Journal of Pain & Relief
ISSN: 2167-0846
Research Article Open Access

The Clinical Profile of Migraine: Since The Molecular Changes Until The Semiological Manifestations

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Abstract

Migraine is a common and incapacitating neurological disorder affecting 10 to 20% of the world population; it is more common between females from 20 to 40 years old.

The objective of this paper is to carry out a brief, analytic, and practical review of migraine through a vision of connecting molecular to clinical perspectives. Migraine was an approach as a primary neuronal network disorder, and some controversial topics were analyzed. New pieces of knowledge have provided innovative possibilities for effective management for intractable cases, and it allows a better understanding of migraine complications.

Keywords: Migraine, Molecular features, Clinical profile

Introduction

Migraine is a common and incapacitating neurological disorder affecting 10 and 20% of the world population [1]. After the tension headache, the migraine is the second most frequent type of primary headache. Migraine affects around 12% of the adults in occidental countries; in US population studies, the prevalence of migraine is nearly 1 of 5 in women and 1 in 20 in men. The most (90%) of the migraineurs patients have moderate or severe pain, the majority (75%) of them have a loss of their labor and familial function during the head pain attacks, and one-third require bed rest during their attacks [2].

Background

Migraine used to have its onset during puberty; however, the major prevalence of patients who suffer this disease is between the 35 to 45 years old [3]; its incidence peaks between the ages of 20 – 24 years in female and 15 – 19 years in masculine [4]; in 9 of each 10 of patients' first attacks occurring before age 40 years [5] exists a peak of disability between 35 and 44 years [6]. Migraine distinguished by recurrent attacks of moderate to severe unilateral throbbing pain, often accompanied by nausea and photophobia, phonophobia, and other neurological symptoms such as enhanced sensitivity to light, sound, touch, and smell [7].

Migraine is classified into two major types: migraine without aura (MO), the most common type, and migraine with aura (MA) [8]. MA occurs in one-third of migraineurs further experience transient neurological symptoms mostly involving the visual system before or during a migraine attack, with visual, sensory, or another central nervous system (CNS) symptoms that appear before the headache and are associated with migraine, in the latter [7-8].Other subtypes have been classified, including chronic migraine and episodic syndromes associated with migraine. The hemiplegic migraine (HM) is a rare, familial, and severe subtype of MA. In this subtype, the migraine manifestations include motor symptoms such as transitory numbness or weakness, affecting one side of the body (hemihypoaesthesia or hemiparesis) [8] and typical aura without headache (TAWH) is a rare type of MA, which incidence is 3% in women and about 1% in men, respectively of migraine with aura patients group [9].

Understanding migraine physiopathology has substantially increased during the last decades. However, some critical knowledge was previously observed; four centuries ago, Sir Thomas Willis suggested vascular inflammation theory to explain migraine. During the 1940s decade, it was proposed that symptoms of migraine with aura could be due to a propagating cortical phenomenon, called cortical spreading depolarization (CSD), this theory was abandoned due to the advent of vascular theory as a central event in this disease proposed by Harold G. Wolff [10];currently, it has been exceeded.

The quest of this review paper is to bring out a brief, analytic, and practical review of migraine through a vision linking molecular to clinical perspectives. Although clinical symptoms were described for a long time, molecular and genetic knowledge has exhibited a new way to understand and management of migraines to reach precision medicine of the century

Migraine pathophysiology: stages and phases

At present, migraine etiology is unknown, and its pathophysiology does not wholly understand; in the last decades, the trigeminovascular system has been related with definitive influences in the physiological alterations in this disease, and this relationship has been confirmed, so that it was modified migraine comprehension. It is widely accepted that migraine must be approached as a complex brain network disorder with a genetic basis. The clinical picture involves multiple cortical, subcortical, and brainstem regions to try to account for the pain and the vast constellation of symptoms characterizing the migraine attack [11-13].

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Received July 18, 2020; **Accepted** August 03, 2020; **Published** August 11, 2020

Citation: Silvia G, Jiménez MKV, Estrada SLA, Suárez SS, Aguilar SQ. et al. (2020) The Clinical Profile of Migraine: Since The Molecular Changes Until The Semiological Manifestations. J Pain Relief 354.

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Some migraine issues have reached consensus. Others are still polemic. It is an agreement migraine is a neuronal network disorder, involving integrated activities across subcortical and cortical brain circuits that are important in headache and altered sensory processing [12]. It is controversial if changes in the brain in migraine are genetically determining or due to chronic pain; in fact, both are possible.

According to the current migraine perspective, this analysis was divided into a) inter-ictal stage (brain alterations in migraine people, without migraine attack), b) ictal stage(premonitory phase, aura phase, headache phase, postdrome phase) and an unanswered question in migraine how does a migraine attack stop? finally, it concisely approaches topics as migraine chronic, CGRP and migraine, migraine and genetics, sleep and migraine, and psychiatric comorbidities in migraine.

The dysfunction in the migraine of the trigeminovascular system is characterized by the release of CGRP (peptide related to the calcitonin gene), causing vasodilation. It is associated with aseptic inflammation that initiates the transmission of the nociceptive impulse to the trigeminal ganglion (GT) until caudalis trigeminal nucleus (first-order neuron). Furthermore, from there to second and third-order neurons where various neurotransmitters such as norepinephrine (NA), Serotonin (5HT) and Dopamine (DA) are involved, and structures play a different role (coeruleus nucleus, periaqueductal gray matter, hypothalamus, thalamus, and cerebral cortex) which are involved in premonitory symptoms, attack of pain and postdrome symptoms.

Inter-ictal stage (brain alterations in migraineurs patient)

The brain of migraine people brain works differently than non-migraine people. However, it does not know how or when changing occurs. The evidence supports that a genetic predisposition and too repetitive ambient events must match in disease devolvement. Triggering events produce a migraine attack only in migraineurs; the brain in migraine has changes of neural cells in basal conditions so that neurons will able to respond to activation for internal or external stimulus [12].

In imaging studies have been observed both structural and functional brain alterations in migraine individuals. Additionally, it has been found in clinical and neurophysiological observations, a chronic hypersensitivity to sensory stimuli, and cortical excitability. All of this may make these patients susceptible to CSD devolvement; both are particular changes in migraine [14-17]; these modifications in the brain of migraine patients can be the result of repetitive exposure to pain and stress; besides that, the brain biology of migraine sufferers appears to differ from healthy controls [18].So that migraine attack may be triggered by several external factors, including lack of sleep, stress, prolonged fast, between others, but these trigger factors only lead to migraine attacks in migraineurs.

Brain changes in migraineurs have been consistently demonstrated. It was recognized structural differences in migraineur's brain vs. control subjects; in structural analysis using the cross-sectional method was observed changes in the via of functional interactions of pain processing areas with the trigeminal system; in Voxel-based morphometry confirmed reduction in the grey matter processing areas of pain. These areas are the anterior cingulate cortex, amygdala, insula, operculum, and the frontal, temporal, and precentral gyri. Peculiarly, grey matter reduction in the anterior cingulate cortex was associated with the frequency of migraine attacks [19].

An interesting Meta-analysis [20] that included eight clinical studies with 390 subjects (191 patients and 199 controls), and five functional studies with 199 participants (93 patients and 96 controls), many morphological and functional modifications were documented. In Activation Likelihood Estimation (ALE) showed that the migraineurs had concordant decreases in the Grey Matter Volume (GMV) in the bilateral inferior frontal gyri, the right precentral gyrus, the left middle frontal gyrus, and the left cingulate gyrus; and GMV decreases in the right claustrum, left cingulated gyrus, right anterior cingulate, amygdala and left parahippocampal gyrus and were related to the estimated frequency of headache attack. Also, activation was found in the somatosensory, cingulate, limbic lobe, basal ganglia, and midbrain in migraine patients. This meta-analysis concluded that gray matter changes in migraineurs could be the mechanism of pain processing and their associated symptoms. Even more, modifications in the frontal gyrus might predispose a person to pain conditions and in limbic regions could be accumulated damage due to the repetitive occurrence of pain-related processes; finally, increased activation in the precentral gyrus and cingulate opposed to GMV decrease might suggest increased effort due to disorganization of these areas and the use of compensatory strategies involving pain processing in migraine.

As well, voxel-based morphometry with T1-heightened 3T MRI showed lower grey matter density in the right hemisphere (inferior parietal, inferior temporal gyrus, superior temporal gyrus), and left temporal pole during the interictal period in migraine without aura patients [21]. These observations suggest plastic changes attendant to the migraine attack that may underlie disorder progression, but it remains unclear if they are the migraine cause or effect.

Also, it has been demonstrated that the possibility to develop migraine attacks can be provoked by functional or structural alterations in pain processing areas such as the anterior cingulate cortex and the trigeminal somatosensory system, again, it is unclear if these changes are the consequence of the episodic migraine attacks or if they are related in its pathophysiology [22].

Basal Nuclei and their connections also have exhibited changes in brain migraine; grey matter in both caudate nuclei are enlarged in migraines with high-frequency attacks vs. patients with low-frequency attack [23]. The somatotopic representation of head and face in the somatosensory cortex is observed increased thickness vs. controls. Moreover, there is a reduced fractional anisotropy in migraineurs along the thalamocortical tract. In migraineurs with aura, this change is also observed in the ventral trigeminothalamic tract, and the ventrolateral periaqueductal gray [24]. An international study 3T scans from 131 migraineurs showed volume loss in patients compared with controls in the central nuclear complex, anterior nucleus, and lateral dorsal nucleus, as well as reduced striatal volume [25].

Hippocampus has been of particular interest in migraine, a review by Liu et al [26] found that there was decreased volume in newly diagnosed migraine patients after one year; it observed an adaptive volume increase to low headache frequency; interestingly, the volume decreases at higher headache frequency as the maladaptive response. Nociceptive activation hippocampal is more significant in patients with migraine compared to healthy controls and correlated to headache frequency. More significant deactivation and higher functional connectivity linked to other pain-processing regions in low frequency compared to high-frequency migraineurs were documented; at resting state (inter-ictal stage), intraregional functional connectivity of hippocampus was lower, and its connectivity to other brain regions was different in patients carrying specific genetic variants so that supporting the genetic origin of this modifications. Also, these authors found more reliable connectivity between the hippocampus and other cortico-limbic regions, and some of the altered connectives are responsible for

migraine-associated allodynia or placebo effect of migraine. Finally, they concluded headache frequency, and the growing number of migraine attacks, the anxiety score, the depression score, and genetic variants can be related to hippocampal morphology and functional changes in people with migraine.

The thalamus is an important sensorial relive; it is a nociceptive nuclei station where arrives information from the dura mater, and cutaneous regions, are conveyed through second-order trigeminovascular neurons. It is considered a central area for the processing and integration of nociceptive stimuli, and its connection to different cortical areas such as the somatosensory, limbic motor, visual, auditory, and olfactory regions can explain the complexity of migraine features [27,28]. Thalamo-cortical transmission is continually modulated by different pathways involved in cognition, emotion, and autonomic responses. It has been reported structural and functional thalamic alterations in migraineurs during the ictal and interictal stages, which can be detected from childhood and might be related to the onset of the migraine attack. The thalamus has shown to be a critical area for the development of sensory hypersensitivity to visual stimuli and mechanical allodynia [24,25,29-33,35].

All these anatomic and functional findings in both ictal and inter-ictal stage support that the brain of the patient with migraine is functional and morphologically different; and can explain why external or internal stimuli produce migraine attacks only in migraine people. More brain structures are in a study in migraines, y surely new knowledge could change the approach of migraines.

During inter-ictal stage migraine, patients kept asymptomatic; again, if these differences are genetics or acquired still debate, of course, both are possible.

Ictal stage

(premonitory phase; aura phase; headache phase; postdrome phase and an unanswered question in migraine. How does a migraine attack stop?)

Premonitory phase

A premonitory phase is a period between alterations homeostasis and the onset of migraine attacks. This phase can begin as early as three days before a migraine headache and allows some patients correctly to predict migraine attack up hours or days before its beginning [ ]. The majority of migraines experience a range of premonitory symptoms well before the typical migraine headache initiates. Despite being described for a long time, their pathophysiological relevance and their clinical implications have been primarily neglected [37].

Patients' symptoms include fatigue, mood changes, food cravings, yawning, muscle tenderness, and photophobia, the involvement of the hypothalamus, brainstem, limbic system, and assured cortical areas during the early stages of an attack have been observed [38,39] From the observation of that in some patients, the migraine attack is triggered at a specific time of day. This "time-triggering" has been associated with circadian alterations in homeostasis. So that, it was suggested that the involvement of chronobiological mechanisms in migraine pathogenesis pointed to the hypothalamus as a potential area of origin of premonitory phase and the migraine attack [8,40,41]. Also, imaging studies using H2O PET show an increase in hypothalamic blood flow during the presence of premonitory symptoms [42] supporting the theory that the hypothalamus is the area of origin of a migraine attack.

Other researchers have focused their study on other diencephalic structures; some are considering the hypothalamus as the first generator of a migraine attack [42]. In positron emission tomography using cerebral blood flow as a marker of neuronal activity in patients with glyceryl trinitrate-induced migraine attacks, activations were observed in the posterolateral hypothalamus region, midbrain tegmental, the periaqueductal gray, in dorsal pons, and various cortical areas during this phase. Moulton et al. [43] using functional magnetic resonance imaging during the interictal phase detected sturdier functional connections between the hypothalamus and other areas of the encephalum related to pain transmission and autonomic function in subjects with migraine compared with healthy controls, which may account for some of the autonomic symptoms manifested during interictal and premonitory phases. Molecules in high concentration in the hypothalamus as Dopamine, Vasopressin, and the orexins are associated with the premonitory phase. Thus, the hypothalamus involvement during the early stage of migraine has achieved an absolute consensus, so that it was postulated that the hypothalamus is a basic structure for facilitating and amplifying pain transmission during a migraine attack. To explain how the hypothalamus participates in migraine attacks have been proposed several theories. One of them proposes that there is an increased parasympathetic activity over the meningeal nociceptors. Another hypothesis involves the modulation of nociceptive signals from the spinal trigeminal nucleus to supratentorial structures implicated in pain processing [44,45]. However, despite the evidence, it has not reached consensus about of hypothalamus role as an initial trigger of migraine attacks.

In the recent International Classification of Headache Disorders 3rd edition (ICHD-3), the migraine with aura has been defined as recurrent and episodic events. These attacks are lasting minutes of unilateral, fully reversible, visual, sensorial, or other CNS manifestations that, in general, develop gradually and are usually followed by headache and other associated migraine symptoms [8]. At least 33 % of migraine attacks are preceded by an aura [46] the most common aura symptoms are visual disturbances, others frequent symptoms include sensory, speech/language, and motor disturbances, plus the disruption of higher cortical function [47]. Aura phase happens immediately preceding or concurrent with the headache.

Cortical Spreading Depression (CSD) is a unique event in the brain of the migrainous during the aura phase. It was described in 1944 by Aristides Lao, which is characterized by a slow, the wave propagation of this depolarization in neuronal and glial cell membranes that is followed by inhibition of cortical activity for up to 30 minutes, strongly coinciding with the initiation and progression of aura symptoms [48-52].

CSD is associated with a phase of hyperemia, followed by a prolonged phase of cortical oligemia [53,54]. This slowly propagating wave of intense but transient regional depolarization of most neurons and glia (possibly all brain cells). That propagates at velocities of ~ 3 – 5 mm/min in brain tissue and ~1.7 – 9.2 mm/min in the gray matter [55], lasting up to a minute or more in otherwise healthy tissue due complete membrane depolarization impedes action potentials and synaptic transmission; it is accompanied by suppression of all spontaneous or evoked electrical activity in that region. Thus it was called "depression"; however, the term depression is a misnomer as the underlying electrophysiological process is a near-complete and prolonged depolarization (i.e., strong excitation) [56].

CSD initiation and propagation mechanisms are not entirely understood. Local elevations initiate the CSD in extracellular potassium (K+) resulting from chronically depolarize cells. This accumulation of extracellular K+ seems to be the consequence of recurrent depolarization and repolarization of preexisting in cortex neurons, and

additionally, accumulation of K+ extracellular produces a depolarize of the same cells from which it was released [50,51,55,57,58].

The excessive efflux of K+ yields significant disruption of cell membrane ionic gradients with the influx of sodium (Na+) and calcium (Ca2), and glutamate is released [58]. The exchange of intracellular and extracellular components during CSD is composed of a sizeable ionic influx (Na+, Ca2+), and water. Furthermore, efflux of K+, H+, glutamate, and adenosine triphosphate (ATP); the increase of extracellular K+, rather than glutamate diffusion, might be the leading event that depolarizes adjacent cells [59,60].

Even more, for CSD propagation, several hypotheses have been proposed; current evidence suggests the propagation is regulated via gap junctions between glial cells or neurons, the opening of neuronal Panx1 mega-channels releases molecules that trigger an inflammatory cascade, which activates neighboring astrocytes and leads to sustained release of inflammatory mediators [50]. Further, many studies support that CSD could activate trigeminal nociception and thus trigger headache mechanisms [61,62]. However, there is no consensus about that CSD is the cause of the initiation of headache [63].

If CSD activates trigeminal nociception and thus triggers headache mechanisms is still controvert, but its relation with the aura, in particular the visual aura, has reached consensus [64] it has postulated that a positive symptom results from cortical hyperexcitability of a cerebral region while the scotoma (negative symptom) is related to an area of diminishing of cortical activity spreading across the visual cortex. The CSD has a congruent temporal pattern, and spread raised the possibility that CSD was the underlying electrophysiological event of the aura in migraine [64].

It is essential to highlight the association of CSD to oligemia. In cerebral blood flow measurements studies in migraine patients were observed phenomena of cortical electrical spreading and oligemia during migraine attacks with aura [65] these modifications were confirmed through imaging and physiological tests and its association to the perception of visual symptoms and CSD-typical, however, in imaging studies were observed that in the hypoperfusion associated to migraine aura, the timing and distribution of this hypoperfusion is not rigorously correlated with specific migraine symptoms [66,67]. Non-visual symptoms of aura as sensorial, sensitive, cognitive symptoms, and others, are a challenger in their explication. Some migrainous with aura sufferer experience sensory and visual symptoms simultaneously (i.e., without succession) thus is possible in addition to spread, CSD may be generated in different cortical regions simultaneously [68].

There have been demonstrated the modifications in sanguine flow and changes in blood vessel caliber during a migraine attack; this change is not always correlated to a specific migraine clinical phase. Clinical relationship between the aura and headache in migraine people are still in debate; while some migraine attack will experience aura without headache both the most of them the aura are accompanied by headache (91%); although, the headache can occur before or simultaneous with aura, in the most of cases (78%) happen after the aura starts (during the aura phase in 28.7%; at the cessation of the aura in 12.1%; or after aura cessation in 37.6% of the attacks) [64,68].

Accordingly, and despite still many events that must be elucidated, cortical spreading depression (CSD) concept was a turning of in our clinical understanding of migraine. However, most of the migraine attacks are not preceding by clinical aura; in fact, the aura may occur after the headache has begun, and some patients may experience aura but not the subsequent headache, so that relationship aura headache in migraine is not definite yet.

Headache phase

Activation of the trigeminovascular system

Trigeminovascular system is one of a critical structure in the expression of migraine headache; this system includes the peripheral axons from the trigeminal ganglion to reach the meninges and intracranial arteries and converge in of the trigeminocervical complex (TCC) that contain the trigeminal caudalisnucleus until the dorsal horn of C1 – C2 segments of the spinal cord.

The complex brain network disorder is kept on control during the inter-ictal phase, but when the control by the brain is of its homeostasis, leading to the activation of the trigeminovascular system and a cascade of events occurs [12]. Trigeminal activation starts in the headache phase; thus, TCC activation is a cardinal event to the cascade of happenings resulting in the migraine pain due to its direct connection with crucial brain centers such as diencephalic and brainstem nuclei [69,70].

TCC outputs fibers converge with projections from extracranial structures neurons that accounts for pain perception in the periorbital, occipital, and cervical-neck regions. Afferent pathways from the TCC transmit multiple signals to different places: the brainstem, thalamus, hypothalamus, and basal ganglia nuclei. These nuclei send connections to multiple cortical areas, including the somatosensory, insular, motor, parietal association, auditive, visual, and olfaction cortices. All these areas are involved in processing the cognitive, emotional, and sensory-discriminative aspects of the nociceptive signals and give an increase to some of the characteristic symptoms of migraine attacks, such asphotophobia, phonophobia, cognitive dysfunction, osmophobia, and allodynia [27,71,72]. Nevertheless, the causes of the losing of brain homeostasis and the subsequent TCC activation are uncertain.

Trigeminovascular pathway activation phenomebegins peripherally after nociceptive neurons from the dura mater are stimulated and discharge vasoactive neuro-peptides, causing signaling along the trigeminovascular pathway. TCC activation takes place by turning on nociceptors that innervate the blood vessels of the skull (starting with the turn-on of trigeminal bipolar neurons, thought to ventral-posterior-lateral thalamic nuclei and, finally, sensitive cortical areas [47]. Perivascular neurons send signals through transmitted by endogenous mediators, among them: a) vasoactive neuropeptides, b) calcitonin gene-related peptide (CGRP), c) substance P, neurokinin A, and pituitary adenylate cyclase-activating peptide (PACAP), as well as the release of vasoactive inflammatory mediators such as nitric oxide associated to meninges inflammation [13,45,46,63,73]. When activation reaches nociceptive neurons that innervate the dura mater, and vasoactive neuropeptides are released, both begin signaling along the trigeminovascular pathway. The arterial vasodilatation, mast cell degranulation, and plasma extravasation are involved, and the physio-pathogenesis remains unclear.

As it was the comment above, some researchers have proposed that CSD beginning the activation of meningeal nociceptors through released of ATP, glutamate, K+, hydrogen ions, CGRP, and nitrous oxide; these molecules diffuse toward and activate meningeal nociceptors; this neuronal activation occurs approximately 14 minutes after CSD had been induced, reliable with the time between the onset of aura and onset of migraine headache. Otherwise, CSD may increase the activity of central trigeminovascular neurons in the spinal trigeminal nucleus, supporting that CSD results in order activation of peripheral and then central trigeminovascular neurons

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released ATP, glutamate, K+, hydrogen ions, CGRP, and nitrous oxide. These molecules diffuse toward and activate meningeal nociceptors; this neuronal activation occurs approximately 14 minutes after CSD had been induced, reliable with the time between the onset of aura and onset of pain headache [62]. Otherwise, CSD may increase the activity of central trigeminovascular neurons in the caudally trigeminal nucleus. All of this is supporting that CSD results in a sequential activation starting with the peripheral and then central trigeminal neurons [74].

Additionally, studies preclinical have exhibited, that CSD can disinhibit central trigeminal sensory neurons by a mechanism intrinsic; and sensory blockade of the trigeminal ganglion did not interrupt CSD-induced activation of second-order trigeminovascular neurons in the TCC [75]. Hence it could elucidate some clinical observations as the development of mechanical allodynia (neck discomfort) before the development of headache. The timing between aura to migraine headache symptoms have been evaluated, and it immensely varies according to the aura symptoms; many patients have manifestations such as nausea (51%), photophobia (88%), sonophobia (73%), and head pain (73%) during the aura phase. Around 11% reported the headache as starting simultaneously with the aura [76].

Peripheral Sensitization.

After peripheral trigeminovascular neurons are activated to become sensitized to dural stimuli, their threshold decreases, and the magnitude of their response increases, which considered to be responsible for the characteristic throbbing migraine headache, and its exacerbation by bending over or coughing. Peripheral Sensitization increases sensitivity to sensory stimulation perhaps by hyper-responsiveness within primary afferent fibers and central neurons; Inflammatory mediators that stimulate activation and sensitization of peripheral trigeminovascular neurons remain no understood [77].

Central Sensitization

Sensitization of trigeminovascular neurons in the TCC and thalamic nuclei are responsible for cephalic and extra cephalic allodynia and produce a raising spontaneous neuronal activity and a heightened response to innocuous stimuli. In Cephalic allodynia from sensitization in the spinal trigeminal nucleus, clinical symptoms are scalp pain and cephalic muscle tenderness; these symptoms develop over 30-60 minutes reaching a maximum after 2 hours. Thalamic sensitization is delayed; it starts after 2-4 hours and is responsible for extracephalic allodynia. This cutaneous allodynia may occur by repeated activation and sensitization of the central trigeminovascular pathways, hence persistent central sensitization increasing the risk for developing chronic migraine [78,79]; hence, sensitization of pain relevant brainstem regions, including peripheral trigeminovascular neurons to dural stimuli, is thought to produce the peculiar sensation of throbbing pain in migraine [38,43].

Besides, nociceptive trigeminovascular signals reaching the thalamus may be modulated by the release of neuropeptides/ neurotransmitters from hypothalamic and brainstem neurons [7]. They are regulating the firing of spread trigeminovascular neurons. The excitatory activity can shift the firing of thalamic trigeminovascular neurons to tonic mode. Contrary, if neurotransmitter is inhibitory, the shift is to burst mode [ ]. The inputs from hypothalamic and brainstem neurons can hence provide high and low setpoints for the allostatic weight (the amount of physiological or emotional stress that can be managed by the brain). In patients with migraine and consequently determine whether nociceptive signals are transmitted to the cortex (pain cortical involvement) [7,81].

Additionally, migraine-associated symptoms, such as nausea, vomiting, thirst, lacrimation, nasal congestion, and rhinorrhea, are revealing central autonomic function dysfunction. There is an alteration in both the sympathetic and parasympathetic systems. The alteration can be observed since the premonitory phase through to the postdrome. That can explain that stress, awakening, or other changes in physiological or emotional to be migraine triggers by increased parasympathetic activity, subsequently activation of meningeal nociceptors [50,82]. The Sympathetic activation into the meninges produces the release of norepinephrine. Turning on the dural afferents fibers, and dural fibroblasts yield pro-nociceptive signaling activity [83].

The kappa-opioids system is activated in response to stress-induced corticotropin-releasing hormone and dynorphin release and may also play a role in stress-induced migraine. These changes involve complex networks projecting to preganglionic parasympathetic neurons in the superior salivatory nucleus. This activation results in peripheral nociceptor activation through the release of neuropeptides of a parasympathetic efferent neuron that innervate the meninges and meningeal blood vessels; sympathetic activation into the meninges encourages norepinephrine release followed beginning to pro-nociceptive signaling through actions on both afferents fibers and fibroblasts dural [84,85].

The complete explanation of the headache migraine remains a challenge. Although during the last decades of the XX century were proposed that migraine may be related to a sterile inflammation of the dura mater (neurogenic inflammation). The pharmacological blockers of specific plasma protein extravasation as acute or preventive migraine treatments can be used [86,87].

In human studies was observed the role of the brainstem regions in migraine headaches. Especially the periaqueductal grey matter (PAG) and the dorsolateral pons (DLP) in migraine attacks, has been called the 'migraine generator' [14,33,88,89]. Subsequent experimental observations supported that the brainstem might act as a driver of changes in cortical activity during a migraine; the role of the rostral ventral medulla, the locus coeruleus, the superior salivatory and cuneiform nucleus—in the modulation trigeminovascular pain transmission and autonomic responses in migraine is well established [11,89,90].

Additionally, there is evidence showing antimigraine drugs such as triptans, ergot derivatives, and CGRP receptor antagonists can precisely modulate activity in the trigeminal-cervical complex, which might explain their effect in aborting migraine [91-96]. Despite these pieces of evidence, the validity of the brainstem generator theory has been widely debated in the last few years, so diencephalic structures and cortical areas have been proposed.

Furthermore, Calcitonin gene-related peptide (CGRP) has gained significant importance in the migraine approach and has been implicated in the development of new therapies for migraine management, which target is this molecule [97]. Nevertheless, in migraine are involved a complex network of structures of Peripheral Nervous System, brain and many molecules, so that, CGRP must not be to consider a panacea for this condition only as a promising option.

Undoubtedly, the activation of the trigeminovascular complex is linked to migraine pain. However, many questions remain still unanswered.

Postdrome phase

The postdrome phase includes diverse clinical manifestations similar to those occurring during the premonitory phase. This migraine

phase has been for a long time neglected; however, its understanding could open new options in migraine management. The findings from studies that have focused on this last phase of a migraine attack indicate that its characteristic symptoms reflect those observed during the premonitory phase [98-100].

A prospective electronic diary study showed that 81% of patients are left disabled with non-headache symptoms in the migraine postdrome. These patients report at least one of them; also, it was documented in Functional Imaging widespread reduction in the blood flow in the postdrome, which may explain the arrays of symptoms experienced [101]. Hence, it is crucial to know this phase better and hope that more effective treatments will become available shortly to lessen the morbidity associated with this phase.

Many and varied symptoms are included into Postdrome syndrome, the more common are: tiredness (71.8%), head pain (33.1%), cognitive difficulties (11.7%), 'hangover' (10.7%), gastrointestinal symptoms (8.4%), mood change (6.8%), and weakness (6.2%); they may follow to the resolution of the headache, persisting for up to 48 hr [100, 101].

It has been proposed that Postdrome syndrome symptoms might reflect a slow decline in migraine processes that could be accounted for by involvement of the whole brain, remarkably the frontal lobes, and the hypothalamus. Thus, these symptoms could be explained by a diffuse cortical and subcortical involvement. Also, It has suggested might be explained by widespread vasoconstriction mediated by an alpha2-adrenoreceptor by activation of brainstem nuclei, and locus coeruleus might play a pivotal role in this process. An alternative hypothesis put forward that hypoperfusion associated with cortical spreading depression is keeping during the migraine headache until the postdrome stage [102], so it remains unclear whether these symptoms initiate in the premonitory phase and persist throughout the headache phase into the postdrome phase, if they may also initiate during the headache phase, or even appear after the headache phase has ended.

Migraineurs commonly relate symptoms of the postdrome phase as an effect of the medication that successfully abolished their headache, indicating that these symptoms may appear or reappear after the headache phase has ended. A meta-analysis of clinical trials revealed that postdrome symptoms are seen in the placebo arm most prominently when pain is relieved. Which does not support that these clinical manifestations are from the pharmacological origin [103].

Innovative neurological techniques will be a valuable noninvasive tool to push the frontiers in the understanding of migraine pathophysiology. These methods may help shed further light on the possible links between fundamental brain areas and their networks that could be implicated in the pathophysiology of the various migraine phases.

Why is migraine over the attack?

For most patients, the migraine attack spontaneously ends after some hours to start. It is also frequent that certain events, such as emesis or sleep, to abort migraine completely; these features imply effective regulation itself, rather than a passive process into the cessation of a migraine attack; but implicated mechanisms are not complete comprehended [104].

It has widely documented that ascending connections from the TCC forward several areas of the brain are involved in the nociceptive somatosensory information from the head and face, which determines how the pain is perceived. Also, many endogenous mechanisms modulate trigeminovascular nociceptive traffic, which can further determine the perception of this information. There is convincing evidence of the brain stem activation and diencephalic nuclei before, during, and after the cessation of the migraine attack, which cannot be explained as solely a consequence of the pain response [33,38,105,106].

Migraine headache triggers a complex endogenous analgesic mechanism; descending modulation of somatosensory processing is knowing since a long time; however, from brain stem modulation can have both a facilitator effect, contributing to chronic pain and an inhibitory influence, through supraspinal and spinal stimulation, on spinal nociceptive processing [107-109]. Some brainstem nuclei can be headache activators and trigger analgesic mechanisms according to the timing of migraine attacks.

Many molecules and neurotransmitters are involved in the endogen analgesic mechanism; knowledge improves about these endogen analgesic mechanisms could provide new and better options for migraine headache management, and understanding to progression to chronic migraine form could help to establish strategies to avoid this progression.

Finally, understanding the factors associated with headache beginning and cessation might provide insights into the mechanisms of attack initiation and termination, and perhaps shed light on the issue of why there being different subtypes of migraine [110-112].

Migraine and genetics

Relationship between migraines to genetic has been studied a long time, but in the last decades has been intensified; its heritability unquestionable, its higher prevalence in women, and the neuronal hyperexcitability have been the essential topics from which the genetic study has been developed.

Heritability is a convincing argument about genetics implications in migraine understanding. A study compared the prevalence and heritability of migraine across six of the countries that participate in the GenomEUtwin project. It was included a total number of 29,717 twin pairs, the heritability it was found from 34% to 57% [113]. Family and twin studies estimate its heritability of 42% (95% confidence interval [CI] = 36 – 47%) for migraine [114]; in other words, 42% of the migraine phenotype is attributable to the genetic material.

The heredity of migraine is likely to differ according to the migraine type. In population-based study relatives, the first degree relatives of probands of migraine without aura had double the risk of migraine without aura (compared with the general population) and 1.4 times the risk of migraine with aura. In essence, the first degree relatives of probands of migraine with aura had nearly four times the risk of migraine with aura and no increased risk of migraine without aura [115-117].

Familial hemiplegic migraine (FHM) is a rare form of migraine characterized by migraine attacks accompanied by transient unilateral motor weakness, with inherited in an autosomal dominant pattern; FHM was the first migraine-type with clear association genetic identified. Genes identified in FHM encode for proteins that modulate the availability of glutamate at synaptic terminals. Thus increasing neuronal excitability and have been classification in three types: a) Familial Hemiplegic Migraine type 1 (FHM1) is related to a mutation in CACNA1A on chromosome 19p13 that encodes for the α 1 subunit of voltage-gated Ca21 channels that control neurotransmitter release at synapses. b) Mutations provoke familial Hemiplegic Migraine type 2 (FHM2) in ATP1A2 on chromosome 1q23, which encodes for the α 2 subunit of Na1/K1-ATPase, which is expressed in the glial cells and

reuptake glutamate from the synaptic cleft. Either FHM1 as FHM2 mutations provoke hyper excitatory activity through the unregulated release and reduced reuptake of glutamate from the synaptic cleft. Furthermore, FHM type 3 (FHM3) results of a mutation in SCN1A on chromosome 2q24 that encodes for the α 1 subunit of voltage-gated Na1 channels which are expressed on inhibitory interneurons and cause unregulated firing of excitatory neurons [118,119].

Even though agreement about FHM is a genetic form of migraine, most of the migraine cases are polygenic and multifactorial (environment) forms; thus to find the genes panel involved for each population is a challenge.

Neurophysiological studies have confirmed the presence of general neuronal hyperexcitability in the brain of migraine patients [120]. This neuronal excitability increasing occurs to respond to a wide range of stimuli (visual, somatosensory, and auditory and brainstem reflexes) in response to nociception. [121,122]. Also, the encephalic structures of migraineurs patients display a lack of habituation in answer to repetitive stimulation [123]. As it has commented above, the brain of migraine patient is hyper-responsive to sensory stimuli during the interictal phase [124,125]. Thus it has been considered that the general neuronal hyperexcitability could elucidate the increased sensitivity to sensory stimuli observed in patients with migraines during the interictal phase [126] and its hyper-responsiveness contribute to the development of central sensitization. It can explain why there is greater activation in pain-facilitating regions and decreased activation in pain-inhibiting regions as a response to painful stimuli in patients with migraine [127]. Once neuronal hyperexcitability and hyper-responsive to sensory stimuli were documented in the brain of migraines patients, the following question was: why do they occur?

Genetic variations associated with migraine may provide insights into the mechanism(s) for the generalized neuronal hyperexcitability seen in these patients [128,129]. Even though genetic association studies have revealed the molecular mechanisms that contribute to pathophysiology, however, understanding has been limited partly because, to date, only a few genome-wide significant risk loci have been identified related to the prevention of migraine.

The underlying basis for cellular hyperexcitability in migraine is unclear. Nevertheless, genetic factors seem to play a crucial role; sizeable genome-wide association studies (GWAS) have identified genetic loci, which could predict susceptibility to suffering migraine both with and without aura. The susceptibility genetic variants identified some of them might regulate glutamate-mediated neurotransmission (MTDH, LRP1, MEF2D genes). In contrast, others regulate growth, evolvement, and plasticity synaptic (ASTN2, FHL5 genes) and ion channels (KCNK5, TRPM8 genes), in addition to ion homeostasis (SLC24A3, near ITPK1, near GJA1 genes) [130-133].

The involvement of the vascular system and migraine has been investigated form a genetic perspective. A meta-analysis [131] of 22 GWAS, Single Nucleotide Polymorphisms (SNP) associating to migraine involved in arterial smooth muscle function, that alterations in vascular smooth muscle function are likely to play a more critical role in migraine pathogenesis; this is consistent with the increased risk of stroke and cardiovascular disease in migraine patient, especially in migraine with aura patient. It is also consistent with the predominance of the central neuronal mechanisms immersed in migraine, assuming a very close anatomical and physiological relationship between the blood vessel and neuronal and glial cells in the neurovascular unit [134]. The regional cerebral blood changes have been different in MA and MO so that some researchers had considered both MA and MO as different entities. However, at present, the most agree both are the same entity [135,136].

For a long time, the participating in genetic in migraines has reached a consensus, which genes and epigenetic mechanisms are involved remain in the study.

CGRP and migraine

Currently, CGRP as a target to management migraine attack is a topic to analyze. What is the peptide CGRP? This CGRP is a 37 amino acid neuropeptide encoded by the calcitonin gene (CALCA) which perform an essential role in cardiovascular, digestive, and sensory functions; CGRP and its receptors are expressed all over the body, predominantly in the central and peripheral nervous systems, the cardiovascular system and the gastrointestinal system [137,138].

The CGRP has been implicated in the neuronal sensitization and pain genesis, most markedly in meningeal vessels in the migraine [139]. Substantial evidence supports CGRP is a crucial player in the pathogenesis of migraine. The CGRP is a potent vasodilator that is localized in afferents innervating blood vessels [139]. CGRP is also working as a neuromodulator that can enhance synaptic transmission mediated by glutamatergic signaling; CGRP can be finding in jugular venous blood during migraine attacks [140]; intravenous application of CGRP triggers migraine attacks only in migrainous patients [141,142].

CGRP seems to act at CGRP seems to act at different levels along the trigeminovascular pathway; peripheral release of CGRP in the meninges sources arterial vasodilatation, and can outcome in sterile inflammation meningeal and activation of meningeal nociceptors; further, by the way indirectly to produce plasma extravasation by increasing substance P release CGRP in the TCC may facilitate nociceptive transmission by increasing the release of neurotransmitters from adjacent primary afferent terminals [138-140].

New strategies in migraine management blocking CGRP receptors are available; they are very promising, particularly in chronic migraine.

Chronic migraine

Chronic migraine is a common cause of chronic daily headache (CDH) disorders, is characterized by the frequency of headache attacks with at least 15 headache days per month; the attacks are less intense and use to be atypical but is associated with worse treatment response. Undertreated headache and associated comorbidities in CM cause a more significant disease burden compared with EM patient [140-141]. It is estimated that approximately 3% of Episodic Migraine (EM) patients evolve to CM per year[142], it is remarkable the bi directionality between EM and CM, it is remarkable the bi directionality between EM and CM about 26% of CM patients remitting to EM in a two-year follow-up [143], which makes it difficult to confirm the accurate prevalence of CM. Although EM and CM are regarded as the same illness [144], pathophysiology CM is not fully understood. However, several predisposing factors have recognized, such as medication overuse, insufficient migraine prophylactic treatment, low socioeconomic status, stressful events, and more [145].

Sleep and migraine

The complex relationships between sleep and migraine point to commonly shared pathophysiology. Although this topic has received significantly more attention over the last two decades, there are still many knowledge gaps. Throughout our review, we have identified several areas in need of further research. Furthermore, our clinical and research approaches should be tailored to view sleep problems as

intimately linked to migraine pathophysiology, in at least a subset of patients. Treatment of sleep problems in patients with migraines may result in an overall decrease in headache days and disability [146].

Likewise to migraine, depression, and anxiety have been associated with increased permeability of the gut. A change to improve the gut microbiota with a reduction of inflammatory activity can have a positive effect on relation gut-brain function. However, either the probiotics may have a beneficial effect on the severity and frequency of migraine there is necessary to make large-scale randomized, placebo-controlled studies in the future to recognize the clinical efficacy and safety of probiotics in migraine headache [147].

Psychiatric comorbidities

Psychiatric comorbidities have a higher prevalence in subjects with migraine than in the general population, the more common disturbers associates are Depression 41 – 47%, Anxiety 51 – 58; Post-traumatic stress disorder 9 – 43%, Childhood trauma 58%, Abuse during adulthood 33%; the hypotheses that can explain this relationship between psychiatric comorbidities can be related with neurotransmission but are not entirely understood. Nevertheless, psychiatric comorbidities seem to increase the development of chronic migraine; those comorbidities decreased the quality of life of migrainous patients, and complicate their treatment. It is important to screen patients with a migraine for these comorbidities. It is necessary to make more studies to explain address this intersection from a therapeutic point of view, given the clinical, functional, and cost implications [148].

Neuropsychological tests can show that migraine attacks are associated with poor cognitive performance compared with control and headache-free periods, consistent with cognitive difficulties subjectively reported during attacks. Most population-based studies have been showing similar cognitive capacity in migraineurs and control subjects in the interictal period. Longitudinal studies do not have evidence of increased risk for cognitive decline in migraine patients. However, there are some studies about worse cognitive performance in chronic migraine patients. Further studies are necessary to establish if it is real and exist cognitive impairment in subjects with migraine and other primary headache disorders [149].

Conclusions

In some topics, the controversy remains somewhat and pivots around two issues: initiation and the origin of the pain. As knowledge increases, it has been possible to establish molecular and clinical genetic physiopathological linkages. It is widely accepted that migraine involves activation and sensitization of trigeminovascular pathways, as well as the brain stem and diencephalic nuclei. The migraine may be considered as altered excitability state of the brain.

Even though the term excitability is frequently used to characterize neurons responses in migraine, a state of hypersynchrony would explain better the clinical symptoms of migraine.

Premonitory y postdrome symptoms in migraines are similar; premonitory symptoms can start days before the headache; postdrome symptoms lasting days after of headache stops. Both are neurological symptoms non-nociceptive of brain origin.

Familial hemiplegic migraine (FHM) is a rare migraine form from the geneticorigin; in most of the most cases, multiple genes have been associated with migraine; identification of a genetic predisposition would provide strong support about that migraine has a substantial genetic component.

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