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Research Article

A Note on the Control of Chronic Migraine (Status Migrainosus) in Adult Men and Women

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Abstract

Migraine is the sixth most common and disabling neurological disorder which affects about 15% people globally. Incidence of migraine before adolescent is almost same in both sexes and after menarche it is higher in females (70%) than males (30%). Sexual dimorphism of migraine points towards the involvement of hormones as women menstruate and men don't. Hypothalamus → hypophysis → adrenals → hormones → minerals and reproductive milestones as pregnancy, lactation, contraception, menopause do influence the occurrence of migraines in women. Different hormones have been found to interfere in mineral metabolism and cause their imbalance. Minerals are essential components of several enzymes which act as catalysts in various metabolic reactions involving synthesis of hormones, vitamins, proteins and energy. Imbalance of some minerals, particularly, iron and copper produce excessive Reactive Oxygen Species (ROS) which induce 'Oxidative Stress". Moreover, ROS are also produced during energy production in the mitochondria which have some physiological functions as induction of protein synthesis, body defense mechanisms in immune system. However, excessive production of ROS might overwhelm the antioxidant potential of the body and result in various diseases. ROS mainly cause oxidation of fatty tissues as myelin sheath. Myelin sheath covers nerves and is essential for nerve impulse transmission. Damage to myelin occur due to oxidation of unsaturated fats which cause microscopic holes in it resulting in naked and highly sensitive neurons. There is extravasation of plasma proteins which cause mechanical pressure at the site of injury resulting in migraine pain. The extent of pain depends on the nature and intensity of injury. Schwan cells are differentiated by zinc which myelinate the peripheral nerves. There is deficiency of magnesium, zinc, selenium, CoQ10, vitamins, melatonin in migraine patients. Nineteen chronic migraine patients, in this study, were supplemented with these deficient minerals and vitamins which gave excellent relief from pain. Our studies revealed that basically cause of migraine is "Oxidative Stress" exerted by ROS which damage myelin sheath by overwhelming body's antioxidant capabilities.

Keywords: Chronic Migraine; Reactive Oxygen Species (ROS)

Introduction

Chronic migraine (CM) is a very complex, multifaceted and most disabling neurological disease of adult human beings. Approximately 1% of the world's adult population suffer from CM at any one time [1]. The cumulative effect of CM is so common that it ranks at sixth position among the most disabling diseases worldwide as per the World Health Organization (2012) [2]. According to the Headache Classification Committee of the International Headache Society, 2013-Beta version, 'Chronic Migraine' has evolved during the last two decades by replacing the existing terms as 'chronic daily headache' or 'transformed migraine' [3]. However, there are still many discussions going on to make further subdivisions and medication overuse headache (MOH) has no longer been considered to be exclusive to CM. Furthermore, menstrual headache, which is primarily a physiological entity, has been putatively included in migraine in the ICHS. However, menstruation in women is a normal physiological phenomenon and during follicular stage of menstrual cycle there is spectacular rise in estrogen which stimulate estrogen receptors in periaqueductal grey and induce headache which cannot be considered a migraine. Migraine means Gr. Fr. Magrin/hemikranea- half head or half skull. Indeed, specific migraine and other headaches, due to variable causes, must be differentially diagnosed for specific control measures.

There is clear-cut sexual dimorphism in the incidence of migraine as it is higher in women (70%) than men (30%) this is because women menstruate and men don't. During the last about two decades most of the investigations into the cause(s) of migraine have revealed that redox active metals as copper, iron, cobalt, chromium etc., are capable of generating 'Free Radicals' during various metabolic reactions [4]. However, many minerals as zinc, magnesium, selenium, iron, copper etc., are essential components of many catalytic enzymes called metalloenzymes which are involved in the synthesis of many neurotransmitters as melatonin, 5HT, glutamate, catecholamines and many more. Such minerals and neurotransmitters play crucial roles in maintaining the normal nerve impulse transmission for several systemic bodily activities. However, fluctuations in reproductive and other hormones induce imbalances in important minerals particularly iron, copper, zinc, selenium, magnesium, molybdenum and some others [14].

Estrogen enhances the absorption of copper and prolongs its half-life. Copper is antagonistic to zinc and hinders its absorption, hence, causing deficiency of zinc. Zinc is essential for the synthesis of serotonin, melatonin, CoQ10, catecholamines as dopamine, adrenaline, nor adrenaline. Therefore, deficiency of zinc induced by excess copper in females has been hypothesized to be one of the most important factors responsible for the higher incidence of migraine in women after menarche [14,15]. These authors further observed that imbalance of some of these metals particularly iron and copper, being transition minerals, induce the generation of "Free Radicals" (FRs) during several metabolic reactions. Most commonly produced FRs are super oxide, Hydroxyl ion, peroxynitrite, nitric oxide etc., which are very reactive and cause lipid peroxidation, neurodegeneration and damage to DNA resulting in mutations.

Magnesium is essential for the removal of nitric oxide (NO) which is produced within the cells during metabolic activities. Magnesium is often deficient in large populations due to which NO, thus produced within the cells, could not be removed and accumulates within the cell which combines with superoxide to form peroxynitrite- a very potent FR which causes lipid peroxidation and damage to neurons. Magnesium has invariably been found to be deficient in migraineurs [5]. Furthermore, copper and Iron are in excess in migraineurs which catalyze the metabolism of catecholamines and produce Hydroxyl ion which damages myelin sheath that cover nerves. These imbalances are quite common in patients suffering from migraine [4].

Excessive production of FRs exert 'Oxidative Stress' and cause oxidation of myelin sheath of the nerves. Myelin sheath act as an insulating membrane, like our domestic electric wiring, and help in smooth nerve impulse transmission. Damage by FRs to myelin sheath and nervous tissue result in the production of malondialdehyde (MDA) and 4-hydroxynoneal (HNE) which are known biomarkers of such oxidative reactions. Such degenerative processes result in the development of various diseases as Parkinson's disease, Alzheimer's disease, Epilepsy, Amyotrophic Lateral Sclerosis and Migraine [6]. The generation of FRs and the damage they cause to nervous tissue resulting in the development of migraine and how to control this malady is depicted here in figure 1.

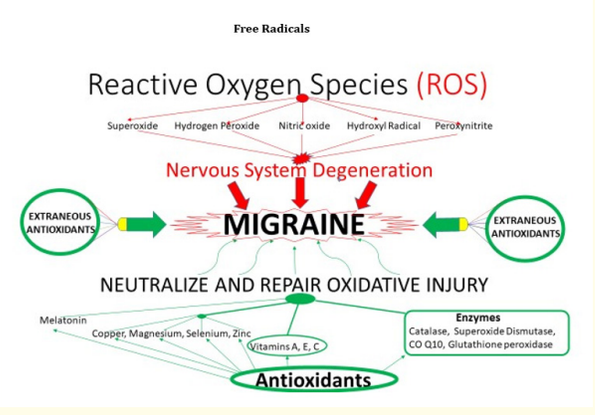

Figure 1: The illustration depicts how ROS damage nervous tissue when they overwhelm the effects of the body's antioxidants. Extraneous antioxidants tip the balance in favor of neutralizing and repairing oxidative injury, thus, controlling migraine pain.

Role of trigeminal nerves in the evolution of migraine

There are twelve pairs of cranial nerves which emerge at the ventral surface of brain and mediate nerve impulse transmissions precisely from the tissues they innervate. Under circumstances of any accidental/biological damage to any of these nerves there is manifestation of specific and typical clinical signs for the nerve and the tissue/organ involved. Out of these cranial nerves the most commonly involved in migraine is the pair of trigeminal nerves (TN V). This nerve plays the major role in relaying sensory information of pain from face, head, neck and intracranial structures, cerebral vasculature and meninges [7]. The processing of sensory impulses occur through the cell bodies of the neurons in the trigeminal ganglia. This sensory information is then relayed to the dedicated brain stem areas and upper spinal cord regions and processed further by hypothalamus, thalamus and specific areas in cerebral cortex where the exact conscious perception of pain occurs which is the mi-

graine proper in the real sense. Furthermore, most of the so called premonitory signs as photophobia, phonophobia, aphasia etc., which might occur during migraine are indeed the comorbidities due to damage of cranial nerves other than the TN V. Such signs may also be present alone even in the absence of migraine pain which presents a wide spectrum of clinical signs. However, there could be a common substrate (Oxidative Stress) between migraine and premonitory signs [8]. These phenomenon indicate that the premonitory signs are quite independent in occurrence and has nothing to do with migraine pain albeit these signs could aid in diagnosing migraine.

Recently, application of very sensitive techniques as functional Magnetic Resonance Imaging (fMRI) of the anatomical structures and related pathobiology of migraine pain have become quite rewarding. Particularly, migraine pain has been considered to be a disorder of the brain rather than involving the dilatation of blood vessels in the cranium [9-12]. Furthermore, trigeminal nerve particularly due to its anatomical situation and laterality of migraine manifestation has squarely been found to be involved in migraine. FRs damage myelin sheath covering of trigeminal nerve where they produce holes in it resulting in sterile inflammation [13]. Due to such injuries by FRs and dilatation of blood vessels due to release of CGRP from trigeminal nerve endings, there is extravasation of plasma proteins which put pressure on naked hypersensitive nervous tissue resulting in mild to severe throbbing pain called migraine.

Increase in blood circulation in the surrounding areas of damage caused by FRs is a normal process of body's defense to increase supply of nutrients, body defense cells, and repair of damage by Schwan cells in the peripheral nerves. Here zinc is essential for the differentiation of Schwan cells which are responsible for myelinating and repairing damaged peripheral nerves. Similarly, there are some other minerals like magnesium, selenium are deficient while copper and iron are usually high in migraineurs. Also, there are imbalances in certain neurotransmitters as melatonin, glutamate, GABA, Serotonin in these patients [14,15].

Many approaches to control migraine have been practiced but without achieving desirable results. Recent observations with complementary and alternative approaches with nutraceuticals as vitamins and minerals which are commonly in imbalanced state in migraine patients and need to be corrected. The interaction of fluctuating levels of hormones and minerals in relation to the occurrence of migraine and its treatment was reported by Dhillon., *et al* 2011. Several investigations have been conducted with individual or in combination of minerals as zinc, magnesium, selenium and vitamins as Riboflavin-Vitamin B2, Vitamin B-complex, CoQ10 etc. [14-20]. These studies revealed significantly positive effects in controlling migraine as far as reduction in number of pain days and intensity of pain. We tested a combination of supplements to control CM affecting adult men and women of different ages with variable migraine periodicity and intensity. The disease (Migraine) in these patients was very common, debilitating and unresponsive to pharmaceuticals in vogue as analgesics and or other drugs. Results are communicated in this short clinical report.

Materials and Methods

Nineteen patients (15women and four men) aged from 35 - 62 years suffering from CM visiting the clinics were recorded. There were four males and fifteen females. Males developed this stage of migraine quite late i.e. 35 - 50 years of age from their usual migraine episodes to chronic form. However, female patients progressed to chronic stage quite fast at early age 20 - 25 years of age and had been suffering from this debilitating malady for a longer duration. All the four men had severe pain but did not progress further to unbearable stage. However, among their counterpart five females attained unbearable intensity who were suffering from migraine episodes for the last 30 - 38 years. There is lot of variation in intensity and frequency of migraine as far as age is concerned. Some patients of migraine could not exactly recollect the number of attacks and gave approximate figures.

Sr. No	Age (yrs)	Sex	Duration (yrs)	Episodes/ Month	Severity*
1	51	F	30	15	+++
2	60+	F	30	16	+++
3	55	F	38	14	++++
4	60	M	22	14	+++
5	46	F	25	12	+++
6	55	F	30	16	++++
7	57	F	35	14	++++
8	45	F	25	10	+++
9	42	F	30	12	++
10	55	F	40	14	+++
11	50	F	35	16	+++
12	50	F	32	16	+++
13	45	F	30	15	+++
14	55	F	42	12	+++
15	56	M	18	18	+++
16	60	M	25	13	+++
17	42	F	35	16	++++
18	37	M	7	14	+++
19	35	F	5	15	++++

Table 1: Showing the specific features of patients suffering from chronic migraine.

* Severity was assessed on the basis of 1 to 4+ scale.

+: Mild, ++: Moderate, +++: Severe, ++++: Unbearable.

MM: Menstrual Migraine (mild); Rare-a mild headache (not exactly migraine); ND: Not Determined.

History is the main subject in such patients of migraine to reach at a proper diagnosis. The diagnosis of CM was based primarily on the background of IHS-Beta version 2013 with some variations. However, patients showing typical signs of migraine as mild to severe throbbing pain on one side of head around temples, nausea/vomiting, frequent urination, gnawing, bulimia (excessive appetite), resistant to usual analgesics, getting relief from dark and calm environments, duration of occurrence (10 - 25 years) with at least more than ten days per month, completely tired (exhausted) and withdrawn at the end of pain phase. Other signs so called premonitory signs were also considered for diagnosis as there appears to be a common substrate for these comorbidities. Nails of both hand-fingers of all patients were examined which showed white spots in five patients (four females and one male), these spots are primarily seen in zinc deficiency.

After the diagnosis of migraine consent of each patient was obtained and the patients were given supplements in a gelatin capsule with drinking water one hour after the meal. The composition of supplements was as under:

- Zinc citrate 50 mg + Vitamin B-complex
- Selenium 100 ugm + Vitamin E 400 IU
- Magnesium citrate 250 mg + Coenzyme Q10 100mg

All the patients were contacted once or twice in a week telephonically and or/in clinics after the start of supplements. The patients were enquired about any side effects and compliance. The patients maintained their normal usual meals and other regular lifestyle habits during the full course of this schedule. Furthermore, patients were advised to taper down (some even stopped) the medications they were taking specifically for controlling migraine.

Results

Observations on the effectiveness of a combination of Magnesium, Co Q10, Zinc citrate, Vitamin-B-complex, Selenium and Vitamin-E, in quantities given above, against CM are presented in table 2. The efficacy of the supplements was spectacular as most of the "Status Migrainosus" patients were free from migraine pain within one week of the start of taking supplements. However, some women did suffer from milder headaches which was typical of menstrual headache in origin as it started 2 days before and remained up to 3 days after menstruation. These headaches were without any premonitory signs and could be effectively controlled by usual pain killers. However, one female patient did suffer from severe daily headaches during the first week of supplementation. On enquiry the patient revealed use of repeated daily doses of over-the-counter medications which were withdrawn during this time. It was a typical case of medication overuse and its withdrawal effects during the first week. However, this patient had only bearable headache after first week of supplementation and had complete relief thereafter.

Sr. No	Age (yrs)	Sex	Duration (yrs)	Episodes/ Month	Severity*	Follow-up Week after Treatment					
						First	Second	Third	Fourth	Fifth	Sixth
1	51	F	30	15	+++	Nil	MM+	Rare	Nil	Nil	Nil
2	60+	F	30	16	+++	Nil	Nil	Rare	Nil	Nil	Nil
3	55	F	38	14	++++	MM+	Nil	ND	Nil	Nil	Nil
4	60	M	22	14	+++	Nil	Nil	Rare	Nil	Nil	Nil
5	46	F	25	12	+++	MM+	Nil	Nil	Nil	Nil	Nil
6	55	F	30	16	++++	Nil	Nil	Nil	Nil	Nil	Nil
7	57	F	35	14	++++	Nil	Nil	Nil	Nil	Nil	Nil
8	45	F	25	10	+++	Nil	Nil	MM+	Nil	Nil	Nil
9	42	F	30	12	++	Nil	Nil	Nil	Nil	-	Nil
10	55	F	40	14	+++	Nil	Nil	Nil	Nil	Nil	Nil
11	50	F	35	16	+++	Nil	Nil	MM+	Nil	Nil	Nil
12	50	F	32	16	+++	Nil	Nil	Nil	MM+	Nil	Nil
13	45	F	30	15	+++	Nil	Nil	Nil	ND	MM+	Nil
14	55	F	42	12	+++	Nil	Nil	Nil	ND	ND	ND
15	56	M	18	18	+++	Nil	Nil	ND	ND	Nil	Nil
16	60	M	25	13	+++	Nil	Nil	Nil	Nil	Nil	Nil
17	42	F	35	16	++++	MM+	Nil	Nil	Nil	Nil	Nil
18	37	M	7	14	+++	Nil					
19	35	F	5	15	++++	+++					

Table 2: Showing the efficacy of a combination of different supplements given to chronic migraine patients.

* Severity was assessed on the basis of 1 to 4+ scale.

+: Mild, ++: Moderate, +++: Severe, ++++: Unbearable.

MM: Menstrual Migraine (mild); Rare-a mild headache (not exactly migraine); ND: Not Determined.

Furthermore, all the patients reported no side-effects from the supplemental therapy during the period of six weeks. Indeed, some patients having signs of anxiety or depression, vertigo and some other premonitory signs before their migraine episodes felt relieved from such comorbidities. The patients showed the absolute acceptance of these supplements and uniform desire to undergo such control measures whenever they needed. The most important observation during this period was the sufferers who experienced sensory/motor signs along with migraine pain also were relieved of these signs. These observations further strengthened the fact that migraine pain is a different entity (a disease in itself) and most probably have a common substrate of cause along with other putative premonitory signs. Hence, migraine alone needs to be separated from premonitory signs as part of migraine. The pre-monitory signs need further differentiation and description as per the specializations in clinical practice e.g., eye, ear, throat, nose etc., for specific diagnosis and control measures.

Discussions

Chronic, episodic migraine called "Status Migrainosus" in four men and fifteen women of different ages (35 - 60 Years) was most effectively controlled by giving orally a combination of nutritional supplements. There was no side effect of these supplements when used continuously for six weeks. There was an absolute check on the dangerously non-responsive cases of clinical CM which was entirely resistant to the commonly prevalent antimigraine remedies available at hand. The history of all these cases was slow progression of mild episodic migraines through continual use of multiple analgesic drugs or irregular use of supplements as magnesium, CoQ10 and other B-complex vitamins, herbals individually or in combinations for quite long periods. Even triptans and Botox were also used quite often which proved ineffective after sometime in controlling any of the episodes which ultimately resulted in CM with ~ > 15 migraine attacks per month in every patient (See table 2).

The main features of migraine investigations reviewed by Dhillon., *et al*. 2011, 2016 are succinctly reproduced 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 serotonin (5HT), melatonin and CoQ10 through activation of vit.B6. Hence, deficiency of Zn exacerbates the deficiency of 5HT, 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 Cu Zn-super oxide dismutase, catalase (Zinc enzyme) and glutathione peroxidase (a selenium enzyme) in the body at optimum levels.
2. Estrogen also increase nociception through extracellularly 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 do 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 peroxynitrite generation.
5. Female hormones lowers magnesium and increase Calcium which increases the incidence of migraines. Transient and sudden changes in metabolic pathways in cerebral cortex is associated with intracellular calcium overload during Cortical Spreading Depression resulting in excitation and oxidative stress.
6. Accumulation of free iron and Cu in deep areas of brain and peripheral nerves catalyzes the oxidation of catecholamines as dopamine, adrenaline, noradrenaline which generate free radical-Hydroxyl ion which cause 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 + one capsule of Vitamin A or E (first ten days) which almost cured all thirty migraine sufferers.
9. Other hormones and neurotransmitters namely prolactin, cortisol, thyroxine, parathyroid hormone, hormone replacement 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.

Expert opinion regarding controlling chronic unresponsive migraines lays specific emphasis on giving preventive therapies. In the past, for quite a long time, theory of cerebral vasodilation was

prevalent as a cause of migraine and control measures were devised as vasoconstrictor drugs which proved palliative with serious side effects. Moreover, theory of vasodilation has now become most controversial and migraine has been observed to be of neurological origin [9,10,11,12,21].

Recent investigations into the cause(s) of migraine, due to its higher incidence in women, have focused on the interaction of reproductive hormones and trace minerals [14,15]. These authors hypothesized that fluctuations of hormones induce imbalances in several minerals with the resultant generation of "Free Radicals" (FRs) - Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). The FRs thus produced cause myelin degeneration which appears to be the basic cause of migraine. There are some other FRs which can be produced by smoking, radiation, Drugs and basic metabolism for the production of energy as Adenosine Triphosphate (ATP). The FRs play several physiological roles in body's defense mechanisms and triggers the syntheses of many essential proteins.

There is ample evidence of ROS playing the major pivotal role in the pathophysiology of migraine. Based on the latest imaging studies and experimental production of migraine in animal models revealed that checking of ROS could effectively control migraines [6]. Pathogenic lesions inflicted by ROS on myelin sheath and neurodegeneration of nervous tissue has lately become apparent in playing a very important role in the pathophysiology of migraine. Therefore, keeping in view the nature of the present cases, a strategic control program with multi-pronged attack on FRs has been adopted for controlling clinical cases of CM.

Melatonin is produced in the Pineal gland during night (darkness). Melatonin is a prodrug as a direct free radical scavenger. It induces certain antioxidant enzymes, e.g. Cu Zn-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 and there is excessive production of estrogen which augments the chances of migraine attacks [23]. 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" (OS). 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 OS. Taken together, the ''free radicals'' thus generated cause lipid peroxidation leading to myelin degeneration and the white matter becomes less hydrophobic and accumulation of water therein exerts mechanistic pressure over the naked hyperalgesic axons culminating in migraine [24]. It has been observed that stimulation of 5-HT B1/D1 receptors 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 [25]. It is well known that zinc plays a pivotal role in the synthesis of 5HT and melatonin which 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 pathophysiology of migraine [26,27].

The consensus is being built on the basic cause of migraine that its pathobiology involves the brain and there are alterations in the sub-cortical sensory modulation of brain [10]. He further suggested to pursue studies targeting glutamate without having any side effects. In our studies reported here it is known that glutamate is converted into GABA by glutamate decarboxylase which is a zinc activated enzyme. In our composition we have included zinc keeping this action in view. Recently, Su and Shengyuan [28] outlined the clinical features, pathophysiology and control measures of chronic migraine. They opined that several structural and functional aberrations and maladaptation of pain modulations and sensitization of trigeminal system appear to be important in the pathogenesis of chronic migraine. Furthermore, recently it has been reported that there is an increased level of sex hormone estradiol and relative deficiency of androgen in men with migraine [29] However, now it is open to study precisely different interactions of hormones and minerals involved in the pathobiology of migraine and hit at the most vulnerable targets. Ours are the preliminary studies in a pilot project and further randomized double blind controlled investigations need to be undertaken for application on clinical cases of migraine. Here the emphasis need to be given to hormones and minerals intricately involved in the etiology of migraine and biomarkers established for proper diagnosis and applying effective control measure for desirable results.

Conclusion

It was concluded that "Oxidative Stress" incurred by transient minerals such as free copper and iron which generate Free Radicals to induce myelin oxidation/ degeneration exposing highly sensitive nervous tissue to the release of CGRP (a potent vasodilator) and Substance P (causes plasma protein extravasation) which put

mechanical pressure on the highly sensitive axones appears to be the basic etiology of migraine. However, this Oxidative Stress was checked by administering, once orally, a combination of antioxidants as Magnesium citrate 250 mgs, CO Q10 100 mgs, Zinc citrate 50 mgs, Vitamin B-complex, Selenium 100umgs and Vitamin E 400 IU. The combination of antioxidants cured all the nineteen patients suffering from chronic migraine.

Disclaimer

There are no competing interests. Information should be applied only after the consultation with the medical expert.

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Volume 2 Issue 5 May 2019