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A new horizon into the pathobiology, etiology and treatment of migraine

Kundan Singh Dhillon, Jasmer Singh *, Jarnail Singh Lyall

Punjab Agricultural University, Ferozpur Road, Ludhiana, 141004 Punjab, India

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ABSTRACT

Sexual dimorphism in the prevalence of migraine (70% women 30% men) suggests the involvement of reproductive hormones in a women's life. Excessive estrogen during menstruation directly stimulate estrogen receptor alpha thickly populated in trigeminal ganglia and periaqueductal gray which manifest as menstrual migraine. In contrast increased progesterone during pregnancy evokes progesterone receptors A/B, which coexist with ERs, providing complete remission from migraine episodes. Moreover, estrogen also increases nociception through extracellularly signal-regulated kinase (ERK) stimulation and down-regulating antinociceptive GABA, IL-R1 and Zn-fingers.

Hormones may provoke migraine indirectly by disrupting mineral homeostasis. Estrogen enhances the absorption and half-life of copper which in turn inhibits the absorption of zinc. Zinc is required for the synthesis of melatonin and CoQ10 essential for growing women. Excess of copper exacerbates the deficiency of zinc, melatonin and CoQ10 typically low in migraineurs. Melatonin is an antioxidant, free radical scavenger and activates antioxidant enzymes like CuZn-superoxide dismutase, catalase, glutathione peroxidase (a Se-enzyme) and glutathione reductase. Zinc deficiency reduces activity of CuZn-SOD. Magnesium and vitamin B6 modulates the level of NO in the cell, both of which are deficient in migraineurs. Magnesium is essential for the removal of trapped NO from within the cell which does not occur under low magnesium levels, which reacts with superoxide generating dangerous peroxynitrite. Iron stimulates nitric oxide synthase producing more NO which is inhibited by zinc, thus, antagonizing peroxynitrite generation. Female hormones lowers magnesium but increase calcium levels which enhance migraine ubiquitousness. Accumulation of copper and iron in deep areas of brain and peripheral nerves typically catalyses the oxidation of catecholamines and generate free radicals involved in lipid-peroxidation, demyelination, denudation of axons and neurodegeneration in specific areas exposing hyperalgesic axons provoking Classical migraine. Furthermore, zinc is an essential component of Zn-fingers (*Krox20* and *Krox24*) which play a pivotal role in the differentiation of Schwann cells-the mainstay for the myelination/remyelination of peripheral nerves.

Taken together, conceptually and logically, 30 migraineurs were administered 75 mg of zinc sulfate orally in water daily for 6 weeks + one capsule of vitamin B-complex + one capsule of vitamin A or E (first 10 days) which almost cured all of them. Placebo controlled trials with incremental doses of zinc sulfate along with magnesium and selenium are proposed to augment recovery involving large population of migraineurs. Monitoring of hair and blood mineral analysis for rational therapy is recommended.

Introduction

Current concepts of migraine etiology are decidedly in favor of its neurological origin, however, the nub of the malady has yet to be unveiled. According to WHO at least 303 million people all over the globe suffer from migraine. The prevalence of migraine prior to adolescence is almost similar in both sexes. But after menarche till menopause its incidence is higher (70%) in women than men (30%), a clear indicator of sexual dimorphism among migraine sufferers. This phenomenon points towards the reproductive milestones among females, e.g., menarche, menstruation, pregnancy, lactation, menopause, etc., directly/indirectly linked to migraine [30,31]. The hormones may contribute directly to the problem but their role in the homeostasis of minerals in the body appears to play a pivotal role in the pathobiology of migraine. The network of hypothalamus → hypophysis → endocrine glands → neurotransmitters → minerals is so meticulously webbed that a slight aberration in it would result in vast pathological manifestations [1,7].

After delving into the biochemical interactions at the molecular level and exhaustive review of literature extant it was conceptually and logically hypothesized that mineral dyshomeostasis,

* Corresponding author. Address: 1217 Forebridge Lane, Lincoln, CA 95648, USA. Tel.: +1 916 543 1771; fax: +1 916 624 1264.
E-mail address: jasmerdr@yahoo.com (J. Singh).

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particularly, of copper, iron, zinc, magnesium and selenium along with hormones/neurotransmitters play a significant role in the occurrence of migraine. The most relevant mechanisms are succinctly explained below:

Hormones, minerals – cause and effect (migraine)

Estrogen

a. 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 melatonin which in turn increases the absorption of zinc. Zinc and melatonin are highly needed by the women but are deficient in migraineurs and excess of copper further exacerbates this deficiency. The deficiency of melatonin contributes significantly towards migraine attacks [2]. Zinc is essentially required by Zn-fingers (*Krox-20* and *Krox-24*) which induce the differentiation of Schwann cells the mainstay for myelination of peripheral nervous system [25].
b. Trigeminal ganglia and periaqueductal gray are densely populated with estrogen receptor (ER alpha and ER beta), which are regulated by estrogen levels and has potential relevance to menstrual migraines. During a menstruation higher level 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-regulated some nociceptive and down-regulated antinociceptive genes as demonstrated by microarray analysis of ER alpha predominantly located in cytoplasm of neurons of trigeminal ganglia *in vitro*. This process appears to be the main cause of menstrual migraines [3].

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-a co-morbidity, 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) and the latter reacts with superoxide to produce peroxynitrite which is a highly reactive species and cause injuries to macromolecules. Moreover, the generation of free radicals is a chain reaction and produce many more reactive species inflicting severe cellular damages [4].

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 [5]. Moreover, there are progesterone receptors A and B (PR-A, PR-B) which coexist with ERs (referred above) but in contrast to ERs, the PRs are most probably antinociceptive in nature and play a major role in calming down or neutralizing the stimulatory effects of estrogen in the cause of migraine in women during pregnancy [3,31].

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 [6].

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 [7]. Furthermore the use of "Copper–T" as a contraceptive is also *in vogue* which adds fuel to the fire through continuous release of copper in the system and increase the incidence of migraine in women.

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 [8].

Women absorb more cadmium which displaces zinc from metallothionein. Smoking persons inhale more cadmium as tobacco contains high quantities of it. There is also reduced production of progesterone in pregnant women and higher cadmium contents in placenta of smoking women. Hence, lower levels of zinc and higher quantity of cadmium increases the incidence of migraine. Cadmium also enhances the accumulation of iron which exacerbates zinc and magnesium deficiency. Nicotine also accelerates copper catalyzed oxidative damage to the nervous tissue [9].

In addition to the above mentioned sex hormones associated directly with migraine, other hormones/neurotransmitters involved in this episodic malady, involved indirectly, are referred to precisely below:

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 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 [10].

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 [11].

Melatonin/neurotransmitters

Melatonin is produced in Pineal gland during night (darkness). Melatonin is a broad spectrum, direct free radical scavenger. It induces certain antioxidant enzymes, e.g., CuZn-superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, etc., which enzymatically neutralize free radicals. It 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 which augments the chances of migraine attacks [12].

The excitatory amino acids such as 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 the 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 water, therein, exerts mechanistic pressure over the hyperalgesic axons culminating in migraine [13].

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 [29]. It is well known that zinc plays a pivotal role in the synthesis of 5HT and serotonin probably 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 hormones and play a significant role in the pathobiology of migraine headaches [30,31].

Lipid peroxidation and myelin degeneration are independent of any inflammatory reaction as no inflammatory cell infiltration was observed in experimental autoimmune encephalomylitis (EAE). 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 [14]. *In vitro* studies have also revealed that copper causes oxidation of phospholipids probably due to their zwitterionic nature [15].

Recently, metal-chelation-therapy has emerged as a very effective technique to combat the increased free radical toxicity to macromolecules. 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 [16].

Zinc being a nonredox divalent metal which possess antioxidant properties can be easily incorporated into the biological system [24]. Zinc showed pronounced inhibitory effect on copper-induced spontaneous lipid peroxidation in whole brain homogenates of rat [17].

Treatment of migraine

While critically analyzing the ongoing observations on the interactions of hormones, minerals and life-style of migraineurs, we planned a pilot project on the treatment of this syndrome. The study involved 30 individuals (males 11 and females 19) aged between 25–45 years. These individuals presented varied frequency, intensity and clinical signs of migraine for the last 3–5 years of duration. A proforma regarding age, sex, duration of occurrence, familial relationship, food habits and any treatments taken was filled by each patient for the records. The treatment schedule was as mentioned below:

a. Zinc sulfate 75 mg daily in drinking water 1 hour after morning meal for 6 weeks.
b. One capsule of vitamin B-complex daily for 10 days from the start of treatment.
c. One capsule of vitamin-A or -E daily for 10 days from the start of treatment.

This schedule was continued for 6 weeks. During the treatment period the patients had the routine excess to their meals as usual. The patients were personally contacted weekly and enquired about their condition in relation to migraine. After 2 weeks of the institution of the medication some patients reported discernible relief from the migraine episodes regarding the frequency and severity. The relief from migraine was so spectacular by the fourth week that most of the patients reported to have almost recovered from the horrible nightmares of the malady. After 6 weeks of this treatment almost all the patients reported to be free from migraine. All the 30 persons were followed-up for 3 years as to know the recurrence of any episode of the malady or side effects, if any, from this treatment. Except two women, who reported rarely having a mild headache during the entire period of observation (which could be an epiphenomenon), none of the other patients suffered from this malady and felt relieved from the perpetual pending fear of 'migraine walking'. No side effect(s) from this treatment was reported by any patient.

Discussion

Copper, iron, zinc, selenium and magnesium are among the most essential metals 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. The nub of this malady has still not been precisely unveiled. Nevertheless, with the advancement of diagnostic techniques the "vascular theory" of migraine has been wrecked with facts and several studies suggest the involvement of nociceptive activation, particularly trigeminal afferent pathways and hypothalamus. There is involvement of multisensory disturbances, e.g., light, sound, smells, nausea, etc., [18]. Brain imaging studies through Magnetic Resonance

Angiography have demonstrated that "migraine headache is not associated with cerebral or meningeal vasodilation" [19].

There is sexual dimorphism in the prevalence of migraine, i.e., 70% in females and 30% in males. 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 [7,29].

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 [20,21]. Further, periaqueductal gray appears to be involved in migraine as it contains higher density of estrogen receptors (ER alpha and ER beta) which may be directly stimulated by higher levels of estrogen culminating in menstrual migraines [3]. However, in contrast to estrogen receptors there also co-exist progesterone receptors which might play antinociceptive role in 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 [22]. 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 [14]. Probably the accumulation of free iron and copper in the vulnerable sites, e.g., trigeminal ganglia, disrupts antinociceptive network processing through myelin degeneration leading to migraine.

As far as the treatment aspect of migraine is concerned several drugs have been developed by certain pharmaceuticals and marketed. The commonly available drugs are triptans, anti-calcitonin gene related peptide compounds, non-steroidal anti-inflammatory drugs, antihistamines, botulinum toxin injection, etc. In the beginning these drugs appeared specious but proved palliative with very serious side effects [23]. Nevertheless, these are still available and being used. Development of more effective drugs against migraine is a continuous process and is underway with many organizations. The hubris of pharmaceutical corporate has often overshadowed the practice of alternative and holistic approach to available or new methods for the control of various ailments inflicting humanity. However, we used zinc sulfate in combination with vitamin B-complex and vitamin A/E, as stated above in the treatment of migraine, which proved very effective for the treatment of migraine in men and women without any side effects. To hit upon this treatment it was hypothesized with the logical concept that under disturbed conditions of homeostasis of copper, iron and zinc the bio-unavailable copper and iron, which are primarily located in the nervous tissue, generate free radicals which cause severe myelin degeneration at specific sites in the nervous system culminating in the manifestation of migraine. Zinc plays a very crucial role in antagonizing these effects since this metal is non-redox, divalent ion and can be easily incorporated into the biological systems both intra- and extra-cellularly. Moreover, zinc being an antioxidant along with metallothionein accelerates the neutralization of oxidative effects induced by copper and iron [24].

Zinc is also an essential component of Zinc-fingers, i.e., *Krox20* and *Krox24* which differentiates Schwann cells vitally required for the myelination of neurons of the peripheral nervous system [25]. Zinc is the harbinger for synthesis of serotonin, melatonin which are potent antioxidants and free radical scavengers. Melatonin is considered a pleuripotent prodrug for the treatment of migraine [26,27]. In addition zinc also antagonizes the lipid peroxidation induced by copper [16]. Iron induces the neuronal nitric oxide synthase (nNOS), the enzyme which catalyses the production of NO radical, this enzyme is inhibited by zinc thus preventing the formation of excess peroxynitrite [28]. From the above discussion it can be concluded that in menstrual migraines ERs play a central role through their direct stimulation by estrogen while PRs in contrast behave antagonistically and provide relief from migraine headaches with or without aura during pregnancy. The generation of free radicals through bio-unavailable copper and iron induce lipid peroxidation, demyelination and neurodegeneration at specific sites provoking unpredictable "Classical migraine" with aura.

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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