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Review Article

Laws of Pathophysiology of Migraine in the Third Millennium

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Abstract

Science is the art of systematic and reproducible measurements, ultimately leading to knowledge supported by a holistic logic. Besides serendipity, there are 6 ways in general to obtain knowledge: authoritarianism; mysticism; rationalism, empiricism; pragmatism; and scepticism. Over the last 100 years, a canonical mythology – cortical spreading depression (CSD) – has prevailed in migraine pathophysiology. Conversely, a well-defined adaptive/protective role has evolved for CSD in locusts, *Drosophila*, and mammals. Additionally, an elaborate but entirely symptomatic nosologic system has arbitrarily evolved in migraine / primary headache. While the so-called systematic but symptomatic classification system of migraine / primary headache keeps on advancing the data-bank exponentially, the cause-effect nexus continues to obscure the most important systematic and insightful components of the knowledge of primary headache. The first step in advancing the cause-effect mystery of migraine / primary headache is to create a conceptual, consistent, and important adaptive-pathogenetic divide in the massive and disparate data-linked pathophysiology of the disorder. Once certain definitive principles (not laboratory/neuroimaging / genetic/epidemiologic data) emerge in the science of migraine / primary headache, we become empowered to understand the complex but key phenotypic blueprint as well as the neuro-pathophysiology / neuropsychiatry of the entity, including the visual (nasal visual-field sparing digitally-displaceable and eyeball-movement-synchronous scintillating scotomata), the lateralizing fronto-temporal-nuchal headache exclusively involving the ophthalmic division of the trigeminal nerve, and the associated features such as 'stress', 'post-stress', 'autonomic storm', 'protean' and 'spontaneous' onset and offset, and headache-aborting nausea-vomiting. In this manner, we have also evolved principles to begin to understand the most complex female predominance of migraine patients in adults [F:M=3:1] as well as the decline of prevalence in migraine attacks following menopause and advancing age. The Laws of the Pathophysiology of Migraine encompass the invaluable neurological / neuro-ophthalmological shift in pathophysiology from the brain to the eye.

More Information

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Introduction

Cortical Spreading Depression (CSD) is implicated in a diverse set of intracranial pathologies, and, in the early 21st Century, with over 100 years of experimentation and deduction, is the generally accepted pathogenetic mechanism linked to neurogenic inflammation (NI) that is widely accepted to underlie migraine [1-6]. With the exception of traumatic brain injury in humans, CSD has been recorded by several methods only in experimental animals. Besides this limitation in human migraine patients, there is a well-known protective/adaptive role for Spreading Depression (SD)-like events in lower vertebrates, such as locusts, for surviving extreme environmental conditions through a highly conserved pathway that may modulate SD in other organisms, including *Drosophila*, and, other mammals [7-12] as well as an exhaustively investigated neurovascular pre-conditioning dependent neuroprotective effect by increasing genome stability, and, neurovascular pre-conditioning effect in rodents [13-17]. These neuronal/neurovascular biologically adaptive/protective effects of CSD / SD that are well-known over 3 decades are systematically excluded in attempted syntheses by a large school of scientists that maintain a pathogenetic hyper-to-exclusive focus for CSD with a potentially therapeutic role for suppression of CSD/SD, particularly for migraine, epilepsy, transient global amnesia, epilepsy or cerebrovascular disorders in the neurocritical care unit [6,14]. Brain neuronal death in CSD-linked otherwise normal brains is not associated with immediate early genes, growth factors/neurotransmitters/neuromodulatory and/or inflammatory mediator systems. Primary/spontaneous or periodic "self-cycling" onset and "self-limited" offset of heterogenous headache as well as nasal visual-field sparing non-homonymous scintillating scotomata/hallucinations/visual experiences that are digitally displaceable by physical pressure and synchronously mobile with eye movements are absolutely inexplicable through CSD / NI or through any other form of primary CNS dysfunction (see below) [18]. Several other forms of proposed or potential systemic CNS

dysfunction/aberration are inconsistent with the primary and inviolable phenotypic principles of migraine [19-24].

Migraine is the most common primary headache, and in the last 100 years, migraine and CSD / SD – have been exhaustively and exponentially investigated. Pain is the most prominent component of migraine, while CSD is typically a painless hypestheic physiologic principle that does not induce aversion but rather promotes eating, drinking, and exploratory behavior [14,25]. CSD in cats, additionally, is not associated with the release of calcitonin-gene-related peptide (CGRP) [26]. CGRP has been the most prominent neurotransmitter/neuropeptide over the last 2 decades in migraine research.

The magnesium-CSD-migraine nexus is untenable and is the outcome of a series of carefully nurtured canonical myths over decades [27]. Primary potential / presumed "periodic/episodic" intrinsic brain magnesium ionic (Mg^{2+}) depletion is central to the variation of CNS hyperexcitability, migraine threshold, and occurrence of the migraine attack [28,29]. Intrinsic brain Mg^{2+} depletion (hypomagnesemia), however, has a significant and fundamentally adaptive function in cardiovascular and cerebrovascular tissues, as well as in many other organ structures with well-guarded supplementation in the Intensive Care Unit (ICU) [30,31]. The brain neurovascular therapeutic effect of exogenous supplementation of magnesium is limited by crossing the Blood-Brain Barrier (BBB) as well as the sustained higher levels in CSF and in the mural level of Mg^{2+} in brain arteries [32]. Across different tissues, the percentage and entry of Mg^{2+} are considerably delayed—variably up to hours [33]. Another reason for the limited exchange of Mg^{2+} with tissues is its binding with water, restricting the bare ion entry through the membrane. Common to all ions, this situation is greater for Mg^{2+} because the radius of its hydrated moiety combined with water is 400 times larger than its ionic radius [33-35]. As such, it is almost impossible for magnesium to pass through narrow channels in biological membranes, opposite to calcium, because of its 'hydration cover' [36,37].

Laws of pathophysiology of migraine – phenotypic principles and evolution of the cause-effect divide

Key phenotypic features of migraine attacks indicate the operation of certain pathophysiologic principles that, in turn, define the role of certain neurologic absolutes. These neurologic absolutes are not otherwise apparent despite the availability of advanced / advancing technology in the laboratory and/or neuroimaging as well as an exponentially increasing data bank. The limitations of the methodology of science of migraine / primary headache have been discussed: there is no physical sign or set of signs or organic aberration to create a robust, generalizable, predictable, or logically-sound pathophysiological blueprint or overview, whereas the sophisticated nosology is purely arbitrary and symptomatic (see above) [38]. On the contrary, and converse to the science of medicine in general, it is the symptoms of migraine, beginning from stress-linked Autonomic Nervous System (ANS) activation / 'storm' along with the noradrenergic-vasopressinergic-serotonergic 'system' that provides the basis for definitive laws of pathophysiology of the disorder. The pathophysiologic role of vasopressin (AVP) in migraine has evolved gradually from systemic vasoconstriction, anti-nociception, and behavior control to [39] to control of migraine-attack related ocular choroidal circulation, control of rise of (or fall in) Intraocular Pressure (IOP) (in contrast to rising in systemic blood pressure), control of the expansion of anterior ocular segment and corneosceral envelope, and spontaneous onset and offset of migraine headache-generating ophthalmic nerve (V1) nociceptive traffic [18, 30,39,40].

Stress, the post-stress phase, missing a meal, alcohol imbibition (weekend migraine headache attack), or insufficient sleep are the commonest precipitants of migraine but have no link to CSD. Post-stress migraine remains enigmatic and involves an adaptive/protective 'stress-related' pre-ictal combined 'pre-prodromal / pre-premonitory' phase that prevents the genesis of the migraine attack for a limited duration (several hours to a few days), through a collective or concatenation of anti-migraine physiological forces. While the role of 'stress / 'pre-stress' / 'occult' stress in migraine attacks cannot itself be studied, the typical delay in stress-linked headache offers definitive clues to its role in the pathogenesis. Lateralization of headache (unilateral, bilateral, side-fixed, or side-shifting) with spontaneous migraine attacks is the most typical stress-alcohol-sleep-linked feature of migraine that has not yet been rationalized (see below). Additionally, experimentally-induced Nitroglycerine (NTG) triggered migraine is unlikely to generate neurologically consistently non-protean lateralizing pathognomonic Scintillating Scotoma (SS) or typical headache of migraine, with consistent onset, duration, or offset; besides, its link to CSD-BBB disruption is also uncertain [41-47]. NTG, in low doses, lowers IOP in varied circumstances (Mishra, et al. 2014). Sustained relatively high-dose intravenous administration of NTG with subtle oculo-sympathetic/parasympathetic – pupil, and by inference, the ocular choroid [48,49] as well as cardiac migrainous ANS deficiency [50-52], as in experimental use of NTG to precipitate migraine, with changes in systemic blood pressure, cardiac pre-load reduction, left-ventricular stroke volume, and ocular vasodilatation can raise IOP but such a study has never been done. There is no brain/brain vascular lesion induced by NTG that might induce recurrent, reproducible yet protean and persistent lateralizing headache of migraine as well as recurrent or persistent pathognomonic SS.

Migraine typically and selectively involves the ophthalmic trigeminal (V1) rather than all three divisions of the trigeminal nerve, a feature inconsistent with diffuse

and/or consistent or repetitive and spontaneous primary propagation of CSD or any other form of CNS modulation / sensory dysmodulation in the trigeminal nerve, but neuro-anatomically consistent with characteristically selective lateralization (unilateral, bilateral, side-shift, or side-fixed) of a headache to the peri-ocular, the fronto-temporal, and the nuchal region, thus formulating the first law of migraine pathophysiology. Osmophobic migraine (involving odours, including scents, foods, and cigarette smoke) and ice-cream headache also clearly reflect a neural circuit exclusively involving V1. No systemic influence (from serotonin to CGRP) can rationalize the lateralizing headache of migraine [53].

A typically protean or unpredictable and delayed onset, duration, offset, and degree/severity of pain and its accompaniments, absenteeism, or presenteeism is a highly characteristic feature of migraine attacks. Experimental (nitroglycerine-induced)/or spontaneous (non-experimental) onset of migraine attacks is not always predictable but commonly indeterminate and with the pre-ictal 'pre-prodromal/pre-premonitory' or 'prodromal/premonitory' phase largely inaccessible or occult to systematic examination or clinical evaluation. Experimentally, not all rodents or humans exposed to NTG develop migraine or migraine-like features. Similarly, while almost all humans (~80%) suffer psychodynamic stress (stress-is-life, life-is-stress, *Hans Selye*) [54], only approximately one/fifth of humans suffer migraine attacks. The concatenation or orchestration of cross-disciplinary pathophysiologic systems that variably manage migraine-related pre-stress/stress/post-stress phases constitutes the second law of migraine pathophysiology. A complex multifocal adaptive mechanism involving intrinsic vasopressinergic-noradrenergic-serotonergic activation, that is, in turn, affected by a very large number of clinical circumstances and situations (endogenous or exogenous or both) likely offers a "protective" effect that significantly delays migraine attacks for several hours or days, prevents experimental migraine in some rodents/four-fifths of humans under protracted stress, or controls the severity and duration of migraine attacks [27]. The multiple end-organ (ocular) effects of this complex adaptive-protective system have been detailed and are briefly mentioned below [18,40,55]. Vasopressin (AVP) surges in the early phases of migraine attacks can generate early nausea/vomiting in migraineurs and abort migraine attacks, a classic adaptive/emotional mechanism that constitutes the third law of migraine pathophysiology. Nausea and/or vomiting are accompanied by intense and rapid AVP release with hyponatremia. Virtually instantaneous increases in plasma AVP from 100 to 1000 times commonly occur with transient nausea, stress, or pain unaccompanied by vomiting or changes in Systemic Blood Pressure (SBP). All adaptive functions have a protean and/or variably complex function across organs in the human body acting to preserve or challenge physiologic body function, e.g. fluid retention has renal and extra-renal manifestations in migraine, whereby it can increase cardiac right/left ventricular stroke volume but create renal overload with urea/creatinine elevation and electrolyte disturbances. Not all migraine attacks are accompanied by nausea-vomiting or the abortion of migraine headache attacks by nausea/vomiting, a classically adaptive manifestation. Amitriptyline is a first-line prophylactic drug for the management of both migraine as well as Cyclic Vomiting Syndrome (CVS), with or without migraine, that can cause hyponatremia and AVP excess, commonly linked to low SBP (and rarely high SBP) with anti-stress mechanisms, choroidal arterial vasoconstriction, ocular hypotension, ocular vasoconstriction, and antinociception [56-58]. Oxytocin may play a role in nausea-based disgust or anticipatory nausea in rats [59]. Oxytocin has no known vasoconstrictive influence, which effect is paramount in keeping migraine in remission or prophylaxis.

Photophobia is not necessarily greater on the side of the headache, and CSD or cortical central visual dysfunction is unlikely to have a major or central role in its genesis [27]. Phonophobia (including rustling of newspaper) and other forms of hyper-reactions or hyper-sensitizations are part of a generalized hyper-reactivity that is also a prominent part of a generalized hyper-sensitivity characteristic of migraine. Further experimental evidence, the surge of Randomized Controlled Clinical Trials (RCCT) with neuropeptides (such as calcium-gene related neuropeptide-antagonists and -receptor antagonists), neuroimaging including cerebral perfusion studies, genotyping, and animal experiments) have made the migraine phenotype increasingly complex while keeping intact the cause-effect conundrum (brain *vs.* eye).

Ocular pathophysiology & fundamentals of migraine

Recently, the primary role of the eye in the pathogenesis of migraine has gained much traction in the Third Millennium, validating the cross-disciplinary integrative KISS principle with both breadth and depth of knowledge of migraine towards a comprehensive and gestaltic synthesis that has defied scientific thinking over 25 centuries. There exist several carefully nurtured myths in migraine pathophysiology that have stymied the creation of such an overarching hypothesis [14,27,60], with the elaborate symptom-based classification system and its variants [38] prominently in the forefront. The study of the fragmented but exponentially expansive data bank of migraine / primary headache and the speculations surrounding its pathophysiology is the best example of the ability of an elaborate classification system in medicine to prevent the emergence of a comprehensive synthesis or fundamental understanding. No systemic belief or canonical myth – including nitric oxide, neuropeptide/ neurotransmitter, dietary, platelet, or cardiac involvement including patent foramen ovale, atrial septal defect, Ebstein's anomaly, coarctation of aorta, or obesity – can rationalize the first law of neurological lateralization of migraine headache

[31]. Sparing of the nasal visual field in Scintillating Scotoma (SS) is an equally if not more demanding neurologically lateralizing pathognomonic phenomenon (see below). The first truly robust, predictable, defensible, and progressive hypothesis regarding migraine was published in the early 21st century with a synopsis earlier in 1990 [30,61].

Pathognomonic-to-classical features of migraine are not reported after enucleation of one or both eyes or following sightlessness [62-66]. Even more importantly, the SS is not distributed homonymously and SS does not expand into the nasal visual field, two absolute features that make brain / central visual field origin of the pathognomonic phenomenon impossible. After enucleation of either or both eyes, the typical paracentral horse-shoe-shaped expanding positive SS as well as the typical migraine headache is not reported [63,64]. Sightlessness markedly attenuates migrainous SS as well as photophobia [66]. The Presence of the eye is essential to manifest typical-to-pathognomonic lateralizing clinical features of migraine, constituting the fourth, and perhaps, the most important clinically absolute law of migraine pathophysiology [27].

Mechanical or physical displacement of the SS is the single most important clinical absolute to determine the site of origin of the positive hallucination or visual pathognomonic phenomenon of migraine [67]. The pathognomonic positive SS of migraine is physically displaceable by digital / finger pressure, and, is thus retinal in origin [18]. Clinical study of SS of migraine on these lines constitutes the fifth law of migraine pathophysiology and forms the crux for understanding this otherwise formidably complex disorder [18].

The crani-ocular pathophysiological system involved in migraine is largely protected during stress, with the post-stress phase manifesting as the commonest cause of migraine attacks. There are several components of this important protective feature of migraine, which can be collectively summed as the sixth law of migraine pathophysiology. Much data has been accumulated about the Autonomic Nervous System (ANS) and migraine at the levels of the pupil and the heart, without any synthesis / co-synthesis emerging across these and several other exponentially enlarging evidentiary banks. Succinctly, migraine is an autonomic storm, that begins often much before the prodrome – a phase most aptly termed the 'pre-prodromal / pre-premonitory' phase, in other words, the truly occult pre-ictal phase of migraine [18]. Migraine philology and philosophy have completely ignored both the generally accepted and scientifically robust adaptive-protective alarm function of the ANS in the animal kingdom as well as its speculative neurological link to CSD / central brain neuronal dysmodulation / sensory dysfunction. Furthermore, speculative pathogenetic involvement of the "intrinsic CNS sympathomimetic system" was proposed as the basis of the biobehavioral model of migraine, a theory that held overriding sway in the last quarter of the last century [18,27,28,40].

Key issues involving stress-protective function of the eye include control of choroidal ocular circulation (adrenergic and vasopressinergic), Intraocular Pressure (IOP), and generation of algogenic/nociceptive impulses in the ophthalmic nerve from mechanical deformation of the corneoscleral junction [18,40]. Maintenance of relative intraocular hypotension delays the onset of migraine attacks. Vasopressin (AVP) raises systemic blood pressure but lowers IOP, a prominent component of the ocular protective influence of stress on the development of migraine attacks. The rate of change of systemic blood pressure rather than an absolute value determines the migraine threshold [30].

The limited duration of the headache of migraine (4 hours - 72 hours) is in itself a clinically typical-to-pathognomonic feature. The components of the tissues of the eye that provide effective ocular tamponade in the face of relative ocular hypertension generating algogenic/nociceptive impulses during migraine headaches are responsible for terminating the migraine attack spontaneously. These ocular features along with external (digital) self-compression of the eye constitute the seventh law of migraine [40].

A combination of these seven pathophysiologic laws underscores the propensity of pubertal/post-pubertal children/adolescents, and adults (F:M = 3:1) to develop migraine, ophthalmoplegic migraine, menstrual migraine, and migraine in the first trimester of pregnancy as well as the tendency of migraine attacks to decline with later trimesters of pregnancy, ageing, and menopause [18]. The migraine-glaucoma nexus (primary open-angle glaucoma/normal tension glaucoma) is gradually becoming more apparent. The protean nature of migraine – even in the same individual on different occasions – does not allow biologically valid conclusions to emerge from statistics (*p* - values) related to randomized controlled clinical trials. Variations of deformability of the corneoscleral envelope in response to mechanical IOP pressure fluctuations with protean/variable generation of nociceptive impulses in V1 is linked to the connective-tissue component of migraine, a key feature that will be discussed elsewhere.

These seven laws detail the biophysics and biophysiology of migraine, keeping mathematical/statistical/nosologic/speculative conclusions or guidelines at bay. Neuropeptides/neurotransmitters do not compose the biology of migraine. In the absence of such basic fundamentals, RCCT and the use of a placebo increase theoretical and therapeutic confusion in migraine/primary headaches [27].

"True progress in science requires the ability to grapple with the immeasurable, the daring to view phenomenology differently, to give birth to and maintain a disquieting but penetrating dys-synchrony, to confront and not be overawed by history or consensus, to sustain searing self-criticism, and to carry curiosity and imagination to a defensible and generalizable conclusion. Canonical authoritarianism,

empiricism, mythicalism, serendipity, cynicism, and irrational skepticism and mysticism over 25 centuries compel the need to refine, redefine, advance, overturn, and crystallize scientific thinking about oculo-cephalic / cephalic pain to a new dimension" [27].

Conclusion

- Cortical Spreading Depression (CSD) has well-defined neuronal/neurovascular 'pre-conditioning' adaptive/protective features in vertebrates (locusts, *Drosophila*) and mammals (rodents).
- The suppressive therapeutic role of CSD in the neuro-critical unit is speculative.
- CSD is absolutely non-nociceptive, promotes eating/drinking behaviour in rodents, and is not relevant to the prominently painful disorder of migraine or its brain-magnesium linked pathophysiology or purely symptomatic nosology.
- There is no pharmacotherapeutic difference between migraine with aura (MWA) and migraine without aura (MWoA).
- CSD in MWA and 'silent' CSD in MWoA are purely speculative.
- Scintillating scotoma is not homonymous, spares nasal-visual field, is digitally/physically displaceable, and moves synchronously with eye movements, all features absolutely against cerebral-visual origin.
- CSD and several other diverse proposed forms of 'primary' involvement of brain cannot rationalize adaptation/protection during pre-stress / stress phase in ~80% of migraine patients; delay in onset of headache following stress/nitroglycerine challenge/alcohol imbibition (several hours to a few days); stress-related migraine; spontaneous but uncertain onset; spontaneous, variable, but limited offset (4 hours - 72 hours); lateralizing headache; and vomiting-induced self-abortion of migraine attacks in a fraction of cases.
- Lateralizing fronto-temporal-nuchal headache (unilateral/bilateral/side-fixed/side-shifting) does not involve all three divisions of the trigeminal nerve.
- Migraine selectively / exclusively involves ophthalmic division of the trigeminal nerve (V1).

Table 1: Clinical Modulation of Migraine Attacks. ↑ Arginine Vasopressin (AVP) Bioavailability with Abortion/Remittance of Migraine.

Nausea / Vomiting	Can immediately abort or reduce the clinical impact of migraine attacks commonly in the early phases. Some patients self-induce vomiting by gag reflex to abort migraine attacks, manage/ameliorate alcohol intoxication, or reduce weight in school wrestling, besides established issues in dentistry and bulimia [68]. Alcohol is a depressant that slows the functions of the nervous system, thus diminishing involuntary processes such as breathing, heart rate, and the gag reflex. Even with the blunted gag reflex with the risk of choking, self-induced vomiting, to a degree, is one method of eliminating alcohol from the system. Eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating) are probably linked with migraine and self-induced vomiting as a weight-control strategy [69]. Common to all these disorders is a stress-management strategy that has gone awry or has become overwhelmed. *https://health.cornell.edu/sites/health/files/pdf-library/self-induced-vomiting.pdf*
Sleep	Well-defined therapeutic effects on migraine, are generally and increasingly regarded as anecdotal [70-74]. While RCCT cannot yield the undisputed scientific evidence required (see below), there is a bidirectional link between sleep and neuropeptides. Sleep stimulates AVP secretion regardless of electroencephalographic sleep state [75,76]. AVP stimulates sleep by reducing Rapid-Eye Movement [REM] sleep, which regulatory central influence, independent of vasopressor effect, is confirmed in humans [77]. Vasopressin neurons in the suprachiasmatic nucleus significantly control the functional output of the biological clock that is contained within it.
Tobacco smoking/nicotine	There is no definite or mechanistic pathophysiologic link between tobacco smoking and migraine. The bias of the investigator(s) is generally reflected in genetic/statistical large-scale evidence. Smoking cessation is not part of any migraine-preventive strategy (Weinberger and Seng, 2023). Nicotine readily crosses the BBB, and releases AVP, β-endorphin, acetylcholine, norepinephrine, dopamine, serotonin, and adrenocorticotropic hormone; nicotine has definitive antinociceptive action [78,79]. Migraine patients may seek relief by smoking tobacco; others smoke to reduce dysphoria and anxiety. Tobacco-released AVP, in turn, can prevent or protect from migraine. Some migraineurs seek relief by smoking tobacco, which evidence is regarded as anecdotal. Severe migraine headaches can develop after the sudden discontinuation of nicotine gum [80]. Almost 2 decades previously, in a prolonged and meticulous 1 single N-of-1 trial case report in a female allopathic medical doctor with severe life-modulating migraine over 20 years, the theoretical basis and potential clinical application of nicotine gum chewing to prevent migraine was fully elucidated [39]. Imbibition of alcohol, the most common intoxicant that precipitates migraine worldwide, in combination with tobacco smoking, as well as nasal nerve-ending irritation by smoke-emission of tobacco-smoking migraineurs as well as non-smoking migraineurs hopelessly complicates the scientific medical issue. Again, RCCT cannot provide clarity of scientific thinking in this field by undisputed evidence due to additional potential carcinogenicity, particularly of lung, protean nature of migraine, and variations in tobacco/alcohol consumption, while a robust synthesis is invaluable (see below).
Physical Exercise	Regular exercise can alter migraine-triggering threshold [81-83]. The frequency, intensity, and modality of physical exercise along with musculoskeletal and balance dysfunctions that can generate and overcome the autonomic 'storm' to prevent or trigger migraine attacks, respectively, (tachycardia, stroke volume, cardiac output, physical conditioning, physical fatigue, ocular autonomic function, ocular blood flow, ocular choroidal function, and IOP) cannot be predicted with precision and can change with time, occasion, training and competition. Individualized osmotic and non-osmotic regulation of AVP may change in competitive events to generate exercise-associated hyponatremia [84]. In such clinical situations, challenges may vary from migraine to death.
Pregnancy	Migraine attacks that begin during pregnancy usually subside within 3 months and a great majority of female migraine patients progressively improve during pregnancy. Fluid overload and relative hyponatremia of pregnancy might restore or enhance AVP efficacy. Elevated estrogen and endogenous opioid levels raise the pain threshold but do not fluctuate. Hypertension raises (13-fold) the risk of worsening of migraine during pregnancy Puerperium (first month) increases the risk of migraine attacks. While breastfeeding lowers the risk of migraine, hypercoagulability is common to both [85].
Estrogen	No definitive vasoconstrictive or anti-nociceptive effect. Anti-stress effects cannot be excluded.
Oxytocin	The antinociceptive effect is probably mediated by AVP; the independent role of oxytocin in pain control is less likely [86,87]. No vasoconstrictive effect that is central to an anti-migraine prophylactic effect. Anti-stress effects cannot be excluded. Elevates IOP when applied to the supraoptic nucleus [88].
Menopause / Ageing	Water retention due to augmented osmotic AVP secretion and renal sodium reabsorption [89,90].
Caffeine withdrawal	Weakly lowers IOP, except in genetically predisposed individuals [91]. At high concentrations, caffeine can increase AVP release [92].

Table 2: Clinical Modulation of Migraine Attacks. ↓ Arginine Vasopressin (AVP) Bioavailability with Precipitation / Triggering of Migraine.	
Alcohol (Morning hangover headache)	Exhaustion of ANS through vasodilatory effect in the external carotid artery decreases peripheral resistance and increases cutaneous blood flow, and tachycardia during exercise / submaximal exercise; increasing initial rate of urine production with no difference in total cumulative urine output [93]. Combined stimulation (osmotic and non-osmotic) and suppression of AVP.
Awakening from sleep with startle / early morning migraine	Exhaustion of ANS 'storm' with startle-induced rise of intraocular pressure.
Psychologic Trauma	Exhaustion of ANS 'storm' with rise of intraocular pressure.
Physical trauma	Exhaustion of ANS 'storm' with rise of intraocular pressure.
Weight-lifting headache	Elevates IOP by Valsalva manoeuver [94].
Constipation / Cough	Elevates IOP by Valsalva manoeuver [95].
Systemic blood pressure (SBP)	Rate of change of SBP [96-98].

- Noradrenergic-vasopressin-serotonergic 'system' (extrinsic and/or ocular) offers vasoconstriction, anti-nociception, behaviour control, while the ocular autonomic nervous system, ocular choroidal circulation, Intraocular Pressure (IOP), anterior ocular segment and corneoscleral expansion, generate and decrease nociceptive V1 neural impulses, thereby advancing the migraine-glaucoma nexus.
- Vasopressin has opposite effects on systemic blood pressure (rise) and IOP (fall).
- Tamponade effect of eye/s that irregularly (4 h - 72 h) but spontaneously stops migraine headache attacks occurs through a combined tissue and neurotransmitter effect.
- Release of Calcitonin-Gene-Related Peptide (CGRP) and/or other neuropeptides/neurotransmitters have no definitive role in 'stress', 'autonomic storm', or genesis/onset/offset of protean unpredictable migraine attacks.
- The ocular tissue/neurotransmitter basis of occurrence of migraine attacks predominantly in females and with declining frequency of attacks in post-menopausal and in advancing age is outlined (Tables 1,2)
- Randomized Controlled Clinical Trials (RCCT), the major methodology of medical science over 50 years, heavily rely on cohort randomization and distribution of variables, mathematics/statistics, and the *p*-value, thereby creating biological confusion. Given the characteristically protean nature of migraine and the use/misuse of placebo, positive RCCT has not been able to offer clear and insightful therapeutic or pathophysiologic guidelines.

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