

## Migraine

*Migraine headache is an episodic headache disorder. It is a common condition with a prevalence of 17.6% in females and 5.7% in males. An American Migraine Study estimated that 23 million persons older than 12 years of age have severe migraine headaches; however, this condition is under-treated and under-diagnosed worldwide. Not all headache sufferers seek medical attention, but those who do generally consult family practitioners, internists or pediatricians, ophthalmologists, and neurologists. The social and economic effects of migraine are staggering--perhaps \$2 to \$17.2 billion are lost in productivity per year. The treatment of migraine has not only medical but also serious economic and social implications. Thus, primary-care physicians should be well versed in the diagnosis and treatment of migraine. Rational migraine treatment necessitates an accurate diagnosis, identification and removal of potential triggering factors, non-pharmacological and if needed pharmacological intervention. Both the avoidance of migraine trigger factors and the use of non-pharmacological therapies have a part to play in overall migraine management (1). Effective management also includes establishing realistic expectations, patient reassurance, and education (2).*

### Symptoms in Migraine

Any attempt to explain the pathophysiology of migraine has to account for the following components of the attack:

#### Premonitory Symptoms(Aura)

The aura may last 20 to 30 minutes and may include one or more of the following:

- Mood changes (commonly a sense of elation associated with hyperactivity)
- Increased appetite (particularly for sweet foods).
- Excessive yawning may precede migraine by as long as 24 hours, on at least some occasions, in about one third of migraine patients.
- Blindspots (scotomata) or visual field cuts may have distinctive scintillations or fortification patterns around them. Typically, the scotomata clear as the headache appears.
- Sensory hyperacuity (light may be perceived as dazzling or may provoke pain, sounds may appear unnaturally loud, and smells may be more intense during (or even before) the headache phase).

#### Focal Neurological Symptoms

- These neurological symptoms may arise from the cerebral cortex, brain stem, or cerebellum and may anticipate the onset of headache as in the prodromal phase of classic migraine or may appear during the headache phase.
- Focal neurological symptoms of classic migraine, whether arising as a prodrome or developing during the headache phase, are accompanied by diminished cortical perfusion of the appropriate part of the opposite cerebral hemisphere. On some occasions a wave of hypo-perfusion may advance slowly over the cortex in association with a slow march of visual or other neurological symptoms whereas on other occasions it may persist as a local or diffuse cortical oligemia. It is clear that the presence or absence of headache does not depend on changes in cerebral blood flow.

#### Headache

- It is unilateral in two thirds of patients. It commonly starts as a dull ache at the occipito-nuchal junction, or in one temple and then spreads over that side of the head or the whole head or may remain localized as a "bar of pain" extending from the eye to the occiput. The pain is usually constant and unremitting but assumes a

pulsatile or throbbing quality when severe, it may consistently affect the same side of the head or may move from side to side, even in the one migraine episode. Pain may radiate down the neck to the shoulder or, in some cases, to the arms and even the leg on the same side of the body, suggesting that the spinothalamic tract has collaborated with trigeminal pathways in the production of pain.

- The frontal branches of the superficial temporal artery become distended in about one third of patients, venous engorgement may be seen, and heat loss increases from the affected area. Most patients appear pale and "dark under the eyes" as the headache worsens, although exceptional patients flush before or during the attack. Sensitivity of the scalp to touch and muscular hyperalgesia may develop during, and outlast, the headache phase.
- However headache of migraine is not necessarily associated with vascular pulsation, dilation of extra-cranial arteries or increased cerebral perfusion.

### **Gastrointestinal symptoms**

- Nausea sometimes precedes the onset of headache but commonly evolves as the attack progresses and may culminate in vomiting. Diarrhea is associated in about 20% of patients. Such gastrointestinal symptoms are mediated by an enzyme, dopamine beta-hydroxylase (DBH) that is the final enzyme in the synthesis of noradrenaline.
- Pain-Sensitive Cranial Structure
- The foundation for any study of the causes and treatments of headache is knowledge of the pain-sensitive structures and pain-conducting pathways within the cranium.
- All available evidence supports an orderly somatotopic representation of the supratentorial pain-sensitive meningeal and vascular structures within the trigeminal system. Pain sensation from posterior fossa structures is carried centrally by the vagus nerve, the upper three cervical nerves, and possibly by trigeminal afferents as well.

## **The Origin of Migraine Headache**

The bones of the skull and brain substance are insensitive to pain because they lack pain sensitive nerve fibers.

Pain is referred to the frontotemporal area of the skull, from the following structures:

- The dura.
- The intracranial segment of the internal carotid artery.
- The proximal few centimeters of the anterior and middle cerebral arteries.
- A portion of the cerebral veins and venous sinuses.
- The middle meningeal artery.
- The superficial temporal artery.

The previously mentioned structures contain pain sensitive nerves with the nociceptors at their ends. The latter can be stimulated by stress, muscular tension, dilated blood vessels and other triggers of headache. Once stimulated, the nociceptor sends a message up the length of the nerve fiber to the nerve cells in the brain, signaling that a part of the body hurts. In periarterial fluid sampled during migraine headache, a polypeptide was found, named "neurokinin". This bradykinin-like substance was postulated to set up a sterile inflammatory response in the vessel, which became pain-sensitive, and is responsible for the transmission of the pain impulse to the brain nerve cells.

Platelet aggregation takes place in subgroups of migraine patients and may be a factor in the vascular thrombosis of "complicated migraine". However the blood platelets in most patients seem to be remarkably normal and their role in migraine is

probably limited to aggregation in some instances and to serotonin release which potentiates the pain-producing effect of bradykinin. Dilation of scalp arteries in this area contributes to the intensity of headache, and compression of the temporal artery eases the pain.

Platelet serotonin content increases before migraine attacks and falls during the headache phase in most migraine patients. A serotonin-releasing factor was found present in the blood during migraine headache. The main metabolite of serotonin, 5-hydroxyindoleacetic acid, is excreted in excess in the urine of some patients during migraine attacks. However it seems unlikely that the amount of serotonin released from platelets during migraine headache would be sufficient to cause any vascular constriction, but it may possibly combine with bradykinin to render the arterial wall sensitive to painful dilation. It has been postulated that free fatty acids might be responsible for the release of serotonin from blood platelets in migraine.

Blood histamine is significantly increased after migraine headache. It is claimed that liberated histamine might contribute to the vascular component of migraine. Prostaglandins, long-chain unsaturated fatty acids derived from arachidonic acid, have potent constrictor and dilator effects. During migraine headache, plasma levels of PGE1 do not alter, but the level of PGE2-like substances has been shown to fall significantly, in contrast with its elevation found in cluster headache.

### **The Mechanisms of Migraine**

Hypotheses for the mechanisms of many aspects of migraine have been extensively studied (3). The aura symptoms are, most likely caused by a mechanism similar to spreading excitation and depression (4).

It has been believed that migraine attack is a specific reaction pattern to an episode of focal cerebral hypoxia. This hypothesis holds that any type of focal brain hypoxia (and thus not only a vasospasm) may provoke a migraine attack. Indeed, as hypoxia is a result of an imbalance between energy supply and energy use, the former can be decreased and/or the latter be increased. Spreading cortical depression, leading to the aura, is believed to be a consequence of brain hypoxia occurring in classical migraine. There are no genuine differences between classical and common migraine, according to the cerebral hypoxia theory. The latter theory may improve our understanding of the mode of action of antimigraine drugs. Certain calcium entry blockers have a direct protective effect on brain hypoxia, but some other pharmacotherapeutic approaches may also prevent cerebral hypoxia via an effect on brain metabolism, vasomotion or platelet behavior (5). It has been postulated that the classic migraine is both spreading cortical depression and localized ischemia linked in a vicious cycle by potassium induced vasoconstriction. The cycle can be initiated by any event that raises the local cortical ECF (extra-cellular fluid) potassium concentration to approximately 20 mM. Such an event could be a localized burst of activity of a group of cells, localized metabolic impairment, or a transient reduction in blood flow to a region of the cortex. Once this level of potassium concentration is reached, it may result in localized depolarization of neurons, releasing more potassium into the ECF. As the concentration continues to rise, vasoconstriction becomes more intense, perpetuating the cycle that results in localized depression of cortical neuronal activity and ischemia. The condition is propagated to adjacent regions of the cortex by diffusion and glial-mediated spread of potassium (6).

Neuronal hyperexcitability between attacks may be due to:

- Mitochondrial disorder.

- Magnesium deficiency.
- Abnormality of presynaptic calcium channels.

Like many others neurological diseases, mitochondrial involvement, by means of abnormalities in cerebral oxidative metabolism, may play a role in migraine(7). The importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. However, the precise role of various effects of low magnesium levels in the development of migraines remains to be discovered.

Magnesium concentration has an effect on:

- Serotonin receptors.
- Nitric oxide synthesis and release.
- A variety of migraine related receptors and neurotransmitters.

The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium. Infusion of magnesium results in a rapid and sustained relief of an acute migraine in such patients. Two double-blind studies suggest that chronic oral magnesium supplementation may also reduce the frequency of migraine headaches (8).

Increased tissue levels of taurine, as well as increased extracellular magnesium, could be expected to:

- Dampen neuronal hyperexcitation.
- Counteract vasospasm.
- Increase tolerance to focal hypoxia.
- Stabilize platelets.
- Taurine may also lessen sympathetic outflow.

Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine.

### **The Humoral-Vascular Theory of Migraine**

The humoral-vascular theory postulates that circulating vasoactive amines constrict the cortical microcirculation, thus causing the neuralgic symptoms and signs classic of migraine and that a subsequent phase of dilatation (predominantly extracranial ) is responsible for headache. Dilatation of extracranial, middle meningeal, or cerebral arteries is thought to cause pain in migraine because the vessel wall has been sensitized by the adsorption of serotonin released from platelets and the periarterial accumulation of histamine and bradykinin, causing sterile inflammatory response around extracranial vessels. In case of normal immune system Opioid-containing immune cells migrate preferentially to inflamed sites, where they release beta-endorphin which activates peripheral opioid receptors to inhibit pain. This immune response is altered in migraine patients. Immunocyte recruitment is a multistep, sequential engagement of various adhesion molecules located on immune cells and vascular endothelium. Selectins mediate the initial phase of immunocyte extravasation into inflamed sites. Anti-selectin treatment abolishes peripheral opioid analgesia elicited either endogenously (by stress) or by corticotrophin-releasing factor. This results from a blockade of the infiltration of immunocytes containing beta-endorphin and the consequent decrease of the beta-endorphin content in the inflamed tissue. These findings indicate that the immune system uses mechanisms of cell migration not only to fight pathogens but also to control pain in injured tissue. Thus, pain is exacerbated by measures inhibiting the immigration of opioid-producing cells or, conversely, analgesia might be conveyed by adhesive interactions that recruit those cells to injured tissue (9).

A significant reduction in peripheral blood mononuclear cell beta-endorphin concentrations was observed in migraine patients with and without aura. Altered transmitter modulation to peripheral blood mononuclear cells may be the cause of this alteration, which could be part of a more diffuse opioid system derangement in migraine subjects (10). The life span pattern of circulating peptide, beta-endorphin (B-EP) is characterized by a progressive increase during prepuberal development, by stable levels in adults with typical circadian and monthly variations, and by a decrease in aging subjects. The concomitant changes in the reproductive system suggested the possible influence of gonads on B-EP plasma levels, as confirmed by decreasing B-EP levels in gonadectomized humans and rats. Headache, which is likely to occur concomitantly with hormonal milieu variations, appeared to be associated with a deficiency in the B-EP system, centrally and peripherally, the lowest values being found in the protracted forms of headache (11). The somatostatin-like (SLI), the neuropeptide Y-like (NPY-LI), and the beta-endorphin-like (BE-LI) immunoreactivities of cerebrospinal fluid (CSF) obtained by suboccipital puncture, or plasma from patients suffering from common migraine were analyzed. The SLI concentration was tendentially decreased in the migraine patients during the attack-free period. During the migraine attack the level of SLI was further decreased. Similar alteration was found in the CSF BE-LI, while the BE-LI in the plasma showed only a tendentious decrease in common migraine patients. The NPY-LI did not change during the attack period in the CSF or plasma. These findings may indicate the possible role of somatostatin in the pathogenesis of common migraine, and support earlier observations that beta-endorphin is involved in the development in this disorder (12). Specific chemical mediator release such as histamine and the prostaglandins (PG2a or PGD2) associated with headaches has been found in a few patients who were repeatedly challenged with specific food (5).

Histamine is able to induce spontaneous-like headache attacks in migraine and cluster headache subjects. Therefore, it has been considered as a possible agent in the pathogenesis of headache. Histamine desensitization is used for the treatment of cluster and other chronic headaches like migraine with interparoxysmal headache (13). A double blind, placebo-controlled trial was performed to establish the duration of action of antihistamines and their ability to attenuate the adverse effects associated with histamine release. It has been found that an adequate dose of antihistamines is recommended to achieve appropriate chemoprophylaxis (14). Headache can be induced by histamine in wine sensitive patients suffering from histamine intolerance, a disease characterized by impaired histamine degradation based on reduced diamine oxidase activity or a lack of the enzyme. As supportive treatment, a vitamin B6 (pyridoxal phosphate) substitution appears useful in histamine-intolerant patients as pyridoxal phosphate seems to be crucial for diamine oxidase activity. Histamine intolerance, based on reduced diamine oxidase activity or a lack in the enzyme, causative for wine/food-induced chronic headache. According to the localization of diamine oxidase in the jejunal mucosa, histamine intolerance is primarily a disease of intestinal origin. A histamine-free diet is the treatment of choice in histamine-intolerant patients suffering from chronic headache. In addition, it is also important to avoid diamine-oxidase-blocking drugs and alcohol which act as inhibitors of diamine oxidase. As avoidance of histamine-rich food is simple, inexpensive and harmless treatment, histamine-containing food such as cheese and alcoholic beverages should be labeled (15).

Platelets aggregation and the platelet release reaction are caused by a plasma substance of low molecular weight, which could be one or more of the free fatty acids liberated by catecholamines secreted as part of a response to stress. A reported case of acute promyelocytic leukemia and disseminated intravascular coagulation presented with migraine with aura as the first sign may support theories

of platelet serotonin involvement in the pathogenesis of migraine (16). Endothelin-1 (ET-1) exerts powerful vasoconstrictive action. The lower plasma level of ET-1 observed in the patients with migraine is consistent with the pathogenesis of migraine, further supporting the hypothesis that a lower ET-1 may be closely related to marked vasodilatation following the vasoconstriction (17).

### **The Neurogenic Theory of Migraine**

This theory postulates that migraine headache involves trigeminovascular and brainstem mechanisms. The ability to trigger an attack may depend on a threshold of brain excitability.

Monoamines have been considered to be the neurotransmitters most likely to be involved in the mechanism of migraine because blood levels of noradrenaline and serotonin fluctuate with the course of headache. The newly acquired knowledge of brain stem monoaminergic nuclei and their influence on cortical activity and cerebral blood flow as well as their participation in the endogenous pain control system makes it feasible to erect a neurogenic hypothesis without completely excluding some aspects of the humoral theory.

Because migraine is a familial disorder, there may well be hereditary anomaly of monoaminergic transmission, that copes well enough under normal circumstances. This mode of transmission is vulnerable to sudden changes in the internal or external environment to emotional stress, or to overload of afferent systems by excessive glare, noise, smells, or other stimuli. All of these factors are known to impinge on the brain stem monoamine nuclei that project diffusely to the cerebral cortex. If monoaminergic systems were genetically unstable in subjects prone to migraine, trigger factors could induce a phase of excessive neuronal discharge followed by a state of monoamine depletion. Finally, in a state of monoamine depletion, the pain gate would be opened, giving rise to spontaneous pain in the head and neck. The conclusion that central monoamine systems play a central role in the pathophysiology of migraine is difficult to escape.

Thus the physiologic and biochemical observations of patients during migraine attacks led to the accumulation of a lot of data awaiting synthesis. The common ground of the various hypotheses for the mechanism of migraine is the involvement of monoamines, neurotransmitters, centrally, and the humoral agents (serotonin and adrenaline) peripherally. This is supported by pharmacological evidence from the results of treatment. Most effective interval therapy for migraine alters the availability or action of serotonin (methysergide, pizotifen), noradrenaline (beta-blocking agents), or both monoamines (amitriptyline, monoamine oxidase inhibitors). Other agents that act directly on vascular smooth muscle, such as the calcium-entry blocking agents, may diminish vasoconstriction, whether produced by humoral agents or by intrinsic monoamine pathways from brain stem to cortex. Non-steroid anti-inflammatory agents presumably suppress the sterile inflammatory responses in vessel walls.

### **When is Headache a Warning of a More Serious Condition?**

Like other types of pain, headaches can serve as warning signals of more serious disorders.

- Migraine is a risk factor for cerebral stroke, particularly in young women. The symptoms and lesions of migrainous stroke suggest the involvement of a mechanism similar to that of migrainous aura, although the infarction process is of greater intensity and lasts longer. Migrainous stroke should be considered an evolutionary complication of aura. Thus, the best treatment consists of adequate control of migraine attacks with the reduction of frequency, intensity and duration. The

avoidance of migraine drugs with marked vasoconstrictive action, and the removal of other vascular risk factors (smoking and oral contraceptives) are additional measures for the prevention of migrainous stroke (18).

In addition to vasoconstriction, activation of clotting factors plays a role in the pathophysiologic mechanism of migraine-related stroke. However cerebro- and cardiovascular evaluation is important in patients with suspected migrainous stroke to exclude the diagnosis of paradoxical cardioembolic stroke through a patent foramen ovale (19).

- Familial hemiplegic migraine (FHM) is an autosomal dominant condition. Attacks start in childhood, adolescence, or early adulthood. They invariably include a unilateral weakness lasting 30 to 60 minutes and almost always associated with visual, sensory, or speech disturbances. They are occasionally very severe with a dense hemiplegia, confusion, coma or fever, but they always completely recover. Brain neuroimaging is normal. In 20% of the families, migraine is associated with permanent neurological signs, mainly nystagmus and cerebellar ataxia (20).
- Migrainous infarction is reported due to severe diffuse intracranial major arterial vasospasm that can be demonstrated by arteriogram. Migrainous infarction is represented by recurrent episodes of migraine with aura, that progress to develop a continuous intractable headache during the course of which cortical blindness and quadriplegia occurs due to extensive and bilateral hemispheric cerebral infarction (21).
- Brain hemorrhage: The connection between brain hemorrhage and migraine has been studied. It has been postulated that the brain hemorrhage might be related to vascular lesion brought about by ischemia secondary to vasospasm (22).
- Intracranial vascular malformations (IVM):Migraine is sometimes the presenting feature of patients with intracranial vascular malformations (IVM). A high prevalence of migraine type headaches and a strong positive correlation between the site of AVM and side of the pain was found (23). Migraine could be the only complaint in patients affected by an intrasellar aneurysm (24).
- Migraine and migraine-like headaches are sometimes associated with acquired types of carotid artery stenosis or occlusion (25).
- Occipital lobe tumor can be presented clinically as migraine with typical aura (26).
- Migraine with aura has been reported as the presenting sign of acute promyelocytic leukemia and disseminated intravascular coagulation. This may support theories of platelet serotonin involvement in the pathogenesis of migraine (27).

### **Danger signals that should alert the physician to consider a potentially sinister cause:**

- Sudden onset of a new, severe headache-"the worst headache ever"
- A progressive headache course.
- Onset of headache with exertion
- Onset of headache during or after middle age.
- Headache associated with a decreased level of consciousness.
- Headache associated with meningeal signs.
- Headache associated with abnormal physical signs including fever.
- Failure of headache to "fit" a benign profile.
- Headache in a patient with a systemic malignant disease, infection or immunocompromised state.

### **Clinical features that suggest the benign nature of a migraine attack:**

- Precipitation by menstruation
- Amelioration with sleep.
- Amelioration during pregnancy

- Appearance after sustained exertion.
- Triggers such as alcohol, odors, foods, or changes in the weather.

### **Trigger Factors of Migraine**

Migraine attacks or other headaches are often triggered (rather than caused) by one or more of the following factors:

- Stress is the most frequently cited precipitant in migraine (28). Patients most commonly recognize stress. Migraine brought on by stressful situations and events. The onset of attacks is usually during the period of calm immediately after such moments of stress (29).
- Odontogenic pathogenic factors (dental problem), good diagnostic examination in the field of tooth-, jaw- and mouth medicine should be conducted in every migraine patient, even in "typical" migraine patients. When indicated, operations should be done (30).
- Weather changes e.g. Chinook weather conditions in the Calgary. Older migraine sufferers appear particularly vulnerable to this effect (31).
- Cheese, chocolate, red wine and beer sensitivity: it is believed that these foods and several others contain vasoactive amines, such as tyramine, which constrict arteries, the first step of migraine process. Others believe that foods cause headaches by setting off an allergic reaction in susceptible people. Food-triggered migraine usually occurs soon after eating (32).
- Gastrointestinal inflammation: Some of the children suffering from migraine with or without aura have been found to have oesophygitis, gastritis of corpus, antral gastritis or duodenitis. It is postulated that there is a gastrointestinal origin of these patients' complaints. findings provide evidence that recurrent abdominal pain is an early expression of migraine and strongly support a causal link between recurrent abdominal pain and migraine(33).
- Female sex hormones fluctuatations: these fluctuations may trigger, intensify, or alleviate migraine. Pharmacological management of migraine in pregnant women must be conservative because of the risks of injury and dependence to the fetus and newborn (34). Motilium and Voltaren have been successfully used for controlling vascular headache developing as a side effect of contraceptive tablets. In case of migraine associated with dysmenorrhoea and/or premenstrual tension the management with triphasic hormone proved to be of therapeutic value (35).
- Minor trauma to the head or whiplash neck injury: ("post-traumatic migraine"- PTM). " The neurologic literature has placed excessive emphasis on compensation neurosis and psychological factors in the etiology of chronic headaches after minor trauma. Physicians must be aware of PTM, as it is both common and treatable (36).
- Low back pain: it has been found that in many patients, headache was found to have begun or exacerbated markedly after onset of low back pain. Potential mechanisms for explaining the high prevalence of migraine following low back pain, include increased muscle tension, psychosocial factors, and analgesic overuse(37).
- Migraine and the eating disorders, particularly bulimia nervosa: Bulimics appear to be more sensitive to the induction of severe migrainous headaches than normal controls following challenge with the 5-HT agonist (38).
- Nitric oxide (NO): it may play a key role in migraine and other vascular headaches since glyceryl trinitrate (a donor of NO) and histamine (which probably activates endothelial NO formation) both cause a pulsating dose-dependent headache with several migrainous characteristics. At relatively high doses of glyceryl trinitrate, migraine sufferers develop stronger and more migraine-like headaches and more pronounced cerebral arterial dilatation than normal controls (39).
- A Common denominator, namely, high levels of blood lipids and free fatty acids are underlying factor in the development of migraine headaches. Biological states that

may cause increases in free fatty acids and blood lipids include: high dietary fat intake, obesity, insulin resistance, vigorous exercise, hunger, consumption of alcohol, coffee, and other caffeinated beverages, oral contraceptives, smoking, and stress trigger migraine attack. Elevated blood lipids and free fatty acids are associated with increased platelet aggregability, decreased serotonin, and heightened prostaglandin levels. These changes lead to the vasodilatation that precedes migraine headache (40).

### **Understanding the Pathology of Migraine assists in Treatment**

It is useful to conceptualize the patient with migraine as having an inherited susceptibility to headache with altered migrainous threshold. The expression of an altered migrainous threshold in headache-prone persons may depend on the balance between inhibitory and excitatory neurocircuits that are influenced by a complex interplay of exogenous and endogenous factors.

The best preventive strategy recognizes the multifactorial nature of migraine and attempts to increase the migrainous threshold through both pharmacological and non-pharmacological interventions.

The serotonergic system:

It consists of the brain stem, with its descending and ascending circuitry, including the ascending pain-modulating projections from the midbrain raphe nuclei. The neural activity within this serotonergic system is an important precursor to migraine.

Serotonin (5-hydroxytryptamine [5-HT])

It is a biogenic amine that is widely distributed throughout the body. It is considered the serotonergic brain stem generator. Any changes of serotonin can alter cranial circulation and trigger a vascular phase. This neurovascular reaction not only produces constriction or dilation of intracranial and extracranial arteries but also activates the nociceptive trigeminal vascular system. Neural connections exist between the cerebral blood vessels and the trigeminal nerve. Stimulation of the trigeminal sensory C fibers by any of the triggering factors releases vasoactive neuropeptides. These vasoactive neuropeptides include, substance P and calcitonin gene-related polypeptide and neurokinin A, an outcome that results in a neurogenic or sterile inflammation, which is blocked by 5-HT sub 1 receptor agonists such as sumatriptan or dihydroergotamine (DHE ).

Seven classes of serotonin receptors have been identified.

Symptomatic agents are believed to act as agonists at the 5-HT sub 1 receptor site. They act either peripherally or centrally.

Prophylactic agents act as antagonists at the 5-HT sub 2 receptor site. They act centrally by "stabilizing" the serotonergic system.

### **Assessment of the Patient with Migraine**

A detailed history is of paramount importance for an accurate diagnosis of migraine. The physician should ask why the patient is seeking medical attention.

The history should include the following factors:

- Age at onset.
- Site of pain.
- Frequency and duration of pain.
- Character, intensity and mode of onset of headache.
- Time between onset to peak pain.
- Associated neurologic, ophthalmologic, autonomic or systemic symptoms.
- Sequence of symptoms.
- Aggravating or precipitating factors.

- Ameliorating factors.
- Prior and current medication use including dose, dosage schedule, and efficacy.
- Caffeine intake.
- History of head trauma.
- Results of prior neuroimaging studies.
- Family history of similar diseases.
- A diary can be helpful for documentation of headache frequency, intensity, compliance, and response to treatment. In addition, a diary may disclose patterns related to lifestyle, diet, menses, or medication overuse.

### Laboratory investigation

Patients with typical migraine:

Neuroimaging or laboratory studies are unnecessary in the routine diagnosis of typical migraine; however, it is sometimes important to obtain an electrocardiogram and baseline laboratory studies such as a hemogram and a chemistry profile before initiation of therapy to ensure the safety of intervention.

Patient with either a new onset of headache or a change in a previously stable headache profile after 50 years of age:

Erythrocyte sedimentation rate, Cranial neuroimaging, high quality enhanced computed tomography. In the case of a suspected posterior fossa lesion in patients with a progressive headache syndrome, papilledema, or abnormal findings on neurologic examination, magnetic resonance imaging should be done. If subarachnoid hemorrhage is suspected, then examination of the cerebrospinal fluid with measurement of the opening pressure is indicated after an appropriate imaging study has excluded contraindication to lumbar puncture. In cases of suspected bacterial meningitis, neuroimaging studies do not need to be performed before a lumbar puncture in the absence of papilledema and focal neurologic findings. Cerebral angiography is indicated in cases of suspected central nervous system vasculitis, arterial dissection, cerebral aneurysm, or arteriovenous malformation.

Pharmacologic Treatment of Migraine (41).

Effective management of migraine includes establishing realistic expectations, patient reassurance, and education.

The choice of medication (abortive, symptomatic) for an acute attack depends on such factors as:

- The severity of the attack.
- The presence or absence of vomiting
- The time of onset to peak pain.
- The rate of bioavailability of the drug.
- The comorbid medical conditions, and side-effect profile.

Effective agents for acute attacks:

- Simple or combination analgesics.
- Non-steroidal anti-inflammatory drugs.
- Ergot derivatives.
- Selective serotonin agonists.

Preventive (prophylactic, interval) medication depends primarily on comorbid medical conditions and side-effect profile.

Preventive agents:

- Beta-adrenergic blockers.
- Calcium channel blockers.

- Tricyclic antidepressants,.
- Anticonvulsant medications.
- Serotonin antagonists.

It is recommended to explain to the patients that they were born with a sensitive neurovascular system that overreacts to internal changes or external stimuli and that the condition can probably be controlled with non-pharmacological and appropriate pharmacological treatment. Patients are more likely to be active participants in their treatment if they have a better understanding of their condition. Patients may be referred to the Migraine Association of Canada for information and support and may benefit from referral to local self-help groups.

It is important to avoid analgesic overuse as it causes rebound headache.

Symptomatic medications, whether prescribed or over-the-counter, when taken on a daily or almost daily basis can result in a chronic daily headache syndrome that can be refractory to treatment. An under-appreciated point is that excessive use of symptomatic medications on a daily basis may render prophylactic and symptomatic medications ineffective.

### **Symptomatic Therapy.**

Symptomatic therapy is the mainstay of migraine management. Effective treatment of the acute migraine attack should terminate or decrease the symptoms of the attack.

- Simple Analgesics. It is recommended to use of ASA and acetaminophen as the treatment of choice for mild to moderate migraine attacks. Enteric-coated ASA , should not be used for migraine because of delayed onset of action. Effervescent preparations are more effective due to more rapid absorption

### **Combination Analgesics**

Two frequently used combination drugs effective in the treatment of mild to moderate migraine attacks contain either isometheptene with acetaminophen and dichloralphenazone or ASA and acetaminophen with butalbital and caffeine. Both combinations can cause a medication-induced or analgesic rebound headache if used frequently. Therefore, we limit use of these agents to no more than 2 days per week.

### **Nonsteroidal Anti-Inflammatory Drugs**

NSAIDs is considered the first-line therapy for mild to moderate migraine attacks. Selected examples include naproxen sodium, ibuprofen, ketorolac, and indomethacin, NSAIDs are contraindicated in patients with active ulcer disease. Potential side effects include nausea, abdominal pain, diarrhea, light-headedness, somnolence, and fluid retention, as well as hepatic toxicity and nephrotoxicity.

### **Ergot Derivatives**

Ergotamine Tartrate is effective symptomatic treatment of moderate to severe migraine attacks that fail to respond to simple or combination analgesics. Although both oral and suppository dosing are available, plasma levels are 20 times higher with rectal administration. A crucial and often neglected point is that a sub-nauseating dose must be used. Such a dose can range from one-quarter to a whole ergotamine tartrate suppository.

Ergotamine tartrate is contraindicated in the following conditions: women considering pregnancy and during pregnancy; sepsis; inadequately controlled hypertension; cerebral, coronary, and peripheral vascular disease; as well as hepatic and renal insufficiency. Major side effects include abdominal cramps, paresthesias, and nausea. The development of chest tightness after use of ergotamine tartrate is a cause for concern and necessitates discontinuation of use of the medication and obtainment of

an appropriate medical referral. Patients should limit their use of ergotamine tartrate to no more than 2 days per week and to take no more than 10 mg per week. Overuse can produce ergotism and chronic daily headaches.

### **Dihydroergotamine**

Unlike ergotamine tartrate, DHE minimally constricts peripheral arteries yet is a potent vasoconstrictor. Unlike ergotamine, DHE does not result in physical dependence. As with ergotamine tartrate, the subcutaneous dose must be determined. Contraindications to the use of DHE are similar to those for ergotamine tartrate.

### **Sumatriptan**

Sumatriptan, a selective 5-HT<sub>1</sub> receptor agonist, has been approved for treatment of acute migraine. Headaches recur in up to 40% of patients probably because of the relative short half-life of 2 hours. Sumatriptan administered subcutaneously has a rapid onset of action, with statistically significant relief being obtained in 10 minutes. Sumatriptan remains efficacious even if given well into the headache phase. Its beneficial effects on associated gastrointestinal symptoms eliminate the need for coadministration of an antiemetic. Sumatriptan administered at the onset of a migraine aura has no benefit. Oral sumatriptan therapy, which was recently approved by the FDA, is similarly effective but has a slower onset of action. Sumatriptan is contraindicated in patients with inadequately controlled hypertension, ischemic heart disease, Prinzmetal's angina, and complicated migraine including vertebrobasilar migraine, as well as in pregnant patients. Side effects of subcutaneous sumatriptan therapy include discomfort at the injection site, diffuse burning, tingling, and, occasionally, neck or chest pain (or both). postmenopausal women, men older than age 40 years, and patients with vascular risk factors such as hypertension, hypercholesterolemia, obesity, diabetes, smoking, and a strong family history of vascular disease without a prior assessment for unrecognized coronary artery disease (CAD).

### **Phenothiazines**

Several controlled studies have demonstrated the efficacy of intravenous chlorpromazine and prochlorperazine therapy. However care must be taken to ensure adequate hydration before use of intravenous chlorpromazine therapy. DHE and prochlorperazine are miscible and can be combined in a single syringe.

### **Corticosteroids**

Prednisone, hydrocortisone, or methylprednisolone can be considered for prolonged migraine attacks that are refractory to the more standard treatment options. 3- to 5-day course of outpatient oral corticosteroid therapy is sometimes used for particularly refractory migraine attacks. Parentally administered corticosteroids are useful for terminating a severe, prolonged migraine attack when there are contraindications to ergot preparations or when ergot preparations have failed to provide relief.

Repeated use of corticosteroid is contraindicated as it causes hormonal imbalance, Cushing's disease, osteoporosis, diabetes hypertension and lower the immune response to infections.

### **Narcotic Analgesics**

Although meperidine is often used as an abortive agent in many emergency departments, clinical trials to support widespread use of this narcotic agent are lacking.

### **Prophylactic Therapy**

Criteria for selecting patients for prophylactic treatment:

- Attacks that occur more than 2 to 3 times a month.
- Attacks that last more than 48 hours.
- Attacks that are severe.
- If the patient is unable psychologically to cope with the attacks.
- Treatment of an acute attack provides inadequate relief or therapy produces serious side effects
- Attacks occur after prolonged aura.

Several additional factors must be considered before prophylactic treatment can be initiated.

Because of the potential teratogenic effect of the prophylactic agents, women of childbearing age should be using a reliable type of birth control. Prophylactic therapy should be considered in patients taking excessive amounts of symptomatic medications, which lead to rebound headaches.

Several pitfalls have been identified in migraine prophylaxis. The dose may be inadequate, either insufficient or excessive--it is prudent to "start low and go slow." The trial regimen of treatment may be inadequate. The minimal time interval for migraine prophylaxis before a beneficial effect is noted is generally 1 to 2 months, especially when calcium channel blockers are being used.

Although elimination of migraine is a worthy therapeutic goal, in actuality, medications for Prophylaxis are seldom more than 55 to 65% effective. The medications used include beta-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, serotonin antagonists, NSAIDs, and MAO inhibitors.

### **Beta-Adrenergic Blocking Agents.**

Beta-Blockers remain the treatment of choice for prophylaxis of migraine, especially if the patient has comorbid hypertension or anxiety. Examples of beta-blockers include propranolol, nadolol, atenolol, timolol, and metoprolol.

Use of beta-blockers should never be discontinued abruptly. Contraindications include asthma, insulin-dependent diabetes mellitus, heart failure, heart block, pregnancy, and Raynaud's phenomenon. Side effects, including lethargy, depression, impotence, and hair loss, limit use of beta-blockers in many people.

### **Calcium Channel Blockers.**

Although calcium channel blockers are considered by some investigators as first-line therapy for migraine prophylaxis, the evidence in support of their efficacy is underwhelming. Some investigators have suggested that verapamil has a marginal benefit in decreasing the frequency of migraine attacks. Several trials have used nifedipine and nimodipine in the treatment of migraine. Nifedipine often causes a dull persistent headache, and nimodipine is approved only for use in subarachnoid hemorrhage and is too expensive to be used as a long-term agent. Contraindications include hypotension, heart block, sick sinus syndrome, and atrial fibrillation and flutter. Constipation can be a troublesome side effect.

### **Tricyclic Antidepressants.**

Amitriptyline is useful for migraine prophylaxis, particularly in patients with coexisting depression, tension headaches, or insomnia. Nortriptyline is as efficacious as amitriptyline, but it has not been formally studied. Contraindications include glaucoma, urinary retention, and cardiovascular disease, particularly ventricular conduction abnormalities.

### **Anticonvulsants**

Divalproex sodium has been shown to be an effective prophylactic agent for migraine in several double blind, placebo-controlled studies. This agent can be considered

first-line therapy for patients with coexisting seizures, mania, or anxiety. Idiosyncratic reactions can include hepatitis or pancreatitis.; clinical monitoring is thought to be the best method for long-term management.

### **Serotonin Antagonists**

Methysergide, a semisynthetic ergot, is effective in preventing migraine attacks. Contraindications include CAD, gastritis, uncontrolled hypertension, connective tissue disease, and pregnancy. The major concern of methysergide is the side-effect profile, which includes potential idiosyncratic fibrotic complications. If the patient's symptoms are relieved substantially, use of methysergide can be slowly tapered after approximately 4 months. The Physicians' Desk Reference recommends a medication-free interval of 3 to 4 weeks after 6 months of continuous treatment. For patients who receive methysergide for 6 months or longer, periodic monitoring should include auscultation of the heart, chest roentgenography, computed tomography or magnetic resonance imaging of the abdomen, and urinalysis. As with all medications, methysergide should be prescribed with complete knowledge of the side-effect profile.

### **Nonsteroidal Anti-Inflammatory Drugs.**

Although NSAIDs can be used for migraine prophylaxis, potential gastrointestinal and renal complications limit its recommendation to short-term use. It is important to monitor the serum creatinine.

### **Monoamine Oxidase Inhibitors**

MAO inhibitors have been found to be effective in patients with migraine headaches refractory to more standard treatment. Before initiation of phenelzine, a dietary consultation is advised. Patients must be given a list of medications and foods that they should avoid, including over-the-counter medications, particularly nasal decongestants.

### **Non Pharmacological Management of Migraine (42)**

Augmentation of the use of non-pharmacological therapies for the acute and prophylactic management of migraine is likely to lead to substantial benefits in both human and economic terms. Both the avoidance of migraine trigger factors and the use of non-pharmacological therapies have a part to play in overall migraine management.

Many of the non-pharmacological therapies are based on the theoretic concept of migraine as resulting from neurochemical instability within the brain. These approaches, which are often "biobehaviouristic," may be complementary or adjunctive to pharmacological treatment or may provide an alternative to it.

### **Patient education**

Patient education refers to "the information provided by health professionals to headache patients. Patient education is a necessary component of any treatment plan, and it is recommended that it include the following items:

- The diagnosis of migraine should be given clearly and confidently after the appropriate history-taking and clinical examination and, when necessary, after investigations have been completed.
- Patients should be reassured that they do not have a serious underlying cause for the headaches, such as a brain tumor.

### **Acute non-pharmacological treatment**

Most of the non-pharmacological measures found to be effective in alleviating an acute migraine headache.

- The application of cold or pressure to the head has been assessed as valuable.
- Reduction of activity and of sensory input in a quiet or dark environment and attempts to sleep.
- Relaxation therapy, hypnosis, transcutaneous electrical stimulation, acupuncture, and occipital or supraorbital nerve blockade have also been used in the acute situation.

## **Biobehavioural measures**

### **Biofeedback**

Biofeedback refers to the use of monitoring instruments to detect, amplify and display internal physiologic processes on-line, so that the patient may learn to alter these processes at will. Various types of biofeedback have been used successfully as prophylaxis for migraine.

A report denying the value of biofeedback has also been published, (36) and it is not possible to predict which patients are most likely to benefit. The effect of combining biofeedback with pharmacological therapy has seldom been studied. Biofeedback requires a substantial time commitment on the part of the patient, which may limit its use.

### **Relaxation therapy**

Biobehavioural approach to migraine comprising relaxation techniques (including progressive muscular relaxation, breathing exercises or directed imagery) may or may not reduce the frequency of episodes. Meta-analysis suggests that relaxation is as effective as biofeedback. Where a treatment effect has been reported, it may be enhanced by the addition of prophylactic agents such as beta-blocking drugs. The usual goal of relaxation therapy is the development of long-term prophylaxis rather than the reduction of pain during an acute attack. However, a few patients can abort a slowly evolving migraine using these techniques.

### **Cognitive-behavioural therapy**

Cognitive-behavioural therapy (CBT) is designed to help patients identify and modify maladaptive responses that may trigger or aggravate a migraine headache. The role of emotional reactivity as a trigger for migraine is considered to be pertinent in many patients, who may indulge in self-blame, hopelessness and catastrophic thinking. CBT is based on the principle that anxiety and distress are aggravators of an evolving migraine headache; it attempts to introduce a more adaptive approach as well as to help develop a specific action plan. Stress-management training is often part of this approach. CBT is usually combined with other behavioural therapies but has been shown to be effective on its own. Individual therapist, group and self-help programs have been used, with variable effects. However, as with other behavioural therapies, such factors as availability, cost, patient acceptance and the time commitment required may restrict their use.

### **Psychotherapy**

It is suggested that psychiatric referral of patients with migraine is indicated solely for the presence of a coexistent psychiatric disorder. However, referral to a psychologist to improve stress management may be appropriate in selected cases. The use of psychosocial interventions appears to be of modest value. Psychiatric referral of patients with migraine is not indicated except in the presence of a coexistent psychiatric disorder.

### **Hypnosis**

Hypnosis may reduce distressing sensory input as it does in other pain disorders and may have a placebo effect. It was more effective than prochlorperazine in one

randomized controlled trial, and a meta-analysis of largely uncontrolled studies also suggested benefit when hypnosis was combined with CBT. However hypnosis may have a limited role in the management of migraine in a small subgroup of patients who are both willing and suitable subjects.

### **Physical measures**

Complementary or alternative therapies may be described as interventions that lack either a valid scientific basis or adequate documentation of their effectiveness in the treatment of specific conditions. Chiropractic, osteopathy and acupuncture have been used in the management of migraine but have rarely been subjected to trial, and evidence for the superiority of any one form of cervical manipulation is lacking. However it has been assumed that chiropractic manipulations reduced migraine frequency and severity while aerobic training may reduce the number but not the severity of migraine headaches.

The value and cost-effectiveness of physiotherapy, osteopathy and chiropractic in the management of migraine have not yet been determined. It is therefore inappropriate for a physician to refer patients for such treatments, but patients who are strongly motivated to seek such help need not be dissuaded as long as they are made aware of the uncertain benefits so far recorded.

### **Transcutaneous electrical stimulation and acupuncture**

Transcutaneous electrical stimulation and have been claimed in small series to provide some relief from migraine. Patients who enquire about transcutaneous electrical stimulation and acupuncture should be made aware of the lack of firm evidence as to the benefits and cost-effectiveness of these treatments in the management of migraine

### **References**

- (1) Pryse-Phillips WE. Dodick DW. Edmeads JG. Gawel MJ. Nelson RF. Purdy RA. Robinson G. Stirling D. Worthington I. Guidelines for the non-pharmacological management of migraine in clinical practice. Canadian Headache Society ,CMAJ. 159(1):47-54, 1998 Jul 14.
- (2)Capobianco DJ. Cheshire WP. Campbell JK. An overview of the diagnosis and pharmacologic treatment of migraine. Mayo Clinic Proceedings. 71(11):1055-66, 1996 Nov).
- (3)Welch KM. Pathogenesis of migraine. Seminars in Neurology. 17(4):335-41, 1997.
- (4) (Spierings EL. Symptomatology and pathogenesis of migraine. Journal of Pediatric Gastroenterology & Nutrition. 21 Suppl 1:S37-41, 1995).
- (5) (Amery WK. Migraine and cerebral hypoxia: a hypothesis with pharmacotherapeutic implications. Cephalalgia. 5 Suppl 2:131-3, 1985 May).  
(Young DB. Van Vliet BN. Migraine with aura: a vicious cycle perpetuated by potassium-induced vasoconstriction. Headache. 32(1):24-34, 1992 Jan).  
Lanteri-Minet M. Desnuelle C. Migraine and mitochondrial dysfunction. Revue Neurologique. 152(4):234-8, 1996 Apr.  
(Mauskop A. Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. Clinical Neuroscience. 5(1):24-7, 1998).  
(Machelska H. Cabot PJ. Mousa SA. Zhang Q. Stein C. Pain control in inflammation governed by selectins. Nature Medicine. 4(12):1425-8, 1998 Dec).  
(Leone M. Sacerdote P. D'Amico D. Panerai AE. Bussone G. Beta-endorphin concentrations in the peripheral blood mononuclear cells of migraine and tension-type headache patients . Cephalalgia. 12(3):154-7, 1992 Jun).  
(Genazzani AR. Petraglia F. Facchini V. Facchinetti F. Cephalalgia. 3 Suppl 1:35-41,

1983 Aug).

- (12) Vecsei L. Widerlov E. Ekman R. Kovacs K. Jelencsik I. Bozsik G. Kapocs G. (Suboccipital cerebrospinal fluid and plasma concentrations of somatostatin, neuropeptide Y and beta-endorphin in patients with common migraine. *Neuropeptides*. 22(2):111-6, 1992 Jun).
- (13) Anselmi B. Tarquini R. Panconesi A. de Leonardis V. Perfetto F. Piluso A. Naldi E. Tarquini B. Serum beta-endorphin increase after intravenous histamine treatment of chronic daily headache. *Recenti Progressi in Medicina*. 88(7-8):321-4, 1997 Jul-Aug).
- (14) (Doenicke A. Moss J. Toledano A. Hoernecke R. Lorenz W. Ostwald P. Administration of H1 and H2 antagonists for chemoprophylaxis: a double-blind, placebo-controlled study in healthy volunteers. *Journal of Clinical Pharmacology*. 37(2):140-6, 1997 Feb).
- (15) (Jarisch R. Wantke F. Wine and headache. *International Archives of Allergy & Immunology*. 110(1):7-12, 1996 May).
- (16) Geller EB. Wen PY. Migraine with aura as the presentation of leukemia. *Headache*. 35(9):560-2, 1995 Oct.
- (17) Komatsumoto S. Nara M. [Lower level of endothelin-1 in migraine with aura]. *Rinsho Shinkeigaku - Clinical Neurology*. 35(11):1250-2, 1995 Nov.
- (18) Leira R. [Migraine due to infarct]. [Spanish] *Neurologia*. 12 Suppl 5:16-23, 1997 Dec.
- (19) Ries S. Steinke W. Neff W. Schindlmayr C. Meairs S. Hennerici M. Ischemia-induced migraine from paradoxical cardioembolic stroke. *European Neurology*. 36(2):76-8, 1996.
- (20) Joutel A. Tournier-Lasserre E. Bousser MG. [Hemiplegic migraine]. [Review] [French] *Presse Medicale*. 24(8):411-4, 1995 Feb 25.
- (21) Sanin LC. Mathew NT. Severe diffuse intracranial vasospasm as a cause of extensive migrainous cerebral infarction. Comment in: *Cephalalgia* 1993 Aug;13(4):231 *Cephalalgia*. 13(4):289-92, 1993 Aug.
- (22) Aldrey JM. Castillo J. Leira R. Suarez P. Sobrido MJ. Noya M. [Cerebral hemorrhage and migraine]. [Spanish] *Revista de Neurologia*. 24(126):183-6, 1996 Feb.
- (23) Monteiro JM. Rosas MJ. Correia AP. Vaz AR. Migraine and intracranial vascular malformations Comment in: *Headache* 1994 May;34(5):287
- (24) Narbone MC. Rao R. Grugno R. Pellicano M. A late 'migraine': the only symptom of an intrasellar aneurysm. *Headache*. 37(8):527-8, 1997 Sep.
- (25) Micieli G. Bosone D. Tassorelli C. Zappoli F. Castellano AE. Nappi G. Internal carotid occlusion associated with migraine syndrome: a case study of a 22-year-old female. *Functional Neurology*. 11(1):45-51, 1996 Jan-Feb.
- (26). Verma A. Rosenfeld V. Forteza A. Sharma KR. Occipital lobe tumor presenting as migraine with typical aura Comment in: *Headache* 1997 Feb;37(2):11) *Headache*. 36(1):49-52, 1996 Jan.
- (27) Geller EB. Wen PY. Migraine with aura as the presentation of leukemia. *Headache*. 35(9):560-2, 1995 Oct.
- (28) Niczyporuk-Turek A. [Factors contributing to so-called idiopathic headaches]. [Polish] *Neurologia Neurochirurgia Polska*. 31(5):895-904, 1997 Sep-Oct.
- (29) Galiano L. Montiel I. Falip R. Asensio M. Matias-Guiu J. [Stress as a precipitating factor in migraine]. [Spanish] *Revista de Neurologia*. 23(122):830-2, 1995 Jul-Aug.
- (30) Lunardon M. Barolin GS. [Odontogenic (concomitant) etiology of headache]. [German] *Wiener Medizinische Wochenschrift*. 147(15):365-8, 1997.
- (31). Piorecky J. Becker WJ. Rose MS. Effect of Chinook winds on the probability of migraine headache occurrence. *Headache*. 37(3):153-8, 1997 Mar.
- (32) Peatfield RC. Relationships between food, wine, and beer-precipitated

migrainous headaches. *Headache*. 35(6):355-7, 1995 Jun.

(33)Mavromichalis I. Zaramboukas T. Giala MM. Migraine of gastrointestinal origin. *European Journal of Pediatrics*. 154(5):406-10, 1995 May.

(34) Silberstein SD. Migraine and women. The link between headache and hormones. *Postgraduate Medicine*. 97(4):147-53, 1995 Apr

(35) Szigethy A. Dienes L. The relation between atypical migraine and multiphasic oral contraceptives. *Therapia Hungarica*. 40(4):185-8, 1992.

(36)Weiss HD. Stern BJ. Goldberg J. Post-traumatic migraine: chronic migraine precipitated by minor head or neck trauma Comment in: *Headache* 1992 Mar;32(3):157-8 *Headache*. 31(7):451-6, 1991 Jul.

(37) Duckro PN. Schultz KT. Chibnall JT. Migraine as a sequela to chronic low back pain. *Headache*. 34(5):279-81, 1994 May.

(38)George MS. Is migraine related to the eating disorders?. *International Journal of Eating Disorders*. 14(1):75-9, 1993 Jul.

(39)Olesen J. Thomsen LL. Iversen H. Nitric oxide is a key molecule in migraine and other vascular headaches. *Trends in Pharmacological Sciences*. 15(5):149-53, 1994 May.

(40)(Bic Z. Blix GG. Hopp HP. Leslie FM. In search of the ideal treatment for migraine headache. *Medical Hypotheses*. 50(1):1-7, 1998 Jan).

(41)(Capobianco DJ. Cheshire WP. Campbell JK. An overview of the diagnosis and pharmacologic treatment of migraine. *Mayo Clinic Proceedings*. 71(11):1055-66, 1996 Nov).

## **N2 Migraine Relief Balm**

Migraine and its accompanying symptoms, complications, warning signs and mechanisms have been extensively studied before designing N2 Migraine Relief Balm. The scientific facts about the herbal ingredients of this remedy have been studied very carefully, with evidence of risks and benefits being made available to consumers.

The N2 Migraine Relief Balm cream is composed of completely natural ingredients that act synergistically. It is applied to the site of pain and nasal mucus membrane. It has the ability to penetrate the skin, the mucous membrane and the fine capillary walls to blood circulation to exert abortive and prophylactic effects in migraines and headaches without side effects.

### **The Mechanisms of N2 Migraine Relief Balm Action**

- Regulates the altered immune response common with migraines, to activate the brain opiate system and control the pain.
- Exhibits sedative and anxiolytic action.
- Inhibits the contractile response of the vascular smooth muscles, relieves the vasospasm and improves the brain circulation that is always diminished during migraine attacks.
- Stops the inflammatory response around the neurovascular system of the brain that is responsible for the migraine pain, through its anti-inflammatory action.
- Inhibits platelet aggregation that might cause cerebral occlusion and neurological complications.
- Inhibits the release of serotonin and histamine
- Improves the mitochondrial energy metabolism which plays an important role in migraine pathogenesis.
- Dampens neuronal hyperexcitation, increases tolerance to focal hypoxia, stabilizes platelets and lessens sympathetic outflow.
- Inhibits arachidonic acid (eicosanoid) metabolism.

## Ingredients

- Feverfew, *Tanacetum Parthenium*.
- Balm, *Melissa officinalis*, Labiatae
- Chamomile, *Matricaria recutita*, compositae.
- Jamaican Dogwood, *Piscidia erythrina*, Leguminosae.
- Linden, *Tilia tomentosa* Moench, Tiliaceae.
- Salmon Calcitonin.
- Magnesium.
- Taurine.
- Riboflavin.

### Feverfew, *Tanacetum Parthenium compositae*

Leaves or infusions of Feverfew, *Tanacetum Parthenium*, have long been used as a folk remedy for fever, arthritis and migraine. Feverfew contains a complex mixture of sesquiterpene lactone and non-sesquiterpene lactone, which are inhibitors of eicosanoid synthesis of high potency, and that these biochemical actions may be relevant to the claimed therapeutic actions of the herb (1).

Extracts of the herb Feverfew was found to inhibit human blood platelet aggregation and secretion of serotonin (14C5-HT) induced in-vitro by arachidonic acid and thromboxane and it has been concluded that this may relate to the beneficial effects of Feverfew in migraine (2).

A bioassay was developed to assess the in vitro activity of *T. Parthenium* and its inhibitory effect on the release of serotonin from bovine blood platelets. Inhibition of serotonin release was shown to be significantly correlated with the content of the germacranolide sesquiterpene lactone, parthenolide (3). The structures of two series of sesquiterpene lactones (the 'alpha'-series 11, 12 and 16 and the 'beta'-series 15, 17 and 18) present in the herb Feverfew have been revised in the light of both X-ray analysis and chemical correlation. The activity of some of these metabolites as well as of the major sesquiterpene lactone present in Feverfew, as inhibitors of human blood platelet function has been determined, The possible relevance of this effect to migraine prophylaxis by Feverfew has been concluded by some authors (4).

Studies showed that parthenolide may be a low-affinity antagonist at 5HAT(histamine) receptors.

In vitro experimental studies showed that extracts of fresh leaves of Feverfew caused dose- and time-dependent inhibition of the contractile responses of the smooth vascular muscles. This inhibitory effects was concluded to be due to Parthenolide (6) and its effect on the contractile responses of the smooth vascular muscles could be a factor in the ability of Feverfew extract to reverse the cerebral vasospasm that occurs in migraine attacks and sometimes leads to cerebral ischemia.

Studies showed that the mean frequency of chromosomal aberrations in the Feverfew user group was lower than that in the non-user group both in terms of cells with breaks (2.13% vs. 2.76%) and in terms of cells with all aberrations (4.34% vs. 5.11%). This difference was small and not significant (7), however, this observation merit further studies to see whether the Feverfew has any effect on the chromosomal aberration found in many migraine patients.

Systematic review was made to look at the evidence for or against the clinical effectiveness of Feverfew in migraine prevention. Two independent reviewers read all

articles. Five trials met the inclusion/exclusion criteria. The majority favor Feverfew over placebo (8).

One of the clinical trials was to assess the effectiveness of Feverfew as a prophylactic therapy for migraine; a double-blind placebo controlled crossover trial was conducted for a period of 4 months. Fifty-seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups were treated with Feverfew in the preliminary phase (phase 1), which lasted 2 months. In the second and third phases, which continued for an additional 2 months, a double blind placebo-controlled crossover study was conducted. The results showed that Feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover; a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the Feverfew-treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms. In contrast, shifting the placebo group to Feverfew therapy resulted in a reduction of pain intensity as well as the severity of the linked symptoms (9).

#### **Balm, *Melissa officinalis*, Labiatae**

Rosmarinic acid (RA), a naturally occurring extract from *Melissa officinalis*, inhibits several complement-dependent inflammatory processes (11).

The sedative effects of *Melissa officinalis* extracts was proved by quantitative EEG analysis and by self-assessment (12)

It has been proved by experimental analysis that *Melissa officinalis*, contained high concentrations of total ascorbic acid (approximately equal to 300 mg/100 g FW) and relatively high ascorbate oxidase activity (10.1-21.1 micro mol min<sup>-1</sup> g FW<sup>-1</sup>) (13). Besides acting as an important cofactor in the modulation of the biosynthesis of catecholamine, ascorbic acid (AA) has an active role in the post-translational modification of neuropeptides. AA in modulates the secretion of immunoreactive beta-endorphin (ir-beta EP) (14). As a result of the latter action it stimulate the brain opiate system for controlling the pain.

An important function of Ascorbic acid is that it exerts anti-inflammatory effects, which was proved by studies in man and animals.

In humans, supplementation with ascorbic acid enhances a number of aspects of lymphocyte function (blood cells responsible for the immune response) (15).

In Europe, *M. officinalis* is used to treat nervous disorders. Experimental studies showed that it exhibited significant analgesic activity(16 )

#### **Chamomile, *Matricaria recutita*, compositae.**

It has been found that en-yne dicycloether one of the constituents of the essential oil of *C. recutita*) could partly inhibit protamine sulfate-induced degranulation (histamine release) of mast cells (17).

Chamomil extract also exerts anti-inflammatory activity (18).

Jamaican Dogwood, *Piscidia erythrina*, Legminosae.

Some of the Lectins prepared from the Leguminosae seeds extracts have been tested in vitro against human platelet and has been found to inhibit platelet aggregation (19).

Linden, *Tilia tomentosa* Moench, Tiliaceae

Components prepared from Tiliaceae were found to inhibit the histamine release induced by antigen-antibody reaction (20).

*Tilia* species are traditional medicinal plants widely used in Latin America as sedatives and tranquilizers. Studies showed that it has clear anxiolytic effect (21).

### **Salmon Calcitonin**

The results of salmon Calcitonin treatment on migraine pain have been studied to verify the mechanism by which Calcitonin induces analgesia. The circulating levels of beta-endorphin, ACTH, and cortisol in patients with migraine during the headache-free period increased after the Calcitonin administration and the maximum increase was obtained in beta-endorphin levels (22).

### **Magnesium**

The importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. Magnesium concentration has an effect on serotonin receptors, and a variety of other migraine related receptors and neurotransmitters. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium. Infusion of magnesium results in a rapid and sustained relief of an acute migraine in such patients. Two double-blind studies suggest that chronic oral magnesium supplementation may also reduce the frequency of migraine headaches (23).

### **Taurine**

Taurine (2-aminoethane sulphonic acid), a ubiquitous beta-amino acid is conditionally essential for man. It is not utilized in protein synthesis but found free or in some simple peptides. Derived from methionine and cysteine metabolism, Taurine is known to play a vital role in numerous physiological functions. Some of the roles with which Taurine has been associated include osmoregulation, antioxidation, detoxification and stimulation of glycolysis and glycogenesis (24).

Taurine administered during hypoxia markedly reduced cellular deterioration due to hypoxia and reoxygenation and led to a significantly greater recovery of cellular function following the hypoxic insult. The responsible mechanisms for the beneficial effects were an improvement in osmotic status and calcium homeostasis and an induction in cellular growth despite oxygen deficiency and reoxygenation. Free oxygen radical generation and lipid membrane peroxidation were not reduced by Taurine. Taurine acted as a potent endogenous agent with multifactorial effects against cellular damage due to hypoxia and reoxygenation (25).

Increased tissue levels of Taurine, as well as increased extracellular magnesium, could be expected to dampen neuronal hyperexcitation, counteract vasospasm, increase tolerance to focal hypoxia and stabilize platelets; taurine may also lessen sympathetic outflow. Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine (26).

### **Riboflavin**

It has been found that Riboflavin regulates mitochondrial oxidative metabolism, which may play a role in migraine pathogenesis. Riboflavin (400 mg) was compared to placebo in 55 patients with migraine in a randomized trial of 3 months duration. Riboflavin was superior to placebo in reducing attack frequency ( $p = 0.005$ ) and headache days ( $p = 0.012$ ) (27).

Clinical data in migraine showed altered immune status in patients during migraine attacks (28). Riboflavin participate in the maintainance of glutathione status, that is a

major endogenous antioxidant and is important for lymphocyte replication. It regulates the altered immune status in migraine. Deficiencies in Riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response (29).

### **Vitamin B6 (Pyridoxal Phosphate)**

As supportive treatment, a vitamin B6 (pyridoxal phosphate) substitution appears useful in histamine-intolerant patients, as pyridoxal phosphate seems to be crucial for diamine oxidase activity, an enzyme essential for histamine degradation and which is deficient in those patients. (30).

### **References**

- (1) Sumner H. Salan U. Knight D W. Hoult J R S. INHIBITION OF 5 LIPOXYGENASE AND CYCLOOXYGENASE IN LEUKOCYTES BY FEVERFEW INVOLVEMENT OF SESQUITERPENE LACTONES AND OTHER COMPONENTS. *Biochemical Pharmacology* 43 (11). 1992. 2313-2320.
- (2) Groenewegen W A. Heptinstall S. A COMPARISON OF THE EFFECTS OF AN EXTRACT OF FEVERFEW AND PARTHENOLIDE A COMPONENT OF FEVERFEW ON HUMAN PLATELET ACTIVITY IN-VITRO. *Journal of Pharmacy & Pharmacology* 42 (8). 1990. 553-557.
- (3) Marles, R. J. Kaminski, J. Arnason, J. T. Pazos-Sanou, L. Heptinstall, S. Fischer, N. H. Crompton, C. W. Kindack, D. G. Awang, D. V. C. A bioassay for inhibition of serotonin release from bovine platelets. *Journal of Natural Products*. 1992. 55: 8, 1044-1056.
- (4) Hewlett MJ. Begley MJ. Groenewegen WA. Heptinstall S. Knight DW. May J. Salan U. Toplis D. SESQUITERPENE LACTONES FROM FEVERFEW, TANACETUM PARTHENIUM -ISOLATION, STRUCTURAL REVISION, ACTIVITY AGAINST HUMAN BLOOD PLATELET FUNCTION AND IMPLICATIONS FOR MIGRAINE THERAPY *Journal of the Chemical Society. Perkin Transactions* 1. (16):1979-1986, 1996 Aug 21.
- (5) Weber JT. Oconnor MF. Hayataka K. Colson N. Medora R. Russo EB. Parker KK. ACTIVITY OF PARTHENOLIDE AT 5HT(2A) RECEPTORS. *Journal of Natural Products*. 60(6):651-653, 1997 Jun.
- (6) Barsby, R. W. J. Salan, U. Knight, D. W. Hoult, J. R. S. Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. *Planta Medica*. 1993. 59: 1, 20-25.
- (7) Anderson D. Jenkinson PC. Dewdney RS. Blowers SD. Johnson ES. Kadam NP. Chromosomal aberrations and sister chromatid exchanges in lymphocytes and urine mutagenicity of migraine patients: a comparison of chronic feverfew users and matched non-users. *Human Toxicology*. 7(2):145-52, 1988 Mar.
- (8) Vogler BK. Pittler MH. Ernst E. Feverfew as a preventive treatment for migraine: a systematic review *Cephalalgia*. 18(10):704-708, 1998 Dec.
- (9) Palevitch D. Earon G. Carasso R. FEVERFEW (TANACETUM PARTHENIUM) AS A PROPHYLACTIC TREATMENT FOR MIGRAINE - A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY *Phytotherapy Research*. 11(7):508-511, 1997 Nov.
- (10) Mustafa T. Srivastava K C. GINGER ZINGIBER-OFFICINALE IN MIGRAINE HEADACHE. *Journal of Ethnopharmacology* 29 (3). 1990. 267-274.
- (11) Peake P W. Pussell B A. Martyn P. Timmermans V. Charlesworth J A. THE INHIBITORY EFFECT OF ROSMARINIC ACID ON COMPLEMENT INVOLVES THE C5 CONVERTASE. *International Journal of Immunopharmacology* 13 (7).

1991. 853-858.

(12) Schulz, H. Jobert, M. Hubner, W. D. The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. *N2dicine*. 1998. 5: 6, 449-458.

(13) Yamawaki, K. Morita, N. Murakami, K. Murata, T. Contents of ascorbic acid and ascorbate oxidase activity in fresh herbs. *Nippon Shokuhin Kogyo Gakkaishi = Journal of the Japanese Society for Food Science and Technology*. 1993. 40: 9, 636-640.

(14) (Yang Z. Copolov DL. Lim AT. Ascorbic acid augments the adenylyl cyclase-cAMP system mediated POMC mRNA expression and beta-endorphin secretion from hypothalamic neurons in culture. *Brain Research*. 706(2):243-8, 1996 Jan 15).

(15) Grimble R F. Effect of antioxidative vitamins on immune function with clinical applications. *International Journal for Vitamin & Nutrition Research* 67(5). 1997. 312-320.

(16) Soulimani, R. Younos, C. Fleurentin, J. Mortier, F. Misslin, R. Derrieux, G. Study of the biological activity of *Melissa officinalis* on the mouse central nervous system in vivo and on rat duodenum in vitro. [French] *Plantes Medicinales et Phytotherapie*. 1993. 26: 2, 77-85.

(17) Miller, T. Wittstock, U. Lindequist, U. Teuscher, E. Effects of some components of the essential oil of chamomile, *Chamomilla recutita*, on histamine release from rat mast cells. *Planta Medica*. 1996. 62: 1, 60-61.

(18) Loggia, R. della. Carle, R. Sosa, S. Tubaro, A. Evaluation of the anti-inflammatory activity of chamomile [*Chamomilla recutita*] preparations. *Planta Medica*. 1990. 56: 6, 657-658.

(19) Bhunia C. Mukherjee M. Chatterjee P C. Some observations on human platelet deaggregation by lectins. *Indian Journal of Physiology & Allied Sciences* 49(4). 1995. 208-211.

(20) Yoshikawa M. Shimada H. Saka M. Yoshizumi S. Yamahara J. Matsuda H. Medicinal foodstuffs: V. Moroheiya: (1): Absolute stereostructures of corchoionosides A, B, and C, histamine release inhibitors from the leaves of Vietnamese *Corchorus olitorius* L. (Tiliaceae). *Chemical & Pharmaceutical Bulletin (Tokyo)* 45(3). 1997. 464-469.]

(21) Viola H. Wolfman C. Stein M L D. Wasowski C. Pena C. Medina J H. Paladini A C. Isolation of pharmacologically active benzodiazepine receptor ligands from *Tilia tomentosa* (Tiliaceae). *Journal of Ethnopharmacology* 44 (1). 1994. 47-53.

(22) (Ustdal M. Dogan P. Soyuer A. Terzi S. Treatment of migraine with salmon calcitonin: effects on plasma beta-endorphin, ACTH and cortisol levels. *Biomedicine & Pharmacotherapy*. 43(9):687-91, 1989).

(23) (Mauskop A. Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. *Clinical Neuroscience*. 5(1):24-7, 1998).

(24) Stapleton P P. O'Flaherty L. Redmond H P. Bouchier Hayes D J. Cornell Univ. Med. Coll., P.O.Box 177, 1300 York Ave., New York, NY 10021, USA. Host defense: A role for the amino acid taurine? *Jpen: Journal of Parenteral & Enteral Nutrition* 22(1). 1998. 42-48.

(25) Michalk D V. Wingenfeld P. Licht C. Protection against cell damage due to hypoxia and reoxygenation: The role of taurine and the involved mechanisms. *Amino Acids (Vienna)* 13(3-4). 1997. 337-346.

(26) McCarty MF. Magnesium taurate and fish oil for prevention of migraine. *Medical Hypotheses*. 47(6):461-6, 1996 Dec.

(27) Schoenen J. Jacquy J. Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis: A randomized controlled trial. *Neurology* 50(2). 1998.

466-470.

(28)Covelli V. Maffione A B. Munno I. Jirillo E. ALTERATIONS OF NONSPECIFIC IMMUNITY IN PATIENTS WITH COMMON MIGRAINE. Journal of Clinical Laboratory Analysis 4 (1). 19.

(29) Grimble R F. Effect of antioxidative vitamins on immune function with clinical applications. International Journal for Vitamin & Nutrition Research 67(5). 1997. 312-320.

(30) (Jarisch R. Wantke F. Wine and headache. International Archives of Allergy & Immunology. 110(1):7-12, 1996 May).

The excruciating stabbing pain of cluster headache arrives suddenly, lasts from 15 minutes to several hours and comes in "clusters" of headaches extending anywhere from a week to a year. Most medications work too slowly to treat cluster headaches, and the pain is too severe to respond to over-the-counter medications. There are some preventive and treatment procedures available, however.

#### **Treating Cluster Headaches**

The key to treating cluster is fast relief. Oxygen and prescriptions that can be absorbed quickly are the first line of defense.

- **Oxygen** Breathing pure oxygen for up to 15 minutes provides considerable relief to most cluster headache sufferers. Raising blood oxygen levels relaxes constricted blood vessels, providing quick relief. It is the most common treatment for cluster headache.
- **Prescription Medications** Ergotamine tartrate (also used in migraine treatment) taken under the tongue to speed absorption is used to treat existing headaches, as is an injection of sumatriptan (also used in migraine treatment). Nasal applications of lidocaine, a local anesthetic, have shown promise in several studies. Nasal applications of butorphanol, a powerful painkiller, have also successfully treated the pain of cluster headache.

#### **Preventing Chronic Cluster Headaches**

Several prescription medications have been successful in treating cluster headaches during a cluster period.

- **Methysergide** Methysergide, which is also used to prevent migraine, is believed to prevent cluster headaches by constricting blood vessels and reducing inflammation. It has serious side effects, however, and can be used only for brief periods, generally for the length of a cluster period.
- **Corticosteroids** Corticosteroids, particularly prednisone and methylprednisolone, are used for short-term cluster therapy, due to potential serious side effects with longer-term use.
- **Lithium Carbonate** Lithium carbonate has been found to be effective in treating chronic cluster headaches, possibly due to its ability to its impact on the electrical system within the brain.
- **Calcium Channel Blockers** Calcium channel blockers, typically used in treating cardiovascular conditions, are used to treat cluster headache episodes and chronic cluster headaches. They may work by blocking the release of neurotransmitters (chemicals in the brain that stimulate nerve cells) involved in causing pain.

Migraine can induce a host of serious physical conditions: strokes, aneurysms, permanent visual loss, severe dental problems, coma, and even death. Furthermore, Migraine can lead to ischemic stroke, and stroke can be aggravated by, or associated with, the development of Migraine. Twenty-seven percent of all strokes suffered by persons under the age of 45 are caused by Migraine, which is why seeking a Migraine medical specialist and exploring all the possible treatment options now available is the most prudent action a Migraineur can take today.

### **PREVENTIVE THERAPY**

First, prophylactic, medications are prescribed to prevent or reduce the number of attacks in patients who experience frequent Migraines, typically two or more per month. In general, these medications act over time to prevent blood-vessel swelling; however, they do not treat the Migraine-associated symptoms and are non-selective. Many sufferers using preventive treatments will still have to take attack-aborting medications to relieve pain and other symptoms. Examples of conventional preventive therapy include: beta-blockers, antidepressants (for their effect on serotonin, not depression), calcium channel blockers, methysergide (potential serious side-effects), and Divalproex Sodium. Examples of non-pharmacological preventive therapy include: vitamin B2 and magnesium supplements, Tanacetum Parthenium (Feverfew Leaf), and Petasites Hybridus (Butterbur root)(For more information on Petasites Hybridus, refer to interview on page 46).

Third, attack-aborting medications are used to relieve the severity and/or duration of Migraine and associated symptoms. In general, most attack-aborting medication should be taken as early as possible in an attack. Certain cerebral vasoconstrictor abortive agents are designed specifically for Migraine. They may be administered by subcutaneous, oral, rectal, or intramuscular means. These medications include ergotamine tartrate, dihydroergotamine, sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan, and isometheptene mucate. An excellent non-vasoconstrictive abortive agent is butorphanol tartrate offered in a patient-administered injection and now a nasal spray. In an ER (Emergency Room) environment, narcotic injections, usually taken with promethazine or hydroxyzine for nausea, can offer a non-cerebral vasoconstrictive option if all the above fail or are contraindicated. An off-label use of lidocaine had had some recent success too. A non-drug abortive approach has been the use of 1g magnesium sulfate through a slow intravenous push during an acute migraine with 85% effectiveness.