

Is migraine a consequence of a loss of neurohormonal and metabolic integrity? a new hypothesis

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Abstract

OBJECTIVE: In 2002 we suggested a new hypothesis of migraine. This hypothesis implies that migraine is a consequence of a loss of neurohormonal and metabolic integrity. The goal of this clinical analysis is to present the evaluation of the effect of a multimodal treatment program in migraine management.

MATERIAL AND METHODS: We evaluated 30 patients ages 16–66 with migraine who were treated with a multimodal treatment program. All patients received a complex program which included: hormonorestorative therapy (HT) with bio-identical hormones; correction of balance between sympathetic and parasympathetic systems and simultaneously calcium/magnesium balance; “resetting” the pineal gland; improvement of intestinal absorption through restoration of normal intestinal flora, and a cleanse from parasitic infestation (if necessary). Serum levels of total cholesterol (TC), pregnenolone, dehydroepiandrosterone sulfate (DHEAS), progesterone, total estrogen, and total testosterone were determined.

RESULTS: All patients responded to this regimen. We do not have patients who still have migraine after they started to use this program. Laboratory finding prior to HT showed the significant deficiency in production of all basic steroid hormones (progesterone and pregnenolone production declined the most). Concurrent symptoms such as fibromyalgia, insomnia, depression, gastrointestinal disorders, and fatigue had disappeared. Total cholesterol completely normalized in 22 (91.7%) patients. No adverse effects or complications related to this program were registered.

CONCLUSIONS: Our findings support the hypothesis that migraine is a consequence of a loss of neurohormonal and metabolic integrity, and that migraine can be managed by a multimodal approach.

INTRODUCTION

The history of the treatment of headaches in general, and migraine in particular, precedes the current millennia. The Pharaoh's courts of ancient Egypt gave the first descriptions of unilateral headaches accompanied by vomiting and malaise, around 1500 BC. Migraine has one of the longest histories of recognition without sufficient understanding. Beset by myths, uncertain etiology, and inadequate treatment, migraine remains one of the most under-treated neurological conditions today. It seems frustrating that despite the long recorded history of migraine, treatment for this ancient complaint, irrational at times and empirical at others, has evolved slowly and tortuously, yet is still without a universal standard (Edmeads 1999).

Migraine affects about 10–15% of populations in different countries (Mathew 2001; Gazerani *et al.* 2003; Lampl *et al.* 2003). Migraine may occur at any age, but prevalence increases from childhood up to 40 years of age (Granella *et al.* 1998). Migraine is more common in women than in men. According to the American Migraine Study, 17.6% of females and 6% of males in the United States currently suffer from severe migraine (Lipton & Stewart 1993).

There are a number of theories and hypotheses concerning the pathogenesis of migraine, but they are frequently in conflict (Rajda *et al.* 1999). For example, the theory of migraine as a result of vasodilatation by sympathetic deficit was suggested in the early 1850s by Brown-Sequard and Claude Bernard. Contrary to the vasodilatation theory, Du Bois-Reymond proposed vasoconstriction by sympathetic overactivity as the cause of migraine in 1860 (Koehler & Isler 2002). The same drug (ergot) was used for both conditions. How could this have happened and where is the truth?!

No hypothesis, at present, readily explains the etiology and pathogenesis of migraine. That is why newer and newer hypotheses are suggested. To a large extent the complex mechanisms involved in migraine are still enigmatic (Allain *et al.* 2000). Large numbers of hypotheses are evidence of the complexity of the problem concerning migraine. The studies on the pathogenesis of migraine have developed into a vast scientific movement in the last years (Prusinski 1995). Here is a very brief list of migraine hypotheses which were suggested and investigated in recent times:

- hypothesis of inadequate regulation of autonomic, especially sympathetic reactions (Pichler *et al.* 1988; Welch *et al.* 1984);
- neuroendocrine hypothesis (Guaschino *et al.* 1985);
- serotonin (5-HT) involvement in migraine (McCall *et al.* 2002);
- migraine as a central biochemical dysnociception (Sicuteri 1976);
- vasoactivity of prostaglandins (PG) is involved in migraine attack (Horrobin 1977; Vardi *et al.* 1976);

- platelet hypothesis of migraine (Hanington 1979; Hanington 1989; Lance 1989);
- reactive hyperaemia due to hypoxia as cause of migraine (Burnstock 1981);
- hypothesis implicating an overreactive temporal artery or skeletal muscle response to stress in migraine (Feuerstein *et al.* 1982);
- primary and familial lipoprotein abnormalities might be associated with predisposes children to the migraine syndrome (Glueck & Bates 1986);
- sensory cortex and hypothalamus could be initiating sites for migraine attacks (Blau 1984);
- migraine with aura is associated with a state of central neuronal hyperexcitability (Welch *et al.* 1990).
- diffuse disruption of central pain-modulating system as reason for migraine (Schoenen *et al.* 1991).

Various guidelines recommended different strategies for treatments of migraine (Lipton *et al.* 2000). Drugs for acute care consist of antiemetics, anxiolytics, NSAIDs, ergots, steroids, major tranquilizers, narcotics, and selective serotonin agonists. Preventive agents include beta-blockers, calcium channel blockers, antidepressants, serotonin antagonists, and anti-convulsants. Behavioral management and relaxation training are important complements to pharmacologic therapy; however, drugs are the mainstay of migraine therapy (Lake & Saper 2002; Diamond 1989; Silberstein & Lipton 1994; Baumel 1994; Cady 1999; Young *et al.* 1997; Lance 1981). Despite a better understanding of migraine and medications designed for the treatment of migraine, many people continue to suffer from unnecessary pain and disability. Drug therapy for preventing and treating migraine remains unsatisfactory for many patients. No miracle treatment has occurred which can cure the migraineur. After reviewing the historical data and clinical studies, we noted that the following observations appear to have some solid basis: 1) systemic derangement of serotonin (5-HT) metabolism, relevant to the peripheral vascular component of migraine pathophysiology, 2) changes in neuroexcitatory amino acids and magnesium, 3) hormonal fluctuations which seem important to set the threshold for an attack, 4) catecholaminergic changes suggesting sympathetic overactivity (Ferrari 1992).

The migraine attack is a complex process that involves both the central and peripheral structures. Migraine is under the control of multiple factors: neurogenic, chemical, metabolic, and myogenic (Dalessio 1990). In spite of the various pathogenetic hypotheses that have been proposed, the pathophysiology of the disease is still unknown. Sympathetic dysfunction in migraine plays an important role on the pathophysiology and the maintenance of the headaches (Ostertag *et al.* 1998). Several studies performed since the '60s have demonstrated the key role of serotonin. It is generally accepted now that migraine is caused by a primary biochemical disorder of the central nervous system

involving neurotransmitters, specifically serotonin. The pineal gland, a primary source of central serotonin and melatonin, contributes significantly to migraine attacks (Toglia 2001; Toglia 1986). Migraine seems to be characterized by low threshold of neuronal excitability which is in turn regulated by genetic factors involving the dopaminergic system (Del Zompo 2000). Vascular disturbances also take place in migraine attacks, but they should be regarded in conjunction with biochemical and central neuronal disorders (Prusinski & Sokolowski 1995). The cerebral circulation is innervated by sympathetic, parasympathetic and sensory nerves which store a considerable number of neurotransmitters. The data shows the involvement of sensory and parasympathetic mechanisms in the pathophysiology of primary headaches (Edvinsson 2000). The ability to trigger an attack may depend on a threshold of brain excitability. Mitochondrial disorders, magnesium deficiency, and abnormality of presynaptic calcium channels may be responsible for neuronal hyperexcitability between attacks (Welch 1997).

Migraine affects more women than men, and is often related to menses. Steroid hormones in physiological concentrations are capable of interacting with the serotonin transport system of patients (Pukhal'skaia 1993; Silberstein & Merriam 1993). Different studies presented controversial results of using estrogens, progestogens, androgens, and DHEA for migraine management (Horowski & Runge 1986; Sarrel 1999; Massiou 2000). Little attention has been paid to androgens (Mattsson 2002; Kudrow 1976). There is a lot of information about the effect of estrogen therapy on migraine in medical literature. Nonetheless, the findings about the benefit of such hormone replacement therapy (HRT) in the prevention of migraine are still very controversial (Damasio & Corbett 1981; Magos *et al.* 1983). It is unclear – what the problem is – too much or too little estrogens? All these factors contribute to the need for more research and knowledge in the area of the altered hormonal state.

Multiple threads of research over the last 15 years have led to a concept that migraine is generated from a hyperexcitable brain. A variety of causes for hyperexcitability of the brain in migraine have been suggested. These causes include low cerebral magnesium levels, mitochondrial abnormalities, dysfunctions related to increased nitric oxide or the existence of a P/Q type calcium channelopathy (Bigal *et al.* 2002). The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium (Mauskop & Altura 1998). Numerous experiments and clinical observations have credited magnesium with a positive influence on the incidence of migraine attacks (Taubert 1994; Mauskop *et al.* 1995).

Many contradictory or never replicated findings in often small patient groups have been published. Medications currently available for the prophylaxis and treatment of migraine provide only limited relief (Leathard

1989). Unfortunately, a total of 44.5% of patients reported adverse events while using migraine drugs, and these were rated serious in the case of 1.7% (Gobel *et al.* 1999). Such adverse events, including dizziness, nausea, headache, paresthesia, cognitive difficulties, fatigue, and other quality of life morbidities indicate the need to find better, safer regimens for migraine (Rapport 2001; Young *et al.* 2002).

THE HYPOTHESIS

All those issues described above and our own observations, led us to hypothesize that migraine is a consequence of the loss of neurohormonal and metabolic integrity. We suggested a unifying hypothesis, which we call the neurohormonal and metabolic dysbalance hypothesis of migraine. Such a hypothesis not only brings together the many seemingly disconnected research findings for the first time, but provides rational guidance for an effective treatment approach.

There are several organ systems involved in a migraine attack. From our point of view migraine is not a single disorder, but a collection of them including the following:

- malfunction in a different place of the hypothalamus-pituitary-steroid hormonal chain with a disruption of normal function of multiple feed back loop mechanism;
- an imbalance between the sympathetic and parasympathetic nervous systems, and as a result, decreased pain threshold of brain nociceptive system;
- lack of equilibrium between calcium and magnesium ions inside and outside of cells, leading to changed electricity of the cell membrane, and a changed condition of calcium channels;
- low production of melatonin or decreased sensitivity of the cell membrane to melatonin;
- altered intestinal flora with abnormal gastrointestinal absorption.

In this article we will provide information about our study in which we investigated a new medical hypothesis of migraine and the role of the simultaneous restoration of neurohormonal and metabolic integrity in the management of migraine.

MATERIAL AND METHOD

Herein we present our clinical experience with a series of particularly difficult-to-treat migraineurs in which we simultaneously restored neurohormonal and metabolic integrity. We analyzed 30 patients with migraine ages 16–66. The mean age is 46.4 years. There are 27 female (90.0%) and 3 male (10.0%). Female/male ratio – 9:1. All patients had used for prophylaxis and treatment of migraine from 1 to 4 drugs and different multiple supplements without significant effect. Illness

duration was from 2 to 46 years. 21 women (77.8%) had used HRT or oral contraceptives (OC). Concurrent symptoms such as chronic fatigue syndrome (CFS), depression, lipid disorders, insomnia, gastrointestinal (GI) disorders, and fibromyalgia were registered in 93.3%, 93.3%, 90%, 86.7%, 70%, and 16.7% respectively (Figure 1). According to medical literature migraine is often comorbid with psychiatric disorders, particularly depression and anxiety, fatigue, insomnia, and fibromyalgia (Sheftell & Atlas 2002; Breslau *et al.* 2003; Bourgault & Gratton 2001; Nicolodi & Sicuteri 1996). Fibromyalgia, chronic fatigue, and primary headaches are common and debilitating disorders and have complex interactions amongst themselves (Peres 2003). Our opinion is that this relationship is based on shared mechanisms and that a successful treatment is possible.

Total cholesterol, pregnenolone, dehydroepiandrosterone sulfate (DHEAS), total testosterone, progesterone, and total estrogen levels were done through routine blood testing during the first time of presentation and serial determinations were made during treatment.

All patients were placed on a multimodal program which includes the following approaches:

- hormonorestorative therapy (HT) with bio-identical hormones, which includes a combination of several agents: oral pregnenolone, dehydroepiandrosterone (DHEA), and triestrogen, progesterone, and testosterone gels;
- correction of the balance between sympathetic and parasympathetic systems and simultaneously calcium/magnesium balance;

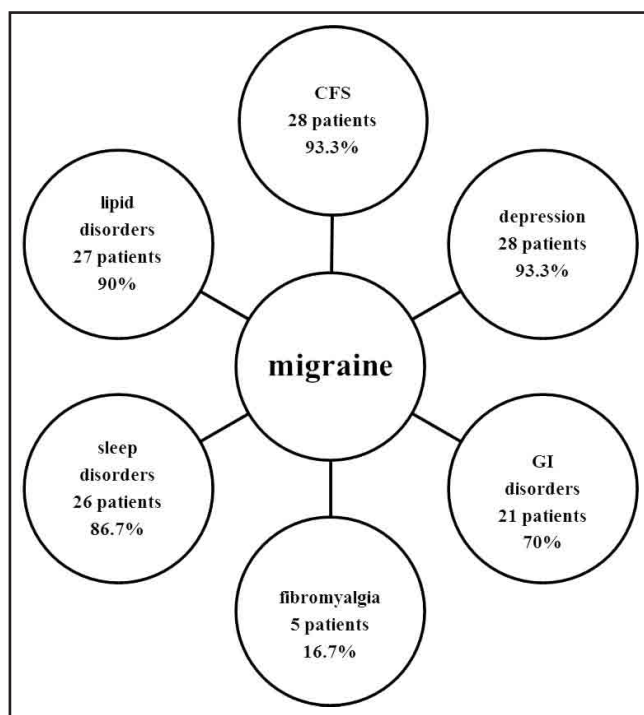


Fig. 1. Concurrent illnesses.

- “resetting” the pineal gland;
- improvement of intestinal absorption through restoration of normal intestinal flora;
- a cleanse from parasites infestation (if necessary).

It is necessary to stress the fact that the above mentioned parts of the program cannot be separated. They are intertwined and work together. For example, using estrogens and progesterone, we restored not only hormonal balance, but we also helped restore a balance between sympathetic and parasympathetic systems activity. The same situation is associated with calcium and magnesium: restoring metabolic integrity, we also optimized the balance between sympathetic and parasympathetic systems.

HT includes a chemically identical formula to human hormones and is administered in physiologic ratios with dose schedules intended to simulate the natural human production cycle. Patients received treatment with oral pregnenolone (15–200 mg), DHEA (15–100 mg), and cutaneously applied triestrogen (1.25–5.0 mg) (estriol 90%, estradiol 7%, and estrone 3%), progesterone (2.5–10%), and testosterone (2.5–10%) gels. The recommended doses to different patients during HT varied significantly and were determined by serum hormonal levels during serial testing. That is why we did not use a standard dose, rigid protocol or traditional design for this study. Doses were individually selected during HT to produce youthful physiologic serum levels. We administered hormones in doses sufficient to achieve circulating plasma levels observed in younger healthy individuals. Our purpose was to achieve the hormonal blood levels of young adults between the age of 20 and 30 at which time the highest level of all steroid hormones naturally occurs. This level is at the high end of the normal range from the testing laboratory.

24 patients (80.0%) had been taking from one to four steroid hormones prior to HT. In spite of that patients had no benefit from replacement therapy and still had migraine before starting our program. All agents such as equine conjugated estrogens, medroxyprogesterone acetate, methyltestosterone, etc. were switched to bio-identical hormones during treatment. Non-physiologic replacement such as estradiol alone was modified to physiologic estrogens ratios. Estrogen was always used with progesterone.

All our patients have been taking:

- magnesium citrate in dose 400–800 mg (at bed time – 400 mg, or 200/400 mg in a.m. and 400 mg at bed time);
- combination of melatonin (3–6 mg), kava root extract (100–500 mg) and vitamin B6 (10–20 mg) (30 minutes before bed time);
- probiotic formula which includes: Lactobacillus group (*L.rhamnosus A.*, *L.rhamnosus B.*, *L.acidophilus*, *L.casei*, *L.bulgaricus*) – 3.5 Billion, Bifidobacterium group (*B.longum*, *B.breve*) – 1.0 Billion, *Streptococcus thermophilus* – 0.5 Billion (in the

morning on an empty stomach). This formula was used for the restoration of healthy natural intestinal flora and for improvement of absorption.

The follow up period ranged from 5 to 77 months.

RESULTS

Our results show that migraine is curable. All patients responded to migraine management. We do not have any patients who still have migraine after they started to use this program. Lipid abnormalities were found in 27 (90%) patients: hypercholesterolemia – 24 (80%) patients (highest level – 360 mg/dL) and hypocholesterolemia – 3 (10%) patients (lowest level – 86 mg/dL). In all patients deficiencies of steroid hormones were found (Figure 2). Pregnenolone and progesterone production declined severely. 29 (96.7%) patients had a low level of pregnenolone, and 18 (60%) of them had less than minimal detectable level (less than 10 ng/dL). 27 (90%) patients had level of DHEA sulfate less than optimal level, 13 (43.3%) of them had less than minimal normal level (less than 65 µg/dL for female, and less than 280 µg/dL for male). Not optimal was defined as level of hormones below one third of highest normal range for all steroid hormones. The level of testosterone in 22 (73.3%) patients was below optimal; 9 (30%) patients had a very low level. Progesterone production was significantly declined in 24 (80%) patients. Only 3 (10%) persons had a good level of progesterone. 9 (30%) patients had a normal level of total estrogens; 8 (26.7%) – a very high, and 13 (43.3%) – a very low level. We did not make a detailed analysis of hormonal change in this study, because of the different purpose, limitation of article size, and because the baseline level of hormones in most patients were below detectable levels (for example: pregnenolone <10 ng/dL). Total cholesterol normalized completely in 22 patients who had hypercholesterolemia prior to therapy. Concurrent symptoms such as fibromyalgia, insomnia, depression, GI disorders, and fatigue have disappeared.

During the follow up period no complications or side effects related to this regimen were a cause for concern. All patients described a significant improvement in quality of life.

DISCUSSION

The old Galen approach of concentrating on the treatment of symptoms was replaced in our study with a treatment of the cause of the disease based on valid research of the past 30 years. From a traditional point of view migraine appears to be a primary disorder of the cerebral vessels, and there were experimentations concerning the role of circulating serotonin, prostaglandins, platelet abnormalities and estrogen level (Spector 1984). We believe that migraine is not a primary disorder, but that it is a consequence of neurohormonal and metabolic disorders.

Migraine most commonly strikes women. Each person who suffers from migraine is unique, so individual treatments are complex and varied. There is no single treatment method. Current treatments for migraine include diet changes, stress management, proper sleep, HRT, supplements, and prescription drugs. During migraine cerebral blood vessels go through a period of constriction and dilation. Imbalance in brain biochemistry may be the cause of this change. Menstrual migraine represents a model that fits perfectly with a neuroendocrine hypothesis which is based upon a faulty chronobiological response of the so-called antinociceptive system (Guaschino *et al.* 1985). Effects of hormone imbalances and deficiencies on vasomotor control are clinically significant and hormone treatment appears to be effective in the management of a variety of conditions due to the abnormal blood flow, including migraine (Sarrel 1990). Estrogens exert their influence by modulating sympathetic control of cerebral vasculature (Welch *et al.* 1984).

Migraine attacks occur during menses in 60% of women and appear to be related to the withdrawal of estrogen. The fluctuations in estrogen levels associated with migraine produce biochemical changes in prostaglandins production, prolactin release, and opioid regulation. Prostaglandin E-2 (PGE-2) is a well-defined mediator of fever and inflammation. Proinflammatory prostaglandins PGE-2 increases vasodilatation and therefore induces pain. Estrogen increases production of PGE-2. An excess of estrogen, deficit of progesterone or dominance of estrogen can be a cause of extra-production of PGE-2 and an appearance of migraine. Elevation of the prolactin level or increased sensitivity to prolactin leads to a decreased level of prostaglandins of group 1 (PGE-1). Patients with migraine may have prostaglandin-induced hypersensitivity to prolactin. PGE-1 is a substance that in fact improves the microcirculation and leads to the development of collateral circuits with a consequent improvement in local hemo-

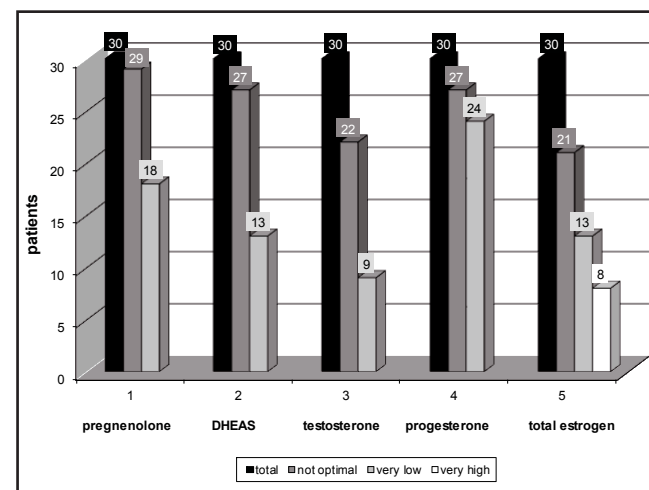


Fig. 2. Lab results prior to therapy.

dynamics. If the patient has dominance of PGE-2 we can expect vasodilatation of major arteries with spasm of the collateral circuit which can be a cause of pain.

In some cases, estrogen replacement therapy for menopausal symptoms induces headache. The incidence and severity of migraine are also affected by oral contraceptives use (OC) (Silberstein & Merriam 1991). Progesterone has an extremely powerful sedative effect. In migrainous women 17-beta-estradiol levels are higher in both ovarian phases, whereas progesterone concentrations and the progesterone to estradiol ratio are lower than in healthy subjects in the luteal phase (Murialdo *et al.* 1986). Menstrual distress was highest during the menstrual and premenstrual phases of the cycle, and these symptoms were related to higher estradiol levels, higher estradiol/progesterone ratios, and increased headache activity (Beckham *et al.* 1992).

Changes in estrogen levels at menarche, menstruation, pregnancy, and menopause may trigger or change the prevalence of migraine. The fall in estrogen that occurs with menstruation is the trigger for menstrual migraine, whereas the sustained high estrogen levels during pregnancy frequently result in headache relief. Estrogen produces changes in prostaglandins, hypothalamic opioids, and prolactin secretion, which may in part account for the genesis of headache. Estrogen and progesterone trigger synthesis of endometrial prostaglandins. In fact, prostaglandins regulate descending norepinephrine pain control systems in the brain, thus increased levels of prostaglandins decrease the pain threshold. In addition, falling levels of estrogen produce dopamine receptor hypersensitivity. Estrogen increases while progesterone and prolactin suppress synthesis of prostaglandins. Several replacement therapies to treat menopausal women with migraine exist. These include adding androgens and reducing estrogen dosage. Some data shows an increase in the severity of migraine among OC users, but other studies find no difference in headache among OC and placebo users (Silberstein 1992).

The control of the menstrual cycle is extremely complex. Migraine during pregnancy is sometimes worse, sometimes better. This stresses the importance of the estrogen/progesterone ratio. We think that the main problem is an imbalance between estrogen and progesterone and not just in absolute numbers. This can explain, for example, why migraine was relieved by temporary ovarian suppression using Zoladex, a gonadotropin releasing hormone agonist analogue (Holdaway *et al.* 1991). It worked, because estrogen and testosterone production was suppressed and the ratio between estrogen and progesterone was improved. Restoration of hormonal levels and balance between them can stabilize a level of prostaglandins.

Simultaneous action of hormones and prostaglandins controls changes during the menstrual cycle. Most female disorders are related to a hormonal imbalance. The reason for this disorder is an absolute deficiency

of hormones (during menopause) or relative deficiency (when the level of progesterone, for example, is less than desirable if we compare it with estrogen level). The loss of hormonal equilibrium is the main reason for the multiple diseases and syndromes. Such conditions as endometriosis and fibroids, for example, related to estrogen dominance. It can be too much estrogen or not enough progesterone. A relative deficit of hormones can be found during premenstrual syndrome (PMS). Changed hormonal sensitivity of target-cells leads to a decreasing of progesterone level. Also, a disorder of the hormonal regulatory system can disrupt the process of ovulation and lead to the malfunction of the luteal phase.

We believe that an elevation of estrogen increases sodium retention which is a cause of interstitial fluid retention and edema. A decreasing level of progesterone is an additional reason for increasing edema. Progesterone has sodium-diuretic action and increase diuresis. If luteinizing hormone (LH) is low, fluid is retained in tissues, including the brain, which can be a cause of migraine. An excess of estrogens leads to hypoglycemia, which is a cause of fatigue and weakness. A decreased threshold of excitability of sympathetic system can be a cause of a condition when normal physiological and furthermore pathological action creates an unhealthy and painful reaction. A change of hormones can be a primary cause of migraine initiation and a changed peripheral nervous system can initiate secondary change of hormonal balance.

An important link between altered sex hormones and changes in neurochemicals is believed to be responsible for migraine (Marcus 1995). In some studies patients with migraine showed a significant reduction of testosterone and a significantly increased cortisol concentration (Facchinetti *et al.* 1986; Waldenlind & Gustafsson 1987; Romiti *et al.* 1983), but not in the other (Epstein *et al.* 1975). Plasma testosterone levels were within the normal range (Epstein *et al.* 1975). We think that a normal level does not mean an optimal one. Our data shows that migraine can be managed only in the case when all basic hormones (pregnenolone, DHEA, testosterone, estrogen, and progesterone) will be close to optimal levels with physiological cycle.

We would like to stress the importance of cholesterol measurement. In our study 90% of patients had a cholesterol disorder (hyper- or hypocholesterolemia). Our data correlated with some studies in which patients with migraine had a significantly higher concentration of total cholesterol in relation to healthy subjects (Maciejek *et al.* 1984). Also, hyperlipemia has been recently described in children with migraine (Castro-Gago *et al.* 1989).

Migraine has been considered a manifestation of sympathetic dysfunction. Serotonin has long been implicated as a key neurotransmitter in migraine (Cassidy *et al.* 2003). The level of serotonin falls during a migraine attack (Selmaj 1979). Several lines of evidence

also support the involvement of the parasympathetic system in migraine (Avnon *et al.* 2003). We agree with the claim that migraine is secondary to autonomic dysfunction and reflects an imbalance between the sympathetic and parasympathetic nervous system (Magos *et al.* 1985; Lehmann *et al.* 1996).

According to classic theory, a migraine attack is initiated by a cerebrovascular spasm followed by extracranial vasodilatation. Cellular hypoxia can cause an increase in the flow of calcium from the extracellular fluid to the intracellular space, resulting in a calcium overload and cellular dysfunction (Gelmers 1985). Steroid hormones influence calcium and magnesium metabolism. Estrogen regulates calcium metabolism, intestinal calcium absorption and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. Alterations in calcium homeostasis (hypocalcemia and hypercalcemia) have long been associated with many affective disturbances. Clinical trials in women with PMS have found that calcium supplementation effectively alleviates the majority of mood and somatic symptoms. Evidence to date indicates that women with luteal phase symptomatology have an underlying calcium dysregulation (Thys-Jacobs 2000). Membrane potentials based on the particular ion involved and the concentration gradient for that ion in the cell. A large number of voltage-gated ion channels, ligand-gated channels, and transporters are involved in maintaining this balance. Normal membrane excitability is tightly regulated by the balance of these opposing influences (Ptacek 1999). A low brain magnesium level can be an expression of neuronal hyperexcitability of the visual pathways related to a lowered threshold for migraine attacks (Aloisi *et al.* 1997). Clinically, it is known that: (1) magnesium supplementation relieves premenstrual problems (e.g., migraine, bloating and edema) occurring in the late luteal phase of the menstrual cycle; and (2) migraine syndromes, particularly in women, are associated with deficits in brain and serum ionizing magnesium levels. Testosterone didn't produce any significant alteration in magnesium level, but estrogen and progesterone did (Li *et al.* 2001). We believe that the restoration of calcium/magnesium balance is one of the key players in migraine correction. As with the supplementation of calcium, the last daily dose of magnesium should be taken at bedtime.

Research has found that the pineal hormone melatonin is low in migraine patients (Claustrat *et al.* 1989). This data suggests impaired pineal function in migraine (Claustrat *et al.* 1997). Additionally, several studies found administering melatonin to migraine sufferers relieved pain and decreased headache recurrence in some cases (Gagnier 2001). The pineal gland could act as the intermediate causative factor of migraine, via a derangement of melatonin (Toglia 1986). The melatonin precursor serotonin showed diurnal variations with opposite phases to melatonin synthesis (Lerchl 1994). Stress and dietary habits lead to deficiencies of both

serotonin and melatonin. A diminished melatonin to serotonin ratio leads to a decline in adaptive processes (Rozenzwaig *et al.* 1987). Also, abnormal circadian rhythms of cortisol may occur in states of decreased melatonin (Maurizi 1984). Our research supports the hypothesis that migraine is a response to a pineal circadian irregularity in which the administration of melatonin normalizes this circadian cycle (Gagnier 2001); i.e., melatonin may play a role in resynchronizing biological rhythm to lifestyle and subsequently relieve migraine.

In addition to melatonin, our program includes Kava (Piper methysticum). Kava has been shown to be effective as an alternative treatment, at least in mild to moderate cases of anxiety. The pharmacological properties of kava are postulated to include a blockade of voltage-gated sodium ion channels, enhanced ligand binding to gamma-aminobutyric acid (GABA) type A receptors, diminished excitatory neurotransmitter release due to calcium ion channel blockade, reduced neuronal reuptake of noradrenaline (norepinephrine), reversible inhibition of monoamine oxidase B and suppression of the synthesis of the eicosanoid thromboxane A(2), which antagonises GABA(A) receptor function (Singh & Singh 2002).

Migraine is a recurrent clinical syndrome characterized by combinations of neurological, gastrointestinal and autonomic manifestations (Diamond & Wenzel 2002). From our point of view the restoration of natural intestinal flora is also a very important element of our program.

Analysis of medical literature and our own experience convinces us that migraine is a complex disorder including malfunctions in a few systems: neurohormonal system which includes feedback loop mechanism between hypothalamus, pituitary gland and glands which produce steroid hormones; sympathetic/parasympathetic systems; calcium/magnesium ions system, pineal gland system, and digestive system. All these changes have a very close interrelationship and each of them can be a trigger mechanism for migraine. Contradictory results with using, for example, serotonergic agonists and antagonists for migraine treatment is additional evidence that the problem is not in high or low activity of sympathetic system, but in imbalance between sympathetic and parasympathetic systems.

Following this logic, the basic method of migraine treatment must be directed to the restoration of integrity between different systems. In our study the simultaneous restoration of neurohormonal and metabolic integrity was an effective approach to the management of migraine (Dzugan & Smith 2003).

CONCLUSION

Our findings support the hypothesis that migraine is a consequence of a loss of neurohormonal and metabolic integrity, and that migraine can be managed by

a multimodal approach. Simultaneous restoration of neurohormonal and metabolic integrity in migraine patients was a very effective treatment approach and was typically associated with a complete management of migraine.

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