EDITORIAL

The Restless Universe of Migraine

O Universo Inquieto da Enxaqueca

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"I'm suffering from a headache and the universe […] My head aches because my head aches. The universe hurts me because my head hurts. But the universe that actually hurts me is not the true one, which exists because it doesn't know I exist, but that other universe which belongs only to me and which, should I pass my hands through my hair, makes me feel that each strand suffers for no other reason than to make me suffer (Fernando Pessoa - The Book of Disquiet)." [1]

Pessoa's restlessness mirrors that of all migraine sufferers, characterized by the anguish stemming from an enigmatic environment that inadvertently inflicts pain. Despite advancements in research during recent decades, the universe of unknown elements pertaining to the pathogenesis of this brain illness remains mostly unexplored.

What have we learned to date? (a) The migraine attack, or a portion thereof, may initiate at the sensory afferents of the first branch of the trigeminal nerve, which innervate the small meningeal arteries, thereby forming the trigeminovascular system. This process involves the release of the vasoactive calcitonin gene-related polypeptide (CGRP) and the subsequent onset of peripheral sensitization[2]; (b) furthermore, in animal models, the activation of the first-order neurons within the trigeminovascular system can be induced by cortical spreading depression (CSD), an electrical phenomenon believed to be the basis of the migraine aura[3]; c) that the hypothalamus and the brainstem collaborate in initiating and potentially terminating a migraine attack, with the former being active prior to the onset of pain during the premonitory phase, and the latter during the painful phase[4]; d) cerebral electrophysiology, assessed via EEG at rest or evoked using sensorial stimuli, is significantly altered during the pain-free phase, likely serving as an endophenotypic marker of susceptibility to subsequent attacks or as a remnant of prior episodes[5]; e) both the micro- and macro-structural aspects of the brain, evaluated through neuroimaging techniques, exhibit distinct alterations contingent upon the interictal, preictal, or postictal phases of the migraine cycle[6]; and f) cerebral hemodynamics in network formation is also atypical in individuals with migraine, even during the pain-free phase.[7] Epidemiological studies indicating familial recurrence, along with recent genome-wide association studies involving a substantial cohort of migraine patients, suggest that the significant and extensive engagement of the central and peripheral nervous systems is underpinned by a genetic foundation.[8] Genetic loci associated with migraine are distinguished by a significant number of genes expressed in vascular and muscle organs. These genes are linked to the control of glutamate levels, nitric oxide, oxidative stress, synaptic plasticity, pain pathways, and the identification of specific therapeutic targets for migraine treatment.[8] This substantial genetic burden may facilitate aberrant activity within the hypothalamic-brainstem-cortical network, resulting in heightened energy demands and a transient or persistent inflammatory state across various organs. Consequently, genetic variables and abnormalities within the specified network

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may establish the foundation upon which diverse modifiable and non-modifiable factors influence the equilibrium of the brain. Sleep disorders, unhealthy diets, hormonal imbalances, emotional dysregulation manifesting as anxiety and depression, irregular working hours, substance abuse, and the presence of other systemic or central pathologies in comorbidity are the most commonly attributed factors.[9]

> *"My head aches today, and perhaps my stomach is the source of its aching. But the ache, once it is suggested by my stomach to my head, interrupts the meditation that goes on behind my thinking brain."* [1]

These factors can substantially affect the threshold for cyclic migraine attacks. For instance, a patient primarily afflicted by a psychiatric disorder may experience migraine attacks due to the activation of the stress response system and subsequent trigeminovascular signaling, even in the absence of a definitive history of migraine symptoms. This system encompasses the hypothalamic-pituitary-adrenal axis, the brainstem monoaminergic system, the thalamic hub, and several cortical regions that constitute the salience network. Numerous studies indicate that the central nodes of the salience network are essential for the conscious integration of feedback and autonomic responses with internal objectives and external requirements.[10] It can be posited that any external or internal event that upsets this extensive system may activate the alarm, resulting in the commencement of a migraine attack. Consequently, the migraine attack serves as a mechanism to maintain systemic stability, aiming to restore normal brain energy consumption and reestablish optimal conditions. In this scenario, the hypothalamus is not the causative agent, but rather a component of the body's stress response. This homeostatic process is relevant both when migraine is the primary pathology and when it is a secondary effect of another condition. It is sometimes stated that, when subjected to specific adverse conditions, all individuals may experience a migraine attack at least once in their lifetime. The activation of the hypothalamic and trigeminovascular systems, which precipitates a migraine attack, compels the individual to rest, avoid excessive sensory stimulation, abstain from food and drink, and refrain from activities that may exacerbate physical and emotional distress.

> *"And so now, because my head aches, I find nothing at all admirable or worthwhile in the show going on outside me which, in this absurd and monotonous moment, I don't even wish to see as the world."* [1]

This putative homeostatic mechanism may elucidate why the treatment of migraine or concurrent illnesses could result in a mutually advantageous outcome.[11]

What are the unknown pathophysiological processes of migraine? Several questions exist, including: (a) the extent and manner in which the trigeminovascular sensitization process is particular to migraine, given its apparent commonality in other headache disorders; (b) the specific brain or peripheral structures that encode the qualitative aspects of headache pain (pulsating, tensive, punctate, electrical discharge); (c) the number of genetic loci identified in GWAS studies that are exclusive to various migraine types (episodic, chronic, with or without aura, comorbid or not) as opposed to other primary headache disorders; (d) whether peripheral mechanisms alone are sufficient to trigger a migraine attack, noting that a subset of patients does not respond promptly or at all to targeted therapies, such as those against CGRP. e) What is the interictal factor that gradually activates the hypothalamic-trigeminovascular system, specifically the connection between interictal electro-functional and anatomical dysfunctions and pre-ictal conditions? f) Which structural and functional abnormalities identified through neuroimaging serve as predisposing traits for migraine, and how many are the consequences of its recurrence? g) What factor correlates interictal electrocortical abnormalities with the onset of aura and, in some instances, pain in humans; why do multiple aura-related focal disorders occur simultaneously or after intervals; and why can an aura present bilaterally?

These are but a few of the unresolved inquiries that render scientists in this domain 'restless,' akin to Pessoa, and constitute the 'universal' queries that patients pose to us daily: who, how, and why triggers a migraine attack? ■

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