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Neurogenic inflammation and vascular changes trigger Migraine : A critical re-evaluation

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Abstract

Migraines are neurological disorder with severe throbbing and pulsing headache, photophobi,nausea,phonophobia and fatigue that negatively affects the quality of life. It affects over 15% of general population.About one third of people with migraine in their lifetime can experience migraine with aura,without aura or chronic migraine .Hormonal changes, stress, weather changes and certain food triggers migraine attacks. Cortical spreading depression activates neuroinflammatory mechanisms that results in trigeminal nerve fiber sensitization which is responsible for intense pain on one side of their head during attack. A number of preclinical and clinical lines of evidence also support the implication of the potent vasodilator and messenger molecule nitric oxide in migraine pathophysiology. Other brain derived molecules are involved in vasodilation of the intracranial vasculature, as well as in the peripheral and central sensitization of the trigeminal system. Migraine is a risk factor for ischemic stroke also. Administration of exogenous hormones may cause worsening of migraine as it may expose migrainous women to an increased risk of cranial vascular diseases. Several studies have explored genetic associations between the functionally important polymorphisms in estrogen receptor 1 (*ESR1*) gene and migraine susceptibility. Life style modification, management of stress along with use of non-steroidal anti inflammatory drugs and proper hormone replacement in menopause can help to reduce symptoms associated with migraine.

Key words : migraine,headache, inflammation, polymorphism

Introduction

Migraines are expressed as pain associated with vasodilatation of cerebral and meningeal arteries and are classified as occurring with or without a visual aura,.Auras include temporary visual changes such as blind spots (scotomas), flashing lights, and zig-zagging lines of color and increased sensitivity of light.. Additional features of aura can include numbness, difficulty with speech and language, episodes of extreme dizziness (vertigo), and double vision. The term Migraine is derived from the Greek word ***hemicrania***. The headache is generally unilateral and is associated with nausea,anorexia, photophobia , vomiting and severe exhaustion,depression and fatigue follows the episode of headache [1]. Cortical spreading depolarization (CSD) is the electrophysiological correlate of the migraine aura . CSD is a slowly propagating wave of neuronal and glial depolarization followed by massive ion fluxes, spreading through the cortex,

and long-lasting suppression of neuronal activity. Chronic migraine is a debilitative neurological disorder that impacts on average 12% of the global population and imposes a significant individual and socioeconomic burden [2].Somatosensory disturbances are observed in chronic patients along with motor weakness,vertigo and decreased level of consciousness. Exsisting reported clinical studies of migraine primarily focus on episodic events of migraine, less is known about pathophysiology of chronic migraine. Profound functional and microarchitectural brain changes, central sensitization and neuroinflammation may underlie chronic migraine mechanisms [3]. The most vulnerable complications associated with migraine are migrainous infarction and migraine aura –triggered seizure**.**

The Migraine Generator : Specific neurons or nuclei of brain are marked hyperexcitable in chronic migraine patients and quickly activate the pathways that initiate the mechanism of pain and associated symptoms.[3,4]. Also the migraine nerve cells are too sensitive to Nitric Oxide (NO),a chemical messenger associated with vasodilation. NO regulates cerebral and extracerebral cranial blood flow and also the circumference of arteries. Inhibition of nitric oxide synthase (NOS) by L NMMA, a non specific NO synthase inhibitor effectively cures migraine without aura [4]. The dorsal raphe nucleus of the brainstem acts as **Migraine generator** which connects to the nerve pathways that leads to meninges. Activation of these pathways leads to release of inflammatory chemicals and dilation of the blood vessels.[5].

Trigeminovascular system, the connection between Migraine generator and nerves and blood vessels of meninges plays a key role in the initiation of pain and aura. Studies conducted with electrical stimulation of the trigeminal ganglion in both humans and cats leads to increases in extracerebral blood flow and local release of both Calcitonin gene related peptide (CGRP) and Substance P (SP). [6] In the cat, trigeminal ganglion stimulation also increases cerebral blood flow by a pathway traversing the greater superficial petrosal branch of the facial nerve, again releasing a powerful vasodilator peptide, vasoactive intestinal polypeptide (VIP). Interestingly, the VIP-ergic innervation of the cerebral vessels is predominantly anterior rather than posterior, and this may contribute to this regions' vulnerability to spreading depression, explaining why the aura is so very often seen to commence posteriorly.[7]

Genetic basis of Migraine : In more or less 50% of the reported families, Familial hemiplegic migraine (FHM) has been assigned to chromosome 19p13. Few significant clinical differences have been reported between chromosome 19-linked and -unlinked FHM families.[7,8] Indeed, the clinical phenotype does not associate particularly with the known mutations. The biological basis for the linkage to chromosome 19 is mutations involving the $Ca_v2.1$ (P/Q) type voltage-gated calcium channel *CACNA1A* gene.[9] Now known as FHM-I, this mutation is responsible for about 50% of the identified families. One consequence of this mutation may be enhanced glutamate release. Mutations in the *ATP1A2* gene have been identified to be responsible for about 20% of the FHM families. Interestingly, the phenotype of some FHM-II involves epilepsy. The gene codes for a Na^+/K^+ ATPase, and the mutation results in a smaller electrochemical

gradient for Na^+. One effect of this change is to reduce or inactivate astrocytic glutamate transporters, leading to a build-up of synaptic glutamate. A mis-sense mutation (Q1489K) in *SCN1A* has been reported as FHM-III [10]. This mutation affects a highly conserved amino acid in a part of the channel that contributes to its rapid closure after opening in response to membrane depolarization (fast inactivation). This represents a gain of function: instead of the channel rapidly closing, allowing the membrane to repolarize fully after an action potential, the mutated channel allows a persistent sodium influx.[8,11].

Neuroinflammation and Migraine : Neuroinflammation plays an important role in pathophysiology of migraine and trigeminal nerve fiber sensitization. The neurogenic inflammation also known as sterile inflammation induces release of Substance P, CGRP from trigeminal innervations which cause vasodilation, leukocyte infiltration, plasma extravasation due to capillary leakage and mast cell degranulation.[12]. Clinical and neuroimaging data suggest that the hypothalamus is implicated in migraine attacks [13]. Changes over time in the connectivity between the hypothalamus and other relevant brain regions for migraine (spinal trigeminal nuclei, dorsal rostral pons nuclei, thalamic neurons projecting to the cortex) may account for the preictal (prodromes) and ictal phases (head pain, associated symptoms and emotional aspects of headache) of migraine, as well as migraine termination. According to this pathogenetic hypothesis, in migraine attack, the hypothalamus in turn may activate the trigeminal nucleus caudalis (TNC) [8,13] therein leading to the activation of the trigeminal ganglion (TG) and the release of calcitonin gene-related peptide (CGRP) from its small to medium diameter sensory neurons (c-fibres).

Mast cells are immune cells derived from hematopoietic pluripotent stem cells which migrate and get matured near the nerves, vasculature and epithelial tissue. Meninges resident mast cell degranulation causes release of proteases, histamine and serotonin and selectively releases pro inflammatory cytokines like IL 1,tumor necrosis factor and also adiponectin [14]. The augmentation in inflammatory cytokines causes an increase in cell adhesion, production of chemical inflammatory compounds and NF-kB dysfunction. VIP can modulate mast cell degranulation and the production of proinflammatory cytokines, such as interleukins, including IL-6 and IL-8 [15].

The innate immune system is a cellular defense of organisms which deals with sterile and infectious insults and responds in a rapid and coordinated manner. The detection of pathogenic signals is recognized by pattern recognition receptors (PRRs) that sense pathogen-associated molecular patterns (PAMPs) and host- or environment-originated danger-associated molecular patterns (DAMPs). In the CNS, these PRRs are primarily expressed in microglia, astrocytes, , macrophages, oligodendrocytes, neurons and recognize metabolic alterations, tissue stress and damage.[16]. PRRs are located both at the plasma membrane and in the cytoplasm. Membrane-bound PRRs include Toll-like receptors (TLRs), which sense extracellular signals. The intracellular PRRs form “inflammasomes” as part of the innate immune response. [15,16]

Mitochondria plays a key role in inflammosome induction in neurons.. The formation of ROS and the release of mtDNA from mitochondria to the cytoplasm are among the cellular signals that play an important role in NLRP3 inflammasome activation which cause IL 1β activation. Abnormal mitochondrial function results in high intracellular calcium levels, increased ROS and reduced rate of oxidative phosphorylation which in turn cause energy deficiency and functional alteration in neurons and astrocytes. [17].The prolonged inflammatory state and CSD induced activation of matrix metalloproteinase 9 can alter Blood Brain Barrier (BBB) permeability and arrangement of gap junctions [18]. Tonabersat, an inhibitor of gap junction which binds to connexin 43, has been shown to be effective in a subset of migraine patients with aura. Under the influence of inflammatory stimuli, microglia can also become efficient mobile effector cells [17]. Microglia activation leads the production of inflammatory mediators and cytotoxic mediators (e.g., NO, reactive oxygen species, prostaglandins) which might disrupt the integrity of the blood brain barrier, thereby allowing leukocyte migration into the brain. [18,19].

Vasoactive Compounds and Migraine : Intracranial blood vessel dilation and vasodilatory peptides like Calcitonin-gene-related peptide (CGRP),nitric oxide (NO), pituitary adenylate cyclase activating polypeptide (PACAP-38) those are potent vasodilators have been implicated in migraine attacks. The blood vessels that carry immune cells pass through the meninges, enter the brain and modulate immunocyte trafficking. CGRP induced vasodilation could not induce nociceptive effect in meningeal nociceptors. Stimulation of the more specifically pain-producing superior sagittal sinus increases cerebral blood flow and jugular vein CGRP levels.[8] PACAP -38 is present in sensory neurons and vascular smooth muscle cells of vessels and intravenous administration of PACAP 38 can elicit a migraine like attack in patients [20] Studies with Magnetic Resonance Angiography of patients concludes that dilation of extracranial arteries was not associated with migraine pain although a slight intracranial dilation of arteries were observed [21] Clinical correlations suggest that CGRP is elevated in the headache phase of severe migraine,[9] although not in less-severe attacks, in cluster headache and chronic paroxysmal hemicrania.[10].

Migraine and stroke in women : Meta-analyses have linked migraine, particularly migraine with aura (MA), with increased risk of ischaemic stroke [22]. One possible mechanism behind this is progressive hypoperfusion, vasospasm and reduction in cerebral blood flow that occurs during migraine .Also long term use of NSAIDs may be a contributing factor to migraine rather than prevention of onset of pain as NSAIDs are associated with high risk of stroke [23] .Elevated concentrations of procoagulants like antiphospholipid antibodies, homocysteines, prothombin in cerebral blood flow also increases the risk of stroke [24] The association between migraine and ischaemic stroke is stronger for women, women younger than 45 years, women who use oral contraceptives and women who smoke. With a biased prevalence toward women (1.7–4.0%) compared to men (0.6–0.7%) [25], chronic migraine incidence peaks during midlife, affecting the most productive years of an individual's life. But due to very low number of outcome events, it is challenging to study the association between migraine and the different

subtypes of haemorrhagic strokes (ie, intracerebral haemorrhage and subarachnoid haemorrhage).

Polymorphism of estrogen receptors : Studies confirmed that 17 *beta* estradiol induces increase in NO level in cerebral and peripheral endothelial cells *in vitro* via eNOS activation and through E2 receptor-mediated mechanisms. Several polymorphisms are associated with familial migraine including genetic variation in Estrogen Receptor alpha (ERα) (G594A polymorphism of exon 8).[26] Estrogen receptors are located within brain nuclei innervating the cerebral vasculature as well as other nuclei regulating cardiovascular function.[26,27] Thus, besides influencing adrenergic mechanisms, estrogen may also modulate central opioidergic tone, release of peptidergic transmitters from trigeminal nuclei, and the GABAergic system, perhaps modulating NO [28,29].

Medications

Current treatment options for chronic migraine include risk factor modification, acute and prophylactic therapies, evidence-based treatments such as onabotulinumtoxin A, topiramate and newly approved calcitonin gene-related peptide or receptor targeted monoclonal antibodies [30]. Unfortunately, treatments are still predominantly ineffective in aborting migraine attacks and decreasing intensity and frequency, and poor adherence and compliance with preventative medications remains a significant challenge.

Nondrug therapies (relaxation, sleep, massage, ice packs, biofeedback) should be tried first to treat migraine in women who are pregnant. For treatment of acute migraine attacks 1000 mg of paracetamol (acetaminophen) preferably as a suppository is considered the first choice drug treatment. The risks associated with use of aspirin (acetylsalicylic acid) and ibuprofen are considered to be small when the agents are taken episodically and if they are avoided during the last trimester of pregnancy [31]. The 'triptans' (sumatriptan, zolmitriptan, naratriptan), dihydroergotamine and ergotamine tartrate are contraindicated in women who are pregnant. Prochlorperazine for treatment of nausea is unlikely to be harmful during pregnancy [32]. Metoclopramide is probably acceptable to use during the second and third trimester. Prophylactic treatment is rarely indicated and the only agents that can be given during pregnancy are the beta-blockers metoprolol and propranolol[1,31].

Conclusion

Migraine represents a substantial health care burden, both clinically and economically. Individuals with migraine and their families consume substantially more health care resources than those without migraine headache. Neuroinflammation can be initiated by chronic stress, diet, hormonal fluctuations, or CSD. The Neuro inflammation -triggering factors may become a possible interventional target preventing the initiation of neuroinflammatory cascade .Understanding the mechanism of Neuroinflammation trigger is essential in migraine research. In

women transdermal estrogen delivery is less likely to trigger migraine than oral estrogen delivery. Obviously this form of supplement is better for migraine patients as because it maintains a more stable delivery of estrogen and avoid fluctuating serum estradiol levels. Future clinical trials will be helpful in identifying treatment strategies for acute migraine attacks and may establish the role of short-term prevention in migraineurs.

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