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Migraine with Dysautonomia Related to Mitochondrial Polymorphisms and Adrenergic Alpha Receptors

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Abstract

Introduction: Migraine has a high prevalence. It is among the first five most disabling diseases worldwide, and it is the most common primary headache in the pediatric age. There are isolated studies of the association of migraine with mitochondrial polymorphism 16519C> T and dysautonomia with polymorphism Arg347Cys of the first adrenergic alpha receptor (ADRA1A). It is common in a pediatric neurology service to find patients where both problems converge in the same subject.

Objective. The purpose of the study was to evaluate a possible association between migraine with dysautonomia and mitochondrial polymorphisms and alpha-adrenergic receptors.

Subjects and methods: An observational, analytical, prospective, and cross-sectional study of 44 participants was designed, divided into four groups: dysautonomia, migraine, migraine with dysautonomia, and controls; a blood sample was taken and analyzed by PCR to determine the presence of mitochondrial polymorphism related with migraine, as well as the most frequent genotypic variant of the alpha-adrenergic receptor 1A.

Results: Both the mitochondrial polymorphism 16519C> T ($p = 0.003$) and the Arg / Arg phenotype of Arg347Cys ADRA1A more frequently migraine groups explained by their multifactorial etiology, with high heterozygous frequency Arg / Cys in the control group.

Conclusion: The high frequency of heterozygotes (Arg / Cys) in the control group can confer a state of normotension and migraine protection in this population.

Keywords: Migraine, dysautonomia, mitochondrial polymorphism, alpha-adrenergic receptors.

Vol. 5, No. 03; 2021

ISSN: 2581-3366

Background

The autonomic nervous system (ANS) is responsible for maintaining homeostasis through automatic mechanisms that regulate breathing, digestion, heart rate, blood pressure, and temperature, activating from the nerve centers located in the hypothalamus, the brainstem, and spinal cord [1,2]. The ANS is pervasive; it distributes its terminal nerves in almost all organs through its two main subdivisions; the sympathetic and parasympathetic nervous system. In each of these components, there are populations of neurons with specific projections and chemical characteristics. Therefore, understanding and parasympathetic neurons are found inside and outside of the central nervous system. The cell bodies of these neurons in the peripheral nervous system are grouped into structures called autonomous ganglia. Their axons project from these ganglia to the target organs; thus, these neurons are known as postganglionic cells. Efferent neurons that send axons from the spinal cord or brain stem to the ganglia and synapse in the dendrites and postganglionic neuron cell bodies are called preganglionic neurons. The preganglionic neuron cell bodies are found in the brainstem and spinal cord [1,3].

All sympathetic and parasympathetic preganglionic neurons are cholinergic, using acetylcholine as a neurotransmitter. All postganglionic parasympathetic neurons are also cholinergic; in the postganglionic sympathetic neurons case, most are adrenergic and use norepinephrine as a transmitter [1].

The sympathetic and parasympathetic divisions of the ANS are integrated and regulated by a central autonomous neural network involved in visceromotor, neuroendocrine, complex motor, and pain modulation control mechanisms. This neural network consists of interconnected areas of the telencephalon, diencephalon, and brainstem [4]. The maintenance of the proper function of the organs innervated by the sympathetic and parasympathetic systems is achieved through a balanced dynamic interaction between the internal and environmental stressors; they can conditioner an autonomous imbalance with an increased risk of problems until disease, including migraines.

The ANS is primarily responsible for regulating responses to postural changes[5]. In an average person, approximately 25% of the circulating blood is in the chest. Upon assuming upright posture, there is a displacement of around 300 to 800 milliliters of blood in the abdomen and lower extremities, representing a volume drop of 25%. Approximately 50% occurs in the first seconds of the stand. This rapid redistribution in blood volume decreases venous return to the heart, with an approximate 40% decrease in systolic volume [4].

Proper adaptation of the prone position when standing requires the activation of various cardiovascular regulation systems and maintaining constant blood pressure and cerebral perfusion; Normally, orthostatic stabilization is achieved approximately one minute [5-7]. The baroreceptor reflex mediates the most crucial mechanism that produces these changes in the aortic arch and the carotid sinus. There are endings specialized nerves capable of recording the fall wall tension arterial due to the displacement of blood to the lower part of the body. This information quickly reaches the center of the solitary tract in the bulb.

Vol. 5, No. 03; 2021

ISSN: 2581-3366

The spinal neurons of the brainstem respond quickly to these signals, which decreases parasympathetic flow to the heart and increases sympathetic activity, producing vasoconstriction and tachycardia [8].

The functioning of any of these components is the origin of orthostatic intolerance. Orthostatic is included in a series of syndromes called dysautonomia, with different clinical forms of presentation, from transient episodes of orthostatic hypotension to progressive neurodegenerative diseases [9]. During childhood, they are mostly benign and self-limited episodes. Frequently or cause trauma due to a fall secondary to loss of consciousness and impair the quality of life of children. Limited knowledge of this pathology makes diagnosis difficult, and most of the time, children are diagnosed with epilepsy and psychiatric disorders. Orthostatic intolerance is the difficulty of standing in position due to cerebral hypoperfusion secondary to automatic nervous system dysfunction, manifested by a variety of signs and symptoms such as the feeling of imminent loss of consciousness, cognitive deficits, visuals alterations, lightheadedness, headache, fatigue, weakness, nausea, vomiting, abdominal pack, tremor, exercise intolerance, tachycardia, paleness, and diaphoresis [9].

Orthostatic hypotension: It is defined as a decrease in systolic blood pressure greater than 20 mmHg or diastolic blood pressure greater than or equal to 10 mmHg for the next three minutes after moving from the prone position to the vertical position [6-8].

Orthostatic postural tachycardia syndrome: It is characterized by daily symptoms of chronic orthostatic intolerance combined with sustained and excessive vertical tachycardia with the absence of postural hypotension. In teenagers, children under 18 are defined as an increased heart rate greater than 40 beats per minute, with the lack of hypotension [10].

During orthostatic hypotension, and to a lesser extent in orthostatic postural tachycardia syndrome, the associated compromise in cerebral blood flow can cause syncope.

Syncope: It is the temporary loss of consciousness and postural tone secondary to global cerebral hypoperfusion; it is of rapid onset, short duration with spontaneous recovery. Vasovagal syncope or medially neural syncope is the most common cause in pediatric patients, which occurs after several minutes in an upright position [10,11]

Migraine has a prevalence of 28% worldwide. In 2016 migraine was the second most disabling disease, depending on the years of life adjusted for disability. It is the most common primary headache in pediatric age. It can begin in early childhood with an increase in frequency between 10 and 14 years of age, having implications such as school absenteeism and adult life in the workplace, decreasing patients' quality of life [12-14].

There are multiple theories about the pathophysiology of migraine. Since remote times it has been considered that the ANS plays an essential role in its pathophysiology, 15 according to different criteria are calculated between 27-73% of patients with migraine are accompanied by cranial autonomic parasympathetic symptoms such as conjunctival injection, epiphora, nasal

Vol. 5, No. 03; 2021

ISSN: 2581-3366

congestion, rhinorrhea, eyelid edema, diaphoresis, facial flushing, myosis, and ptosis as well as nausea and vomiting [15,16]

The nucleus of the solitary tract and the gray periaqueductal substance, both functional structures of the central autonomic red neuronal, have an essential role in both pain processing and cardiovascular control. The gray periaqueductal importance receives nociceptive entries from the spinal dorsal horn and trigeminal and initiates sympathetic responses in fight or flight situations, which produces norepinephrine (NE) release, hypertension, and tachycardia [4].

Vascular theory and neuronal dysfunction theory are the most accepted theories for the pathogenesis of migraine. The vascular theory proposes that alterations in the diameter of the dura and extracranial blood vessels underlying the pain associated with migraines. A decrease in sympathetic tone or an increase in parasympathetic tone could perform cerebral vasodilation. The theory of neuronal dysfunction in which the caudal trigeminal nucleus in the brain stem plays the most crucial role. The dura and proximal portions of the large intracranial vessels have high sensitivity to pain [17]. The trigeminal sensory senses of these meningeal and vascular structures converge in the nucleus of the solitary tract, which ascends to the synapse in the ventral posteromedial nucleus of the thalamus. The solitary nucleus tract gives afferent to different areas of the central autonomic red neuronal. The activation of the dorsal nucleus also leads to the activation of the trigeminal-vascular system that can alter the monoaminergic modulation of pain.

Thus, it has been proposed that the cause of autonomic dysfunction during a migraine is a pattern of elevated sympathetic and decreased parasympathetic activity. Independent biomarkers have been studied in patients with migraines compared to healthy controls, finding a sympathetic-parasympathetic imbalance [18,19].

The molecular basis of migraine continues to be studied, suggesting that some migraine subtypes may be related to mitochondrial dysfunction [20]. Based on the hypothesis that alterations of mitochondrial oxidative metabolism can contribute to the pathogenesis of migraine by interrupting the correct nervous system functioning [21,22].

The brain and muscle are highly dependent on oxidative metabolism, and they are the tissues most affected by mitochondrial disorders.

The mitochondrial encephalopathies such as MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy ragged red fibers) have recurrent episodes of migraine. Histopathologically, abnormal mitochondria have been found in the walls of the cerebral and intramuscular arteries of patients with MELAS. These mitochondrial structural abnormalities in cutting the meningeal vasculature could explain the high sensitivity to different external factors in patients with migraines [21].

Migraine and dysautonomia considered several functional diseases specific pathways in their pathophysiology with overlapping symptoms between individuals and within families; due to the

Vol. 5, No. 03; 2021

ISSN: 2581-3366

apparent maternal inheritance, common genetic factors in functional diseases may be encoded in mitochondrial DNA [22,23]. Many patients with primary autonomic disorders are affected by migraines; It is unknown whether dysautonomia is the cause of migraine, its consequence, or independent diseases caused by the exact mechanism. Thijs et al. found an incidence greater than 1.48 times of syncope in patients diagnosed with migraine than in healthy controls [24]. Migraine is common in POTS syndrome, affecting approximately 25% of patients [25]; it is also common in cyclic vomiting syndrome and chronic fatigue syndrome. The latter also considered functional diseases Polymorphisms associated with dysautonomia and migraine.

Human mitochondrial DNA (mtDNA) is a circular, closed, and double-stranded structure, with an enlarged size of 16569 base pairs, contains 37 genes, of these 2 encoded for tRNA, 2 for rRNA (12S and 16S), and 13 encoded for the latter messenger RNAs involved in the oxidative phosphorylation chain [26]. Changes in the mitochondrial genome sequence have been modified, with possible physiological implications in populations of different lineages. In studies, previous patients association of mtDNA polymorphism 16519C> T in patients with migraine and cyclic vomiting [23, 27].

The α1-adrenergic receptors (α1A-AR, α1B-AR, and α1D-AR) are transmembrane receptors coupled to G proteins that mediate actions in the sympathetic nervous system through the binding to norepinephrine and epinephrine [28], their genetic variants have been related with pathologies and drug sensitivity [29-31]. The α-1 receptors regulate smooth muscle contraction, inotropic cardiac muscle, and hepatic glucose metabolism. Their activation by α1-adrenergic agonists initiates transduction by activating the protein Gq / 11. This protein enables Phospholipase Cb and hydrolyzes phospholipid membranes releasing to second messengers: Inositol Triphosphate (IP) and Diacylglycerol (DAG), which Increase intracellular calcium and activate a protein in smooth muscle contraction to Kinase C, which translates [32].

The α-1A adrenergic receptor (ADRA1A) plays an essential role in the heart, arterial resistance vessels (arterioles), and prostate tissue. Its gene is located on chromosome 8q21.2; nine polymorphic sites have been specified; the most studied is a single base polymorphism (SNP rs1048101) at position 1441 where change the cytosine nucleotide for thymine (C> T) non-synonymous variant that codes for the amino acid, arginine at location 347 and changes for a cysteine (Arg347Cys) located at the end C-terminal [33,34]

In the daily practice of pediatric neurology consultation, there is an annual frequency of 5% of patients who come for a diagnosis of migraine, and 1 to 2% for dysautonomia, clinically observing association between both pathologies. The presence of autonomic symptoms supports this relationship during the migraine picture. The pathophysiology of migraine is not well clarified. Recently, an autonomic nervous system imbalance has been found as a factor for their development and mitochondrial dysfunction, so it has been proposed that both devices can be interwoven in their pathogenesis.

Before the recurrence of dysautonomia and migraine episodes, our patients decrease their quality of life, being affected at this stage of life both academically and socially.

Vol. 5, No. 03; 2021

ISSN: 2581-3366

In the department of pediatric neurology, a previous study of the association of two mitochondrial polymorphisms with migraine was performed, finding statistical significance in migraine patients with aura and family history, 35 continuing this line of research and also studying a new alpha-adrenergic polymorphism. It helps to know and understand the pathophysiology of the disease.

Do we hypothesize that patients A diagnosis of migraine with dysautonomia have a higher frequency of mitochondrial polymorphisms and alpha-adrenergic receptors concerning healthy adults? The objectives of this study are to evaluate the association between migraine with dysautonomia with mitochondrial and alpha-adrenergic receptor polymorphisms; to determine the presence of mitochondrial polymorphisms 16519C → T and the alpha-adrenergic receptor Arg347Cys in pediatric patients diagnosed with migraine, dysautonomia, migraine with dysautonomia, and healthy adult controls, and to evaluate the epidemiological characteristics of patients with migraine and dysautonomia.

MATERIAL AND METHODS.

Observational, analytical, prospective, and transversal research study, designed as a pilot study. It was realized in the Central Hospital "Dr. Ignacio Morones Prieto," in the city of San Luis Potosí, S.L.P. Mexico.

The universe of the study was taking of selected cases from child patients diagnosed from the pediatric neurology outpatient clinic and adult controls without a diagnosis of migraine or dysautonomia or personal neither a family history of these pathologies.

We found that the association of migraine and dysautonomia with mitochondrial polymorphisms and alpha-adrenergic receptor polymorphisms was not published in the medical literature. In the neuropediatric consultation, we have observed that both pathologies can coincide, so we want to develop a study that will serve as a basis for further research with more significant resources [36]. A sample of 44 individuals, were distributed as follows: a) Group 1. Migraine (11 patients), b) Group 2. Dysautonomia (11 patients), c) Group 3. Migraine with dysautonomia (11 patients), d) Group 4. Healthy adults as controls (11 participants without personal o familial history of migraine or dysautonomia).

The inclusion criteria were: a) Pediatric patients aged 5 to 15 years. b) Diagnosis of migraine according to the criteria of the international headache society in its third edition. c) Diagnosis of dysautonomia with a suggestive diagnosis by Holter or inclination test associated or not with migraine. d) With signed authorization and informed consent by the parents or guardians and the child's consent in children over 12 years.

The subjects with secondary dysautonomia were excluded. The control group was made by adult subjects without dysautonomia and migraine or family history of these.

We took a small sample of blood stored in EDTA K2 tubes analyzed in the molecular biology laboratory of the Department of Biochemistry of the Medicine Faculty from the UASLP.

Vol. 5, No. 03; 2021

ISSN: 2581-3366

The polymorphism of nucleotide 16519 C> T of the mitochondrial genome was analyzed by the PCR-RFLP method was detected in DNA purified from venous blood. Around 200 nanograms of DNA were used with about 20 picomoles of oligonucleotides that flank polymorphisms site and amplify a 190 bp product, with a protocol of 95 ° C, 5 minutes. This procedure was followed by 94 ° C 30 seconds, 58 ° C 30 seconds and 72 ° C 1 minute, for 35 cycles, finished with a 7-minute extension at 72 ° C (Adapted from Zaki et al.) 27 Verified the 190 bp amplification product for region 16519 on agarose gel at two%. The PCR product was incubated with ten units of HaeIII restriction enzyme at 37 ° C overnight. The digestion products were separated by 3% agarose electrophoresis to obtain three 89, 61, and 40 base pairs for the typical sequence 16,519 and 2 of 89 + 101 bp for the C> T polymorphism. The nucleotide polymorphism 1441 of the α1A adrenergic receptor was detected in the series of Hernández-Pacheco et al., 2014 and Shibata et al., 1996,37 using the sequences 5′-5'- ATGCTCCAGCCAAGAGTTCA-3 ′ and 5′-TCCCAAGAAGAGCTGGCCTTC-3 ′, and cycles 94 ° C 5, min, followed by 94 ° C, 40 sec, 60 ° C 30 sec and 72 ° C 1 min, the final extension of 72 ° C 7 minutes. The 502 bp product was incubated with the restriction enzyme Pst1 and analyzed as above by electrophoresis.

The statistical analysis was performed in Excel with the Mega Stat version 2010 application. We look at the demographic characteristics of the study population, arithmetic average, standard deviation, minimum and maximum for age, and percentages for distribution by sex were considered.

Due to the low frequencies derived from a small sample, the hypergeometric distribution (Fisher's exact probability) was used. The multi-hypergeometric issuance was extended when more than two groups had to be compared [38].

The authorization was done for the Research Ethics Committee of the Central Hospital, "Dr. Ignacio Morones Prieto."

The diagnostic procedures inherent in the study were considered to be minimal risk and did not violate the rules of the Helsinki Conference of 1964 and its 2013 revision.

RESULTS

Tables 1 and 2 shows the distribution of 44 individuals; 33 with the disease according to the three already specific groups and 11 controls with distribution for sex and age, as shown in

	Female		Male	
Group	N°	%F	N°	%M
Dysautonomia	8	72.7	3	27.3
Migraine with dysautonomia	9	81.8	2	18.2
Migraine	5	45.5	6	54.5
Controls	6	54.5	5	45.5
Total	28	63.6	16	36.4

Vol. 5, No. 03; 2021

ISSN: 2581-3366

Table 1. Distribution by sex in each study group.

	Dysautonomia	Migraine/ dysautonomia	Migraine	Controls
Media	11.27	13.27	11.36	38.45
SD	2.42	1.48	2.71	9.09
Min	5	10	5	18
Max	14	15	14	49

Table 2. Distribution by age in each study group.

The female was predominant for the groups; dysautonomia (72.7%), migraine with dysautonomia (81.8%), and 54.5% of the control, but no for the case of migraine (45.5%). In migraines with dysautonomia, the average age between the migraine and the dysautonomia group (11.27 and 11.36 years) was 13.27 years.

For the mitochondrial polymorphism 16519C> T, we observed that its frequency differs significantly between the groups (multi-hypergeometric distribution p = 0.03), with a higher rate for migraine (72.7%) and the controls the lowest (27.3%) — table 3.

Group	Positive	Negative	Total	%Positivity
Dysautonomia	6	5	11	54.55
Migraine with dysautonomia	6	5	11	54.55
Migraine	8	3	11	72.73
Control	3	8	11	27.27

Table 3. Frequency of mitochondrial polymorphism in each group.

Polymorphism was not statistically significant in the migraine group with dysautonomia (p = 0.19), although in percentage, the frequency is double (54.5% vs. 27.27%). In the case of the migraine group, we found that polymorphism increases the risk (p = 0.04, OR = 7.1: 95% CI 1.2 - 43.2) when compared with the control group.

The genotypic frequencies of the alpha-adrenergic receptor are described in the following table:

	Arg/Arg (CC)		Arg/Cys (CT)		Cys/Cys (TT)	
Group	N	%	N	%	N°	%
Dysautonomia	2	18.18	7	63.64	2	18.18
Migraine with dysautonomia	2	18.18	7	63.64	2	18.18
Migraine	4	36.36	3	27.27	4	36.36
Controls	1	9.09	9	81.82	1	9.09

Table 4. Genotypic frequencies of the ADRA1A receptor polymorphism in each group.

Vol. 5, No. 03; 2021

ISSN: 2581-3366

We found that all groups showed a balanced frequency of genotypic frequencies analyzed by the Hardy-Weinberg law.

The genotypic frequency Arg/Arg is different between the groups with a statistical significance p = 0.015, finding a higher rate for the migraine group (36.36%). We found not a significant difference for migraines with dysautonomia (p = 0.25). In the case of migraine, we found p = 0.08, which, although it is not statistically significant, shows a clear tendency. It is essential to point out that the frequency tends to be higher regarding the control group (36.3% vs. 9.09%) as indicative of a possible association.

In the combined analysis of the presence of both mitochondrial polymorphisms, we found a statistical significance p = 0.014 of the frequency of distribution in all groups, with a higher rate in migraine (27.27%), versus the control group p = 0.05. It is notorious that no control was positive for both variants, and mathematically we cannot calculate the OR. Table 5.

Group	Positive	Negative	Total	%Positivity
Dysautonomia	1	10	11	9.09
Migraine with Dysautonomia	2	9	11	18.18
Migraine	3	8	11	27.27
Control	0	11	11	0.00

Table 5. Frequency of the combination mitochondrial polymorphisms + ADRA1A per group.

DISCUSSION.

The interaction of genetic variants and environmental factors may explain the origin of common diseases. Both; dysautonomia and migraine have a high frequency in the general population, predominantly in the female gender; the pathophysiology of both is not entirely clear, but they share pathways in their pathogenesis and are considered autonomic dysfunctions, frequently are presenting together [39].

The association of the mtDNA polymorphism 16519C> T to migraine Zaki et al. 23 found statistical significance 16519C> T in 52% of patients with migraine without aura compared with 27% of healthy controls. In 2016, Morales et al. found in the Mexican population a statistical significance (p = 0.03, OR 6.67) for this polymorphism in migraine patients with aura and maternal antecedents [35], in our study, it was observed that when comparing the four groups the frequency of this is higher in the migraine group (multi -hypergeometric distribution p = 0.03).

The Arg347Cys polymorphism of the ADRA1A receptor has been associated with regulating blood pressure and the autonomous control of the heart. Poor management of systemic blood pressure may be related to the polymorphic character of ADRA1A, which can be explained by the favorable response to alpha-adrenergic agonists such as midodrine in patients with postural hypotension [39].

Vol. 5, No. 03; 2021

ISSN: 2581-3366

Different population studies have described that the frequency of the normal allele (Arg) ranges from 0.35 to 0.48, and the rate of carriers is 0.499 +/- 0.019 [41]. In our study, the frequency of Arg was 0.5. Freitas et al. observed in young subjects homozygous for the Cys allele a tendency to increase systolic blood pressure and a longer PR interval [42]. Sorrentino et al., in a study of polymorphisms of alpha and beta-adrenergic receptors in population.

Italian with a diagnosis of vasovagal syncope, found no statistical significance for the frequency of polymorphism (Arg / Arg 32%, Arg / Cys 49%, Cys / Cys 19%) [31]. Hernández et al. They found statistical significance for the Arg / Arg genotype (OR = 13.21: 95% CI 3.69–54.99, p = .001), attributing a predisposing factor for vasovagal syncope [29].

We found no difference in the frequency of homozygous Arg / Arg and Cys / Cys genotypes among patients in the same group. We noted that the migraine group presented a higher incidence of the Arg / Arg variant (36% vs. 18% in dysautonomia with and without migraine), which makes us think it is related to its vascular theory. The control group had the highest frequency of heterozygotes (81.8%). This phenomenon could be explained by the heterozygous advantage (being a carrier of the Arg / Cys variant gives power in survival) over the normal homozygote and homozygous mutant [42,43].

In our knowledge, there are no studies in the literature that show an association of mitochondrial polymorphism 16519C> T plus the Arg347cys of the 1A adrenergic alpha-receptor with migraine and dysautonomia. When analyzing the combination of these, statistical significance was found in the frequency for migraine p = 0.05 compared to the control. It is striking that both polymorphisms presented a higher frequency in the migraine group related to its multifactorial etiology.

CONCLUSIONS

In our population, contrary to the study conducted in Mexico City, no association was found between the alpha-adrenergic receptor polymorphism in patients with dysautonomia, which may be influenced by differences in the environment and the characteristics of the study population.

Finding a higher frequency of alpha-adrenergic receptor polymorphism and mitochondrial polymorphism in patients diagnosed with migraine, we think that its pathophysiology may be mediated by genetic variability.

The high frequency of heterozygotes (Arg / Cys) in the control group can confer a state of normotension and protection against migraine in this population. We consider it necessary to expand the sample size in subsequent studies to confirm our results.

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Vol. 5, No. 03; 2021

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Vol. 5, No. 03; 2021

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