Migraine

Diagnosis and treatment

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BACKGROUND Migraine is a genetically determined recurrent pain syndrome accompanied by neurological and gastrointestinal features, involving interaction of external triggers and internal pathophysiology and the cause of considerable disability to sufferers.

OBJECTIVE This article discusses the pathophysiology and diagnosis of migraine and outlines a patient centred approach to management.

DISCUSSION Establishing the correct diagnosis is essential for success. Discussing a structured approach ('a puff, a gust, and a gale') in the recognition of a developing migraine attack can assist patients in appropriate self management. A 'stepped care' approach to management of acute migraine involves initial nonpharmacological methods followed by antiemetics and simple analgesics or nonsteroidal anti-inflammatory medications. Moderate episodes are treated with antiemetics and migraine specific medications. More severe migraines often require parenteral medications and sometimes intravenous fluids. Prophylaxis involves adoption of a chronic disease model, identifying and avoiding triggers and causative factors for migraine, nonpharmacological methods such as dietary modification and biofeedback, and for some patients, pharmacological prophylaxis.

Migraine is a feature of the human condition that has long intrigued and exasperated both sufferers and their physicians. In the USA and Europe the condition affects about 12% of the population[1] and is the most common of the disabling primary headache syndromes.[2]

Migraine is a genetically determined recurrent pain syndrome accompanied by neurological and gastrointestinal features, involving interaction of external triggers and internal pathophysiology. Migraine is currently considered a complex interplay of different processes such as an alteration of pain and sensory input, increased sensitivity of the cortex leading to aura phenomena, central pain facilitation, neurogenic inflammation and brainstem nociceptor sensitisation.[3] It affects mainly the brainstem and diencephalon[4] and is an example of abnormal amplification and sensitisation of pain pathways in these regions.

DC-magnetoencephalography in migraineurs has demonstrated increased amplitudes of slow cortical potentials, representing hyperexcitability of cortical networks.[5] In this context, it has been shown that antiepileptic medication such as sodium valproate and topiramate may beneficially affect migraine by inhibition of voltage gated sodium channels, inhibition of high voltage activated calcium channels, or by promoting inhibition by gamma-aminobutyric acid (GABA).[6] There is increasing recognition of the similarity in pathophysiology between migraine and epilepsy.[7]

The triptans exert their effect in part by producing selective carotid vasoconstriction via 5-HT1B receptors and by pre-synaptic inhibition of the trigeminovascular (sterile) inflammatory response via 5-HT1D/5-ht1F receptors.[8] With these new insights into the pathophysiology of migraine, the current goal in treatment is to modulate neurotransmitter systems rather than to affect intracranial vessel tone.[9]

There is evidence that the condition is progressive in a significant number of sufferers. In about 4% of the American population, a gradual transformation from episodic migraines into a chronic daily headache syndrome punctuated by peaks of acute migrainous features takes place.[10] This process is characteristic of the phenomena of progressive 'central and peripheral sensitisation'.[8,11] These clinical changes are

mirrored by structural changes such as iron deposition in the periaqueductal grey matter, the emergence of hyperintensities on magnetic resonance imaging (MRI) representing cerebral ischemic lesions which in turn may lead to cognitive and visual impairment, and in some cases, stroke.[12] Migraine therefore has the potential to develop into a disabling chronic pain syndrome.

Management of the patient

To manage migraine effectively, physicians must have more than just a prescribing knowledge of the latest triptans. They must be able to make the diagnosis of migraine with confidence and understand the pathological basis for this primarily neurological condition, while grasping the patient's social, psychological and medical situation. The practitioner must have a sound understanding of the different modalities of treatment for both acute attacks and the prevention of attacks in order to craft the best management plan for the individual.

Making the correct diagnosis

Establishing the correct diagnosis is essential for success. Clinicians sometimes ignore the presence of a dull, daily background headache of 'transformed' migraine, the short duration of cluster headaches, and the pain characteristics and lack of associated features of tension type headaches, and term these conditions 'migraines'. These mistakes inevitably lead to ineffective management.

Criteria for diagnosis

The International Headache Society[2] diagnostic criteria for migraine are:

- the attack should be episodic
- the duration of the attack should not be shorter than 4 hours and not longer than 72 hours (paediatric migraines may be shorter, and occasionally migraines may be more prolonged)
- the headache itself should be characterised by at least two of the following:
  - the headache should be unilateral
  - the quality of the pain should be throbbing
  - the headache should be aggravated by movement, and
- the pain itself should be in the moderate to severe range
- one of the following characteristics should be present: either nausea/vomiting, or both photophobia and phonophobia.

If some or all of the main features for migraine are present, an additional 'clustering ' of associations often helps to clinch the diagnosis with confidence (*Table 1*).

Prodrome

About 20% of migraineurs will experience prodromal changes of hypothalamic involvement before the actual aura or pain commences. These can be a craving for food, thirst, and altered emotional states.

Aura

About 25% of migraineurs have either visual or sensory phenomena that are repeatedly associated with migraine. The aura usually lasts between 5 minutes and 1 hour, however prolonged auras may occur. Sensory symptoms are less frequent than visual ones and usually consist of numbness and 'pins and needles' paraesthesiae of the upper limbs or around the mouth. Visual auras may take the form of central loss of vision (central scotoma) or a hemianopia. Often there are scintillations that may occur separately or as part of the shimmering edge of the scotoma. Some migraineurs experience zig-zag formations (fortification spectra) with double or triple outlines, and in some, the visual phenomena will move slowly across the visual field; this is almost pathognomonic of migraine. The presence of a typical aura – as an isolated phenomena without the headache – indicates a migraine. This is particularly important in the elderly where the headache of migraine is often absent, causing diagnostic confusion with transient ischaemic attacks. The aura of migraine is distinct, and quite different from vascular phenomena such as amaurosis fugax and other episodic conditions such as epilepsy.

Management of the acute attack

Awareness of patient expectations is essential. Two independent surveys[1] have found that the following results were most desired from acute therapy:

- complete relief of pain
- rapid onset of pain relief
- no recurrence of pain, and
- lack of adverse reactions.

Although it is difficult to come up to these expectations in every case, certain guidelines are useful in getting optimal results.

Early treatment

The earlier treatment is initiated, the better. Although not proven in randomised controlled trials, there is anecdotal evidence for this.[13] The recognition of a migraine attack should prompt the early use of medication, even as early

as in the aura phase (except in the case of triptans, which are not effective at this stage).

Prophylactic treatment in severe cases

Prophylactic medication often results in milder and less stubborn acute attacks, so – in difficult cases – the relatively early commencement of prophylactic measures is useful. Prophylaxis can be attenuated later as the condition comes under control.

Early assessment of the patient's needs

Aggressive early management can reduce anxiety produced by loss of work hours and family disruption, and in fact may prevent disease progression.

A strategic approach to management

Explain the model

This consists of a description of triggers interacting with centrally situated migraine 'centres' to produce a cascade of events resulting in vascular reactivity and resultant pain. This is useful in allaying fears of what is often a devastating medical event.

A structured approach

Discuss a structured approach ('a puff, a gust, and a gale') in the recognition and management of a developing migraine attack. Ask the patient to be aware of levels of pain – as objectively as possible – to allow a 'stepped care' approach to management.

Explain the use of medications

Patients need to share a rational approach to management. Simple nonmedical measures are often effective in aborting an attack. If these fail, there are two main types of medication. The first group contains disease nonspecific medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and simple analgesics, while the second contains disease specific drugs such as ergot derivatives.[2] The first group is most useful early while the migraine is still developing and not severe ('a puff of wind'), while the second group is accessed when the condition escalates into a full-blown migraine ('a gust of wind'). When there is a 'gale' blowing, medical advice should be sought. All important possible side effects from the medication must be discussed.

Acute treatment cascade

Stage 1 (a puff)

The patient is aware that a migraine is commencing but the level of pain lies between 1 and 2 on a scale of 0–10.The patient applies nonmedical measures such as lying or sitting down in a dark room with a cold cloth on the forehead, and some form of relaxation technique. If these measures are not effective, a combination of antiemetics, simple analgesics, and NSAIDs can be used (*Table 2*).

Whether or not there is nausea, it is often useful to 'prime' the analgesic or NSAID by administration of an antiemetic 5 minutes earlier. This relieves the gastric stasis that sets in at the onset of a migraine attack, hindering absorption of medication. Double blind controlled clinical trials have shown the efficacy of simple analgesic combined with an anti-emetic.[13] Apart from nausea and abdominal irritation, side effects rarely occur. Rectal administration of NSAIDs, analgesics or antiemetics in cases of severe or early nausea may be useful.

Stage 2 (a gust)

When the level of pain is 3 or more on a scale of 0–10, the use of antiemetics followed by migraine specific medications such as ergotamine or combinations of ergotamine with caffeine, should be considered. The combination of antiemetic, ergot derivative, NSAID and an analgesic such as codeine or a codeine-paracetamol combination is useful. At this stage, as an alternative to the above, the use of triptans may be considered.

Triptans

There is a plethora of triptans available,[2,9] but they are costly and there is significant frequency of headache recurrence (30%).[14] Moreover, on a number needed to treat basis, they are only marginally more effective than the combination of an antiemetic with simple analgesics.[14] In a double blind placebo controlled study,

Table 1. Additional common features of migraine

- Positive family history
- More common in females
- Onset in childhood or adolescence
- Stereotyped triggers
- Headaches triggered by a time in menstrual cycle, or change in pattern with pregnancy
- Presence of prodome
- Presence of aura
- Hypersentivity to sensori stimuli (noise, light, smell, touch)
- Bilateral headache with side shift during and between episodes
- Prompt response to specific antimigraine preparations

tolfenamic acid was shown to have comparable efficacy to oral sumtriptan.[15] Zolmitriptan has the potentially lowest number needed to treat, while naratriptan is the least potent.[14] Sumatriptan is the only injectable 5-HT1B/D agonist, and although expensive, this format of administration is useful in certain circumstances where there is early vomiting, where oral medications are not well tolerated, or where there is very rapid onset of migraine.[2] The triptan nasal sprays are available in Australia and have few if any advantages over tablet form.[2] However, the nasal route may be useful in patients with early, severe nausea.[2] Serious cardiovascular side effects from triptan use is extremely low, but their use is not advised in patients with known coronary heart disease.[14] There are wide individual variations in response to triptans, and for certain patients they remain the preference.

Stage 3 (a gale)

This is the stage where simple nonpharmacological measures, nonspecific drugs, and disease specific drugs have been ineffective. This is the stage where medical help should be sought and parenteral medications and sometimes intravenous fluids considered (*Table 2*).

- Outside hospitals and emergency departments, narcotics should not be used. In the inpatient setting for very severe cases of migraine, narcotics such as pethidine are used, but this is under controlled circumstances. Drug dependency (either psychological or physical) is a real danger, and very difficult to break in general practice
- If feasible, the patient should be in a dark, quiet environment
- Avoid early discharge home as this frequently results in re-presentation.

Table 2. Useful medications for acute migraine

Nonmigraine specific analgesics
Aspirin (900 mg)
Paracetamol (1000 mg or as required)
Naproxen (500–1000 mg or as required)
Ibuprofen (400–800 mg)
Oral antiemetics
Metoclopramide (Maxolon) (10 mg)
Prochlorperazine (Stemetil) (5–10 mg)
Domperidone (Motilium) (10 mg)
Migraine specific medications
Ergotamine preparations
Ergotamine with caffeine
Triptan preparations
Parenteral medications for severe attacks
Dihydroergotamine (DHE)
Metoclopramide (Maxolon)
Prochlorperazine (Stemetil)
Chlorpromazine (Largactil)
Promethazine (Phenergan)
Subcutaneous sumatriptan (6 mg)
Others
Intravenous valproate
Intramuscular droperidol

Intravenous fluids

Vomiting, lack of fluid intake, and the potential for dehydration may necessitate the administration of intravenous fluids such as normal saline or dextrose water.

Parenteral medications

With the fluid replacement, the parenterally administered medications either alone or in varying combinations are useful (*Table 2*). Dihydroergotamine should be the mainstay of treatment, in conjunction with either prochlorperazine or metoclopramide. It may be combined with chlorpromazine and promethazine. Analgesics such as codeine phosphate (50 mg rectally or intramuscularly) or tramadol (50 mg intravenously) can be added. These medications, alone or in combination, can be administered every 6–8 hours. In severe refractory migraines, adding corticosteroids (dexamethasone 4 mg) to the above regimens is useful.[14] As an alternative to the above, subcutaneous sumatriptan (6 mg) may be considered.

Intravenous valproate

In a recent open label study,[16] intravenous valproate was shown to be effective and largely free of side effects in the treatment of acute migraine. Randomised, double blind, controlled studies are needed, but this appears to be a potentially exciting option for the future.

Droperidol

This neuroleptic with dopamine receptor antagonist actions has been shown in a large, randomised, placebo controlled trial[18] to have significant effect on headache and migraine related symptoms after intramuscular injection, but it has a high rate of akathisia (31%), somnolence (20%), and anxiety (16%). Droperidol use should be limited to emergency departments for patients unable to tolerate triptans and who have severe nausea and vomiting.[9]

Prophylactic management

A very important aspect of the management of migraine is the prevention of future attacks. If considering prophylaxis it is vital to ensure the condition being treated is truly migraine and not

- chronic daily headaches with occasional migraine peaks, or
- episodic tension type headaches

where the management differs quite substantially.[2] As a general rule, if there are more than two migraines per month it is worthwhile considering prophylaxis. If the decision has been made to begin prophylactic measures as opposed to treating attacks ad hoc, there are two important considerations.

Encourage patients to adopt a chronic disease model

Effective management of migraine requires from the patient the same discipline and attention to detail as is required of the chronic asthmatic or insulin dependent diabetic. If the patient understands the long term, noncurable nature of the disease – and the need for ongoing doctor-patient cooperation – an interactive model of care can be established with good results.[2]

Determine whether or not there is medication overuse

Overuse of medication is frequently the direct cause of the development of chronic daily headache from an episodic form of migraine. Medication overuse will result in a refractoriness of headache frequency and severity that is very difficult to break. Overuse of acute antimigraine drugs frequently negates the effectiveness of prophylactic medication.[17] Definitions[17] for overuse are:

- ergotamine intake on ≥10 days per month on a regular basis for >3 months
- triptan intake (any formulation) on ≥10 days per month on a regular basis for >3 months
- intake of simple analgesics on ≥15 days per month on a regular basis for >3 months
- intake of combination analgesic medications on ≥10 days per month on a regular basis for >3 months.

As a rule of thumb, if the patient is using rescue ergot preparations, analgesics (especially codeine), or triptans on more than 2 days per week, there is the real potential for rebound headache to develop.

Stages of migraine prevention

Stage 1 – avoidance of triggers

Triggers may be as mundane as a sensitivity to perfume or cleaning agents, the eating of certain foodstuffs, menstruation, or emotional ups and downs. Patients may need prompting to recall triggers such as lack of sleep or too much sleep, or specific times of the week when migraines tend to occur; but in the majority of cases the patient will be aware of their unique triggers. Advocating the avoidance of those triggers is simple, but sometimes lifestyle factors are difficult to change and the process may require repetition and psychological support. Creative advice from an independent medical observer is often invaluable. Although the cause of the dramatic increase in prevalence of migraine in both children and adults in past decades is unknown, environmental factors such as dietary changes, social instability, and stress have been implicated.[18] If recognised triggers (eg. exercise) cannot be avoided, NSAIDs taken before such a trigger can be useful.

Stage 2 – nonpharmacological methods

Patients will often express the wish to use 'natural' methods to prevent migraines, and it is wise to implement these before prescribing medications. There are many nonpharmacological methods advocated for prevention of migraine that have not been tested in a rigorous, double blinded fashion.[2,19] Two approaches seem to be worth considering: dietary manipulation, and biofeedback.

Dietary change

Migraine sufferers are aware that certain foods can precipitate a migraine attack. These include cheese, chocolate, monosodium glutamate, artificial sweeteners, hot dogs, citrus fruits and wine. Low fat diets appear to reduce the intensity and duration of migraines.[20] Although a meta-analysis of studies related to the effect of biogenic amine challenge in migraine causation found no significant effect,[21] the subject remains controversial with other authors suggesting that abnormally high circulating levels of 'elusive amines' (tyramine, octopamine, synephrine) may be implicated in migraine genesis and that dietry restrictions of foods containing high levels of these may be helpful.[22]

Behavioural interventions

Paediatric studies have indicated that biofeedback is useful. Biofeedback as an adjunct to migraine management is based on the assumption that patients with migraine have unique and sustained autonomic responses to a variety of external or physiological triggers. Meta-analysis of studies on behavioural interventions (stress management, biofeedback, relaxation) have shown a 35–50% reduction in migraine activity.[23]

Stage 3 – pharmacological methods

Medications such as propranolol, metoprolol, amitriptyline, pizotifen and methysergide have been used for several decades and are well accepted, proven prophylactics. However, response is idiosyncratic, and the initial choice should be guided by individual contraindications such as the use of beta adrenergic receptor blockers in asthmatics. Medications are then trialled according to clinical response and the development of side effects.

Newer medications with demonstrated efficacy are valproate, flunarazine and topiramate. The first is readily available and effective, the second requires authority for special consideration, the third is not on the Australian Pharmaceutical Benefits Schedule (PBS) for use in migraine, although it has been shown to be effective in double blind, placebo controlled trials.[8] Topiramate is a broad spectrum antiepileptic drug that appears safe, well tolerated and has the advantage of promoting weight loss.

The use of botulinum toxin is as yet unresolved. One recent randomised, double blind, placebo controlled study failed to demonstrate any efficacy of botulinum toxin A in prophylactic treatment of migraine.[24] Other studies have shown positive results,[9] but the selection of patients, the sites of injection, and optimal dosage are as yet unresolved. Botulinum toxin is not PBS listed in Australia for use in migraine.

Candesartan, an angiotensin converting enzyme inhibitor, has been shown to be effective in migraine prevention in a recent prospective placebo controlled trial.[8]

Both riboflavin and magnesium supplements are reported to be useful, and can be considered in patients not willing to be take conventional drugs.[15] There are other medications that are widely used, but for migraine prophylaxis there is little or no evidence of efficacy. These include selective serotonin reuptake inhibitors (SSRIs) and verapamil.

Conclusion

Migraine management can be very effective. If the condition is approached systematically and with careful attention to detail the result can be satisfying for both the patient and treating doctor. Explanation and preparation of the patient is essential. While migraine is an inherited biological condition that is not curable, adherence to an ongoing discipline and the application treatment algorithm based on its understood pathophysiology can benefit sufferers greatly.

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