Treatment of Clinical Cases of Migraine

Abstract

According to WHO nearly 303 million people, of all ages, are affected with migraine. Migraine does occur among children but the incidence is almost same in both the sexes prior to adolescence. However, after menarche the incidence among women is higher (70%) than men (30%). Moreover, even in women incidence varies with the periodicity of the reproductive milestones as menstruation, pregnancy, lactation, menopause and use of contraceptives. These phenomena points towards the implication of hormonal changes during these phases of reproduction. Hormones may influence the induction of migraine directly. The trigeminal ganglia and periaqueductal gray are densely populated with estrogen (alpha and beta) and progesterone (A and B) receptors which regulate primarily the headache signs. During menstruation, increased level of estrogen stimulates the alpha receptors and activates ERK present in neurons having peripherin, a known marker of nociceptive neurons, thus, causing menstrual migraine. Estrogen also down-regulates antinociceptive GABA, IL-R1 and Zn-fingers. During pregnancy increased levels of progesterone stimulate A/B receptors which are antinociceptive in nature and result in milder or almost complete remission of migraine attacks.

Hormones may induce migraine indirectly by disrupting mineral homeostasis. Estrogen enhances the absorption of Cu and increases its half-life which interferes in the absorption of Zn. Zinc is required for the synthesis of melatonin and CoQ10 essential for growing women. Hence, the deficiency caused by estrogen exacerbates the deficiency of zinc, melatonin and CoQ10 which are always typically low in migraineurs. Melatonin has been considered as a prodrug which stimulates the most important antioxidant enzymes namely CuZn-superoxide dismutase, catalase, glutathione peroxidase (a se-enzyme), and glutathione reductase. Moreover, Zn deficiency reduces the activity of ZnCu-SOD. Magnesium deficiency is quite common in migraineurs and Mg is very essential part of many enzymes which play roles in the production of energy as ATP. Mg and vit.B6 modulates the level of NO in 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 in the cell and generates peroxynitrite which is a potent free radical resulting in myelin degeneration at specific areas denuding hypersensitive neurons inducing migraines. Iron stimulates nitric oxide synthase and produce more NO but this enzyme is inhibited by zinc thus antagonizes more NO production. Furthermore, there is adrenal fatigue, depression and somnolism in migraine patients. There is reduced production of cortisol from adrenal cortex which stimulates the synthesis of ceruloplasmin (a copper transporter) and transferrin (an iron transporter) in the liver. Both iron and copper are transition metals which become free and stored in deep areas of the brain and peripheral nervous tissue where these ions catalyse the oxidation of catecholamines and produce highly reactive radicals which also cause neurodegeneration, lipid-peroxidation and demyelination exposing hypersensitive neurons inducing migraines. Moreover, Zn is an essential part of Zn-fingers (Krox20 and Krox24) which induce the differentiation of Schwann cells responsible for the myelination/remyelination of peripheral nerves. Zinc in itself is an effective antioxidant and protects nervous tissue in general, hence, prevents and/or help in the treatment of migraine. Other hormones and neurotransmitters

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as prolactin, thyroxine, parathyroid hormone, Vit. D, insulin, melatonin, 5HT, GABA, etc., also play very important roles in homeostasis of minerals and indirectly aids in the induction of migraine. This imbalance causes myelin degeneration, due to generation of free radicals, at specific sites of nervous system. It can be treated most effectively by restoring this imbalance with exogenous administration of zinc sulfate 75 mg+200 mg magnesium citrate twice daily+one capsule Vit. B-complex+one capsule Vit. E 400 IU+200 mg Coenzyme Q10 twice daily. All these medications were given orally for six weeks. This line of treatment was more effective than our previous one in amelioration of migraine in all the 27 patients. Further studies on large population of migraineurs with different mineral and vitamin combinations are required before finally adopting in general practice of medical treatment.

Keywords: Migraine; Nervous system; Minerals: Myelin degeneration

Introduction

The prevalence of migraine has been estimated to be about 303 million people globally. There is clear-cut sexual dimorphism in the occurrence of migraine as 70% of women and 30% men, in their adult stage, are affected. However, migraine does occur in children before attaining adulthood but classically the prevalence is almost equal in both the sexes. Furthermore, during pregnancy the migraine attacks becomes rare, if any, that too very mild or there may be complete remission from migraine attacks. Hence, these observations indicate the involvement of reproductive hormones in its development. This phenomenon points towards the periodicity of the reproductive milestones in females such as menarche, menstruation, pregnancy, lactation, menopause etc. Moreover, the use of contraceptives, which are mostly composed of estrogen and/or progesterone analogues, worsens the migraine episodes in women who previously had migraine problem and badly affect visual, sensory and motor aura (prodromal phase) along with migraine. The hormones may directly contribute to the migraine as estrogen stimulates the estrogen receptor alpha which is thickly populated in trigeminal ganglia and periaqueductal gray which manifest as prodromal signs and menstrual migraine. There are also progesterone receptors A/B alongside ERs which provide complete remission during pregnancy due to its higher levels during pregnancy. These hormones also play very crucial roles in the homeostasis of minerals, e.g., copper, iron, zinc, magnesium, selenium, cadmium, etc., and their intricate involvement in the development of migraine has already been described [1].

The network of hypothalamus, hypophysis, endocrine glands, neurotransmitters and mineral homeostasis which is meticulously webbed and a slight aberration in it might result in disastrous pathogenic manifestations as migraines [2]. The earlier theory of migraine’s cause as to be due to vascular changes has been wrecked with facts [3]. Brain imaging by Magnetic Resonance Angiography have clearly demonstrated that “migraine headache is not associated with cerebral or meningeal vasodilation” [4].

However, in the exhaustive investigations into the cause of migraine has been reported precisely that migraine attacks often begin with prodromal signs capable of inciting nervous tissue which precede the start of headache pain [5]. Recently, [6] also concluded from their studies that primarily there is involvement of hypothalamus, brain stem and cortex which induce transient neurological symptoms that manifest as nausea, vomiting, sense of smell, abnormal sensitivity to light, noise and other symptoms involving muscles, e.g., fatigue, muscle tenderness, etc. Nevertheless, the nub of the cause of migraine still remains an imbroglio.

While going through the literature extant we found that it appears that not only hormones but the involvement of some important trace minerals are also intricately connected with the development of migraine. After delving into various biochemical interactions of hormones and minerals we hypothesized that the basic etiolo of migraine appears to be hormonal and mineral dyshomeostasis [1]. These were our preliminary observations which we extended further and are precisely reported in this short communication.

The main features of our previous investigations are succinctly enumerated below

1. Estrogen enhances the absorption of Cu and increases its half-life. Zn and Cu are natural antagonists and excess Cu further reduces the Zn levels. Zn plays an important role in the synthesis of melatonin and CoQ10 through activation of vit.B6. Hence, deficiency of Zn exacerbates the deficiency of melatonin and CoQ10 which has always been recorded as low in all the migraineurs. Melatonin and CoQ10 are most potent antioxidants as free radical scavengers and activates CuZn-super oxide dismutase, catalase, glutathione peroxidase (a Se-enzyme) and glutathione reductase in the body.

2. Estrogen also increases nociception through extracellular
signal-regulated kinase (ERK) stimulation and down-regulating antinociceptive GABA, IL-R1 and Zn-fingers.

3. 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 NO trapped within the cell which does not occur in Mg deficiency and reacts with superoxide ion resulting in the generation of peroxynitrite-a very dangerous oxidant.

4. Iron stimulates nitric oxide synthase producing more NO which is inhibited by Zn, thus, antagonizing peroxynitrate generation.

5. Female hormones lower magnesium and increases Calcium which increases the incidence of migraine.

6. Accumulation of free iron and Cu in deep areas of brain and peripheral nerves catalyses the oxidation of catecholamines which generate free radicals inducing lipid-peroxidation, demyelination, denudation of axons and neurodegeneration in specific areas exposing hyperalgesic axons provoking Classical migraine.

7. Furthermore, Zn is an essential component of Zn-fingers which play a pivotal role in the differentiation of Schwann cells which are required for myelination/remyelination of peripheral nerves.

8. Treatment with 75mg of zinc sulfate in drinking water daily for 6 weeks, one capsule of vitamin B-complex for six weeks as in our previous study. All the patients were followed-up for 1-3 years during which time two women reported mild headache which could be an epiphenomenon, i.e., from some other cause. This treatment did not produce any untoward side effect. These were the preliminary studies which might form the basis for further exhaustive investigations to unfold the mysteries of its cause(s) and radical treatment/prevention of this dreaded disease-a common cause of disability called “migraine walking” affecting humanity.

**Discussion**

Trace minerals, e.g., copper, iron, magnesium, selenium and zinc play very important roles in the metabolic pathways as being part of enzymes. The balance of these minerals in proper proportion is very crucial. Any disturbance in the homeostasis of these minerals result in very disastrous results and migraine is the one such malady. The balance of these elements is commonly affected during variation in the hormonal secretion during different phases of reproduction. Their imbalance result in the generation of free radicals which cause lipid peroxidation, oxidative stress and demyelination resulting in denudation of axons [7]. Migraine is a very complicated disorder which implicates the whole network of hypothalamus, central nervous system, endocrine glands, neurotransmitters and minerals [1, 2, 6, 8, 9]. There is sexual dimorphism in the occurrence of migraine as 70% in women and 30% in men. Excessive estrogen during menstruation directly stimulate the estrogen receptors alpha which are thickly populated in trigeminal ganglia and periaqueductal gray that manifest as menstrual headache/migraine [10]. There is also progesterone receptors A/B alongside of estrogen receptors which are antinociceptive and are stimulated during pregnancy, hence, there is mild or complete remission of migraine attacks during pregnancy.

Hormones may provoke migraine indirectly by disrupting mineral homeostasis [1]. Estrogen enhances the absorption of copper and increases its half-life which in turn hinders the absorption of zinc. Copper and zinc are natural antagonists and excess Cu exacerbates the deficiency of zinc. Zinc is required for the synthesis of melatonin and Coenzyme Q10 essential for growing women. Zinc, melatonin and CoQ10 are strong antioxidants which are typically low in migraineurs. Magnesium and vitamin B6 modulates the level of nitric oxide in the cell both of which are deficient in migraine patients. Nitric oxide when trapped in the cell combines with superoxide and forms peroxynitrite which

**Line of Treatment**

These investigations involved twenty seven (seven males and twenty females) migraine cases attending the clinics of private medical practitioners. All the patients were given a proforma to fill and the consent of patient/family member was taken for the treatment. The patients were in the age of 34-68 years. Hair mineral analysis showed low zinc:copper ratio. All these patients were given the following modified line of therapy, use of contraceptives, GABA, melatonin, 5HT, Vit. D, etc., involved in the dyshomeostasis of minerals leading to the development of migraine have also been discussed.

1. Zinc sulfate 75 mg daily in drinking water an hour after breakfast for six weeks
2. Daily one capsule of vitamin B-complex for six weeks
3. One capsule of vitamin E 400 IU or Coenzyme Q10 (CoQ10) 100 mg for six weeks as an antioxidant
4. One tablet of Magnesium citrate 200 mg twice daily for six weeks

During the treatment period the patients were given free excess to their routine feeding and life-style as usual. The patients were contacted weekly for the follow-up of the progress in the effect of the treatment regarding migraine. It was reported by all the patients to be having a discernible relief from the frequency of migraine attacks and the severity of pain after one week of the start of this medication. There was almost complete recovery from fatigue, somnolence and disrupted routine physical activity after two weeks of this medication. However, there were still mild migraine episodes in some patients during third week of treatment. The relief from migraine after four weeks of the medication was so spectacular as none of the patients reported any trouble from the migraine episodes. Nevertheless, the treatment continued for six weeks as in our previous study. All the patients were followed-up for 1-3 years during which time two women reported mild headache which could be an epiphenomenon, i.e., from some other cause. This treatment did not produce any untoward side effect. These were the preliminary studies which might form the basis for further exhaustive investigations to unfold the mysteries of its cause(s) and radical treatment/prevention of this dreaded disease-a common cause of disability called “migraine walking” affecting humanity.
is very dangerous free radical and cause myelin degeneration- the basic cause of migraine [11]. Accumulation of free copper and iron in deep brain areas and nerves catalyzes the oxidation of catecholamines and generate hydroxyl ion which is most potent free radical involved in lipid-peroxidation, demyelination, denudation of axons and neurodegeneration in specific areas exposing hyperalgesic axons provoking Classical migraine. Furthermore, zinc is part of zinc fingers (Krox20 and Krox24) which play a pivotal role in the differentiation of Schwann cells that are essential for the myelination/remyelination of peripheral nerves. However, zinc antagonizes such lipid-peroxidation through silencing free radicals [12].

There are other hormones namely cortisol, thyroxine, parathyroid hormone, melatonin and some neurotransmitters as glutamate, 5HT, etc., which have been implicated in the mineral homeostasis and indirectly appear to aid the induction of migraine [1, 2]. Furthermore, use of contraceptives which are mostly composed of estrogen and progesterone provoke worse type of migraine with aura episodes preceded by prodromal signs as sensory, visual problems. Hormone replacement therapy after menopause presents a variable picture and attacks of migraine with aura may start for the first time after its start [13]. From the ongoing discussion it appears that migraine is a very complicated malady inflicted by a combination of several factors which is preceded by prodromal signs of aura and vertigo culminating into classical migraine. However, the quest must continue to unfold the basic etiology and control of this migraine walking and dreaded disease inflicting human beings.

Altogether, conceptually and logically the treatment schedule stated above was adopted which proved highly successful in curing migraine. However, investigations into this problem need to be undertaken on large population with different combinations of treatment schedules.
References

1. Dhillon KS, Singh J, Lyall JS (2011) A new horizon into the pathobiology, etiology and treatment of migraine. Medical Hypotheses 77: 147-151.

2. Gupta S, Mehrotra S, Villalobos CM, Perusquia M, Sexena PR (2007) Potential role of female sex hormones in the pathophysiology of migraine. Pharmacol Ther 113: 321-340.

3. Goadsby PJ (2009) Scientific commentary: The vascular theory of migraine—a great story wrecked by the facts. Brain 132: 6-7.

4. Schoonmann GG, van der Grond J, Kortmann C, van der Geest RJ, Terwindt GM, et al. (2008) Migraine headache is not associated with cerebral or meningeal vasodilation—a 3T magnetic resonance angiography study. Brain 131: 2192-2200.

5. Noseda R, Burstein R (2013) Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 154: 544-553.

6. Burstein R, Noseda R, Borsook D (2015) Migraine: Multiple processes, complex pathophysiology. The Journal of Neuroscience 35: 6619-6629.

7. Halliwell B (2006) Oxidative stress and neurodegeneration: Where are we now? J Neurochem 97: 1634-1658.

8. Talebi M (2011) Relation between serum magnesium level and migraine attacks. Neuroscience (Riyad) 16: 320-323.

9. Afshin S, Nabioollah A, Raheb G, Jafar A (2012) Blood magnesium levels in migraineurs within and between the headache attacks: A case control study. Pan Afr Med J 11: 46.

10. Vanderhorst VG, Gustafsson JA, Ulfnak B (2005) Estrogen receptor-alpha and -beta immunoreactive neurons in the brainstem and spinal cord of male and female mice: Relationships to monoaminergic, cholinergic and spinal projection system. J Comp Neurol 488: 152-179.

11. Mauskop A, Altura BM (1998) Role of magnesium in the pathogenesis and treatment of headaches. Chem Neurosci 5: 24-27.

12. Meloni G, Faller P, Vasak M (2007) Redox silencing of copper in metal-linked neurodegenerative disorders: reaction of Zn7 metallothionein-3 with Cu2+ ions. J Biol Chem 282: 16068-16078.

13. Silverstein S.D, de Lignierse B (2000) Migraine, menopause and hormonal replacement therapy. Cephalalgia 20: 24-21.