Commentary

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Pathophysiology of migraine: an increasingly complex narrative to 2020

Vinod Kumar Gupta*,[1]

[1]Migraine-Headache Institute, Gupta Medical Clinic, S-407, Greater Kailash Part Two, New Delhi 110048, India

*Author for correspondence: Tel.: +91 9911756123; dr_vkgupta@yahoo.com

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Migraine has been known to afflict humankind since antiquity as an intense pulsatile painful neurological entity [1,2]. Migraine headache is currently the third most common disease with an estimated global prevalence of 15%, and, is also ranked among the top ten debilitating diseases imparting substantial suffering to the family in addition to the sufferer, being the fourth most burdensome disease in women according to the 2012 Global Burden of Disease study that, in desperation, propels medication abuse, yet by general consensus its etiology remains uncertain [3–5]. Management of both episodic and chronic migraine has a massive escalating fiscal impact in developed countries, as the poorly understood frequently refractory noncommunicable disorder(s) with a typical but only partially defined genetic component [5–9] continues to challenge current human problem-solving capacity despite impressive technological advances. Increasingly frequent multicenter often industry-specific bottom-line driven randomized clinical trials (RCTs) in the face of incomplete scientific logic or commonsense add data into a profusely confused perspective [10–12]. Without a salient and robust pathophysiologic matrix, all therapies advocated at the tertiary-care level are empirical cart-before-the-horse strategies poorly translated at the level of the general population, leading to research frustration [12]. Precisely for the same reason, migraine has the broadest possible spectrum of potential therapies, both pharmacological and nonpharmacological, including surgery. Although, by wide consensus, migraine is regarded as a primary brain disorder [3–9,13–15], disruption of the blood–brain barrier (BBB) during attacks has not been established [13], and, first-line hydrophilic preventive drugs that clearly influence the primary pathogenetic processes(es) or 'afferent limb' of migraine aura-headache such as atenolol and nadolol [16–19] do not freely cross BBB or influence occipital- or brainstem neuronal function [10]. Application of nitroglycerin ointment to skin of fronto-temporal region precipitates headache in migraineurs without involving the CNS [20]. This unacknowledged pharmacologic–clinical disconnect is being steadily widened by logic-challenging RCTs and meta-analyses, both being commonly used to sustain assumptive but intrinsically weak pathogenetic theories and therapies through mathematic extrapolations.

While there has been an exponential accumulation of data, opinion and reviews in migraine (and other primary headache) literature, pathophysiologic certitude has proven elusive. Experiment, statistical sophistication and extreme nosologic 'splitting' has left reflection and logic far behind data in evolution of migraine as a discipline, while observation – never itself completely objective – has no scaffolding to be arranged into a meaningful matrix. Interpretation of the biologic significance of a large, fragmented, disconnected, burgeoning but disparate and often controversial body of data encompassing recorded peripheral and central changes in the laboratory including neuroimaging remains unresolved [10–12]. Biology of migraine is not synonymous with 'laboratory' or 'nonenvironmental' but is the elucidation of the concatenation of physiologic forces that push or pull the migraine patient towards either the aura/headache phase or the aura/headache-free state [11]. While perceived psychophysical stress as well as occurrence of reactive oxygen species stress is both ubiquitous and nonspecific, migraine affects approximately only up to a fifth of humankind, with an apparently inexhaustible adaptive cranial/brain intrinsic noradrenergic-serotonergic-vasopressinergic mechanism keeping the majority of the human cohort free from the disorder [11,21]. Conversely, despite a nebulous clinical and scientific landscape, some researchers believe that

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understanding of migraine pathophysiology is advancing rapidly [14,15]. Supporting evidence for such enthusiastic belief for an imminent breakthrough, is, however, conspicuously absent.

The chance discovery of cortical spreading depression (CSD) in experimental animals by Leão (1944) [22], the presumed cortical origin of personal experience of scintillating scotomata (SS) without headache attacks by Lashley (1941) [23] and the assumed linkage between these two sets of cross-species events by Milner (1958) [24], set stage for a prolonged philosophic commitment by leading researchers to CSD as the neural/neurologic domain of migraine well into the 21st century [25]. How CSD or any other form of 'self-cycling' visual cortical 'hyperexcitability' or brain neuronal 'hypersynchronization' or 'oscillation' [26,27] might spontaneously arise and cease ('start-stop' cycle *de novo* or *per se*) in the first instance to generate characteristically self-limited (4–72 hours) periodic and protean lateralizing headache (with varied frequency and periodicity, severity, duration, gender predisposition (F:M::3:1), characteristic remission and precipitation) and varied associated symptoms (including autonomic and nonautonomic features) while involving only a distinct part of the ophthalmic trigeminal nerve – mainly the temples and the periocular regions – is a significant, most likely, absolute impediment to such theories [10–12]. Amitriptyline, the second most commonly prescribed drug for migraine prevention at tertiary-care headache centers is unarguably a serotonin agonist that effects the serotonin syndrome – a pharmacologic absolute. Propagators of hypotheses, however, are never wrong [28]. Old theories, therefore, never die. In every generation, assumptions and myths are reconstituted in the prevalent or emerging hues. For example, the hypothesis of 'malfunctioning ion channels' proposed to modulate pain circuits was revived by discovery of mutations in the potassium channel – TWIK-related spinal cord potassium (TRESK) channel recently linked with inherited migraine – as well as several other molecular mechanisms – but with the basic pathophysiologic mechanisms still remaining poorly understood, little headway was made [29]. Another momentous but equally serendipitous event in migraine research six decades ago was the discovery of the preventive role of beta-blocker drugs without intrinsic sympathomimetic action [30,31], placing the generally accepted adaptive function of the autonomic nervous system (ANS) into uncertain pathogenetic complexities. Next, the impressive saga of the biochemistry of migraine started the neurotransmitter bandwagon with measurements of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid also in the 1960s. Exhaustive studies of 5-HT receptor subtypes and PET imaging linked-metabolomics did not, however, yield the much-expected biologic or pathophysiologic dividend, but the migraine headache abortive agent triptan did gain center stage [5]. The bio-behavioral model of migraine, a complex assumption widely quoted in the late 20th century primary headache research, emerged two decades later [32], placing counter-intuitive and counter-adaptive emphasis on aberration of the intrinsic brain noradrenergic function, a belief that failed to gain traction [10,11].

Early in the 21st century, PFO-closure for prevention of migraine – again a chance-spun exercise with poor pathogenetic and therapeutic logic – captured the imagination of a wide divide of scientists as a high-profile but controversial interventional management strategy, and, gained momentum through a combination of intense lobbying from the Amplatzer PFO-closure device manufacturer and a fervent hope-hype froth that enveloped trialists at a time during which device(s) began to determine the science of migraine rather than the converse [12]. PFO-closure for migraine has become the therapeutic equivalent of CSD [10–12], with calcitonin-gene-related peptide (CGRP)-antibodies running neck-to-neck (see below). Since migraine attacks are predictable (menstrual) or unpredictable but discrete events over a lifetime, the paradoxical embolism across the interatrial septal defect is imaginatively expected by proponents of PFO-closure, to repetitively unveil itself during a precisely timed right-atrial twin-event involving passage of platelet-serotonin-linked thrombo-embolus across the defect into the systemic circulation in consonance with a rapid elevation of the right atrial pressure to enable the passage from the low-pressure right atrium into the higher-pressure left atrium; it is, then, further envisioned that an entirely imaginary idiosyncratic rheologic pathway will allow it to lodge in the same precise segment of the cerebrovascular circulation to generate recurrent stereotypic but distinct aura-headache attacks. The presumed migraine-generating thromboembolic plug is several thousand times (or more) heavier than air bubbles used to establish the diagnosis of PFO, and, far less susceptible gravitationally and rheologically to pass across a PFO. What prevents the presumed thromboembolic plug from entering and obstructing the pulmonary circulation and generating infarcts and secondary pulmonary hypertension? Not only must the thromboembolic plug hover over the PFO to exclusively generate well-timed periodic migraine attacks, it must be ushered deftly and recurrently into a particular part of the cerebrovascular circulation over decades! Atrial fibrillation management [33] and noninvasive vagal nerve stimulation [34] have now joined the device-determined (un)scientific race to the finish.

Since the science of migraine has evolved by chance, all therapeutic options and claims, including triptans, PFO-closure and CGRP-monoclonal antibodies, and the pathophysiologic extrapolations therefrom remain empirical

and uncertain [10–12,33–35]. Does it make sense to diffusely and bilaterally block cranial-CGRP release or effect, long term for months on end (and even years or decades), for a phasic/intermittent lateralizing primary headache in a sizable segment of the human population? With the advent of monoclonal antibodies in migraine management, it is inevitable to reflect whether we are simplistically treating an infective disorder. The brain is kept in homeostasis by a vast interconnected network of influences that work in synergy (either in concert or in dissonance) [35]. Immediately after administration of any agent, drug or pharmaceutical, or release of any biological substance within the body/brain, another set of counter-regulatory chemicals will be released under neuro-endocrine and ANS control. All neuropeptides reflect neuronal function, not the other way around. Neuropeptides are neuronal messengers operating at the surface [11,35]. Simply because neuropeptides are measurable in the laboratory does not mean that neuronal truths have been unraveled. Similarly, brain magnesium depletion is central to several migraine pathogenetic hypotheses, but hypomagnesemia is very common among hospitalized patients, and, exogenously administered magnesium does not freely cross BBB [10,11]. Whereas biochemistry and genetics of migraine appear far more advanced, they are in essence rudderless as there is no inkling about the cranial tissue that lends to migraine its eponymous pathognomonic feature, that is, lateralization of headache (unilateral, bilateral, side-shifting, or fixed).

Most leading researchers concede large gaps in the 'theory' of CSD and in other brain-centric hypotheses with the assumed in vogue but unsustainable 'self-cycling' concept [26,27], but simultaneously point to incredible and prodigious futuristic progress over the last 100 years, while some other more enthusiastic investigators outline an imminent concept of cure for migraine [36]. Such contrasting viewpoints are, however, unsustainable together. There is nothing intrinsically improper with serendipity in science as long as the chance-principle is knitted back into the theoretic and therapeutic mainstream matrix. Despite a series of chance discoveries, such an evolutionary synthesis has not been generated for migraine pathophysiology in the last 100 years.

Fundamentally, what makes the brain in migraine patients intermittently either more or less susceptible to the presumed attack-provoking CSD remains unknown [6,37]. The lateralizing principle of migraine does not become apparent from an in-depth study of characteristic headache triggering or remitting stimuli as well as any systemic or diffuse cranial influence including meningeal involvement. More importantly, migraine headache-triggering factors are neither quantified (or quantifiable) nor consistent in their pathogenetic effect. Next, a variable but remarkable cumulative or barrage effect in precipitation of migraine headaches exists. Finally, once a migraine-headache attack is initiated, the characteristic triggering factors appear to lose their pathogenetic cranial nociceptive potential. A pathophysiologic system that is responsive to but lies within as well as outside known physiological effects of migraine triggers, and, has a degree of intrinsic ANS protection likely underlies the disorder [11]. The single most important factor in the quest for understanding migraine pathophysiology is delineation of the physiological mechanisms that underlie poststress migraine. The ANS is the single most important factor in grasping the basis of adaptive mechanisms that offer variable and exhaustible but definitive protection to the migraine patient during psychophysical stress [11]. Since nausea/vomiting commonly aborts migraine headache, a hyperfocus on vasopressin is the single most important factor to understand the basis of psychophysical stress handling by migraine patients [21].

A widening gap, at the research level, between SS of migraine, considered the only truly pathognomonic feature of migraine, and, the flood of data/opinion regarding PFO-closure, botulinum toxin administration, noninvasive vagal nerve stimulation, CGRP-antagonist therapies for headache management appears to be developing [10–12,33–35]. SS of migraine are not distributed homonymously and do not expand into the nasal visual fields [38]. Typical paracentral horse-shoe-shaped expanding positive SS and typical migraine headache and are not reported after enucleation of one or both eyes [39–42]. Sightlessness markedly attenuates migrainous SS as well as photophobia [43]. The eye has a fascinating relatively unexplored neuroanatomically consistent role in migraine pathophysiology with a significant degree of ANS protection during psychophysical stress, distinct from the prevailing neuronal/vascular/neurovascular hypotheses for migraine [44]. Presence of the eye is essential to manifest typical to pathognomonic clinical features of migraine.

Every research question has a different approach. 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.

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