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Review Article

Sexual Dimorphism in Migraine by Fluctuating Sex Hormone -Induced Mineral Imbalance: A Review

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Abstract

Migraine is a chronic, neurological, episodic and most disabling disease. It affects women 2-3 times more than men which points towards reproductive milestones as women menstruate and men don't. During menstruation, fluctuating level of estrogen (alpha and beta) and progesterone (A and B) receptors modulate headache signs. Estrogen activates ERK (extracellular signal-regulated kinase) present in neurons having peripherin, thus, causing menstrual headache (migraine?). Estrogen also excites mast cell degranulation resulting in histamine release which cause headache. Estrogen also down-regulates anti-nociceptive factors as GABA, IL-R1 and Zn-fingers. During pregnancy increased level of progesterone stimulate A/B receptors which are anti-nociceptive and result in mild or complete remission of migraine attacks. Men with migraine have higher levels of estrogen and lower levels of testosterone. Hormones produce headaches by directly stimulating their receptors and involve whole areas of head. Moreover, these headaches are often controlled by usual analgesics. Hormones may induce migraine indirectly by disrupting mineral homeostasis. Migraines are throbbing, pulsating, mostly one sided but very rarely both sides of head, and are unresponsive to usual analgesics. Estrogen enhances the absorption of Cu and increases its half-life which interferes with the absorption of Zn. Zinc is essential for the synthesis of serotonin, melatonin and CoQ10 which disturbs sleep/wake cycle. Melatonin stimulates antioxidant enzymes namely Cu-Zn-superoxide dismutase, catalase, glutathione peroxidase (a selenium-enzyme), and glutathione reductase. Mg and vit. B6 modulates the level of NO within the cell, both of which are deficient in migraineurs. Due to deficiency of Mg the trapped NO within the cell is not removed which combines with superoxide and generates peroxynitrite- a potent free radical. Iron stimulates nitric oxide synthase and produce more no but this enzyme is inhibited by zinc thus antagonizes excess NO production. Due to adrenal fatigue in migraineurs there is reduced production of cortisol resulting in free copper and iron which gets deposited in deep areas of brain tissue where they produce ROS and cause 'Oxidative Stress'. These Free Radicals damage myelin sheath covering nerves and normal nerve impulse transmission is disrupted. Moreover, Zn is an essential component of Zn-fingers (Krox20 and Krox24) which induce the differentiation of Schwann cells responsible for myelination/remyelination of damaged peripheral nerves. Hence, migraines has been logically and conceptually regarded as a neurological disease.

Keywords: Free Radicals; Oxidative-stress; Migraine; Nervous system; Minerals; Myelin

Introduction

Migraine is a neurological, episodic and most disabling disease prevalent worldwide affecting women 2-3 times more than men and peaks during their most productive period i.e., 30-39 years of age [43]. The reason for this variation has invariably been assigned, directly or indirectly, to the fluctuating reproductive hormones. Furthermore, recent functional magnetic resonance imaging (fMRI) studies have convincingly unveiled various anatomical and functional changes in relevant areas of the brain throughout the menstrual cycles in women which make them hypersensitive who develop migraine/headache. The frequency and severity of migraines during different milestones of reproduction as menstruation, pregnancy, lactation, menopause and contraception does vary to a larger extent. Plasticity of brain is influenced by several factors as environmental, genetical, lifestyle, neural signals, inflammatory reactions, hormones and of course many drugs used. As the age advances the brain networks modify structurally and functionally. There is segregation of local brain regions and integration

of distant regions of body disparately, thus, altering response to external/internal stimuli dependent on brain maturation. These changes continue to occur during different stages of development even after teens. During these changes our brain, immune system, lifestyles, foods and environments are also manipulated due to the neuroplasticity and neurogenesis of the brain. Remarkably migraine is one such disease which is expressed differently in young children, pre- and post-adolescent stage and its prevalence changes markedly with advancing age [1,2].

During infantile stage when neuronal networks are still in resting state and developing the migraine signs might be associated with colic, irritability, facial pallor, mood changes and disturbance in sleep [3]. These migraines in children are called "abdominal migraine" which may be considered as representing the behavioral level of brain development. Changes in the cortex of such infants have been found in thalamocortical connections which are believed to be of migraine [4,5]. The occurrence of migraine in boys and girls before puberty (10-11yrs of age) is similar and is ~ 3-10%. The symptoms in these cases are benign paroxysmal torticollis, vertigo, abdominal migraine and frequent cyclic vomiting probably due to brainstem effectors. Thereafter, it differs in both the sexes which is ~6% in males and 15-17% in females. Puberty usually begins at 8-14 in girls and 9-15 in boys at which time the Gonadotrophic Hormone Releasing Factors (GnRF) are secreted from the hypothalamus. These factors act on specific reproductive organs/glands to produce particular hormones as estrogen, progesterone, testosterone, prolactin and others. These hormones have specific receptors in various regions/tissues of the brain and other organs for specific functions. During the stages of development, functioning of hypothalamus is adjusted and modified continually depending on the requirements and preset needs [6,7]. As far as incidence of migraine is concerned there is ample evidence of sex differences in brain structure [8], and also aberrations in brain functioning, connectivity, visual and language systems [9,10]. These hormones play important roles for the development of various systems in the human body as per the reproductive stage [11,12].

Hypothalamus (Greek- hypo means under, thalamus) is a part of the brain situated below thalamus and have different nuclei which perform wide spectrum of functions, The most important relations of hypothalamus is its connection through pituitary portal system with pituitary gland which produce endocrine hormones. Pituitary gland has two parts i.e., anterior and posterior pituitary. Anterior lobe hormones regulate many physiological functions such as growth, stress, reproduction, lactation. Posterior pituitary regulate oxytocin and vasopression. Other hormones control hunger, thirst, body temperature, parenting, behaviorism, fatigue etc. Hypothalamus has rightly been described as the "Biological Clock" of human body. Most of these hormonal effects occur along with headaches/migraines which are putatively considered as 'premonitory signs' of migraine. These signs, though very important, shall be addressed separately in another forthcoming publication.

Here we discuss the sexual dimorphism in migraine which had been considered to be due to fluctuating hormone levels in women. It was conceptually and logically hypothesized that fluctuating levels of hormones interact with minerals which many a times result in their imbalance [13]. Many minerals act as part of enzymes and during metabolism generate Reactive Oxygen Species (ROS) called 'Free Radicals'. These ROS have quite a number of physiological functions in defense, immunity and synthesis of nucleotides. However, whenever there is excessive production of these species which overwhelms the bodily antioxidant mechanisms create 'Oxidative Stress' leading to neurodegenerative disorders. This is particularly true with iron which is essential for oxygen carrying and other metabolic enzymes. About 25% of total oxygen consumption in the body is by brain metabolic processes during which ROS particularly hydroxyl ion is very toxic for phospholipids. Myelin sheath which covers the nerves is primarily composed of these phospholipids which regulates the normal nerve impulse transmission. The ROS thus produced cause oxidation of phospholipids, particularly of trigeminal nerve which is the hub of the origin of migraine disease [14]. Keeping these observations in view it is opined that migraine is a neurological disease [39,44]. In this communication we explain that how mineral imbalances in copper, iron, zinc, magnesium, calcium, selenium along with hormones/neurotransmitters play a significant role in the evolution of migraine. These interactions of hormones and minerals are succinctly explained here.

Estrogen

Estrogen enhances the absorption of copper and prolongs its half-life. Copper is a natural antagonist of zinc and interferes in its absorption from the gut. Zinc is essential for the synthesis of serotonin, melatonin, dopamine, adrenaline, noradrenaline etc., which play pivotal roles in pathobiology of migraine. These transmitters are highly needed by adult women but are deficient in migraineurs and excess of copper further exacerbates this deficiency. The deficiency of serotonin and melatonin contributes significantly towards migraine attacks [15]. Zinc is essentially required by Zn-fingers (Krox-20 and Krox-24) which induce the differentiation of Schwann cells the mainstay for myelination/remyelination of peripheral nervous system [16].

Trigeminal ganglia and periaqueductal gray are densely populated with estrogen receptors (ER alpha and ER beta), which are

regulated by estrogen levels and has potential relevance to menstrual (migraines?) headaches. During menstruation higher/lower levels of estrogen directly stimulates ERs and activates extracellular signal-regulated kinase (ERK) which is present in neurons having peripherin, a known marker of nociceptive neurons. Estrogen also up-regulate some nociceptive and down-regulate antinociceptive genes as demonstrated by microarray analysis of ER alpha predominantly located in nucleus and cytoplasm of neurons of trigeminal ganglia in vitro. This process appears to be the main cause of menstrual headaches [17].

These headaches, however, need to be separated from migraine because perimenstrual headaches are by the excitation of estrogen receptors in trigeminal ganglia, periaqueductal grey and some other adjoining areas. Moreover, menstruation is a normal physiological phenomenon and not a pathological condition as has been assumed along with migraine. Higher levels of estrogen cause degranulation of mast cells which release histamine a known cause of headaches. Furthermore, menstrual headaches can be easily controlled by usual analgesics to which migraines are refractory. Hence, there is conclusive evidence that menstrual headaches are a different entity but not a true migraine.

Progesterone

During pregnancy progesterone is produced by corpus luteum and placenta throughout the gestation. Progesterone is antiestrogenic and also enhances the absorption of zinc during pregnancy. There is significant improvement or may be complete remission in the occurrence of migraine during pregnancy [22]. The progesterone receptors A and B (PR-A, PR-B) which coexist with ERs are antinociceptive in nature and play a major role in calming down or neutralizing the stimulatory effects of estrogen in the cause of headache in women during pregnancy.

Prolactin

There is an inverse relationship between prolactin and zinc. Moreover, in lactating, non-pregnant (menstruating) women there is excessive absorption of copper due to higher estrogen levels which increases the incidence of migraine. However, there is protective effect of breast feeding from migraine during first trimester of postpartum which is probably due to the low levels of estrogen or increased levels of oxytocin and vasopressin, which have antinociceptive properties [18]. Due to activity of vasopressin which is controlled by hypothalamic secretion of Anti –Diuretic-Hormone (ADH) there is frequent micturition during migraine episodic attacks.

Testosterone

Sexual differences, in men and women can also be modulated through testosterone as in men with migraine have lower levels of testosterone and relatively higher concentration of estrogen. Zinc is also essential for the synthesis of testosterone in the body, but zinc is quite low in migraineurs, hence, lower levels of the male hormone-testosterone [41]. Testosterone also reduces pain in transsexuals treated for hormone imbalances. It has been observed that female-to-male transsexuals treated with testosterone reduces pain while in male-to-female treated with estrogen pain is increased [19]. Nuclear testosterone receptors are present in dorsal root ganglion and CGRP-positive neurons which are not expressed after castration [20].

Cortisol

Cortisol produced by adrenal cortex stimulates the synthesis of ceruloplasmin (a copper transporter) and transferrin (an iron transporter) in the liver. Migraine is often accompanied by depression which results in 'adrenal fatigue'. Under such circumstances there is deficiency of ceruloplasmin and transferrin resulting in free copper and iron. Though these metals are present in the system but usually bio-unavailable. Free copper and iron being transition metals have high ''redox potential'' and generate free radicals, e.g., superoxide anion, hydroxyl radical, nitric oxide (NO). The latter reacts with superoxide to produce peroxynitrite which is a highly reactive species and cause injuries to myelin sheath and macromolecules. Moreover, the generation of free radicals is a chain reaction and produce many more reactive species inflicting severe cellular damage.

Free radicals cause oxidation of phospholipids which is major component of myelin sheath covering nerves. Myelin helps in the smooth transmission of nerve impulse and act as an insulation as our domestic electrical wiring. Hence, when myelin is damaged by free radicals the naked nerves get exposed to extravasation of plasma proteins which cause mechanical pressure on the exposed nerve areas resulting in migraine. However, the intensity of migraine pain varies with the severity of damage which depends on the level of "Oxidative Stress" exerted by free radicals.

Use of contraceptives

Hormonal contraceptives are mostly composed of estrogen or progesterone analogues. The women previously suffering from migraine with aura experienced worsening of their attacks after starting with oral contraceptives. This observation was further

substantiated by the occurrence of visual, sensory and motor aura along with migraine [21]. Furthermore the use of ''Copper–T'' as a contraceptive is also in vogue which adds fuel to fire through the continuous release of copper in the system and increase the incidence of migraine in women due to higher copper levels.

Menopause

Before and during menopause the occurrence of migraine usually worsens but improves significantly thereafter. The hormone replacement therapy (HRT) thereafter, presents a variable picture. Attacks of migraine with aura may start for the first time after the start of HRT. Women absorb more cadmium which displaces zinc from metallothionein. Also smoking women inhale more cadmium in tobacco which reduce production of progesterone in pregnant women due to higher cadmium contents in placenta of smoking women. Hence, lower levels of zinc and higher quantity of cadmium increases the incidence of migraine due to 'Oxidative Stress'. Cadmium also enhances the accumulation of iron which exacerbates zinc and magnesium deficiency. Nicotine also accelerates copper catalyzed oxidative damage to the nervous tissue [23].

Thyroxine

Thyroxine opposes or balances estrogen. There is a concomitant hypothyroidism among women migraine sufferers. Iron status and thyroid functions are reciprocal as copper antagonizes iron absorption and deficiency of iron can impair thyroid function culminating in migraine. Excess copper can also affect thyroid function through insulin, though, indirectly. Insulin is known to antagonize thyroid function. Elevated level of estrogen is associated with higher levels of insulin. Moreover, during the last trimester of pregnancy insulin levels are the highest as also the levels of estrogen along with the concomitant episodes of migraine. Zinc is required for the storage of insulin. Possibly the antagonism of zinc by higher levels of copper (estrogen) during the last trimester of pregnancy there is flooding of insulin into plasma. Further, the synergistic effect of copper, calcium and vitamin-D in which there is increase of calcium retention which is known to mediate the release of insulin. Taken together, these interactions result in increased frequency and intensity of migraine [24].

Parathyroid hormone (PTH)

PTH is essential for the synthesis of vitamin D. PTH and vitamin D, both are required for the absorption of magnesium. Magnesium and vitamin B6 moderates NO levels. Magnesium and vitamin B6 are usually low in women suffering from migraine. Magnesium is essential for the release of trapped NO from within the cell which in lower levels of magnesium does not occur. The trapped NO within the cell combines with superoxide to form peroxynitrite which is a most potent free radical and cause oxidative stress through lipid peroxidation and cause myelin degeneration. Moreover, levels of estrogen are negatively correlated to cytosolic concentration of magnesium and its levels are consistently low in migraineurs [25].

Serotonin, melatonin/neurotransmitters (Neurotransmitters)

Serotonin is produced during day time and is called the 'Feel Good' neurotransmitter. Melatonin is produced in Pineal gland during night (darkness) which is mainly concerned with sleep/wake or 'Circadian cycle'. Melatonin is a broad spectrum, direct free radical scavenger. Moreover it induces certain enzymes which are most potent antioxidants in the body's defense e.g., Cu Zn-superoxide dismutase, catalase (Zinc containing), glutathione peroxidase (selenium containing), glutathione reductase, etc., which enzymatically neutralize free radicals. It also prevents free radical generation and scavenges reactive oxygen species (ROS) resulting in attenuation of 'oxidative stress'. Melatonin production is lowered in night duty persons, particularly in women. There is excessive production of estrogen in such women which augments the chances of migraine attacks [26].

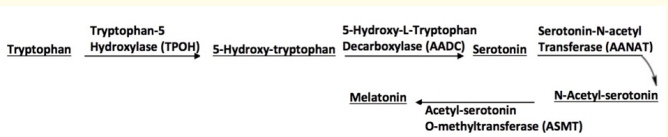

Figure 1: Synthesis of serotonin (5 HT-Feel Good) and melatonin (sleep/Wake cycle).

Synthesis of these neurotransmitters are shown below:

Description: Tryptophan is an essential amino acid and is an obligatory substrate for the synthesis of 5-hydroxy-tryptophan (5-HT) and melatonin. Hydroxylation of tryptophan by enzyme tryptophan-5-hydroxylase has an absolute requirement of pyridoxal phosphate (PLP) i.e., Vitamin B6 which can be activated by a zinc dependent enzyme pyridoxal kinase. Therefore, deficiency of zinc in migraine patients, synthesis of 5-HT (serotonin) and melatonin is disrupted resulting in very low levels of these two molecules, hence, the role of zinc in the causation and treatment of this malady need not be overemphasized.

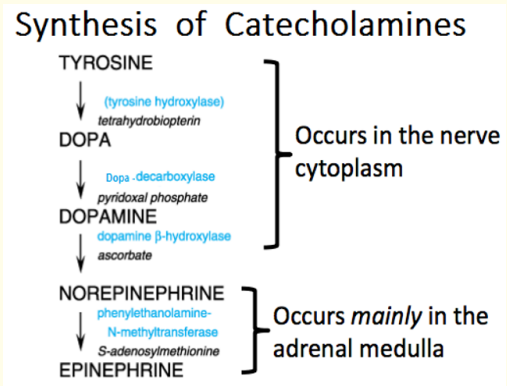

Figure 2

Description: Tyrosine is first hydroxylated to 3, 4, dihydroxyphenylalanine (DOPA) and DOPA is converted to dopamine by dopamine-decarboxylase and this enzyme has the absolute requirement of activated pyridoxine (vit. B6) to pyridoxal phosphate (PLP). Conversion of pyridoxine to PLP is catalyzed by a zinc dependent enzyme called pyridoxal kinase. Dopamine is then converted to Norepinephrine and Epinephrine by the respective enzymes shown in above figure. Dopamine-beta-hydroxylase is also a zinc dependent enzyme. Furthermore, it has been observed that the activity of dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase is reduced in zinc deficiency. Dopamine has always been found to be low in brain tissues (cortex, cerebellum, hippocampus). Hence, the deficiency of zinc in the mediation of migraine development.

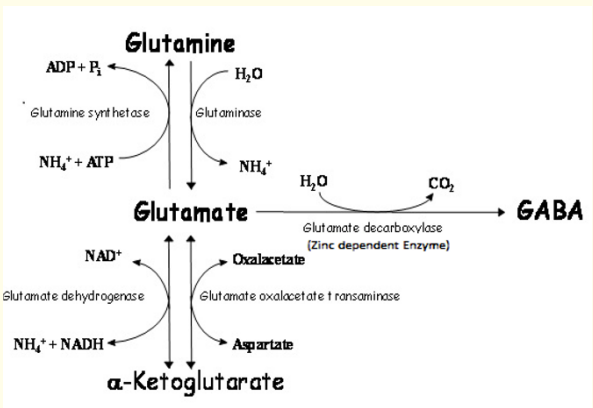

Figure 3: Synthesis of Glutamate (excitatory) and Gama Amino Butyric Acid (Pacifier).

Description: Glutamate has been recognized as an important neurotransmitter which plays very crucial roles in neuronal transmission and development of neurodegenerative diseases. Glutamate is synthesized from glutamine and play an excitatory role in nerve impulse transmission at synaptic junctions. However, an excess or less of a good thing may also prove disastrous. Under physiological conditions glutamate normally is converted to gamma-amino-butyric- acid (GABA) which is pacifier in action. This conversion from glutamate to GABA is catalyzed by glutamate decarboxylase which is a zinc dependent enzyme. Therefore, zinc deficiency in migraine patients exacerbates the occurrence of migraine due to accumulation of glutamate at the synaptic junctions. Hence, the role of zinc in migraine control need not be overemphasized.

The excitatory amino acid glutamate enhances the generation of endogenous hydroxyl radical. Oxidation/autoxidation of dopamine, epinephrine and nor-epinephrine catalyzed by iron and copper generates more free radicals which further accelerates oxidative stress. The excitatory amino acid receptors suppress the synthesis of melatonin. Myelin is composed of 80% lipids containing unsaturated fatty acids which are very sensitive to oxidative stress. Taken together, the ''free radicals'' thus generated induce lipid peroxidation leading to myelin degeneration and the white matter becomes less hydrophobic and accumulation of fluids, therein, exerts mechanistic pressure over the hyperalgesic axons culminating in migraine [27].

It has been observed that stimulation of 5-HT1b/1d receptor in the periaqueductal gray inhibits nociception. These studies show that there exist some more brain loci other than trigeminal nucleus which might play a role in the occurrence of clinical migraine [28]. It is well known that zinc plays a pivotal role in the synthesis of 5HT or serotonin which modulates the nociceptive process through these antinociceptive pathways in the brain stem. Furthermore, the neurotransmitter systems, e.g., serotonergic, glutamatergic, noradrenergic, GABAergic and opiatergic, are most prominently affected by sex hormones and play a significant role in the pathobiology of (migraine?) headaches.

Lipid peroxidation and myelin degeneration are independent of any inflammatory reaction as no inflammatory cell infiltration was observed i.e., "sterile inflammation". Moreover, evidence of excess redox active copper in the peripheral nerves well before myelin lesions or macrophage activation is consistent with copper-induced oxidative stress leading to myelinopathy [29]. *In vitro* studies have also revealed that copper causes oxidation of phospholipids

probably due to their zwitterionic nature [30]. It has been demonstrated that metallothioneins play a pivotal role in the homeostasis of zinc and copper. Studies show that Zn7MT3 in the presence of ascorbate completely quenched the copper catalyzed hydroxyl radical production and most efficiently silenced the redox-active free copper ions [31]. Zinc being a nonredox divalent metal which possess antioxidant properties can be easily incorporated into the biological system. Zinc showed pronounced inhibitory effect on copper-induced spontaneous lipid peroxidation in whole brain homogenates of rat [32].

Dicusssion

Copper, iron, zinc, selenium, calcium and magnesium are among the most essential minerals which act as cofactors and catalyze various biological reactions when in proper proportions. However, any disturbance in their homeostasis result in devastating effects through the generation of free radicals, with ensuing lipid peroxidation, oxidative stress, demyelination and denudation of axons. Migraine is a very complex disorder of brain which involves several neuronal pathways and neurotransmitters in its pathobiology. The network of hypothalamus, central nervous system, autonomic nervous system and hypophysis appears to be of paramount importance which is suspected to be *locus in quo* for migraine. Recent advancements in diagnostic techniques of migraine the ''vascular theory'' of migraine has been denounced and several studies suggest the involvement of nociceptive activation, particularly trigeminal afferent pathways and hypothalamus. However, brain imaging studies through Magnetic Resonance Angiography have demonstrated that ''migraine headache is not associated with cerebral or meningeal vasodilation'' [33-35].

There is sexual dimorphism in the prevalence of migraine, hence, the female hormones contribute immensely, directly or indirectly, to the higher incidence of migraine in women than men. The changes in the reproductive milestones in women's life (from menarche to menopause) are in tandem with the frequency and severity of migraine. The female hormones enhance the neuronal excitability by elevating calcium and decreasing magnesium concentrations. Female hormones also modulates the release of NO, serotonergic, adrenergic and GABAergic systems which are implicated in migraine pathogenesis [28].

Recent investigations have revealed that estrogen regulate several genes on the trigeminal ganglia with a potential relevance to migraine. Probably the antinociceptive genes are down-regulated while nociceptive one's are up-regulated resulting in the activation of extracellular signal-regulated protein kinase (ERK) in the neurons containing peripherin which is a marker of nociceptive neurons [36]. Further, periaqueductal gray, trigeminal ganglia and some other brain parts are densely populated with ER alpha and ER beta which may be directly stimulated by higher levels of estrogen culminating in menstrual headaches. However, in contrast to estrogen receptors there also co-exist progesterone receptors which might play antinociceptive role in the remission of migraine during pregnancy.

Magnetic Resonance Imaging (MRI) revealed increased deposition of iron in periaqueductal gray in migraine patients which suggests the interruption of central antinociceptive neuronal network. Further, it was observed that there was repeated migraine attacks associated with increased iron accumulation in multiple deep brain nuclei involved in the central pain processing system and migraine pathophysiology [37-39]. Iron being a transition metal as free in the brain would generate hydroxyl radical by catalyzing the oxidation of catecholamines.There is also accumulation of dietary copper in the peripheral nerves where it causes variable degrees of myelinopathy [40]. Probably the accumulation of free iron and copper in the vulnerable sites, e.g., trigeminal ganglia, periaqueductal gray and adjoining areas disrupts antinociceptive network processing through myelin degeneration leading to migraine through generation of highly reactive hydroxyl radicals [45,46].

From the above discussion it can be concluded that in menstrual headaches ERs play a central role through their direct stimulation by estrogen. Moreover, men with migraine had higher levels of estradiol and relative deficiency of androgen [41,42]. Hence, higher levels of estradiol also activates estrogen receptors in men as in women and they also lacked the protective effect of testosterone against headache/migraine. Free copper and iron in nervous tissue produce ROS which cause "Oxidative Stress" that overwhelms the body's antioxidant defense mechanisms and establish "Neurogenic sterile Inflammation' and induce lipid peroxidation, demyelination and neurodegeneration at specific sites causing migraine with or without aura. Basic etiology of genesis of migraine pain appears to involve the sensitized meningeal afferents with their cell bodies present in trigeminal ganglion that project to higher centers for signal transmission in higher brain centers for execution in trigeminal nociceptors.

Conclusion

Prevalence of Migraine before adolescent is similar in boys and girls but after menarche it has been reported to be ~2-3 times more in adult women than men. This phenomena of sexual dimorphism points towards the involvement of sexual reproductive milestones as women menstruate and men don't. During this period there is fluctuation of hormones secreted by gonads. Estrogen in higher levels stimulate its alpha and beta receptors present in trigeminal ganglia, periaqueductal gray and adjoining areas and cause headaches during perimenstruation i.e., two days before and three days after menstruation which are physiologically normal. Indeed these headaches are not migraines, however, called menstrual migraines. Moreover, during pregnancy Progesterone through its receptors A/B which lie alongside estrogen receptors provokes very mild or there is complete remission in migraines. In males testosterone hormone is also antinociceptive, hence, occurrence of migraine is lesser in males. However, hormones interact with minerals as Zinc, Ca, Mg, Iron, Copper, Selenium etc., resulting in creating imbalances in them. As fluctuating (higher) levels of estrogen increases the absorption of copper which antagonizes zinc absorption and creating zinc deficiency-a biomarker of migraine. These ions are part of various metalloenzymes which play an integral role in the synthesis of very important molecules as serotonin, melatonin, CoQ10, dopamine, adrenaline, noradrenaline which are usually low in migraine patients. Imbalances of these enzymes results in the production of Reactive Oxygen Species (ROS) also called 'Free Radicals". These ROS cause oxidation of myelin sheath which covers the nerves for normal nerves impulse transmission. Such oxidation cause degeneration of fatty tissues resulting in naked axons which are very sensitive to mechanistic pressure of extravassation of plasma proteins causing pain called migraine headache which is pathological disease. There ensues sterile inflammation along with interleukines, prostaglandins, histamine resulting in severe pain. This pain condition is primarily due to imbalance of minerals and overwhelming oxidative stress over the protective antioxidants of the body. These observations have been discussed in detail in this manuscript.

Conflict of Interest

Disclaimer: Certified that there are no conflicts whatsoever among the authors, and no financial support was obtained from any source.

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