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A REVIEW STUDY ON MIGRAINE

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ABSTRACT

Migraine is a common disabling condition mostly in adult population and shows female predominance. Unilateral throbbing type moderate to severe intensity headache is a common manifestation of the migraine though it may present with varied presentation. Even though there is rapid advancement in the knowledge of path physiology leading to development of novel treatment, evidence based treatment for migraine specially in developing nations is still unmet needs.[1] Migraine, a significantly disabling condition, is treated with acute and preventive medications. However, some individuals are refractory to standard treatments. Although there is a host of alternative management options available, these are not always backed by strong evidence. In fact, most of the drugs used in migraine were initially designed for other purposes. Whilst effective, the benefits from these medications are modest, reflecting the need for newer and migraine-specific therapeutic agents. This article reviews the pathophysiology, clinical features, diagnosis and evidence based approach for management of migraine.[2]

INTRODUCTION

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache.[1] Amongst these, the migraine headache is ubiquitous, prevailing, disabling and essentially treatable, but still under-estimated and under-treated.[2]

Migraine has a lifetime prevalence of around 15% of the population, affecting women (18%) more than men (8%).[3] It has been termed the seventh disabler due to its considerable impact on the quality of life (QOL) of patients.[4] A subset of patients progresses from having episodic migraine (EM) to chronic migraine (CM), the latter affecting 1%-2% of the population. It has been termed the seventh disabler due to its considerable impact on the quality of life (QOL) of patient.[5]

A subset of patients progresses from having episodic migraine (EM) to chronic migraine (CM), the latter affecting 1%-2% of the population.[6] This is a gradual process, initially changing from low-frequency EM to a high-frequency stage and eventually to CM.[7] CM is defined as a headache on ≥15 days per month for ≥3 months, of which ≥8 days meets the criteria for migraine with or without aura or responds to migraine-specific treatment.[8] Migraines have significant psychological, social, and economic impacts. Around 75% of patients experience impaired functioning during an attack and around half of them require help from others.[9]

PATHOPHYSIOLOGY

1. Vascular and Neurogenic theories

The cause of migraine headache is still not completely understood. Historically, two independent theories, the vascular theory and the neuronal theory, explaining the etiology of migraine headache were proposed. The vascular theory was introduced by Thomas Willis where he recognized that “all pain is an action violated” and argued the pain from headache is caused by vasodilatation of the cerebral and meningeal arteries. The alternative neurogenic theory focuses on the cause of migraine pain and is currently linked to activation of the trigeminovascular system.[10]

2. Cortical Spreading Depression

The alternative and widely accepted theory suggests that cortical spreading depression (CSD), a wave a neuronal hyperactivity followed by an area of cortical depression, accounts for the aura and that the headache depends on activation of the trigeminovascular pain pathway. In Chronic Migraine (CM), atypical pain processing, central and peripheral sensitization, cortical hyper excitability, and neurogenic inflammation all have a role to play. Cortical hyper excitability is thought to be another major factor participating in transformation of EM to CM.[3]

3. Cortical Hyperexcitability in Migraine

As is the case for many episodic disorders, the trigger for migraine attacks has not been precisely identified. Many clinical factors such as diet, alterations in sleep and stress are known to predispose individuals to attacks. It is particularly intriguing that photic stimulation can trigger both migraine attacks and epileptic seizures. How these factors bring on a migraine attack is not known. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraineurs. The techniques that have been used to generate this evidence include psychophysical studies; visual, auditory, and somato sensory evoked potentials; magneto encephalography; and transcranial magnetic stimulation of the motor cortex. In all cases, there is evidence of heightened reactivity between migraine attacks.[11]

CLINICAL FEATURES

Women have an 18% risk of having a migraine compared to a 6% chance in men. The higher prevalence in women is typically attributed to hormonal fluctuations especially estrogen. Migraines typically begin during puberty or between the ages of 35 and 45 years.[12]

Migraine has two major subtypes: Migraine with aura which is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, and depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptom such unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, during headache nausea and/or vomiting or photophobia and phonophobia can occur.[13]

DIAGNOSIS

The International Headache Society criteria are very helpful in the diagnosis of migraine. These criteria can be too restrictive and therefore may be interpreted flexibly by experienced clinicians. There are two main types of migraine: migraine without aura (MO), and migraine with aura (MA). Many people have both; MO is at least three times as common as MA. Note that family history, trigger factors, and treatment response have no additional diagnostic value.

Migraine without aura

Formerly called common migraine, the diagnosis of MO is suggested by a history of episodic disabling headache lasting between a few hours and a few days, accompanied by gastrointestinal symptoms or by heightened special senses. The International Headache Society criteria may be fulfilled when pain is mild or generalised: it does not have to be severe or unilateral. It is unusual to be able to distract oneself from MO with exercise or hard work, in contrast to TTH. The frequency and periodicity of migraine is important: migraine-like headache more than twice every week is unlikely to be MO alone, but it may be MO complicated by MOH and/or TTH. This is common in patients referred with "intractable migraine" or "status migrainosus".

Migraine with aura

In MA, formerly called focal or classical migraine, the aura evolves over time, usually many minutes; one aspect of the aura improves while another is deteriorating. Visual aura usually leads to easy diagnosis. Auras affecting sensation, movement, cognition, vestibular function, or consciousness may be difficult to distinguish from thromboembolism, or from epilepsy (especially occipital seizures). People presenting with recent onset MA often give a longer history of MO, mistakenly diagnosed as "bilious attacks", "sinusitis", or "normal headaches". Visual symptoms are positive (seeing things which are not there), homonymous and binocular, though some patients insist that visual aura is monocular, raising the possibility of retinal origin. Aura typically precedes migraine headache, though can occur at any time in relation to pain. Aura is not always contralateral to pain. Migraine aura without headache is common, especially in middle age: a flurry of MA episodes without headache often triggers referral fearing transient ischaemic attacks (TIA). Thromboembolism may be accompanied by headache (especially with vertebral or carotid dissection, in which pain usually precedes impairment), but is distinguished from MA by abrupt, non-evolving associated impairment, confined to a single vascular territory. MA is much more common than TIA at all ages: around 40 years of age, MA is about 2500 times more prevalent than TIA, and is still about 15 times more common at 70.[14]

Take a detailed history

Accurate history taking is vitally important in the diagnosis of migraine. It is important to give patients time to describe their attacks fully (it may well be the first time that anyone has listened to them talk about their pain), and also to clarify the history with specific questions

aimed at filling out the gaps in what the patient has told you spontaneously. The diagnosis of migraine lies in the history, and that the purpose of examination is primarily to look for other problems that may be exacerbating an underlying tendency to migraine. This may in most cases be restricted to fundoscopy, inspection and palpation of the head and neck structures, and a brief screening cardiovascular and neurological examination, unless, on the basis of the history, serious intracranial or systemic pathology is suspected.

It is useful to begin with questions about the pattern of the pain, including when, and how headaches begin; whether they are continuous, episodic or (as is often the case in chronic migraine) continuous with episodic exacerbations; the duration of episodes or exacerbations; and if there are any triggers or exacerbating factors. After this questions can be asked about the nature of the pain, such as its location, character, severity (using a verbal report scale of 0–10, where 0 is no pain and 10 is the worst imaginable). Then the presence of associated symptoms that accompany the pain should be ascertained; these include symptoms that precede attacks suggesting a prodrome or aura, such as excessive tiredness or energy, yawning, excessive urination, neck stiffness, vertigo, visual or sensory disturbances; symptoms that accompany attacks such as nausea, sensitivity to lights, noises, smells, touch, or movement; and symptoms suggesting alternative primary or secondary headache disorders such as eye watering, conjunctival injection, nasal congestion, ptosis, eyelid oedema, sweating, agitation, fever, neck stiffness or rash.

It is also important to ask questions about the patient's previous medical history (including questions about depression, anxiety and sleep disorders), current nonheadache medications, allergies, family history (especially of headache), and social history (including occupation, smoking status, and levels of alcohol and caffeine consumption).[15]

TREATMENT

- **Non Pharmacological treatment**

Migraine is the most common type of headache leading patients to consult a physician. For most patients, a combination of non-pharmacologic and pharmacologic interventions should be used to control the headache disorder. Many of the non pharmacologic 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 pharmacologic treatment or may provide an alternative to it. William EA. et al

has developed guideline for the non pharmacologic management of migraine in clinical practice which includes the application of cold or pressure to the head, reduction of activity and of sensory input in a quiet or dark environment and attempts to sleep and are supplemented by the use of pharmacologic therapies when not adequate in isolation. Relaxation therapy, hypnosis, transcutaneous electrical stimulation, acupuncture, and occipital or supraorbital nerve blockade have also been used in the acute situation and are considered. Other specific treatment includes biobehavioral measures which includes Biofeedback, Relaxation therapy, Cognitive-Behavioral therapy, Psychotherapy, Hypnosis and physical measures such as chiropractic, osteopathy and physiotherapy.[16]

- **Pharmacological treatment**

The acute management of migraine attacks aims at achieving rapid pain relief. Several drugs have been shown to be effective in placebo-controlled trials. In many patients, simple analgesics are usually sufficient for controlling pain during an attack. However, some individuals have a suboptimal response to analgesics and can be offered other medications such as 5-HT1B/1D receptor agonists, which are migraine-specific. Opiates should be avoided as far as possible for the treatment of acute migraines.

Analgesics

Analgesics are the drugs of first choice for migraines of mild or moderate severity. Aspirin[17,18], paracetamol[19], ibuprofen[20], naproxen[21], diclofenac[22], phenazone[23], and tolfenamic acid[24] have all demonstrated efficacy in placebo-controlled trials. Paracetamol has the advantage of causing less gastric irritation. Ibuprofen is probably the most widely used nonsteroidal anti-inflammatory drug (NSAID) and, while is at least as effective as aspirin, it may also cause less gastric side effects. Diclofenac has a rapid onset of action whilst naproxen, which has a longer half-life, has a slower onset of action. Effervescent acetylsalicylic acid has a faster onset of action (depending on the formulation) than regular tablets and has shown efficacy similar to that of sumatriptan 50 mg. In addition, the combination of aspirin, paracetamol, and caffeine is more effective than either drug taken alone or in combination without caffeine.[25] Valdecoxib, a COX-2 inhibitor, has been shown to be effective for acute migraine treatment.[26] These analgesics should be taken as soon as the headache starts. The concomitant use of an antiemetic is recommended to treat nausea[27]; also antiemetics are believed to improve the absorption of analgesics.[28] There is no evidence, however, that the combined use of an antiemetic with an analgesic is more effective

than the analgesic alone. To avoid medication overuse headache (MOH), patients should use these analgesics as infrequently as possible and on less than 15 days per month.

5-HT1B/1D Receptor Agonists (Triptans)

The so-called "triptans" are considered to be the gold standard symptomatic treatment. They are considered as a second line when patients have inadequate response to simple analgesics. Seven triptans, all of which have strong evidence of efficacy, are marketed, namely, sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. They are thought to act via three potential mechanisms: cranial vasoconstriction[29], peripheral neuronal inhibition[30], and inhibition of transmission through second-order neurons of the trigeminocervical complex.[31] However, they differ in terms of their pharmacodynamics and pharmacokinetic properties and are therefore expected to exhibit differences regarding their efficacy and tolerability profile. With the exception of naratriptan, the oral triptans provide headache relief within 30 to 60 minutes. Response rates at 2 hours range from 50% to 80%, with 20% to 50% of patients being pain-free. Triptans are associated with medication overuse headaches, but the withdrawal is shorter in duration and less in severity than other patients using ergots and other analgesics. Contraindications for the use of triptans are untreated arterial hypertension, coronary heart disease, Raynaud's disease, history of ischaemic stroke, pregnancy, lactation, and severe liver or renal failure. Triptans should not be taken on less than 10 days per month to avoid the emergence of MOH.[32]

Flunarizine

Flunarizine is a calcium channel antagonist, has moderate action as antihistaminics, serotonin receptor blocking and antidopaminergic. The starting dose is 5mg/day for initial 21 days which is increased to 10mg/day after it. Common side effects noted in flunarizine are drowsiness, depression and weight gain.[33]

Beta blockers

Even though Beta blocker like propranolol, atenelol, metoprolol and bisoprolol had shown the efficacy against the migraine headache, most evidences demonstrate maximum efficacy in favor of propranolol. The staring dose of is 20 mg/day. This must be increased slowly since adverse effects can occur prior the prophylactic effects and impair patient compliance. The prophylaxis should be maintained for a minimum of 3 months before efficacy evaluation. The successful prophylactic treatment should be continued for 12 months. Thereafter,

discontinuation can be attempted but drug doses should be decreased slowly, in order to avoid tachycardia or hypertension.[34]

Tricyclic antidepressants

Among the tricyclic antidepressant, amitriptyline hydrochloride is the choice of drug for migraine management. The starting dose is 10 mg can be titrated up to 75 mg to achieve the maximal therapeutic effect. Response to these agents of usually within 4 weeks of starting of treatment. Dry mouth, weight gain, postural hypotension, drowsiness are common side effects of these agent.[35]

Divalporex Sodium

Divalporex sodium reduces the frequency of migraine attacks compared to the placebo (P-≤0.05). Starting dose of divalporex Sodium is 500 mg/day can go up to 1500mg/day. nausea, dizziness and tremor are common side effects of it.[35]

Topiramate

Topiramate works by inhibition of glutamatergic excitatory amino acid transmission, inhibition of voltagegated calcium channels, enhancement of GABA-evoked currents, fast Na+ channel blockade, and carbonic anhydrate inhibition.[36]

Ergot Derivatives

Placebo-controlled trials addressing the efficacy of ergot derivatives are scarce, although experience with their use is not lacking, having been available for many years. Data from comparative trials have shown ergot derivatives to be inferior to triptans. Ergotamine tartrate and dihydroergotamine (DHE) are the only two compounds with sufficient evidence of efficacy. Some patients who have an inadequate response to triptans will benefit from DHE, the preferred ergot derivative. It is available as a nasal spray and can also be injected subcutaneously or intramuscularly. The main side effects include nausea, vomiting, paraesthesia, and ergotism. It is contraindicated in cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, and pregnancy and lactation.[32]

PREVENTION OF MIGRAINE

Lifestyle management Management of lifestyle can appear to be very helpful, though evidence is largely anecdotal. Regularity of biorhythms is the key. The avoidance of relative

hypoglycaemia, with a regular, fibre containing diet is probably the most helpful strategy. Dietary exclusion is rarely helpful, and should be abandoned if ineffective. Change in sleeping times at weekends and irregular shift work may usefully be avoided, as is the abrupt let-down from stress. Trigger factors often summate—for example, at times of international travel.

Alternative therapies

These are often acceptable to patients though are rarely evidence based. Large doses of vitamin B2, and magnesium, may be effective with several months' latency to benefit. Manipulative treatments seem to be helpful for soft tissue pain or tenderness. Homeopathy is ineffective. Acupuncture probably has only an acute analgesic effect.

Hormones and migraine

Migraine is more common in women, the sex difference beginning at puberty. Menstruation is a migraine trigger in 10% of women with migraine. This is often overestimated by the patient: true menstrual migraine can be diagnosed only after examining a few months of the headache and menstrual diary. The oestrogen-containing contraceptive pill (OCP) may lead to an improvement, but this ameliorating effect is then lost during the pill-free week. Tricycling the contraceptive pill, and using transdermal oestrogen, can be helpful. Migraine, especially MA, is possibly an independent risk factor for stroke, though confidence intervals of case–control studies are wide, making risk assessment difficult. MA is a relative contraindication to the OCP. Intrauterine devices and progesterone only contraceptives affect neither migraine nor stroke risk, so are preferable to OCPs for women with any form of migraine. Migraine typically improves during the second and third trimesters of pregnancy, though can be troublesome in the puerperium. The climate and menopause are associated with worsening of migraine, as often as with improvement. Transdermal, not oral, hormone replacement therapy is often helpful, though high doses may trigger MA.[37]

CONCLUSION

Migraine is common cause of headache, early diagnosis and prompt treatment of migraine enhances the quality of life; prevent conversion of episodic migraine to chronic migraine. It is vital to make a diagnosis and ensure that any concomitant medical or psychological conditions are treated in parallel with interventions aimed at reducing the biological tendency to headaches. It is also important to set patients' expectations as to what can be achieved. The tendency to migraine is genetic, and will rise and fall in people's lives; migraine cannot be

'cured' in any sense. It can be managed, however, and often very successfully following the lines outlined in this article.

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