher's exact test and continuous data by t-test or Mann-Whitney test.

Results

A total of 156 participants, 73 migraineurs and 83 controls, were evaluated. The -889C>T variant of IL-1α was not associated with increased susceptibility to migraine when evaluated in allelic, codominant, dominant, or recessive models. The C allele, the lowest producer of the cytokine, was associated with a higher frequency of osmophobia in patients with migraine (65.5% vs. 48.2%; p=0.038).

Conclusion

No association was identified between the -889C>T variant of IL-1α and susceptibility to migraine. Its effect on osmophobia should be further investigated. However, the present work is a partial analysis whose main limitation is the small sample size.

Keywords:
Migraine
Interleukin 1
Genetic polymorphism
Pathophysiology

Received: February 16, 2022
Accepted: February 21, 2022

Introduction

The main characteristic of migraine is headache, and it belongs to the group of primary headaches because it causes physiological changes in the nervous system, which determine the pain.[1] In this context, it can be understood as an inflammatory disease resulting from the interaction of genetic, environmental, hormonal, and metabolic factors.[2]

This disease can present up to four phases: prodrome, aura, pain, and postdrome.[1,2] Thus, the crises are a sum of these phenomena and can last five to six days.[1] It is rated as the third most disabling disease in the world 1, affecting 10-20% of the world's population, as well as 15.8% of Brazilians.[3,4] It is noteworthy that it affects females three times more often than males, with a first peak of incidence at 18-29 years of age and a second one at 40-49, with a reduction in prevalence concomitant with menopause.[5,6]

The pathophysiology of migraine is not yet fully understood, but it is known that cytokines play a key role in pain. Substances such as interleukin 1 (IL-1), interleukin 10 (IL-10), interleukin 4 (IL-4), interleukin 13 (IL-13), interleukin 2 (IL-2), and tumor necrosis factor-a (TNF- a) may be relevant to the condition.[7]

Therefore, as the pathophysiology of the disease involves a neurogenic inflammation, pro-inflammatory genes, such as interleukin 1 alpha, may interfere in the manifestations of migraine.[8] This interleukin is produced by macrophages, monocytes, fibroblasts, and endothelial cells in physiological situations and in situations of cellular injury due to infection and inflammation.[9,10] Specifically in the brain they are produced pathologically by astrocytes, oligodendrocytes, microglia and neurons.[10] IL-1 induces endogenous pyrogenic phenomena and influences the hematological, metabolic, and central nervous systems.[11]

One of the genetic variants found in the IL-1 ALPHA gene is the - 889 C > T, which consists of the exchange of a cytosine for a thymine in the regulatory region of the DNA. In the case of migraine, only one study has addressed this issue and concluded that patients homozygous for the T allele (T/T) have a greater chance of early onset of headache than patients with CC and CT genotype migraine.[10] Furthermore, this same study found a higher prevalence of aura in patients homozygous for the T allele (TT) than other genotypes.[10]

Hence, the present study aims to analyze the association of clinical aspects of migraine and the IL-1alpha -889 C>T gene polymorphism (rs1800587) and to verify a possible association of genetic variants and disease activity.

Methods

Ethical Considerations

The present study was carried out after approval by the Research Ethics Committee (CEP) of PUCPR, according to report 3.029.972, by means of Informed Consent Form (ICF) signed by the participants, after a detailed explanation of its development, being in accordance with resolution 466/2012 of the National Health Council.

Study Population

The universe of this study was made up of a convenience sample with 156 participants - 73 patients and 83 controls, and the participants were seen at the PUCPR Headache Academic Outpatient Clinic - Londrina Campus, Paraná, Brazil.

Inclusion Criteria

Patients and controls between the ages of 18 and 60 years of age, of both.

Exclusion Criteria

Individuals with severe and uncontrolled neurological, psychiatric, and inflammatory diseases were excluded.

Study design

This is a retrospective longitudinal case-control study investigating the possible association between clinical aspects of migraine, sociodemographic variables, and genetic polymorphism of IL1-α and TNF-α in individuals seen at the Academic Outpatient Clinic of PUCPR Londrina Campus, Brazil.

Instruments used

The diagnosis of migraine was made according to the 3rd International Classification of Headache, published in 2018. The interview was structured and based on the form developed electronically by the Headache Research Group of the PUCPR Londrina Campus, through the Google Forms tool®. Composed by the following topics: demographic data, diagnostic criteria, and temporality of

migraine; associated clinical characteristics; crisis triggers, medications used, lifestyle habits, performance of aerobic physical activity, sleep time, and comorbidities. The following scales were applied MIDAS (*Migraine Disability Assessment*)[12] HIT-6 (*Headache Impact Test-6*)[13] and form Y-STAI (*State-Trait Anxiety Inventory*).[14]

Genotyping

To obtain DNA, extraction was performed from peripheral blood leukocytes by venipuncture in tubes containing EDTA (0.6%) and DNA extraction- kit Pure Link Genomic DNA (Invitrogen, Carlsbad, EUA) was used, following the guidelines provided by the manufacturer. The extracted DNAs were stored in a freezer at -80° C. The quality and quantity of DNA was measured by means of absorbance analysis in a spectrophotometer (NanoDrop 2000 – Thermo Scientific) at 260 nm and 280 nm. Next, DNA was diluted in ultrapure water Milli-Q® to a final concentration of 100 ng/uL. Genotyping of genetic variants of the cytokine IL-1α -889 C>T (rs1800587) was performed by PCR with allele-specific sequence primers (PCR-SSP) described by Bunce.[15]

Results

Table 1 presents the main characteristics of the population analyzed in this study. The mean age of patients with migraine was 31 years old. There was a prevalence of migraine in females of 82.2% of patients (p=0.036), as well as a higher prevalence in Caucasians than other ethnicities. It was found that majority of the patients did not have associated comorbidities such as diabetes and hypertension.

Table 1. General characteristics of participants with migraine and controls

		Migraine		Control		*p*
		n	%	n	%	
Age		31		26		
Sex	Male	13	17.8	27	32.5	0.036
	Female	60	82.2	56	67.5	
Ethnicity	Caucasian	61	83.6	58	81.7	0.767
	Non caucasian	12	16.4	13	18.3	
Hypertension	Yes	5	6.8	7	8.4	0.711
	No	68	93.2	76	91.6	
Diabetes	Yes	2	2.7	5	6	0.323
	No	71	97.3	78	94.0	
Body mass index (average in kg/m²)		24.6		24.0		

Another relevant finding is that the -889C>T variant of IL-1α was not associated with increased susceptibility to migraine when evaluated in allelic, codominant, dominant or recessive models (Table 2). However, the C allele, a lower cytokine producer, was associated with higher frequency of osmophobia in patients with migraine (65.5% *vs.* 48.2%; p=0.038). This same allele is associated with higher presence of aura in patients. However, it is observed that there was no association with the classification (episodic or chronic) and other symptoms associated with migraine (Table 3).

Table 2. Assessment of genetic susceptibility to migraine of the -889 C>T variant

		Control		Migraine		*p*
		n	%	n	%	
Allylic Model	C	97	58.4	90	61.6	0.564
	T	69	41.6	56	38.4	
Codominant Model	CC	22	26.5	24	32.9	0.674
	CT	53	63.9	42	57.5	
	TT	8	9.6	7	9.6	
Dominant Model	CC	22	26.5	24	32.9	0.384
	CC + CT	61	73.5	49	67.1	
Recessive Model	CC + CT	75	90.4	66	90.4	0.992
	TT	8	9.6	7	9.6	

Table 3. Evaluation of comparative clinical characteristics in T and C alleles

		C		T	
		Count	%	Count	%
Type of migraine	Episodic	46	52.3	34	60.7
	Chronic	42	47.7	22	39.3
Migraine with aura	Yes	38	42.20	20	35.70
	No	52	57.80	36	64.30
Phonophobia	Yes	78	86.70	46	82.10
	No	12	13.30	10	17.90
Photophobia	Yes	82	91.10	50	89.30
	No	8	8.90	6	10.70
Osmophobia	Yes	59	65.60	27	48.20
	No	31	34.40	29	51.80
Allodynia	Yes	43	47.80	19	33.90
	No	47	52.20	37	66.10
Prodrome	Yes	69	76.70	41	73.20
	No	21	23.30	15	26.80
Postdrome	Yes	75	87.20	43	76.80
	No	11	12.80	13	23.20
MIDAS_dico	Mild or no disability	28	33.30	18	33.30
	Moderate to severe disability	56	66.70	36	66.70
HIT6_dico	Moderate to no impact	13	15.30	13	23.60
	Substantial to severe impact	72	84.70	42	76.40

Discussion

In agreement with the epidemiological data presented in the literature, the results found in the present study indicate that patients in the migraine group are mostly female and Caucasian.[6] In addition, individuals aged 15-49 years are the most affected, as evidenced by the average age of the patients analyzed, i.e. 31 years.[10]

Studies show that women with migraine are 15% more likely than women without migraine to develop hypertension. However, the correlation of comorbidities with migraine in the present analysis was divergent from the evidence in the literature.[16]

The scarcity of studies in the literature that definitively correlate the genotype of such polymorphisms and migraine incidence is equivalent to this study, since there was no relevant change in susceptibility in any genetic model. However, the association of the C allele with osmophobia and aura reinforces the need for further research.

Finally, it is believed that, since this is a partial analysis, with a reduced sample size, there are losses. Thus, it is necessary to continue the analysis.

Contribution authors: All authors had the same contribution.
Funding: No
Conflict of interests: The authors report no conflict of interest.

Maria Paula Bertoletti Juliani
https://orcid.org/0000-0002-7168-1232
Amanda Brant Rocha
https://orcid.org/0000-0002-5196-7727
Giovana Ortiz Zendrini
https://orcid.org/0000-0003-4508-575X
Valéria Aparecida Bello
https://orcid.org/0000-0001-7919-6218
Regina Célia Poli-Frederico
https://orcid.org/0000-0003-4631-4606
Aline Vitali da Silva
https://orcid.org/0000-0001-7797-9227

References

1. **Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition**. *Cephalalgia* 2018;38(1):1-211 Doi:10.1177/0333102417738202
2. Charles A. **The pathophysiology of migraine: implications for clinical management.** *The Lancet Neurol* 2018;17(2):174-182 Doi:10.1016/S1474-4422(17)30435-0
3. Burch R. **Migraine and Tension-Type Headache: Diagnosis and Treatment**. *Med Clin North America* 2019;103(2):215-233 Doi:10.1016/j.mcna.2018.10.003
4. Speciali JG, Kowacs F, Jurno ME, Bruscky IS, Carvalho JJF, Malheiro FG, . . . Prado GF. **Protocolo Nacional para Diagnóstico e Manejo das Cefaleias nas Unidades de Urgência do Brasil**. *Soc Bras Cefaleia* 2018;1(1):3-14 [Internet] Available from: https://sbcefaleia.com.br/images/protocolo%20cefaleia%20urgencia.pdf
5. May A and Schulte LH. **Chronic migraine: risk factors, mechanisms and treatment**. *Nat Rev Neurol* 2016;12(8):455-464 Doi:10.1038/nrneurol.2016.93
6. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML and Stewart WF. **Migraine prevalence, disease burden, and the need for preventive therapy**. *Neurology* 2007;68(5):343 Doi:10.1212/01.wnl.0000252808.97649.21
7. Ates O, Kurt S, Altinisik J, Karaer H and Sezer S. **Genetic variations in tumor necrosis factor alpha, interleukin-10 genes, and migraine susceptibility**. *Pain Med* 2011;12(10):1464-1469 Doi:10.1111/j.1526-4637.2011.01200.x
8. Persico AM, Verdecchia M, Pinzone V and Guidetti V. **Migraine genetics: current findings and future lines of research**. *Neurogenetics* 2015;16(2):77-95 Doi:10.1007/s10048-014-0433-x
9. Oliveira CM, Sakata RK, Issy AM, Gerola LR and Salomão R. **Cytokines and pain**. *Rev Bras Anestesiol* 2011;61(2):255-259, 260-255, 137-242 Doi:10.1016/s0034-7094(11)70029-0
10. Rainero I, Pinessi L, Salani G, Valfrè W, Rivoiro C, Savi L, . . . Grimaldi LM. **A polymorphism in the interleukin-1alpha gene influences the clinical features of migraine**. *Headache* 2002;42(5):337-340 Doi:10.1046/j.1526-4610.2002.02103.x
11. Mayer-Barber KD and Yan B. **Clash of the Cytokine Titans: counter-regulation of interleukin-1 and type I interferon-mediated inflammatory responses**. *Cell Mol Immunol* 2017;14(1):22-35 Doi:10.1038/cmi.2016.25
12. Fragoso YD. **MIDAS (Migraine Disability Assessment): a valuable tool for work-site identification of migraine in workers in Brazil**. *Sao Paulo Med J* 2002;120(4):118-121 Doi:10.1590/s1516-31802002000400006
13. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, . . . Tepper S. **A six-item short-form survey for measuring headache impact: the HIT-6**. *Qual Life Res* 2003;12(8):963-974

Doi:10.1023/a:1026119331193
14. Spielberger CD, Gorsuch, R. L. y Lushene RE. **C de ansiedad, Estado-Rasgo SMT. Manual STAI, Cuestionario de Ansiedad Estado Rasgo.Adaptación española**. *Tea Ediciones* 1997;1(7):7-16
15. Bunce M, O'Neill CM, Barnardo MC, Krausa P, Browning MJ, Morris PJ and Welsh KI. **Phototyping: comprehensive DNA typing for HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 & DQB1 by PCR with 144 primer mixes utilizing sequence-specific primers (PCR-SSP)**. *Tissue Antigens* 1995;46(5):355-367 Doi:10.1111/j.1399-0039.1995.tb03127.x
16. Rist PM, Winter AC, Buring JE, Sesso HD and Kurth T. **Migraine and the risk of incident hypertension among women**. *Cephalalgia* 2018;38(12):1817-1824 Doi:10.1177/0333102418756865